Computer Simulations and the Changing Face of Scientific Experimentation

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Edited by

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To Kassandra Pomper, for her support and companionship
during all the stages of this book
—Juan

To Rolf Ital who spoiled me by buying me my first computer
for my twelfth birthday
—Eckhart

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INTRODUCTION

William Aspray recorded the first use of computers for scientific usage between 1952 and 1957. By June of 1952, the IAS computer was finished and ready to be tested; although it needed some extra months for repair and general maintenance, the major issue for the team of scientists and engineers was to understand the new instrument. The digital computer, built and designed on solid theoretical foundations, presented a significant challenge; namely, it was necessary to dedicate some extra time to learn the operation of the machine, identify appropriate algorithms, and determine the range of mathematical applications within the computer's capacity (1990, 155). By the time the computer became a more knowledgeable and reliable instrument, scientists and engineers began to use it with great success in specific scientific applications. By 1954, the calculation of the energy band structure of iron that would test the theory of ferromagnetism became the first scientific application to run on a digital computer (1990, 159).

In the years following 1954, the digital computer proved to be a fundamental tool for the development and advancement of scientific understanding. Today, despite their short history, computers are leaving an indelible mark on numerous and disparate scientific disciplines such as particle physics, astronomy, behavioral science, psychology, sociology, and economics. Arguably, there is virtually no scientific discipline that has not been involved, in one way or another, with the digital computer. This durable presence extends widely along the uses and needs of scientific practice. For instance, the numerical experiment of calculating the energy band structure of iron qualifies, in contemporary parlance, as a computer simulation. The main topic of this book is precisely to address the uses of and needs for computer simulations in contemporary scientific practice. In this context, computer simulations are discussed from a philosophical, historical, and scientific point of view.

Nowadays, there is a renewed interest in understanding the role that computer simulations play in scientific practice. Do computer simulations belong with the calculator and the test tube, or do they belong higher in the epistemic hierarchy, closer to theories and experiments? Are they just scientific models implemented on the digital computer, or do they represent a novel way of doing science? Given the centrality of the issue, it

is not surprising to find that there have been many attempts to theorize about the nature of computer simulations as experimental devices. Admittedly, these questions have been around for quite some time. As early as 1967, Naylor, Burdick and Sasser, define a computer simulation as:

> A numerical technique for conducting experiments with certain types of mathematical and logical models describing the behavior of an economic system on a digital computer over extended periods of time (…) The principal difference between a simulation experiment and a 'real world' experiment is that with simulation the experiment is conducted with a model of the economic system rather than with the actual economic system itself (1967, 1316).

It is astonishing to note the similarity of this quotation with more contemporary literature on the topic. Current philosophical inquiry also engages in similar efforts, such as distinguishing between a computer simulation and a 'real world' experiment, or exploring the methodological implications of implementing a scientific model as a computer simulation.

Yet, despite these few similarities, much of the contemporary philosophical investigation is simply not the same as in the late 1960s. From a historical perspective, the introduction of silicon based circuits, and the subsequent standardization of the circuit board significantly helped the industry and the growth in the computational power of computers. Such growth in speed of calculation, size of memory, or the number of programming languages forcefully challenged the established ideas and encouraged the seeking of new questions and answers.

One of the leading questions on this issue has been whether computer simulations stand for a new way of conducting scientific practices, or if they simply represent another computational method subsidiary of experimentation. The work of Rohrlich (1990) sets the grounds in this direction. He argues, computer simulations do provide a qualitatively new methodology for the physical sciences, lying somewhere intermediate between theoretical physics and empirical methods of experimentation.

However, Frigg and Reiss (2009) deliver the most pressing contemporary discussion on the philosophical relevance of computer simulations. The authors understand computer simulations in the context of the philosophy of models and, as such, with no significant distinctions from other uses of modeling in experimental practice. Humphreys (2009) answers their skepticism by indicating that the way the argument is presented is misleading, for it illuminates only computer simulations from the perspective of a philosophy of models. To Humphreys' mind, computer

simulations raise questions that cannot be answered by a familiar philosophy, but rather need to be addressed at face value.

Beyond the specific contribution that this discussion can offer to the philosophical study of computer simulations, there is general agreement that computer simulations raise important questions for the general philosophy of science. One interesting example is the search for general criteria that distinguish computer simulations from experiments. Such a search has ramifications on studies about the epistemic power of computer simulations, the ontological and epistemological status of simulation data, the importance of new methodologies involved in the design and building of a computer simulation, and similar questions.

From September 21st to September 23rd 2011, the interdisciplinary workshop "Computer Simulations and the Changing Face of Scientific Experimentation," sponsored by the University of Stuttgart and the Stuttgart Research Center for Simulation Technology (SRC SimTech), brought together philosophers, historians, sociologists, and scientists into a common discussion with the purpose of revisiting some of the questions here mentioned, and addressing the new challenges that computer simulations pose to scientific practice.

We have divided this book into three mutually related parts. Part One (Theory) is dedicated to the theoretical understanding of the relation between simulations and experiments in the current philosophy of science. Part Two (Practice) fleshes out some of the theoretical conceptualizations presented in Part One by illustrating case studies from current scientific research on computer simulations. These case studies highlight the shift from experiments to computer simulations that is observed in current scientific practice, and describe the patterns of interaction between simulation methods and experimental methods in current scientific research. Part Three (History) broadens the perspective by offering case studies on the historical development of "computer experiments" as a research method.

The first part of the book is dedicated to the diversity of views among philosophers regarding existing distinctions between computer simulations and experiments, the epistemic power of computer simulations, and the new methodologies that they represent.

In the first contribution ("What Are Data About?"), Paul Humphreys calls our attention to the discussion about the status of data produced by a computer simulation. His paper focuses on the content of data produced, instead of the source that produces such data. According to the author, the origins and modes of production of these data show that the empiricist

point of view is no longer an attainable position in the philosophy of science. This argument derives its force from what the author calls 'causal-computational instruments'; that is, an instrument that relies on a causal process that links the data source in nature with the measurement, but that also requires further post-processing for rendering reliable data. In Humphrey's mind, then, such causal-computational instruments cannot be interpreted in the same way as Hacking discusses microscopes, where a realist interpretation of the images is justified by the independent access to the same phenomenon through different observational instruments. The decisive point here is that the data delivered by a causal-computational instrument, like a CT scan, are the result of deliberate engineering. Depending on the particular purpose, say, whether the data is meant to be "read" by a human agent or further processed in the computer, the appearance of the engineered data may differ considerably. In order to determine its representational content, it is therefore central to take into account the origin of the data as well as the engineering steps by which it is formed (and transformed). Causal-computational instruments, then, pose a significant challenge for philosophers interested in traditional problems of empiricism, realism, and the notion of data.

If Humphreys reminds us that there is a considerable amount of engineering involved in the production of the empirical data by causal-computational instruments, Anounk Barberousse and Marion Vorms ("Computer Simulations and Empirical Data") attack the problem from the opposite side; that is, by examining whether the data produced by a genuine computer simulation can, with any good reason, be considered empirical data. Starting from the assumption that empirical data are about physical systems, Barberousse and Vorms challenge the opinion that the data produced by computer simulations cannot be new or surprising. It is frequently assumed that computer simulations, because they rely heavily on pre-existing theoretical background knowledge of the simulated objects, are less capable of producing genuinely novel and surprising insights about their target system than observations or traditional experimentation. The authors support the claim that this assertion is mistaken with the example of computer simulations of deterministic chaos.

While this conclusion emphasizes the capacity of computer simulations to produce empirical data that are as novel and surprising as that of experiments or observations, Eckhart Arnold points out the differences that remain between simulations and experiments as scientific methods ("Experiment and Simulations: Do They Fuse?"). Most notably, he argues that the results produced by computer simulations cannot go beyond what

lies in the deductive closure of their premises. According to Arnold, a simulation, unlike a material experiment, cannot be employed as an *experimentum crucis*. The chapter therefore contains an elaborated criticism of some, in Arnold's opinion, misguided philosophical conceptualizations of computer simulations. With respect to the borderline between simulations and experiments, however, one question remains that is not so easily dismissed: How can a measurement that involves the computational refinement of its data properly be distinguished from a computer simulation that makes use of input data of empirical origin? To this question, Arnold gives a tentative answer based on the *measuring a cause by its effect pattern*, a pattern that is typical for many traditional measurement methods already.

The contribution by Juan M. Durán ("The Use of the 'Materiality Argument' in the Literature on Computer Simulations") continues the discussion on the differences between computer simulations and experiments, but this time from a meta-critical point of view. Durán's main concern is to unpack the underlying rationale that has been guiding the argumentation in current literature. By addressing the so-called "materiality argument" present in three different conceptualizations, the author shows that there is a common argumentative structure that inevitably shapes the final epistemological evaluation of computer simulations. Specifically, Durán presents what he calls 'the materiality aftermath,' a meta-criticism that exposes the rationale underlying the arguments in the current literature on simulations. In the author's mind, 'the materiality aftermath' is the result of the philosopher's ontological commitment to computer simulations, from which epistemological consequences are drawn. The author believes that adapting the philosophical investigation to this rationale leads to a conceptual corset in the inquiry of the epistemology of computer simulations. Durán's conclusion is sober, and aims at endorsing the philosophical investigation on computer simulations as neither restricted by, nor limited to, ontological commitments, but rather addressed at face value.

The contribution by Pío García and Marisa Velasco ("Exploratory Strategies: Experiments and Simulations") turns the discussion to a notion of 'exploratory strategy' applicable to computer simulations. Particularly, the authors analyze exploratory strategies in experiments and computer simulations, and elucidate the methodological and epistemological role in both domains. Their proposal, then, consists first in drawing some distinctions between computer simulations and experiments. Second, the authors make explicit the concept of 'exploratory strategy,' establishing a further distinction between exploratory experiments and other types of

experiments. This second step allows them to present their own proposal as a different way to approach the epistemic and methodological aspects of scientific practices, particularly, computer simulations. Some relevant cases of experimental and simulation activity are considered in the context of 'exploratory strategies.'

In the second part of the book, the focus is shifted from the abstract and theoretical philosophical discussion to the analysis of concrete examples. The first of these papers is the study of simulations of cardiac electro-physiology by Annamaria Carusi, Blanca Rodriguez and Kevin Burrage ("Model Systems in Computational System Biology"). Their case study concerns multi-scale models of cardiac electro-physiology. These models represent a challenge from a technical as well as a philosophical point of view. Defying any sharp distinction between simulations and experiments, the authors claim that "the basic unit of analysis when considering questions of the validation and epistemic warrant of computational methods in systems biology" is the model-simulation-experiment-system (MSE). In particular, the target system cannot be understood simply as a given reality, rather it is co-constructed with the MSE system. The construction of the target domain is inevitable because the validation data need to be comparable to the MSE system. However, the term 'construction' must not be misunderstood as implying a relativistic understanding of science in this context. The validation experiments remain independent in the sense that they do not make use of any data that have been used for model construction.

Anne Marcovich and Terry Shinn's contribution ("Computer Simulation and the Growth of Nanoscale Research in Biology") explores three links between computer simulations and nanobiology research. First, they show that there is a correlation between nano-related biology publications in the early 1990s and the introduction of computer simulations in scientific practice. Second, computer based research contributes to the cognition of nanobiology through the creation, organization, and consultation of databases. Finally, the authors show that "simulation molecular graphics generate images that are informationally and analytically rich, and that offer a fundamental input into novel forms of epistemology." Their contribution shows not only how the academic agenda is strongly driven by the introduction of new technologies, but also how computer simulations can provide a genuine understanding of their simulated target system, requiring a novel form of epistemology.

In their contribution, Lucía Ayala and Jaime Forero-Romero ("Computer Simulations in a Cosmological Context") discuss the case of

testing hypotheses in cosmology. Physical cosmology represents a special case in the natural sciences with regard to the available methods for testing a hypothesis. Since direct experiments are excluded, observations and simulations must carry out this testing function. In their contribution, the authors discuss the special case of numerical simulations as an essential tool for understanding the observed large-scale structures in the Universe. This discussion is followed by a description of the limitations of simulations in understanding such large-scale structures. For instance, the physical nature of computer simulations becomes a limitation. As the authors point out, time, data storage, and data transfer rates are restricted. Ultimately, theory, observations, and simulations work together and, with their different potentials and limitations, mutually complement each other in contemporary astronomy.

Muniza Rehman traces the latest developments in the use of simulations and experiments in the pharmaceutical industry ("Experimentation and Simulations in the Pharmaceutical Industry"). Rehman places simulations between traditional experimentation and theoretical accounts. To the author's mind, two kinds of simulation studies are common in the pharmaceutical industry: Computer-assisted trial designs (CATD) and computer-simulated clinical trials (CSCT). The former are employed to study the experimental design of clinical studies, before they are conducted. The latter are used to estimate the outcome of clinical trials, potentially rendering some of these trials unnecessary and thus reducing the number of clinical trials that actually have to be conducted. Some philosophers have disputed that simulations provide a true novelty over traditional modes of modeling and theoretical exploration. Nevertheless, given how strongly the use of computer simulations has affected the practice of drug testing in the pharmaceutical industry, Rehman concludes that from this perspective simulations are indeed a *sui generis* activity in a Humphreyan sense.

The third and last part completes the book with historical case studies. Wolfgang Brand ("Designing the Membrane Roof of the Munich Olympic Stadium using Supercomputers") presents a historical case study of the deployment of the first supercomputers in architecture and civil engineering. The events around the design of the tent-shaped membrane roof of the Munich Olympic Stadium for the 1972 Olympic Games demonstrates how physical models of constructions enable technologies for the construction of naturally shaped buildings. It is argued that the 1960s mark the period in which the usage of high performance computers triggered the change toward architectural design processes. The technology

available had already reached a state where model building was no longer necessary. It is shown how two groups using different methods on the same computing infrastructure designed the roofs inspired by the ideas of Frei Otto. They developed wide-spanning lightweight structures consisting of pre-stressed cable nets covered by transparent tiles. The group of John H. Argyris relied on the Finite Element Method, which he co-invented. While another group headed by Klaus Linkwitz used least-square fitting and developed the new Force Density Method, all influenced by geodesic methods. Both attempts were successful and led to the landmark Olympic Stadium in Munich, as we know it today.

A somewhat different perspective on simulations is introduced by Michael Resch ("What's the Result? Thoughts of a Center Director on Simulations"). As head of the high-performance computing center in Stuttgart, Resch addresses the technological procedures (and their limitations) by which simulations are implemented and executed on the computer. In this respect, Resch proposes an addition to Winsberg's (2010) layered model of simulations, which also includes numerical schemes, program structures, programming models, and hardware architectures. All of these influence the capabilities as well as the limitations of the simulation approach. Resch, then, embeds his 'prototypical workflow' into a broad philosophical perspective, covering the question of verification and validation, as well as the need for rendering simulation results comprehensible to human beings. The latter issue does not only concern the specialist user of simulations, but also is of interest for society –as the example of climate simulations may illustrate.

We hope that readers from different humanistic and scientific fields that concern themselves with computer simulations find the broad perspective of our book useful. The editors would like to thank the University of Stuttgart and the SRC SimTech for financial support that made the workshop possible. This book is a publication of the papers presented at that workshop. We are in debt to the participants for making the workshop a successful event. Most of all, we would also like to thank all the authors that, with their excellent contributions, made this book possible.

Juan M. Durán and Eckhart Arnold

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PART I:

THEORY

CHAPTER ONE

WHAT ARE DATA ABOUT?

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Empiricism is no longer a tenable position in the philosophy of science. As a result, it is worth examining what it was that made empiricism such an attractive position for so long and if anything valuable can be salvaged from that tradition. The debates about empiricism usually contrasted knowledge obtained from observation and experiment on the one hand with knowledge obtained from theories on the other. Because computer simulations are firmly entrenched as a third mode of pursuing scientific inquiry, one way to explore what made empiricism important is by contrasting data that are provided by experiments and observations with data that are generated by computer simulations. In doing so, my paper will indirectly address one of the original philosophical issues about computer simulations: in what ways, if at all, do computer simulations differ from scientific theories on the one hand and experiments on the other?[1] Early in the discussions, claims were made that simulations had some kind of intermediate status between theory and experiment, while also standing as sui generis methods. More recently, claims have been made that simulations can be used in place of material experiments under certain circumstances.[2] Although it is true that there are similarities between certain aspects of simulations and experiments, pointing out analogies between laboratory experiments and computer simulations, such as the ability to manipulate variables and control for confounders, do not address one of the central epistemological questions that arise once

[1] This issue was present almost from the inception of computer simulations. Explicit attitudes towards it can be found in (Ord-Smith and Stephenson, 1975, 3), (Rohrlich, 1991), (Humphreys, 1994).
[2] See Norton and Suppe (2001), Winsberg (2003), Parker (2009).

simulations are brought into the picture. This question is: Are the data produced by computer simulations different in kind and in content from experimental and observational data, and from data generated by traditional scientific or mathematical theories? If we have reasons to agree that they are different in a scientifically relevant way, then that is one dimension along which simulations occupy a distinct scientific niche. Empiricists have usually treated the issue of the empirical source of data within a methodological context such as confirmation, verification, or falsification. I shall focus instead on content. One important question is this: what is it for a datum to have empirical content?[3] An answer to that question is provided in (Humphreys forthcoming); here we can make additional progress by addressing a related question: what are various kinds of data about?

What are Data?

In order to remain as ontological neutral as possible about data, I take a datum to be the value of a variable. The term 'variable' will be used here in a way that is neutral between items such as a mathematical function that represents a property and the property itself.[4] This dual use carries with it certain dangers because the role of representations in computer simulations is crucial, but where appropriate I shall explicitly note which use is in play. The variable can be scalar and discrete valued, which covers situations in which the datum concerns a qualitative monadic property such as "is red," or it can be vector and continuous valued, capturing relational features such as "has velocity v with respect to frame F." Other possibilities can be accommodated. I shall not distinguish between atomic and non-atomic data because nothing that follows depends upon making that distinction. Finally, although the expression "data" often carries the force of something given, something fundamental, those connotations must be rejected. Data can be the result of processing, transformations, and interpretation, and we can and often do question the data.[5]

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[3] There are other epistemological issues about simulations and experiments including: 1) the a priori versus the a posteriori content of data from each, 2) the empirical versus the formal content of data from each, and 3) the relative rates of reliability as truth generators for data from each.

[4] The variable can be purely formal and hence represent nothing.

[5] The distinction between data and phenomena drawn in Bogen and Woodward (1988) and other papers is compatible with the definition of a datum given here, although their emphasis on the causal production of data perhaps indicates a narrower use of the term "data" than is considered here.

Data can be assessed on their own terms, without regard for what generated them and an important aspect of our definition is that it does not mention the origins of a datum, allowing data to originate from computational processes, from experiments, from theory, and perhaps other sources. Yet, if we are to address the question of what the data are about we must solve the *inverse inference problem*. The inverse inference problem consists in making, and providing a justification for, an inference from the data to its source. In the debates between scientific realists and empiricists, the issue is usually cast as one of whether terms in scientific theories that purport to refer to unobservables genuinely refer, but it can be recast as the problem of what objects' and properties' existence can justifiably be inferred from the empirical data. In these terms, inferring the existence of Saturn's rings and their properties from what is observed through a low powered telescope is an inverse inference problem, as is inferring the existence of a virus from an electron microscope image. The converse of the inverse inference problem, the direct inference problem, is the problem of what data will be available given the existence of the source.

To see how addressing the inverse inference problem and assessing the content of data make a difference to how we evaluate data, consider the traditional division between empiricism and rationalism.[6] For empiricists, data that are the result of direct perceptual experience, or on a slightly more liberal agenda, data that are a result of observations by elementary equipment that include the human senses, are the most desirable and, for many, are the only source of genuine knowledge. The reasons for this desirability vary. On the one hand there is a widely shared belief that the origins of the data in the causal world make their content more desirable than the content of data whose origins are whatever produces a priori knowledge. On the other hand the empiricists' starting point was the content of the datum and not its origin, an orientation that deliberately left open the possibility that the external world might not be the source of the empirical datum and might not even exist, leading either to a lack of commitment to the existence of that data's origins, as in constructive empiricism, or to an outright denial, as in idealism.

[6] What constitutes empiricism and rationalism is, and probably forever will be, a matter of scholarly dispute. I am using the terms here as surrogates for broad epistemic attitudes that I assume most philosophical readers will recognize. For the record, I subscribe to the view that although it is often a matter of historical contingencies when a particular philosophical issue is raised and becomes the subject of focused discussion, the issue itself transcends those historical contingencies.

Empiricists have granted privileged status to observational data for a number of other reasons. One was that data about directly observable entities seem to have the certainty that was lacking in data that were about unobservables. This certainty was a reason for refusing to provide a solution to the inverse inference problem and it was the intrinsic content of the data to which any certainty attached. A second reason was that data about observables were supposed to act as a theory independent basis for deciding between rival theories. On what might now seem to be rather naive grounds for taking the intrinsic content of a datum to be theory-independent, this gave privileged status to such content, and a bonus was that by avoiding making inverse inferences, no theory was needed in that capacity either. A third reason was that empirical data were taken to be the only reliable source of information about contingencies existing in our world; a priori methods were incapable of that degree of specificity. For various reasons, all of which are plausible, the first and second of these reasons no longer have the force once attributed to them and in light of the well-known arguments formulated by Quine (1951), the distinction between the a priori and the a posteriori is now seen to be a much more difficult distinction to make than was originally imagined.

It is a different issue that lies behind some of the difficulties in assessing the status of data from simulations and experiments. The issue is the extent to which inverse inference problems need to be solved in order to decide what the data are about. One set of solutions to this problem, following the empiricist tradition, attempts to attribute content to the data without taking into account their origins. This approach starts with data and avoids making inferences about their origins as far as is possible. If the content of data from simulations and from experiments is equivalent under this approach, then data from the two classes are inter-substitutable. Thus, if a simulation of independent tosses of a coin with parameter p is based on an accurate model of a sequence of tosses of a real coin with that degree of bias, the data from the simulation can replace the data from the experiment and we can ignore the origins of the data.[7] Another set of solutions suggests that the origins of data in material systems make those data about something different than data coming from a computer simulation and so inferences that are often not easy to justify are required to use data from simulations in place of data from experiments. These are complicated issues and I can only sketch a solution here, but the overall view is that the origins and mode of production of data must be taken into account.

[7] This is the position taken by Kästner and Arnold (2012) in which well-confirmed theories play a central role. See also Winsberg (2009)

Simulations and Experiments

In recent years, there has been considerable discussion about whether computer simulations can serve as a replacement for material experiments. Those who have argued for relevant similarities between simulations and experiments tend to emphasize methodological considerations.[8] Barberousse, Franceschelli and Imbert (2009) (hereafter BFI) have drawn an important distinction between two types of data, $data_E$ and $data_A$. BFI define $data_E$ as being 'of empirical origin, namely produced by physical interactions with measuring or detection devices' (2009, 560). It seems clear from this definition, and also from the examples used to illustrate the definition, that $data_E$ are data produced by purely causal instruments. In contrast, $data_A$ are about a physical system. BFI note that $data_A$ may be produced by $data_E$ 'but also via other processes, among them analytical or numerical pen-and pencil-computed solutions of systems of equations representing the target systems, and computer simulations' (2009, 560) In the present context I shall take simulations to be like traditional pencil and paper solutions in the sense that they are drawing out consequences of formal representations.[9]

The distinction drawn by BFI is important and helpful and their insistence that it is the representational aspects of computer simulations that constitute the dividing line between experiments and simulations is exactly right, but we shall need to see how the distinction plays out in the realm of causal-computational instruments (see section "Causal-computational instruments" below). The distinction also opens up some important

[8] In this paper, 'simulation' refers to a digital computer simulation and 'experiment' refers to a laboratory experiment. In the latter, all known relevant variables except for explicitly specified independent variables are controlled and the manipulations of the independent variables are epistemically transparent in the sense that the causal effects of the manipulations on those variables are known. The point of the experiment is then to identify the causal effects of the independent variables on the dependent variables. The situation with a single independent variable and a single dependent variable is a special case.

[9] This assertion is consistent with my position (Humphreys 1994, 2004) that the physical implementation of computer simulations places constraints on simulation methods that are not present in traditional a priori mathematics and that epistemic opacity, including the need to make inductive inferences in place of deductive inferences, is usually present. Despite some claims in the literature to the contrary, I have never endorsed the view that running simulations on material computers is itself a reason to justify substituting data from simulations for data from experiments. Numerical experiments are significantly different from material experiments.

philosophical questions. One is how to interpret data that have transformations applied to them after their origination. Suppose we grant that we can correctly specify what counts as a measurement or a detection device.[10] Then, in the case of $data_E$, consider what happens when a representation of an empirical datum has a formal transformation applied to it. Suppose that we have a square divided into two so that the left hand side is white and the right hand side is black. An imaging device (consider a digital camera for simplicity) takes a photograph of the square and forms a digital visual image that duplicates the original square. The image is unquestionably a representation of the square and the data, which are a spatial array of black and white pixels, are about that square. It is easy to perform a formal transformation on that data set so that all of the pixels on the right hand side are transformed from black to white and all of the pixels on the left hand side are transformed from white to black. What is this second image a representation of and what is it about? Exactly the same image could have been obtained by a purely causal process by using a mirror to produce the left-right inversion. So one answer to these questions is that it is a mirror image of the original square, hence a representation of it and that the $data_A$ are about the original square. Now consider the case where only the formal transformation of the right hand side from black to white is carried out. The resulting image is a completely white square. What is this a representation of and what is it about? A variety of answers are plausible. To preserve consistency with the first and second cases, it seems we should give the same answers: The purely white square is a representation of the original square and the data are about it. Yet, it is such an extremely poor representation that one wonders in what sense it counts as a representation at all.

To see more clearly what is at issue, suppose that we have a digital photograph of a couple, Jack and Jill, against a white background. A computer algorithm removes the pixels representing Jack, replacing them with white pixels, leaving only a visible image of Jill. This image contains $data_E$ according to the above definition, and this is surely correct, but what is it about? Most people would say that the image, which consists of a spatial data array, is about Jill. Clear enough, although this answer deviates from the criteria we used for the black and white squares example. So now consider a parallel example in which the original photograph is of Jill alone, but an algorithm transforms white pixels into a colored array that is a representation of Jack. What is this new image about? It is a representation of Jack and Jill, and it is therefore about Jack

[10] This is not at all easy and I shall not attempt to solve the problems here.

and Jill, although it is a photograph of Jill only and so, on an origins view of data content, about Jill only.[11] The pixels that make up the image of Jill are all $data_E$ as well as $data_A$, whereas the pixels that make up the image of Jack are $data_A$ only.

We have here a familiar set of philosophical issues. $Data_A$ can be about the causal sources that give rise to $data_E$. Emphasis on the causal origins of the data, typified by causal theories of reference and perception, lead to one set of answers regarding what $data_A$ are about. But what $data_A$ are about can have nothing to do with the relevant $data_E$ and the interpretation is imposed by the intentions of an interpreter of the data. We thus need to say more regarding what the $data_A$ are about. Under the causal view, for an individual datum we can plausibly say that it is about whatever gave rise to that datum regardless of the accuracy of its content. In this there is an echo of the causal theory of reference in that all of the descriptive content of a piece of referential apparatus can be wrong and yet that apparatus can successfully refer. Thus, rather than begin with the datum itself, we begin with a realist attribution of the existence of the source. The inverse inference to that source is underdetermined, but this is an additional complication that is unavoidable and I set it aside here.[12] The underlying problem here is this: when philosophers still believed in pure observations, the idea was that such things gave us direct access to what was being observed. In contrast, we required inverse inferences to know what the referents of theoretical terms were. That view about direct access seems quite naive now, but we can retain one element by highlighting the fact that there is a causal pathway connecting the observation with the entity observed. Yet, we lose that causal pathway not only with simulations but also with a widely used class of imaging devices. The point here is that what data are about is a vexed and complicated issue that is intimately tied to an adequate theory of reference. BFI were right to draw our attention to this aspect of the simulations versus experiments debate. The origins of the data, whether material or not, are insufficient to determine the content of $data_A$. So let us generalize the concept of $data_E$ to $data_O$ where $data_O$ are data generated either by causal or computational sources. Here the 'O' indicates that the origin of the data be included in a specification of the data.

[11] Definitions of 'photograph' stipulate that the image must have been formed by electromagnetic radiation (usually visible light) falling on some recording device.

[12] This is not to suggest that underdetermination problems in inverse inference methods are unimportant. Both theoretically and in practice solutions to these problems must be found.

Causal-Computational Instruments

To help clarify matters, it is useful to consider a particular type of instrument, those that I shall call causal-computational instruments. Almost all discussions of scientific instruments implicitly restrict themselves to what I shall call non-computational instruments.[13] By a non-computational instrument I mean that the instrument receives some physical process as an input, the instrument causally interacts with the input to transform it, the instrument's output is another physical process, and none of these processes or interactions is a computation.[14] All of the familiar scientific instruments discussed in the philosophical literature are of the non-computational kind: optical telescopes and microscopes, magnetometers, oscilloscopes, and so on.[15] In the last fifty years or so, a potentially different class of instruments has been developed that I shall call causal-computational instruments. These take physical processes as inputs and at some point in the operation of the instrument, they convert physical states into digital representations that undergo computational transformations before producing the instrument's output.[16] Of course, these causal-computational instruments have causal aspects not only because of their inputs but because the implementation of the computations is carried out by causal processes. Yet, causal-computational instruments fall into a class intermediate between purely causal instruments and computer simulations because inferences and representations play a crucial role in their operation but, unlike pure simulations, the causal inputs to the physical device also play a central role in the interpretation of the output.

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[13] One of the few exceptions is Israel-Jost (2011).

[14] For our present purposes, what counts as a computation will involve only those in the class of Turing computable discrete functions. This rules out the view that all physical processes are computations and provide the basis for a principled distinction between computational and non-computational instruments.

[15] I am in this paper excluding the human perceptual system as an example of a scientific instrument because it is too difficult to disentangle interpretations of the datum from the causal processes that lead to the datum, although in a more general context there are epistemological advantages to viewing the human perceptual apparatus as simply another instrument that produces data.

[16] Many traditional instruments now use digital displays for their outputs but that does not by itself introduce a computational element into the instrument. Although the distinction is perhaps not easy to make completely clear, an instrument in which the display types are antecedently fixed does not count. Under computational theories of vision, parts of the human perceptual system may count as a computationally enhanced instrument.

I shall take as examples of causal-computational instruments the category of medical imaging devices that includes computed tomography (CT) and positron emission tomography (PET) instruments.[17] Although the physical operation of specific types of instruments is crucial for understanding how they produce data, most of the philosophical points I make here generalize from the specific examples discussed. A generic diagram of scientific instruments is given in Figure 1-1.

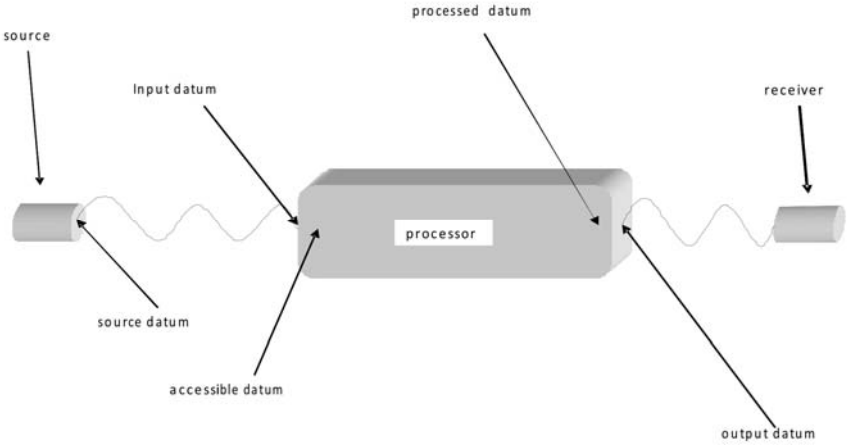

Figure 1-1

What I have called the processor can be either a purely causal transformation device, such as a telescope lens, or a computational device. The generic case that I consider has the source as an object with a single spatially varying quantitative property represented by a continuous or discrete function *f(s)* on the space $\mathbb{R}^2$ or $\mathbb{R}^3$. Values of *f* are the source data. For concreteness, take as the running example the situation in which *f* represents the intensity of X-rays in a spatial region or the spatial distribution of some radioactive biological marker, where the spatial region includes some target such as a human body. The task is then to estimate the mathematical form of *f* or specified values of *f* using the receiver data. The input data are often the result of complex physical

[17] The principal use of PET scans is for imaging of brain tumors, epilepsy, strokes, and Alzheimer's disease. Magnetic resonance imaging (MRI) devices use different methods than do PET and CT devices.

processes within the system that must be modeled in order to infer both the general form and the specific values of *f*.

Both CT and PET instruments construct a two dimensional (sometimes three dimensional) image from a sequence of one dimensional projections. The construction process, which is inescapably computational, involves a set of inverse inferences from the receiver data to the source of that data. A number of different mathematical techniques are used for these inferences (here I shall discuss one of the most frequently used methods, filtered backprojection). Although such inferences run against the primary direction of causation from input to output, this does not violate the causal component of these instruments. Similar inverse inferences are made in purely causal instruments, such as refracting telescopes, to the conclusion that the image at the eyepiece is an image of the source object.

In two dimensional computerized tomography instruments, X-rays, collimated to lie in a plane, traverse the object to be imaged and impinge on detectors on the far side of the object.[18] Each detector receives a one dimensional projection of the target object along a given ray, and the computational algorithms combine all the projections around a 180º arc to construct a two dimensional image of a cross section of the target. The energy of the X-rays is attenuated by traveling through the object, and the degree of attenuation depends upon the densities of the materials through which the X-ray is traveling. Although Hounsfield's CT prototype used matrix inversion methods, these are no longer used to recover the values of attenuation coefficients because there is a relatively high level of noise in the projections and this can cause instabilities in direct inversion techniques. In addition, the large amount of data collected makes the computational load on matrix inversion methods infeasible. The choice of mathematical techniques is thus affected by both technological constraints, and the fact that the physical system does not satisfy the idealizations needed for matrix inversion to be effective. Instead, backprojection algorithms or iterative methods are used.

The backprojection methods that make inverse inferences from the detected intensities to the attenuation coefficients use inverse Radon transforms.[19] The basic idea is that the total attenuation along a ray is the sum of the attenuations in each pixel, and the backprojection method adds back the attenuation in each voxel by performing a line integral along the direction of the ray. By taking rays in many different directions, the 2-D

[18] For simplicity, I take the X-rays to be parallel rather than distributed in a fan-shaped beam.

[19] I note that some of these mathematical techniques had been developed previously for use in astronomical imaging using radio telescopes.

matrix of pixels can be reconstructed. But the bare mathematical method assumes that the physical processes are idealized in certain ways and in order to eliminate artifacts one needs to know how the image was constructed.

In order to argue for the view that the generating conditions of the data must be known, consider an argument that Ian Hacking (1983) has used in favor of entity realism. The argument goes like this for the case of microscopes. It is sometimes possible to observe the same structure with the aid of microscopes that use different, independent, physical processes, such as ordinary optical microscopes, fluorescent microscopes, interference microscopes, polarizing microscopes, and so on. Hacking argues that it would be incredible to assert that there was no common physical structure that was giving rise to these common observations from different instruments: "If the same structure can be discerned using many of these different aspects of light waves, we cannot seriously suppose that the structure is an artifact of all the different physical systems" (Hacking, 1983, 147). This argument is flawed because it does not properly take into account the fact that the observed structure is deliberately engineered.[20] We can easily see this in the case of the medical imaging techniques discussed here. Consider the example of a sinogram, which is a representation of the raw data produced from a CT scan with the frame of reference attached to the detectors and which rotates around the target object. The intensity of the radiation received at a detector is plotted against the angle of rotation of the radiation source relative to a fixed baseline in the object's frame of reference.[21] To almost all readers of this essay, sinograms do not represent anything familiar. However, when inverse Radon transforms are applied to the pixels constituting the sinogram, it is transformed into something familiar, such as an image of a human skull but that familiar image has its 'obvious' representational structure imposed by choices of the instrument designers. The intentional content is useful to us because of the perceptual apparatus of human observers, but for a computer, the sinogram is at least as useful a representational device and results from a coordinate transformation between the two frames of reference. We could say that the sinogram and the familiar image of the skull are both in an equivalence class of representations where the equivalence relation is determined by a set of

[20] For arguments that this point also applies to traditional causal instruments, see (Humphreys, 2004, 33-37). One difference between causal and causal-computational instruments in this regard is the relative ease with which images can be constructed in the latter instruments.

[21] For images of sinograms see Webb (2003).

transformations on the set of individual data points. If so, what those images are about cannot be determined from the output of the instrument alone or from the intentions of the observer. Decisions about $data_A$ require knowledge of what causal processes were involved in producing the individual data and what transformations have been performed on the individual data points.

This simple example illustrates the point that images from causal-computational instruments are deliberately constructed, and the 'structure' that is allegedly invariant across different imaging devices is the result of deliberate engineering. There are no limitations on how the individual pixels in a $data_A$ representation generated by a causal-computational instrument can be computationally re-arranged to form an output image. This construction process does not mean that the resultant image is arbitrary. The output will be tailored to the needs of the data user, whether it is a human scientist, an automated scientist, or some other epistemic agent. Since truth is an epistemic goal for most scientific enterprises, representations of the target object that systematically misled the users of the instrument should be avoided, although other situations, such as one in which the intelligence services of a country insert rogue software into an enemy's spy satellites, would not be subject to this constraint. Further discussion of these issues is contained in the section on artifacts below.

This ability to construct the output image is also present in purely causal instruments although these are constrained by laws of nature in ways that the computational components of causal-computational instruments are not. In order to obtain useable outputs from such instruments, a great deal of deliberate engineering is required. This tends to be disguised by the fact that the physical design of the instrument produces the constructed image automatically, and correction mechanisms, such as those for chromatic aberration, are physically built into the instrument. One reason Hacking's argument seems plausible is that we can appeal to optical laws such as that light travels in straight lines and is refracted and diffracted in regular ways that allow gross spatial structure to be preserved. In the case of CT images, for each datum, we can make a case that a datum *j* is about a cylinder of tissue lying along the ray traversed by the X-rays detected by detector *j*. The causal relations between the adjoining spatial parts of tissue are, in the idealized models, absent in both the $data_A$ and in the $data_E$ and this is why it is initially not obvious what the collective $data_A$ are about. Although this lack of determination of the collective representation by the local data has always been present, the ability to easily rearrange the $data_A$ in computerized instruments makes this problem much more pressing for those

instruments. Similar considerations show that what, collectively, the data points in a sonogram are about is not determined by what the individual data points are about but requires knowledge of what transformations have been performed on the detector data.

Artifacts

We have seen that with all causal-computational instruments the final image is constructed and cannot be taken as a 'given.' What I want to suggest is that although all data collected from these instruments requires interpretation, simply noting that such data is 'theory-laden' is uninformative. What is important is that with sufficient knowledge of the causal and computational processes that generated the data, data can be corrected to eliminate, or partially eliminate, artifacts.

In CT imaging devices an artifact is a systematic discrepancy between the real attenuation values and the values inferred from the measurements taken at the CT detectors.[22] Although artifacts of an instrument are often considered as properties of the output of the instrument, in the present case the artifacts can be considered as properties of a numerical data set just as much as a feature of a graphical image. It is probably not possible to provide a sharp division between a misrepresentation and an artifact, but there is an important conceptual difference that should be maintained. There are two kinds of artifacts to consider – artifacts that are the result of causal interactions and computational artifacts that result from approximations in the numerical methods. A standard example of the former are lines present in an image due to beam hardening, which is the progressive increase in mean X-ray energies due to the total absorption of lower energy rays by tissue. This can be corrected for either by physically filtering out lower energy X-rays before the beam enters a target region or by using software correction algorithms.

An example of the second occurs in continuous helical scans. Because the plane of the beam is tilted at an angle to the target due to the helical path, when traversing an object with a non-uniform cross-section, the beam will present a slightly different set of projections at an angle of $(\theta + \pi)$ than it will at θ. This results in a distortion of the shape of the cross-section that in the case of liver scans; for example, can be mistaken for a tumor and the errors must be corrected by software.

We can now ask the question: is an image of an artifact a representation and if so, of what? To answer this question, recall the

[22] Barrett and Keat (2004).

earlier point that what $data_A$ are about can result from two quite different sources – the origins of the data or from an interpretation that is independent of the origins. Taking the definition of an artifact, if we emphasize the $data_A$ as resulting from $data_O$ then the image of an artifact represents the systematic error. In contrast, if the interpretation of the $data_A$ is made without consideration of the $data_O$, the $data_A$ can be taken to represent not an error, but a non-existent entity such as a liver tumor. Similar issues arise for computational artifacts that occur in simulations of fluid dynamics.

Issues about distinguishing what is real from what is an artifact thus hinge on whether $data_A$ are interpreted with reference to $data_O$ or not. It is the ability to distinguish between artifacts and genuine features of the target system, not the existence of the 'unobservable' processes used to construct the representation that is the important issue here. No operator of computed tomography instruments doubts the existence of X-rays, radioactive matter, biological cells, cancerous tissue, and so on. The issue is one of accurate representation, not of the existence of 'unobservables.'

The model dependence of data might be thought to have the consequence that there is an inseparable mixture of theory and observation in the data. This created a serious problem for empiricists in two cases. One was when the user of the data was unaware of what the theoretical component was, a situation that can occur when a theory or paradigm is so dominant that its effects have become invisible to practitioners in the field. The second case occurs when the data user cannot separate and remove the effects of the theory or model. This can occur when we do not have a good theory of how an instrument works, as well as in the first kind of case. But when the methods used in the models are explicit and invertible, the effects of theory and modeling can be corrected. The computed tomography example is valuable because there are many models embedded in the processing of the data and we can correct for most of them. Indeed, many correction algorithms are used in modern instruments ranging from image stabilization methods in digital cameras to optical enhancement algorithms for telescopes. Similar remarks can be made about simulation artifacts, which are a problem in molecular dynamics simulations, simulations with periodic boundary conditions, fluid dynamics, and some other areas. They often result from numerical integration methods and finite size effects.

It has also been suggested that instruments have theory built into them. Whether or not this is correct for purely causal instruments, it is clearly true for causal-computational instruments in the sense that correction models based on knowledge of the physical and computational processes

occurring within the instrument are frequently used.[23] Empiricists extolled the virtues of direct, theory-free access to data, and the use of models can seem to degrade our access to the world. There are identifiable dangers of using models to correct data sets, but unmediated access to an object is not always epistemically superior to access mediated by physical or mathematical intermediaries. Look at the windshield of a car on a bright day with your unaided vision. Then don a pair of polarizing sunglasses. You will be now able to see objects inside the car that were not previously visible. If you believe these objects are artifacts of the polarizers plus windshield, simply remove the sunglasses, open the car door, and use your unaided senses, including touch. The important thing is to know how the instrument works. With the computational parts we have this knowledge because we have designed them.

Could we avoid needing to know how an instrument works by accumulating inductive evidence of successful uses? Eckhart Arnold has suggested the following thought experiment.[24] Suppose a working CT scanner with a generator is washed up on the shore of an island the inhabitants of which have never seen such an instrument and know nothing of modern physics. After experimenting with placing various familiar objects into the scanner and seeing that their internal structure is reproduced accurately, they are in a position to use the scanner in similar ways to their own visual sense, the workings of which they also do not understand. This is an ingenious suggestion, but the situation with respect to CT images and artifacts is not quite so straightforward. Because the inverse Radon transform that is used to obtain the value of the function f within a given pixel is constructed by backprojecting all of the rays received at detectors between 0 and π, each reconstructed point is dependent upon the whole data set. This means that artifacts produced by factors in one part of the target can produce errors in another part. Although it is possible that inductive evidence could be obtained about the appearance of such artifacts, there would need to be a sample base of objects sufficiently similar to each future object used in the instrument in order for such artifacts to be recognized in each case.

What does all of this say about simulations? Much of what I have said about imaging devices transfers, with obvious modification, to the simulation case. A decision must be made regarding whether what the data are about is determined by reference to the origins of the simulation data, which will be the (interpreted) model upon which the simulation is based

[23] Morrison (2009) has noted that instruments often require models in order to extract meaningful data.
[24] Personal communication.

if one exists, or is determined by an intentional attribution to the output from the simulation. I have argued that an informed attribution under the second method cannot be made without knowledge of the generating conditions of the output data, in which case the origins of the simulation data also play a role in this approach. It is an unfortunate fact that in the philosophy of reference an emphasis on the conventionality of object-sign relations and social accounts of meaning has distracted attention from other, more refined, ways of representing the world.[25]

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CHAPTER TWO

COMPUTER SIMULATIONS AND EMPIRICAL DATA

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Introduction

Because computer simulations are intensively used in most parts of contemporary science, both as substitutes for, and complements to, laboratory experiments and field observations, the question arises whether they are able to produce empirical data and, if they are, whether the quality of these data is similar to that of data produced via experiments. Can a computer provide us with empirical evidence? Aren't experiments and observations our main sources of empirical data, and the most legitimate ones?

The comparison between computer simulations and experiments has recently been explored in a number of papers (Guala, 2002; Morgan, 2002; Winsberg, 2003, 2009; Parker 2008, 2009; Barberousse et al., 2009; Morrison, 2009). These papers mostly focus on the building of empirical knowledge from the outputs of computer simulations. They address questions such as: How are the results of simulations validated? What is the role of models in the confirmation process when applied to the results of experiments? These questions have received various answers. In the present paper, we focus on the production of *data* by contrast to the production of *knowledge*. We explore how data are produced within contemporary science and how they are transformed into pieces of knowledge.

For a computer simulation user in the empirical sciences, the questions mentioned in the first paragraph may seem surprising, as her work is based on the assumption that computer simulations do provide empirical data.

On the other hand, simulation non-users often rely on the opposite assumption, as testified by the following dialogue (reconstructed from a discussion on ScienceBlogs):

> Scientist#1 (defending the privilege of experiments): "Can any scientist really doubt that models and simulations have lesser status, scientifically, than observational/experimental data? This is THE cornerstone of empiricism and science. […] Yeah, there is a whole spectrum here, since extracting data from observations/experiments usually takes some kind of models, but the general rule is pretty simple - each step away from direct observation, each layer of theory, model or simulation, lowers the reliability of the conclusions."
>
> Scientist#2 (defending the legitimacy of simulations): "You have a bias here towards observational data. Need to recognize that a lot of data comes from models and analyses."
>
> Scientist#3 (denying the legitimacy of the distinction with respect to data): "As a professional data torturer, I don't see any difference in principle between 'real' and simulated data: it's all information that is to be processed."

Consequently, the debate remains open even among practitioners of science. In this context, the aim of the present paper is to assess whether there are any reasons to give epistemological precedence to data produced through experiments with respect to data produced through computer simulations. In "Empirical data," we analyze what empirical data are. In "Comparing measurement results and simulation outputs," we draw a systematic comparison between data produced through experiments and data produced through simulations. The criteria of comparison on which we focus are evidential features, reliability, and novelty of data.

Empirical Data

Definitions

In order to compare computer simulations and experiments as far as the production of empirical data is concerned, it is first necessary to say a few words about what are called "empirical data." The word "data" itself, although intensively used in contemporary science, has a rather vague meaning. We propose the following working definition, which is meant to hold in the context of empirical investigation:

> Working Definition 1: Data are elements of information that are taken for granted at a given step of a specific investigation, and on which one can rely in the course of the ongoing investigation.

Let us take an elementary example. When a magnet comes close to iron fillings, they move toward it and align themselves perpendicular to its surface. This observation can be made an indefinite number of times; it can constitute a set of data for the further investigation of magnetic phenomena. From these data and others, an elementary knowledge of the origin and properties of magnetic fields can be built up. During this process, the behavior of iron fillings and magnets will be considered as a piece of information that remains stable and unquestioned insofar as no contrary observation occurs. In contrast, hypotheses about the cause of the alignment of fillings, the intensity of the magnetic field, etc. may vary during the knowledge-building process. The main difference between data and hypotheses is thus that data are not susceptible to being modified during the investigation. Data are associated with some notion of epistemic stability, at least at a given step of an investigation. This does not mean that the validity of these elements of information cannot be re-assessed in future steps.

Working Definition 1 is functional: it is based on the *role* data play in empirical investigation, without any commitment toward their constitutive nature. Functionally, data are the building blocks of scientific knowledge. As the notion of information is intentional, the notion of data is intentional as well: data are basically *representations* (cf. van Fraassen, 2008, for whom measurement outputs are representations). It follows that what counts as data are relative to (1) a given context of inquiry, and (2) the scientists leading the inquiry.

In physics and in many domains of biology, "raw data" consist of (very large) series of numbers, which are usually automatically generated by detection or measurement instruments. Raw data cannot be identified with the usable pieces of information that are the object of Working Definition 1. Raw data are not usable at all by the human mind. They have to be heavily processed in order to become usable; that is, to participate in knowledge-building. Once processed, they achieve the status of data as defined above.

Let us now turn to *empirical* data. Our next working definition is as non-committal as possible about the meaning of empiricity, because we do not want to beg the question of the relationship between empiricity and the presence of physical interactions:

> Working Definition 2: Empirical data are elements of information *about* physical (biological, social, …) systems that are taken for granted at a given step of a specific investigation, and on which one can rely in the course of the ongoing investigation.

Just as it is clear from the definition, we consider empiricity (with respect to data) as an intentional notion. This feature results from our decision not to include the origin of data in the definition. Traditionally, the precise way empirical data are produced (their "origin") is considered as an essential element of this notion. Causal interactions are thus often referred to when empiricity is defined. In contrast, our purpose is to explore whether it is possible to do without the mention of causal interactions in the definition of empirical data. This is the reason why Working Definition 2 is intentional. In the remainder of this section, we argue for the legitimacy and interest of this purpose.

Let us focus on empirical data produced through experiments or field observations. In this case, empirical data are series of numbers produced in the course of physical interactions between instruments and the investigated phenomena. The crucial point is that these series of numbers need to be *interpreted* in order to be considered as empirical data. Without this interpretative step, no empirical information, and no information of any sort, would be available. This aspect of the production of data in the context of experiments or field observations leads us to adopt a definition of "empirical data" that is non-committal with respect to the origin of data. As our aim is to focus on the *uses* of data in the context of scientific inquiry, the interpretative step is at least as important for us as the step resulting in raw data. In fact, our bet is that the precise way in which raw data are produced may be left open in the definition of empirical data. This view thus differs from Humphreys' (this volume), who maintains that the origin of data must be taken into account.

By emphasizing the importance of interpretation in the epistemic process ending with empirical data, we do not mean to underestimate the role of physical interactions between a detection or measurement instrument and the investigated process, but we want to insist that physical interactions are not sufficient to obtain data. We want to emphasize that the interpretative process that allows for the production of empirical data is a central part of the scientific investigation itself. It is open to discussion and criticism, and overtly revisable.

Certainly, Working Definition 2, because of its neutrality with respect to the origin of data, might look surprising, if not shocking. In the remainder of the paper, we argue that it is not. Our strategy is as follows. In section "Comparing measurement results and simulation outputs," we

examine three epistemic features of empirical data that seem to advocate the privilege of data coming from experiments: evidential features, reliability, and novelty. Whereas it is relatively easy to admit that outcomes of computer simulations can be as evidential and as reliable as data coming from experiments, it seems very difficult to accept that genuinely novel data can emerge from computer simulations. The capacity to yield *new* empirical data seems to be exclusive to experiments. In section "Novelty," we present arguments against this view. For the time being, we further explore the notion of empirical data.

What are Empirical Data About?

In the preceding section we suggested that, in order to assess whether computer simulations can yield empirical data, it is better to define "empirical data" as neutrally as possible in regards to their origin, and to focus on the intentional aspect of the notion. We now have to be more precise with respect to the elements upon which empirical data rest, and to the inferences that have to be drawn in order to acquire the desired information.

When analyzing experiments, it is common to introduce a distinction between the "object" of the experiment and its "target." The object is the material system, which is manipulated during the course of the experiment, or the parts of it that interact with detection or measuring instruments. It is spatio-temporally localized. In contrast, the target of the experiment is the system about which the scientists look for new or more reliable information. It may be the same as the object of the experiment, for instance when physicians look for information about a tumor in a patient. In many cases, however, the object and the target of the experiment are different systems. It also happens that the target is not a particular system but rather a class of systems.

Whatever the specific relationship between the object and the target, the series of numbers that are gathered during the experiment need both automatic and human-inferential processing before they can be further used as data. That is, there are many inferences to be drawn before we can be sure that these numbers (once automatically processed in order to acquire a readable format) provide scientists with the information they desire. This inferential task is usually extremely difficult to fulfill. Most of these inferences are grounded on, and warranted by, background information about both the object and the target; they are of course, fallible. The most important question to assess is whether the object is

representative of the target; that is, to what extent the information gained about the object can be interpreted as also having a bearing on the target.

Let us now compare the epistemic situation obtaining in experiments with the use of computer simulations. In the case of computer simulations, it is unclear whether there is an object of any experiment, but the targets are of the same type as the targets of experiments. What is different is the way in which the inferences from the outputs of the simulation to the target are warranted. Here, the crucial aspect is whether the computer model correctly *represents* the target. The important relation is, thus, the relation of *representation*. The quality of the representation is itself grounded on, and warranted by, background knowledge on the computer program and on the target.

Let us further develop the comparison between experiments and computer simulations with respect to the inferences they allow us to draw about the target. The assessment of the representative quality of the object of experiments with respect to the target is usually based on several models, at least a model of the object and a model of the target, and more often than not a model of the experimental setup; namely, of the way in which the instruments acquire data. Models are, thus, central to data production both through experiments and through computer simulations, as emphasized by Morrison (2009). As a result, the representative character of the object of the experiment cannot be warranted unless there is a way to draw inferences about the model of the target, from the model of the object.

It might seem that when the object is one member of the target class; that is, when it is made from the same material, the inferences drawn from the object about the target would be easier to assess. Even in this case, however, scientists usually rely on a model of the investigated system (that is, a model of both the object and the target) and on a model of the experimental setup (that is, of the interactions between the object and the instruments).

The example of model organisms illustrates this point. In this case, a specific organism, or set of organisms, let us say mice, are submitted to various modifications, say genetic modifications. The experiment aims at discovering the effects of these modifications on the mice phenotypes. The observed modifications are then interpreted in order to assess which part of the genetic manipulations is responsible, and to what extent, for the phenotypic modifications. Such a judgment relies on detailed models of the mouse's genome, genetic-phenotypic path, physiology, etc. Now, the target of the experiment is usually not the specific mouse (or set of mice) whose genome has been modified. The models are thus used for inferences

about further mice: first, other laboratory mice and, second, wild mice, which are known to differ significantly from their more artificial siblings, and which are also known through (less precise) models. In some cases, the inferences are extended to a larger class, like mammals, including humans. Models of the differences between the relevant features of mice and humans are then used. What is true of experiments with model organisms is also true of experiments on inanimate properties and their relations. In both cases, the fact that the object and the target are of the same substance (they are both mice, or both mammals, or both made of iron) is not a sufficient condition for the drawing of reliable inferences about the target. The quality of these inferences is based on the validity both of the underlying model of the target and of the model of the experimental setup.

Does this mean that measurement results, produced by physical interactions, play a minor role in experiments? Of course not; by insisting on the fact that reliance on models is pervasive both in experiments and in computer simulations, we want to emphasize that measurement results make only sense in the context of the above-mentioned models. Measurement results provide data (usually after heavy computer processing) in cases where the underlying models are valid. Otherwise, they do not. In the same way, simulation outputs are only likely to deliver data if the underlying model of the target is valid. In order to establish whether this condition is sufficient, we now turn to a systematic comparison between measurement results and simulation outputs.

Comparing Measurement Results and Simulation Outputs

In this section, we investigate the epistemic features of measurement results and simulation outputs according to three dimensions: their evidential character, their reliability, and their novelty. Evidential character, reliability, and novelty appear as crucial features of empirical data originating from physical interactions. In the building process of scientific knowledge, data may be used to establish (or refute) the validity of hypotheses; in this case, they need both to provide evidence about the investigated phenomenon and to be reliable. Data may also be used to improve detection or measurement instruments; in this case, their reliability is indispensable. Evidential character and reliability are, therefore, important epistemic properties of data. The capacity to provide scientists with new knowledge is also a highly desirable property.

Our strategy is to explore the conditions under which empirical data originated by physical interactions are evidential, reliable, and new, in

order to assess whether these conditions also obtain for simulation outputs. We begin with the first two criteria, leaving novelty for section "Novelty." As mentioned above, our aim is to explore whether it is possible to remain neutral with respect to origin in the definition of empirical data. At first glance, it seems that: (1) physical interactions are required in order to confirm hypotheses; (2) data coming from physical interactions are necessarily more reliable than data coming from computer simulations; and (3) computer simulations are totally unable to yield new empirical data. As we shall see, intuitions (1) and (2) are relatively easy to criticize. In contrast, intuition (3) seems particularly robust. The capacity to yield new empirical data seems exclusive to experiments. By further developing our analysis of computer simulations, however, we suggest that this might not be so clear.

Evidential Features and Reliability

How are reliability and evidential features of measurement results established in an experiment? A major part of this task lies in the control of the experimental setup, especially through benchmarking procedures. The essential thing is to check whether the experimental setup yields correct data in known cases. This is usually a matter of delicate and lengthy tuning operations, involving both manipulations and modeling.

Besides the control of the experimental setup, many underlying assumptions have to be assessed in order for the resulting data to be evidential and reliable: for instance, the assumption that the measurement procedures allow scientists to make the measurement they had in mind, or that they are as precise as required. Checking whether information is gained on the right aspect of the object with sufficient precision might also require lengthy tuning and modeling. More generally, the presence of artifacts of any kind has to be checked and eliminated.

An important aspect of the control procedures that are needed to warrant the evidential feature and reliability of the measurement results is that their implementation relies on models. At this point of our analysis, it is important for us to define what we call a "model" in our general analysis of empirical data produced through experiments. We propose the following working definition:

> Working Definition 3: A model is any coherent set of detailed hypotheses about the investigated phenomena (usually at least three models are available: of the object, of the target, and of the experimental setup).

Models guide the building of the experimental setup as well as the various actions that need to be performed in order to obtain the relevant information. Therefore, the final judgment about the quality of the produced data depends on the quality of the involved models.

Let us now turn to computer simulations. The evidential character and the reliability of their outputs are also established by comparison with results already known. The benchmarking procedures play no lesser role than in the case of experiments even though they are different, only involving the transformation and checking of lines of code. Two other kinds of procedures are currently used in order to assess the validity, evidential character, and reliability of the outputs, called "validation" and "verification." The aim of the validation procedure is to check whether the underlying theoretical model, as transformed into algorithms and lines of code, is valid for the investigated phenomenon. The verification procedure guarantees the consistency and "good behavior" of the computation. It is necessary in order to avoid abrupt stops or breakdowns of the computation, as well as abnormal results owed to cutting-off, round-up errors, and other sources of bugs. These procedures involve delicate tuning of the computer program; their implementation can be very lengthy.

Many aspects of the assessment of evidential character and validity are common to experiments and computer simulations. They involve checking that the apparatus (a set of laboratory instruments or the computer program as it is implemented on a particular machine) is functioning well; that is, that it delivers the expected information. Although the checking procedures fall under the same heading, they seem to correspond to highly different types of activity: material object-oriented on the one hand, strictly intellectual on the other. Let us analyze this difference further.

In the case of experiments, the control procedures usually rely on manipulating pieces of apparatus, aligning them, purifying chemical material, maintaining pressure at a low level, etc. They require specific skills in terms of coping with reluctant artifacts as well as highly situated know-how. All these activities require scientists and technicians to collaborate and coordinate themselves in situ. They are entirely different from what is involved in checking and rewriting lines of code.

In the case of computer simulations, the material aspect of the control procedures is limited to typing on the keyboard and eye-checking on the screen, by scrutinizing series of symbols or images. The core of this activity is symbolic: it has to do with the writing, deleting, and transforming of meaningful series of symbols, not with the handling of material objects. What is relevant here is abstract; it lies in the realm of meanings and computation.

Are these differences more important than the common goal of these control procedures; namely, assessing the epistemic quality of resulting data? The question we want to tackle here is whether the fact that material interactions are involved in the case of experiment makes a difference to the assessment of evidential character and reliability (Tal, 2011 also tackles this question from a different perspective). Undoubtedly, as we have emphasized, it makes a difference to the involved activities of the scientists and technicians, but it seems to us that the common goal of these activities; namely, warranting that the resulting data are evidential and reliable, counts more than the differences in the ways in which this goal is implemented. To put it another way, we argue that the right way to analyze the differences in the involved human activities is *functional*. All these activities, which seem at first sight entirely different in nature, are ways to fulfill the same epistemic function; namely, retrieving useful information about the target of the experiment (or of the computer simulation).

The next step in our argument is to assess whether or not, by functionalizing the analysis of the control of data production, we beg the question of the (un)importance of materiality in data production. In the current discussion about the status of computer simulations as compared with experiments, the most difficult but most important task is to avoid begging the question of whether physical interactions are necessary to produce data. In functionalizing the analysis of the control of data production, do we not beg the question the other way round, by assuming that the weight of physical interactions is less than their epistemic function? Our answer is that if one accepts the working definitions we have proposed so far for "data" and "empirical data," one cannot but accept our functional analysis.

Novelty

It might seem that only experiments, because they involve physical interactions, are likely to yield new empirical data; in contrast, the outputs of computer simulations are somehow already contained in the inputs. In this section, we probe this widely shared intuition. In order to analyze it further, we first try to isolate the conditions in which the comparison between experiments and computer simulations is relevant when it comes to the production of new empirical data. There are obvious cases in which experiments are the only way to obtain new empirical data; however, the question remains whether there are also other cases in which this is less clear. Our second task is to distinguish between types of computer

simulations: simulations based on the discretization of differential equations perform differently from cellular automata and agent-based models with respect to the theme of epistemic novelty. Third, we distinguish between the various meanings that the term "new" in "new empirical data" can take. At the end of the section, we reveal the reasons why, and the circumstances in which, new empirical data emerge from computer simulations.

Is the Question ever Meaningful?

There are domains of phenomena of which we know a few regularities and not much else. For instance, at the end of the 1960s, liquid crystals were known to exist and some of their properties had been observed, but condensed matter physicists had no idea of the underlying laws governing their behavior. In such domains, computer simulations will probably yield hardly any empirical data. They will at most inform us about the general, structural features of these phenomena, but will be unable to provide us with any prediction about a particular phenomenon. Field observations and experiments are the only ways to obtain empirical data, because these domains still need to be further explored. They are terrae incognitae. In these domains, the question of whether computer simulations can yield new empirical data is meaningless; it does not arise.

There are also domains of phenomena about which we know a lot, however. We know many regularities and how they operate, sometimes forming hierarchical relations. This knowledge enables us to model particular phenomena and to achieve precise predictions. We have obtained these delicately articulated pieces of knowledge through observations and experiments; that is, by deliberately producing highly specific physical interactions the effects of which we were able to interpret as measurement results. The sets of measurement results have been further interpreted as indicating, or testifying to, regularities at various levels. In those domains, the question whether computer simulations are able to yield newer empirical data is meaningful. We address this at the end of this section.

Finally, there are intermediate domains where some pieces of knowledge are available. It seems to us that in these domains the question of whether computer simulations can yield new empirical data is legitimate, particularly for those areas where there is enough knowledge to render empirical exploration unnecessary.

Types of Computer Simulations

As we have argued above, the question of whether computer simulations can yield new empirical data is only meaningful in limited domains. We must further emphasize that its meaning not only depends on the domain of investigation but also on the type of computer simulations at hand. As far as we can see, computer simulations based on cellular automata and agent-based models, which are based on discrete, local rules, are more susceptible to being considered as yielding novelty. Their outputs are often qualified as "emergent," a term including a sense of novelty.[1]

Even if one considers the outputs of cellular automata and agent-based models as emergent, it is still unclear in which conditions they might count as empirical and, further, as data. We leave this discussion for a future occasion. In the rest of this paper, we focus on computer simulations based on discretized differential equations, because they are probably the hardest case: whereas the association of cellular automata and agent-based models with novelty seems natural enough, simulations based on discretized differential equations are usually associated with a symbolic process in which nothing new can occur.

The Meanings of Novelty

We have begun our analysis of the question whether computer simulations can yield new empirical data by first restricting its scope and, second, by distinguishing between types of computer simulations. We need to introduce further distinctions about the meaning of "new" in order to analyze the expression "new empirical data." Our discussion will be entirely general, returning to computer simulations only at the end in order to keep different questions strictly separate.

Let us first note that the most straightforward sense of "new" occurs in the terra incognita context, when the information about the domain of phenomena is scarce, and when systematic exploration is the only way to obtain it. Let us call this sense the "primary sense" of epistemic novelty. As we have already mentioned, the primary sense cannot possibly apply to computer simulations. Using this as our base, we introduce other senses.

The first distinction that seems important to us is the distinction between *surprising* and *unsurprising* or *expected* novelty. To our mind,

[1] The outputs of computer simulations based on discretized differential equations are sometimes said to be "emergent" in a rather different sense, related to computational irreducibility. It is unclear whether computational irreducibility is related to epistemic novelty.

novelty in the primary sense is surprising by default, because in the case of novelty in the primary sense, scientists have no expectations about what they are going to learn. In contrast, there are cases in which they learn new information through experiment and this information does not come as a surprise: for instance, when they already had an idea of the range of the values they obtained in the experiment. These are cases where the achieved epistemic novelty is unsurprising.

It might be argued that "unsurprising novelty" is an oxymoron, a juxtaposition of words that does not carry any genuine meaning. We maintain, however, that when the value of a given variable in a specific situation is learned by experiment to a certain degree of precision, whereas the available hypotheses could only allow a range of values for this variable, something genuinely new has been obtained. The resulting value falling within the predicted range does not ignore the fact that the available hypotheses did not explain how to reduce the range, so that when the experiment allowed such a reduction, it resulted in a new piece of information.

Now that we have introduced the distinction between surprising and unsurprising novelty, we might wonder in what situations surprising novelty can obtain, except in terrae incognitae. Can surprising novelty occur in domains of phenomena whose main regularities are well established? It might seem that in those cases, of which particle physics is a paradigm example, experiments can only yield expected results. The experimental setups are built precisely to yield the values scientists want to know about; this can only be achieved if they already know, or can reasonably predict, the range of these values. One could even claim that if an experiment yielded an unexpected value, it would be considered as a failure and the scientists would immediately check the setup in order to discover where the error originated. It thus seems that in the domains of phenomena about which a lot is known, surprising novelty is highly … unexpected. Is it really the case?

In order to answer this question, we introduce a second distinction that pertains to the case we have just discussed, the distinction between surprising novelty arising within the available theoretical framework and surprising novelty arising outside the available theoretical framework. By "theoretical framework" we mean the set of all available knowledge about the domain of phenomena at hand, be it of theoretical or empirical origin. It is the set of all that is known or expected, based on theoretical reasons. We have indicated above that the case of surprising novelty arising within the theoretical framework seems less likely than surprising novelty arising outside the framework. To put it another way, in domains already

endowed with a rich theoretical framework, surprising novelty seems more likely to come from theoretical change than from experiments. Moreover, it also seems that computer simulations are even less likely to yield surprising novelty in such domains. There is, however, at least one well-known example in which surprising novelty occurs within a rich theoretical framework, by the use of computers.

To our mind, the study of deterministic chaos as performed in the 1970s through digital computation exemplifies the notion of surprising novelty within the available theoretical framework. The theoretical framework is differential calculus augmented by Poincaré's topological innovations at the end of the nineteenth century, a rather old framework. What scientists discovered, however, when they implemented a system of non-linear differential equations on their computers, astonished them.

The computer-aided study of deterministic chaos is a nice illustration of surprising novelty arising within an available theoretical framework. Moreover, this novelty was achieved by the use of computers. Even though it is questionable whether the results are empirical as opposed to mathematical, this example shows that surprising novelty can obtain within an established theoretical framework and that machine computation is by no means an obstacle. Why is it that computer simulations based on discretized differential equations are commonly thought of as forbidding the production of surprising epistemic novelty? We answer this question in the following section.

Machine Computation and Human Reasoning

The main reason why machine computation is usually conceived as incapable of producing surprising novelty lies in the way in which machine computation (including computer simulation) is commonly analyzed. Machine computation is correctly described as a series of deductions in the sense that the series of physical states instantiated by the computer are systematically interpreted as logical states. Given this description, it is tempting to infer that the outcomes of any specific computation are "already contained" in the inputs, so that nothing new can occur in the computational process. Our main thesis is that one should refrain from such an inference as it relies on confusion about the notion of "content."

Let us make it clear why such confusion arises. When the notion of deduction is applied to human reasoning, it is commonly associated with the notion of the conclusion being already "contained" in the premise. In this sense, the conclusion of a deduction is not supposed to be "new" in

any interesting sense. Of course (paper and pencil) mathematical calculation provides an example of series of deductions yielding new results in the sense that they were unknown beforehand, but this novelty is usually judged uninteresting, because the word "novelty" is commonly associated with "discovery" and not with reasoning.

The underlying assumption is that when the conclusion is already "contained" in the premise, it is only necessary to perform mechanical actions to find it. This is precisely what computers are supposed to do. It seems to us, however, that it is a mistake to analyze machine computation on the model of human reasoning: what counts as "mechanical actions" for human beings (for instance, the basic operations of arithmetic) is different, as far as the production of knowledge is concerned, from the transition of one physical state of a computer to another. These "mechanical" actions, as fulfilled by human beings, are "mechanical" only in a metaphorical sense, whereas the physical transitions within a computer are truly mechanical. When a human being makes an arithmetical operation, s/he keeps track of its meaning to her/him; it is inseparable from her/his epistemic aim. In this sense, it is not "mechanical." To put it briefly, we claim that it is a mistake to compare machine computation with human reasoning when it comes to analyzing the notion of epistemic novelty. It is unlikely that a surprising novelty can result from deductions made by human beings, but this does not preclude surprising novelty resulting from a computational process.

Another way to formulate the above analysis is to question the relevance of the notion of "deductive closure." It might seem that the frontier between uninteresting and genuine novelty can be defined in terms of the deductive closure of a set of premises: what is inside might be new to a particular person, but it is not new in the genuine sense of the term. If one demarcates trivial and genuine novelty at this point, then it is true that computer simulations cannot possibly yield any genuinely novel empirical data. In contrast, our proposal is to shift the boundary and to count some elements that fall within the deductive closure of a set of premises as genuinely novel, as explained above.[2]

In this section, we have tried to explain why computer simulations based on discretized differential equations are usually considered as incapable of providing scientists with surprising epistemic novelty. Two reasons can be cited. First is the fact that these simulations are paradigmatically set up within a rich theoretical framework, which seems

[2] We warmly thank Eckhart Arnold for a challenging e-mail about deductive closure.

to exclude the possibility of surprising novelty. As we suggested in the preceding section, however, surprising novelty can occur even in rich theoretical frameworks. Second is the equivocality of the description of computer simulations as series of deductions. It appears that the word "deduction" does not have the same epistemological meaning when it applies to human reasoning and to the description of a computational process. When these two meanings are confused, it appears that no surprising novelty can emerge from a computational process. Distinguishing between the epistemological significance of deductions for human beings and that for computers shows, however, that nothing precludes computational processes yielding surprising novelty, as the example of deterministic chaos attests. It seems to us that the arguments we put forward at the beginning of section "Comparing measurement results and simulation outputs" suggest that nothing precludes computational processes yielding surprisingly new empirical data.

Conclusion

Starting with an analysis of the notions of data and empirical data, we have investigated the question of whether computer simulations are capable of yielding empirical data. We have focused on a systematic comparison between the results of experiments and the outputs of computer simulations with respect to three criteria: Evidential features, reliability, and epistemic novelty. Our conclusion is that the outputs of computer simulations, once relevantly processed, are capable of counting as genuine empirical data in terms of these criteria. Our analysis of the question of whether computer simulations can provide scientists with new results allowed us to shed light on some conceptual obstacles explaining why computer simulations are usually conceived of as incapable of yielding new empirical data.

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CHAPTER THREE

EXPERIMENTS AND SIMULATIONS: DO THEY FUSE?

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Introduction

In today's science, computers have become an indispensable tool. They are used for the evaluation of scientific data, for storing data, for the preparation of results, and for communication among scientists. However, computers are not only tools that help scientists to process and evaluate scientific data, but also they produce scientific data when they are used for running computer simulations. This raises the question of whether the data that computer simulations produce is the same as other kinds of scientific data, in particular experimental data. What speaks for this assumption is that the data produced by simulations are usually previously unknown to the scientists, often cannot be derived mathematically, and may yield the same or at least similar kinds of information about a simulated empirical system as an experiment yields. What speaks against this assumption is the fact that simulation data stems from a calculation performed with a computer and that it is not the result of an empirical measurement, or not directly the result. This is also the stance that I am going to take in this chapter.

I will set out the reasons for taking this stance in detail in the following section, when I review the debate on the relation of simulations and experiments. In particular, I will argue that computer simulations are not material in any sense that would liken them to experiments (as maintained by Parker, 2009) and that experiments are not intertwined with models to such a degree that the function of models in experiments becomes indistinguishable from the function of models in simulations (as maintained by Morrison, 2009).

But there is also a further possible line of reasoning against a strict separation of simulations and experiments that is not so easily dismissed.

According to this line of reasoning, simulations and experiments cannot strictly be separated because, at least in some instances, the role that empirical data take can appear indistinguishable in simulations and experiments. The question arises for those simulations that do in one way or another make use of empirical input data, and for those experiments that in one way or another involve the computational post-processing of the measured data. In both cases, the computer produces some kind of output data by processing empirical input data. The question, then, is precisely: what kind of output data?

We can define those scientific procedures that involve both empirical input data and computational processing of these data collectively as *hybrid methods*. The problem of hybrid methods can then be formulated as follows:

> *What, if anything, distinguishes a computer simulation that makes use of empirical input data from a measurement that involves the computational refinement of empirical data?*

It is not entirely clear whether this question is the right way of formulating the problem. I will briefly discuss different alternatives in the third section of this chapter as well. The answer to the problem of hybrid methods that is advocated here treats it as a partly conventional matter whether the outcome of hybrids is considered as empirical data or as theoretical data (which includes simulation data). The convention proposed here is that *hybrids* should be considered as empirical methods, if

1. The output data represents quantities that are either causally responsible for the values of the input data or that are mathematically connected to them.
   It may appear paradoxical that the output should be causally responsible for the input, but a simple example suffices to explain what is meant: assume that you measure force with a simple spring. Then what you actually measure is the extension of the spring (input data) and the scale on the spring allows you to "compute" the force in Newton (output data). Now, it is of course the force (i.e. the output) that is causally responsible for the extension (i.e. the input). At the same time, it is true that the output value depends on the input value, but this dependence is computational and not causal. I hold that this pattern is typical for any measurement where the quantity that is measured is only indirectly accessible.

2. And the output data characterizes factors that operate in close spatiotemporal proximity to the input data or, more precisely, to the source data.

In order to defend this convention, I am going to argue that it is in harmony with the self-ascription by the scientists using these methods, with the traditional understanding of measurements, and with our intuition.

The Current State of the Debate

The philosophical debate on the epistemic status of computer simulations can be traced back at least until the early 1990s. One of the popular slogans that already appeared as early as that in the debate was that of simulations as a "third way of doing science" (Axelrod, 2006; Küppers and Lenhard, 2005; Rohrlich, 1990), indicating that computer simulations neither fully resemble material experiments nor conventional forms of theory or model building, but that they are something in between. While this is a fair characterization of the activity of conducting computer simulations, which in many ways resembles experimentation but also requires specific practical skills and virtues that differ from those of experimenters, it is doubtful whether computer simulations can be characterized as a "third way" in an epistemological sense. For scientists themselves it has been clear most of the time that computer simulations are not an empirical method of science, even though they resemble experiments, and that therefore computer simulations, just like theories and models, are in need of empirical validation themselves, rather than being able to confer empirical validation on theories (Gilbert and Troitzsch, 2005; Heath, Hill and Ciarello, 2009). This view is also reflected in much of the philosophical literature on computer simulations of the 2000s (Guala, 2002; Humphreys, 2004; Morgan, 2003).

However, in the latest installments of the philosophy of simulations, this view has come under attack. In the context of a sometimes confused debate about the alleged materiality of simulations, philosophers have denied that there is any fundamental or epistemologically relevant difference between simulations and experiments. Or, if there is, then at least "any epistemically relevant differences between experiment and simulation [are] very difficult to articulate" (Morrison, 2009, 48). I am convinced that this is a mistake. First, therefore, I am going to set out some of the core arguments against the epistemic difference between simulations and experiments and I will try to show why all of them are wrong, some of them quite obviously so. Then, I am going to put forward

positive arguments for the differences between simulations and experiments. Finally, I explain why, in spite of the clear conceptual distinction, hybrids still provide a challenge for the epistemology of simulations.

Arguments against the Difference between Simulations and Experiments

The philosophers who are the most critical of the attempts to draw a clear distinguishing line between simulations and experiments are Wendy Parker (2009), Eric Winsberg (2009, 2010) and Margaret Morrison (2009). Wendy Parker argues that simulations in a sense are also "material" and that at any rate what matters is not materiality but "relevant similarity" (Parker, 2009, 484), which can be quite independent from the material status of the experiment or simulation. Winsberg does not go quite as far as Parker, but he, too, argues that simulations and experiments cannot be sharply distinguished by their materiality or by any similar criteria. The only distinction he concedes is that the way in which scientists justify their belief that the object under study (in a simulation or an experiment) can stand in for the target differs between simulations and experiments. As we shall see, he cannot advocate this view without contradiction, because the justifications cannot differ without referring to some other difference on which the different justifications are based. But then, the different kind of justification is not the only difference any more.

Morrison, in contrast to Parker, does not diminish the difference between simulations and experiments by arguing that simulations are also somehow material and, thus, somehow like experiments. But, quite the contrary, she argues that experiments in advanced science are somehow like simulations, because "the way models function as the primary source of knowledge in each of the (…) contexts [simulation and experimental] is not significantly different" (Morrison, 2009, 43). As we shall see, she overlooks the simple fact that in simulations a model also functions as the source of data while in experiments, the data is at least coproduced by nature.

I will now explain the flaws of the central arguments by Parker, Winsberg, and Morrison in more detail.[1] Parker offers several arguments, which are partly independent from each other. As mentioned, one argument is that simulations like experiments are also "in a sense" material. The sense in which simulations are material is this:

[1] Still I have to confine myself to the most important points here. For an even more detailed criticism see the working paper by Kästner and Arnold (2012).

> The experimental system in a computer experiment is the programmed digital computer – a physical system made of wire, plastic, etc. As described in the last section, a computer simulation study involves putting a computing system into an initial state, triggering its subsequent evolution (the simulation), and collecting information regarding various features of that evolution, as indicated by print-outs, screen displays, etc. It is those data regarding the behavior of the computing system that constitute the immediate results of the study. In a computer simulation study, then, scientists learn first and foremost about the behavior of the programmed computer. (Parker, 2009, 488ff)

But, obviously, the kind of materiality that computer simulations enjoy because they are run on a material system (i.e., the computer hardware) does not at all liken them to real material experiments. It is misleading to say that the data that is presented on the printouts and screen displays is "data regarding the behavior of the computing system." For the data of a simulation usually does not convey any information about the computer on which it was produced, but only information about the simulated system. It would be equally awkward if someone makes a calculation with pen and paper to consider the resulting figure as data regarding the pen and the paper. In particular, the person could potentially perform the same calculation with the same result in her head, which would imply that the result written on the paper must also be data regarding the brain of the person. Clearly, this is absurd. But then it is also wrong to say that the data that results from calculations performed on a computer is data regarding the computer. If this is not true, then also Parker's basic contention that "any computer simulation study classified as an experiment is first and foremost a material experiment" loses its ground.

The same confusion of different levels of consideration (i.e., the symbolic or, if preferred, the "semantic level" (Barberousse, Franceschelli, and Imbert, 2009)) on which a computer simulation operates and the material level of the hardware on which it is implemented, is carried over by Parker to her reading of intervention. In Parker's opinion, *intervention* in a computer simulation study occurs when the user sets up the simulation and puts it into an initial state, for which purpose the user has to interact materially with the computer. What Parker appears to misunderstand at this point is that it is not the interaction between the experimenter and the experimental machinery that is at stake when one speaks of *material experiments* in contradistinction to *computer simulations* or *computer experiments* but the interaction between the investigated experimental object and either the machinery or the experimenter or both. Now, in a computer simulation, the experimental object is either a fictional symbolic object or a symbolic (or "semantic" for that matter) representation of a

material object. In any case, intervention on the "experimental" object of a computer simulation always occurs on the symbolic level (e.g., by assigning certain values to certain control variables). Thus, if one classifies computer simulation studies as experiments on the grounds that they involve intervention—which is, admittedly, one of several typical (though not exclusive) characteristics of experiments—then one still must concede that there exists an important difference between simulations and experiments regarding the type and kind of this intervention: in computer simulations, it remains purely symbolic and only in experiments it is material.

That is not to say that Parker is entirely unaware of the representational nature of computer simulations. At one point Parker even contrasts the representational quality of computer simulations with the property of involving interventions that experiments have:

> These characterizations imply at least the following fundamental difference between simulations and experiments: while a simulation is a type of representation — one consisting of a time-ordered sequence of states — an experiment is an investigative activity involving intervention. (Parker, 2009, 487)

However, apart from the fact that the there is at least a counterpart to the representational quality of the simulation model; namely, the representative quality of the experimental object, it is not at all clear why a simulation does not involve intervention. In both the simulation and the experiment, intervention consists in setting or changing certain conditions of the experimental system in a controlled way. Moreover, for both simulations and experiments there exist examples where this kind of intervention is achieved by: a) determining the boundary conditions through the setup before the experiment or simulation starts, or by b) user interaction during the simulation or experiment. While this line of reasoning might appear to strengthen Parker's point about the comparability of simulations and experiments as scientific methods, it still does not alleviate the counterargument that experiments operate on material objects while simulations operate on symbolic representations.

If we say that the experimental object is a representative, this means that it is a part or an instance of the target system of the experiment (i.e., the system in nature) the investigation of which was the purpose of the experiment. It is clear that the programmed model that represents the target system in nature in a computer simulation can never be a representative in this sense. On the other hand, there exist experiments where the object is also not a representative, but merely is some kind of

representation. An example would be a ripple tank that is used to study such phenomena as reflection and interference of waves. Although the waves in the ripple tank are water waves, the ripple tank could also be used to learn something about waves of another kind, like sound waves or light waves. In this case, the waves in the ripple tank are not an instance of the target system and therefore the experimental object would not be called a representative of the target system. One can, in this special case, speak of the experiment as an *analog simulation* and consider the experimental object as a representation of the target system, just as in the case of a computer simulation. There still remains one obvious and one more subtle difference, nevertheless: the object of an analog simulation remains a material object, while the object of a computer simulation is always symbolic. This difference does not have any epistemic relevance in the case of analog simulations. The more subtle, but potentially epistemically relevant difference is that in the case of the analog simulations, there is still some kind of isomorphism involved between the object and the target, while in the case of computer simulations the relation remains purely representative.

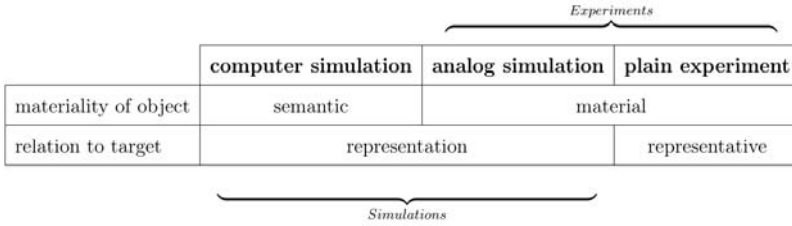

Figure 1: Conceptual relation of simulations and experiments

The different types of simulations and experiments that have just been described are summarized in Figure 3-1. Failure to distinguish properly between computer simulations and analog simulations is a constant source of error in both Parker's and Winsberg's treatment of simulations. For example, Parker complains "the proposed distinction implies that no study as a whole can be simultaneously both a simulation of some target system T and an experiment undertaken to learn about that same target system T, since the required relationships with T are mutually exclusive" (2009, 486). Then, she continues by presenting an example of a study that according to her interpretation is simultaneously an experiment and a simulation. Not surprisingly, her example of the San Francisco Bay Model concerns an analog simulation. However, this merely shows that the

categories of simulations and experiments are not mutually exclusive in the first place. At the same time, it does not imply that there is no epistemically relevant difference between (computer) simulations and experiments that are not analog simulations, which is the conclusion that Parker suggests. In a similar vein, Winsberg (2009) complains that "if we can never be sure if something is an experiment or a simulation" it would not be worth knowing that, as Mary S. Morgan (2003) maintains, "experiments are more epistemically powerful than simulation" (Winsberg, 2009, 582). However, doubts whether something is an experiment or a simulation can arise only in the case of analog simulations. Even here it is possible to distinguish analog simulations from plain experiments by their relation to the target system, as depicted in Figure 3-1.

Another point that Parker makes deserves more consideration; namely, that "what is ultimately of interest when it comes to justifying inferences about target systems is not materiality, but relevant similarity" (Parker, 2009). This is quite true, because material similarity does not automatically transform into epistemic reliability. In addition, numerical representations of nature in computer simulations can be quite accurate at times. Still, being of the same material stuff can be a good reason to assume relevant similarity (which Parker concedes); in some cases, it may be the sole reason. It must be expected that this is particularly true for those processes in nature about which we do not yet have comprehensive theoretical background knowledge in terms of either fundamental laws or at least well-tested phenomenological laws. Parker seems to be faintly aware of the connection between the existence of background knowledge and the possibility to simulate: "especially when scientists as yet know very little about a target system, their best strategy may well be to experiment on a system made of the 'same stuff'" (Parker, 2009, 494). However, she does not seem to be aware that in this case it is not just an option ("best strategy") but a necessity to conduct real material experiments. As the frontier of science is being pushed forward, one can assume that greater and greater regions of nature fall into the realm of what can reliably be simulated based on our scientific background knowledge. However, there will always remain scientific questions for which material experimentation is unavoidable.

Winsberg, in his paper entitled "A Tale of Two Methods" (2009), maintains that simulations and experiments can only be distinguished by how scientists argue for their validity. He does not notice that it would be impossible to argue in different ways for the validity of either simulations or experiments if there did not exist other differences on which the

different arguments could be founded.[2] Indeed he implicitly admits this when he says of the experimenter that "She believes the inferences she will make are legitimate because she is prepared to argue that the two systems are, in relevant respects, the same kind of system, made out of the same material, and can be expected to exhibit relevantly similar behavior" (Winsberg, 2009, 590). However, this means that the experimenter relies on a relevant material similarity. So then, relevant material similarity must be another difference between simulations and experiments, besides the different justifications given for the respective methods. If it were not, it would not be understandable why the simulationist should not appeal to the same reason when justifying his or her procedure. Regarding the simulationist, Winsberg claims that he or she "will want to argue . . . that the computational model of his computer is relevantly similar to a good model of the behavior of the gas jets that interest him" (Winsberg, 2009, 590). However, this is an argument based on formal similarity, which means that formal similarity in contrast to material similarity must be an exclusive feature of simulations, if the justification based on formal similarity is to be exclusive to the simulationist. Otherwise, Winsberg's thesis that simulations and experiments differ by the way they are justified would be empty. Thus, Winsberg is forced to admit the validity of Guala's (2002) distinction between material and formal similarity that he tries to deny in his paper.

This is not the only contradiction in Winsberg's paper. In order to explain his point, Winsberg sets out with the thought experiments of two physicists, one using a tank of fluid, the other using a digital computer to study fluid interaction. In other words, one scientist is conducting a material experiment; the other, a computer simulation. At one point he concretizes his story as follows: "what if we were to find that both of our original physicists' primary area of interest is astrophysics? The systems that actually interest them are supersonic gas jets that are formed when gasses are drawn into the gravitational well of a black hole" (Winsberg, 2010). With respect to this setting, Winsberg remarks: "neither physicist, then, is actually manipulating his or her actual system of interest. Neither

[2] Against this criticism of Winsberg, an anonymous referee objects, "two claims can be justified in different ways but have the same epistemic warrant." However, since the epistemic justification of a scientific procedure usually consists in explaining or pointing out what its epistemic warrants are, it is hard to see how this is possible in this context. Moreover, as the passages quoted in the following pages from Winsberg demonstrate, he is unable to uphold his position that simulationists and experimenters rely on the same epistemic warrants when they justify their method.

one is even manipulating a system of the same type, on any reasonably narrow sense of the term" (2010, 52). Thus, we are to assume that simulation and experiment cannot be distinguished by whether the actual system of interest is manipulated. However, only a few lines later Winsberg maintains exactly the opposite: "in some respects, the physicist's tank is an instance of the system of interest, since it is in fact an instance of a supersonic interaction of a pair of fluids." Now, how can a system that is not a "system of the same type, on any reasonably narrow sense of the term" be at the same time an "instance of the system of interest"? Winsberg denies that there exists a distinction between simulations and experiments that is more fundamental than the different kinds of justification for experiments and simulations respectively. It seems, however, that this denial rests in part on a self-contradictory analysis of the central thought experiment of his paper.

Another objection that Winsberg raises against the distinction is "on the Simon/Guala definitions of simulation and experiment, they are both success terms. An investigation will count as an experiment only if it is successful in the sense that the relevant material similarity between object and target actually obtain" (Winsberg, 2009). He concludes from this that in this definition if an experiment failed to establish a relevant material similarity then it would not be a failed experiment but it would simply fall into the other category (i.e. simulation), which seems wrong to Winsberg. With respect to this, he worries that "if experiment and simulation are success terms, then investigators may never be in a position to know if they are conducting a simulation or an experiment." However, Winsberg (2009), following a suggestion from Parker, already offers the obvious counterargument against his objection; namely that "simulation studies are characterized by the fact that the investigators aim for their objects to have relevant formal similarities to their targets and that ordinary experiments are characterized by the fact that the investigators aim for their objects to have relevant material similarities to their targets." Winsberg never answers this counterargument. Instead, he continues: "I do not think this works. I think the whole idea of formal versus material similarity is confused, no matter how much it is tempered by 'relevant,' 'aimed for,' or whatever." That is, Winsberg reasserts his opinion but does not offer an argument.

Margaret Morrison does not buy Parker's argument that computer simulations are also somehow material: "locating the materiality of computer experiments in the machine itself, however, carries with it no epistemological significance," she notes (2009). Nevertheless, she reaches the similar conclusion that "the modeling features of simulation are co-

extensive with its experimental character making any epistemically relevant differences between experiment and simulation very difficult to articulate." More precisely, her claim is "that the way models function as the primary source of knowledge (…) is not significantly different" (Morrison, 2009). But this is obviously false, because in a simulation it is a model that produces the data, which is impermissible in a material experiment.[3] In a similar vein, Morrison maintains "experimental measurement is a highly complex affair where appeals to materiality as a method of validation are outstripped by an intricate network of models and inference" (Morrison, 2009). However, one of her own examples, magnetic resonance imaging (MRI), suggests the opposite. For, in order to validate that an MRI scanner works correctly, it is, among other things, tested with material objects. And when it is put to use in medicine, it is done so because it is able to reveal material features of the body or body part under examination and thus is able to validate or refute assumptions about health or illness by an appeal to materiality.[4] Because devices like an MRI scanner are diligently built to determine material properties of the objects under study, one could say that the "intricate network of models and inference" is tailored to the expression of the materiality of the object, rather than outstripping the appeal to materiality.

As we have mentioned earlier, with the scientific frontier moving onward, it is imaginable that increasing ranges of natural phenomena can be simulated, thereby potentially outstripping the need for experiments. This is, however, something completely different from maintaining that the appeal to materiality can be outstripped by models and inference in those cases where material experiments are still conducted. One might

[3] See also Peschard (forthcoming) who utters a very similar criticism of Morrison and nicely summarizes her complaints: "Admittedly, we 'know' of the features of the system that affect the instrument only in so far as we 'know' of the relation between these features and the state of the instrument; that is, only in so far as we have and are justified in using a given model of the instrument. But to say that this mediating role of model makes causal interaction in experimentation epistemically irrelevant looks like saying that the role of language in expressing our sensory experience makes the sensory character of this experience epistemically irrelevant."

[4] According to an anonymous referee I have misunderstood the point that Morrison wanted to make with her example of MRI. I am aware that Morrison has several things to say about MRI. It is just this specific consequence about the relative epistemic weight of material factors and models that I intend to criticize. In the worst case my criticism only touches an unfortunate formulation by Morrison. Because Morrison formulates more or less the same idea in different ways at several points of her paper, I am inclined to believe that she means what she says at this point.

speculate that in future science there will be a growing dependence on observations that are made with intricate and highly technicized measurement devices and continuously less reliance on ordinary sense perception. However, it is doubtful whether the point where sense perception becomes superfluous as a means of scientific investigation will ever be reached. One can say with Humphreys (2004) that this increases the epistemic opacity or that a greater and greater part of the epistemic processes that lead to knowledge will take place hidden from our eyes. But even then, humans will remain in the epistemic center, because it is humans that build and design the epistemic machinery that they make use of. However, the path—or, more likely, some of the paths—to the periphery where the epistemic machinery gets into contact with the world will continuously be extended.

Morrison may have been mislead into likening experiments to models by her own historical example, which she presents at the beginning of her paper. For the purpose of commenting on the contemporary discussion about models and experiments, this example unfortunately does not appear to be particularly well chosen. The example concerns Lord Kelvin's interpretation of electrodynamics. "As I mentioned at the outset, Kelvin saw mechanical models as intimately connected to measurement and experiment. He considered numerical calculation measurement as long as it was performed in the context of model construction, testing, and manipulation. All of these features enabled one to know an object 'directly' rather than simply becoming acquainted with a mere representation." (Morrison, 2009). This can be misleading if applied to the contemporary discussion, because it seems that Kelvin's notion of knowing an object "directly" rests entirely on an ontological commitment of Kelvin's in favor of mechanical models and explanations. Other than that, his jelly bowl (Morrison, 2009, 37) is just another example of what we call analog simulations and as such, it is just as remote from its target system as Maxwell's mathematical equations. Therefore, the example of Kelvin is not a good example for showing, as Morrison seems to intend, that material experiments do not have a more direct relation to their target systems than simulations and that appeals to "knowing an object directly" through a certain kind of scientific method are badly founded. The appeal is merely badly founded in Kelvin's case. Incidentally, we see again how important the clear distinction between plain experiments and analog simulations is for the whole discussion.

Briefly summing it up: none of the arguments against the separation of simulations and experiments by Parker, Winsberg, and Morrison appear to

be pervasive.[5] However, there is one point by Parker that ought be kept in mind; namely, that in any concrete case what ultimately matters is not the materiality of the procedure nor primarily whether the relation to the target system is a material or a formal similarity, but whether a relevant similarity can be established.

Arguments for the Difference between Simulations and Experiments

Having refuted the arguments against making a difference between simulations and experiments, the question remains: what positive arguments are there for drawing a strict distinction between simulations and experiments? There appear to be at least three fundamental and important differences between simulations and experiments, which I will discuss below.

Only experiments can operate on a representative of the target system

Operating on a representative of the target system means that the object that is manipulated and studied in the experiment is either a part of or an instance of the target system or is the target system itself. In contrast, both analog and computer simulations operate only on a representation of the target system. In the case of analog simulations, this is true in virtue of the definition of an analog simulation as an experiment that operates on a representation of, rather than on a representative of, the target system. In the case of computer simulations, this is true by necessity as long as the target system is a target system in nature.[6] Both the relation of being representative of and that of being a representation of a target system raise

[5] According to an anonymous referee, this misrepresents Winsberg's, Parker's and Morrison's position, because none of them believes that simulations and experiments are one and the same thing, but only that in some cases they may have the same epistemic warrants. My primary goal is not to criticize Winsberg, Parker and Morrison, but to refute those arguments that have been put forward against the difference between simulations and experiments. I have pointed out above some of the few concessions these authors make in the discussed papers in favor of the distinction between simulations and experiments. In no way do the discussed papers support the conclusion that Winsberg, Parker, and Morrison restrict themselves to *some* cases only. But even if restricted to some cases, most of their arguments remain false and seriously misleading.

[6] One can also conceive of a model as a target system of a computer simulation. But this is a special case which in an epistemic connection is not at all comparable to the case where the target system is a system in the real world.

the analogous question of whether the respective relation truly holds. But this does not mean that both questions are one and the same. For establishing either of these relations provides a different challenge. Generally speaking, establishing the relation of representation requires comprehensive background knowledge about the target system, while the relation of being a representative can be established (though, as always, with a probability of error) on the basis of other indicators. For example, if one wants to know whether some kind of wood burns at 250°C it suffices to take a piece of that wood to establish the relation of *representative of* (in this case, in the sense of being part of it). However, before one could be sure that a certain computer model of a piece of wood is truly a *representation of* that kind of wood, one would either need a comprehensive knowledge of the chemical structure of the kind of wood in question and of the chemical laws guiding oxidation, or one would at least need to know sufficiently detailed phenomenological laws about the burning of wood as to allow one to draw conclusions about the temperature at which the particular kind of wood in question starts to burn. Thus, the difference between *representation of* and *representative of* is a highly relevant epistemic difference.

This difference in relation to the target system can also be described as the difference between *material similarity* and *formal similarity* (Guala, 2002). Material similarity is the relation between the experimental system and the target system in the case of an experiment. Formal similarity holds between the simulation system and the target system in the case of computer simulations.

The case of analog simulations is ambiguous with respect to this terminology, and requires clarification as to whether *material similarity* also covers the similarity of different materials that obey the same laws. If this clarification is made or if the case of analog simulations is excluded, then Winsberg's (2009) criticism of this terminology can be circumvented. Another phrase that has been used to describe material similarity is the phrase "same stuff." This phrase is less ambiguous than the phrase "material similarity," because it clearly suggests that the material must be the same.

Only experiments can deliver knowledge to us that goes beyond what is implied in our background knowledge

Because computers are merely calculating machines, they cannot provide us with any knowledge about the world beyond what is implied in the premises of a computer simulation. As the premises must be rooted in

our prior knowledge, the insights one can gain from computer simulations is limited to this prior knowledge and its implications.[7] The same does not necessarily need to be true of analog simulations. In order to be meaningful, an analog simulation only requires that the mapping relation (typically an isomorphism) between the object that serves as a stand-in for the target and the target system itself is known, but not that the laws of nature that govern the object are known as well. Therefore, the object could potentially reveal a behavior that is not merely a logical consequence of our prior knowledge. If we assume that the mapping relation is applicable nonetheless, then the novelty exposed by the object's behavior carries over to the target system as well. It may of course be disputed whether this assumption is true or whether it has much practical impact. But the case is at least imaginable.

Because of this limitation, computer simulations can be best thought of as tools for evaluating the consequences of an existing stock of knowledge. But only experiments (potentially including analog simulations in the hypothetical case just described) can break through the epistemic barrier that is determined by our prior knowledge and to which computer simulations are inevitably confined.

One can speculate whether one day our background knowledge will be so complete that we can deduce any possible further knowledge about the world from it. This, however, is pure science fiction and it seems as good as impossible within the limitations of the *conditio humana* that it should ever become real.

Only experiments can be used to test fundamental theories

Can simulations be used to test hypotheses? They can, but only against the background of an existing theory. It may be the case that this theory can in turn be tested via simulations against another more fundamental theory. But at some point we reach a most fundamental theory, which cannot be tested by a simulation any more, because no theories or principles remain upon which such a simulation could be built. Thus, it is for basic reasons impossible to replace an *experimentum crucis* by a simulation. And this is true for both computer simulations and analog

[7] It is important here to understand the difference among a) things that are not logically implied in our prior knowledge, b) things that are logically implied in our prior knowledge but unknown to us and c) things that are logically implied in our prior knowledge and known to us. For category a, simulations cannot help us, only experiments can help. For category b, simulations and experiments can help us. Finally, for category c neither is needed because we know it already.

simulations, because an *experimentum crucis* requires that the investigated object be a representative of the target system, the particular nature of which is in question.

What counts as fundamental theory is, of course, historically relative. For example, Galileo's laws of motion and Kepler's laws of the movement of the planets were both fundamental theories at the time of their invention. Both, however, can be derived from Newtonian mechanics and, therefore, they lost the status of fundamental theories, which was then taken by Newtonian mechanics. Once Newtonian mechanics were accepted, Kepler's laws could also be tested by simulation (though this is strictly speaking unnecessary, because they could be derived mathematically already). But then this simulation does not replace an *experimentum crucis* of a *fundamental* theory anymore. Since at any past, present, or future point in the history of science there will exist at least one theory that is the most fundamental theory, material experiments will still be needed to test at least this fundamental theory. Even if we assume the hypothetical scenario above, where humanity has accumulated sufficient knowledge to derive everything else that is worth knowing from this knowledge, material experiments would still be needed to justify the fundamental theories that are part of this set of knowledge.

Further differences and conclusions

One can easily think of further differences between simulations and experiments: as mentioned earlier, experiments are material in the sense that the object under investigation is a material object. Simulations in contrast are virtual in the sense that the object that is investigated is a semantic representation. The criterion of materiality should not be confused with the relation of material similarity. Materiality as such concerns only the object under investigation and not the relation between object and target (see Figure 3-1). With respect to the relation of material similarity, materiality is a necessary but not a sufficient condition, because an analog simulation is also material but not of the "same stuff" as its target. Since it does not allow us to distinguish analog simulations from other experiments, materiality alone is a comparatively less important criterion for the distinction than, say, material similarity.

Yet, another difference is that experiments are an empirical method while computer simulations remain purely theoretical. Again, the case of analog simulations may be a cause of ambiguity, because by virtue of the materiality of their object, analog simulations could be considered

empirical just like ordinary experiments, but they do not deliver empirical knowledge about the target system to us.

Overall, we find that there are sufficiently many and sufficiently important differences to warrant an epistemological distinction between simulation methods and experimental methods. This said, it cannot be denied that it is a fact that in modern science both methods, the experimental method and the simulation method, are frequently used in close connection with each other. Does this mean that they merge into complexes where simulations and experiments become indistinguishable? We will now turn our attention to this question.

The Challenge of Hybrid Methods

In contemporary science, experimental methods are often closely intertwined with simulations or with simulation-like computational procedures. Simulations can be used to determine the optimal experimental design before experiments are carried out (Kramer and Radde, 2010). Computational methods can be used to select experimental data for further analysis while the experiment is run, as is done in particle accelerator experiments (CERN, 2011). They can furthermore be employed to post-process the raw data from measurements as, for example, in computed tomography (Lee and Carroll, 2010). In economics, experiments usually involve real human subjects that are placed in an artificial environment that differs substantially from the sort of real-world environments to which scientists try to apply results from the experiments and draw conclusions (Guala, 2002, 2012). Sometimes the artificial environment contains computer agents that interact with humans in the experiment. In the natural sciences, we also frequently encounter cases where empirical measurements and simulation methods jointly function as sources of data. Multiscale models of electrocardiac physiology, described by Annamaria Carusi, Kevin Burrage, and Blanca Rodriguez in another chapter of this book as model-simulation experiment systems, may serve as an example.

To give a name to these kinds of sophisticated procedures, we can speak of them as *hybrids of simulations and experiments*. Hybrid methods constitute a challenge for the philosophy of science in several respects. They challenge the distinction between simulations and experiments that has been defended above. Doing so, hybrid methods also challenge the logic of scientific research in general. For the logic of scientific research, as understood by most scientists and by many philosophers of science, rests on the testing of hypotheses against empirical data. This presupposes,

one should assume, a clear distinction between the empirical and the theoretical. To put it in another way, if we cannot uphold the distinction between the theoretical and the empirical, then we would have to reconstruct the whole logic of scientific research.

The distinguishing features between simulations and experiments presented earlier do not really solve the problem of hybrids, because they only tell us what the difference between the categories of experiment and simulation are. However, they do not allow us in all cases to decide whether a particular procedure belongs to the class of simulations or to that of experiments. If we follow the reasoning of the first part of this chapter, then we know that only experiments can operate directly on the target system. But we may not be sure in a particular case whether some scientific procedure that makes scant use of some sort of empirical data and heavy use of computation falls into this category.

To solve the problem of hybrids, several quite different approaches are imaginable. One can even say that so far neither the framing nor the exact formulation of the question is clear. I am not going to attempt to give a comprehensive list of approaches to the problem of hybrids that have been proposed so far or that appear imaginable, but I will confine myself to the discussion of three approaches. Other authors have suggested two of these approaches; I briefly present them here since I consider these promising. After that I am going to present my own best guess at how the problem of hybrids could be solved.

Hybrids as Mixtures of Empirical and Virtual Data Sources (Zacharias/Lenel)

Guala (2002) considers as hybrid methods economic experiments where real human agents act in an artificial laboratory situation. Let us, for the sake of simplicity, imagine an experiment where human agents interact with computer agents. Generalizing from this case and adjusting it to the terminology developed in the first part of the paper, this leads to one possible definition of hybrids as procedures where the data source is partly empirical and partly virtual.

How does this relate to our earlier distinction between simulations and experiments in light of the material or formal similarity of object and target? Well, the example shows that both the object under study and the target can be complex entities that are made of different components. The material similarity that makes the method an experiment may hold only for some components of the object and target but not for others.

As a consequence of this, the differences between simulations and experiments that have been described earlier apply only insofar as such components of the object under investigation are concerned that do actually bear a material similarity to (parts of) the target system. One could classify hybrids (in the just-defined sense) as experiments, if one were willing to weaken the formulations of the differences a bit; for example, by allowing that it suffices that at least one component of the object is a part of or an instance of some part of the target system. However, this would be a somewhat strained attempt to keep up a strict dichotomy between simulations and experiments.

A much better solution has been proposed by Moritz Lenel and Sebastian Zacharias (unpublished). They give up the strict dichotomy in favor of a cross-classification of simulations and experiments (first dimension) and of laboratory and field methods (second dimension). In order to do, so they drop the idea of a monolithic target system. Instead, they differentiate between the target object and the target situation. Experiments and simulations are then distinguished by whether they operate directly on the target object or on a representation thereof. Laboratory research is distinguished from field research by whether it takes place in the target situation or in an artificially crafted laboratory environment. This classification scheme works quite well for economic experiments and simulations and for the social sciences in general. Economic experiments would most of the time fall under the category of laboratory experiments, but there is also room for laboratory simulations, field simulations, and field experiments.

It is an open question how well this or a similar scheme could work in the natural sciences. In addition, the case where human agents act together with computer agents in the same situation on an economic experiment might strain the classification. Still, it is so far one of the most convincing answers to the problem of hybrids.

Classification in Terms of the Degree of Materiality (Morgan)

A quite natural approach would be to examine to what extent the method employed depends on materiality (i.e., material data sources, material interaction, material output) throughout the course of the simulation or experiment in question. This is the approach that Mary S. Morgan (2003) has taken. Doing so, she reaches a fine-grained classification that ranges from lab experiments over "virtually experiments," "virtual experiments" (which are not the same as "virtually experiments"!) to mathematical model experiments. Morgan takes into

account the material status of input, intervention, and output, but also the relation between object and target where, again, she carefully distinguishes between "representative of," "representative for," and "representation of." Morgan's "Experiments without material intervention" (2003) is also one of the few attempts to explicitly deal with hybrid methods. I will not attempt to do justice to her careful and well-reasoned examination here. However, a few remarks are in order.

First, while it seems reasonable to consider the materiality or nonmateriality of the intervention for distinguishing degrees of virtuality, it is not equally clear why the material or nonmaterial status of the inputs or outputs should really matter. A simulation can start with empirical input data of some system and then calculate the future evolution of the system. However, this would not make the simulation any more experimental. The most that can be said is that materiality of input data is a necessary but not sufficient requirement for a procedure to be an experiment or empirical measurement. As will be argued below, it is, if anything at all, the relation between the input and the output what makes a hybrid an experiment or a simulation.

Mary Morgan's distinction between representative and representation is more convincing. Although it is very helpful for distinguishing experiments from simulations, it does not seem fit to solve the problem of hybrid methods, because—as has been argued above—the problem arises when both relations are present in the course of one and the same procedure. As sample cases, Morgan examines two different simulations of hipbones. They differ in the way the model of the hipbone is obtained on which the simulation is carried out. In one case, the model is obtained by cutting one particular hipbone into slices and determining the three-dimensional structure of the hipbone from these slices. In the other case, the scientists started with a stylized bone model that is then refined: "the individual side elements within the grid are given assorted widths based on averages of measurements of internal strut widths (taken from several real cow bones) and are gently angled in relation to each other by use of a random-assignment process" (Morgan, 2003, 222). Only in the first case is the input data clearly of empirical origin. The other case could— from the description given by Morgan—alternatively be interpreted as an example of a theoretical model that is adjusted or corrected with empirical data. For Morgan, the first simulation is therefore more like a material experiment than the second, and both lie somewhere between pure material experiments and pure mathematical modeling.

The stance I have adopted leads to a different evaluation, though. According to the view I advocate, both examples are clearly simulations.

The reason is that the empirical origin of the input data alone is not sufficient to classify a procedure as experimental, or even partially experimental. In either of the two cases described by Morgan, it is only the input data what is empirical. The object that is manipulated during the study, however, is obviously a model. According to Morgan's description, "in both cases (…) the experiment consists of the 'application' of a conventionally accepted (…) mathematical version of the laws of mechanics (…) The computer experiment calculates the effects of the 'force' on individual elements in the grid and assembles the individual effects into an overall measure of the strength due to structure" (2003, 221).

The last description seems to fit one of our earlier characterizations of simulations in contrast to experiments quite well; namely that in a simulation it is a model and not a material object that produces the simulation data. This characterization is not as clear as it may seem at first glance though, because it requires that we can always distinguish the case where a model that is set up with empirical parameter values produces simulation data from cases of mere refinement of empirical input data, like, for example, by noise reduction algorithms. In the examples that Morgan presents, however, it seems clear enough that the data is produced by programmed models in a way that goes beyond the typical inferential patterns that can be found in measurements. That the models have been created from empirical data does not contradict this finding.

Classification in Terms of the Relation between Input and Output

In the following, I present my own best guess at how to answer the problem of hybrids. As stated earlier, the best way of framing the question in my opinion is to ask how computer simulations that make use of empirical input data can be distinguished from empirical measurements that involve the computational refinement of raw data. The difference can, I believe, easily be made clear with the help of examples.

Think for example of a climate simulation: a climate simulation calculates the future development of the climate. In order to do so it is fed empirical data. Thus, both components of a hybrid—empirical input data and the computational processing of this data—are present. Yet, it is clear that a climate simulation is a simulation and not a measurement, because it is impossible to measure something that lies in the future.

Now take as another example an MRI scan: again both components of a hybrid are present: the object or the person in the scanner from which the

empirical input data is recorded in form of electromagnetic waves that are emitted in response to the prior excitation of its H-atoms and the computational processing, which in this case produces a visual image of the internal structure of the object from the input data. While the classification may be not quite as indisputable as the example of the climate simulation, it still appears reasonably clear that this is an empirical measurement, because the object's structure is reconstructed from data that reflects this structure.

As clear as the example cases may be, it is more difficult to find general criteria by which to decide whether a particular method or procedure belongs to the class of simulations or to that of measurements (or experiments for that matter). In the following, I am going to attempt an answer in two steps. The uniting idea for both steps is the assumption that the difference between simulation-like hybrids and measurement-like hybrids can best be spelled out in terms of the relation that exists between quantities that the output data represents and the quantities that the input data measures.[8]

A first approach: The same-system formula

Following the idea that one feature that distinguishes experiments from simulations is that experiments can operate on the physical target system itself, one can formulate the following criterion:

> *Same*-system *formula*: a hybrid procedure is a measurement if its output data describes the same system in the same state as its input data.[9]

One can easily check that this criterion works well with the two examples given above: the output of the MRI scan is obviously data about the very system that the input data is taken from, and it is about the system in exactly that state in which the input data was recorded. Although in the case of the climate simulation one could say that the input and output

[8] The relation between input and output that is meant here is not to be confused with the transformation function that transforms the input data into output data. Rather it concerns the relation of the input and output values within the target system. Examining the nature of the transformation from input to output might provide yet another alternative way to deal with the problem of hybrids. Nevertheless, this alternative is not examined here.

[9] It might be worthy of notice that the input of the computational part of a hybrid always has a precisely and unambiguously defined magnitude; namely the digital data as it is entered into the computer (either by hand or by a digitizing device) before any calculations on this data have been carried out.

system is the same; namely, the climate system, the output clearly concerns the system in a future state and therefore in another state than the input. The same-system formula therefore correctly places it in the class of simulations.

The same-system formula works well enough in many cases, but unfortunately not in all cases. Imagine a similar case as Mary Morgan (2003) discusses: we determine empirically the structure of a particular hipbone. Then, we run simulations where pressure is put on the hipbone in order to estimate the strength of this hipbone. The hipbone's strength is thus inferred by a calculation from its structure. Now, measurements often involve some kind of inference, but usually this is backward inference, where we measure the deeper causes of a phenomenon by some overt phenomenon (e.g., we measure the temperature by the extension of the liquid in a thermometer). However, in the case of the hipbone, the inference goes in the other direction. It therefore appears very doubtful whether one could call this a measurement of the hipbone's strength.

A second approach: The measuring-the-cause-by-its-effects pattern

Since the same system formula fails as a sufficient criterion for classifying hybrids, a subtler criterion is needed. Spelling out the same idea that only experiments operate on the physical target system itself, I propose the following two criteria for classifying hybrid procedures as measurements:

1. *Spatiotemporal* concordance of source and output: the output values have the same spatiotemporal location as the source values.
2. Causal dependency of input on output: the output values are either a necessary (!) cause for the input values, or the output values are linked by definitions or mathematical laws to the input values.

The first criterion makes sure that neither prognoses nor retrodictions (i.e., inferences about past events based on present observations) are accidentally classified as measurements. The second criterion reflects the well-known pattern of measuring a magnitude by its causal effects. For example, if one measures the force through the expansion of a spring. The further qualification that a link by definition or mathematical laws suffices is meant to capture such simple cases such as measuring the density by measuring and then dividing the weight and the volume of an object. If a hybrid procedure is found to be a measurement by these criteria, then we can also speak of the input data as *raw data* and the output data as *refined data*, thereby indicating that in the case of a (computationally enhanced)

measurement, the input and the output data still concern one and the same thing. There exists an overlap between both criteria insofar they exclude prognoses, although this overlap is harmless. One can easily verify that neither criterion is superfluous in the sense of preempting the other criterion.

We speak here of "values" rather than "data," because data is, strictly speaking, an entity located in a computer and causally linked to the software that processes it. What matters here, however, are the magnitudes in nature that the data informs us about. We understand "values" as always having the time, location, and causal connection to their occurrence in nature. In addition, it should be noted that in the first criterion we do not refer to *input* values but to *source* values.[10] This accounts for the fact that the measuring device can be located more or less remotely from its object. For example, a person observing an explosion may hear a noise and see a flash of light, both of which occur at a different time to the observer. Because of this, it would not be useful to require spatiotemporal concordance of the *input* values. Admittedly, introducing the concept of source values here raises questions regarding the relation between source values and input values. Since the source values cannot directly be observed, it requires at least a further inferential step to reconstruct the source values from the input values. It would take us too far afield to go into this problem here. Therefore, it must be noted as an open question.

In order justify the proposed criteria for classifying hybrid methods, we will briefly go through a number of typical examples of hybrid methods and try to show that the classification according to these criteria is sound in the sense of matching the intuitions one might have about the particular examples.

I have already mentioned climate simulations as probably the most well known example of simulations in science. Climate simulations are based on empirical input data, but clearly they do not constitute experiments or empirical measurements themselves. The output of climate simulations concerns the future development of the earth's climate. It would seem awkward to consider climate simulations as a measurement of the possible future climate. As the output does not fall into the same spatiotemporal region as the source, climate simulations are also not measurements according to our two criteria listed above. Thus, the classification of climate simulations according to our criteria is in harmony with our intuition and the self-ascription by scientists.

[10] This distinction relates to Paul Humphreys' distinction between source data and accessible data. See Figure 1-1 of Humphreys' article in this volume.

Another famous example of the most advanced kind of "technoscience" is the Large Hadron Collider (LHC). An interesting peculiarity of the Large Hadron Collider is that from the enormous number of events occurring during one second in the collider, only a number of events that is several magnitudes smaller is preselected[11] by automatic procedures for further examination (CERN, 2011). This nicely illustrates the idea of epistemic opacity, which, according to Humphreys (2004), is one of the characteristic features of modern computer-based science: It is the computer that decides which data will be selected and it is in principle impossible for any human agent to double-check each individual decision, even though the algorithms for that decision were of course developed by humans.

According to our criteria, which remain neutral with respect to the selection and preselection of data, the LHC data still counts as experimentally measured data. This is in accordance with the self-description of the LHC project, which also speaks of experiments. It is reasonable to do so, because the events selected by the computer for further analysis are still empirical events that occurred in the collider itself.

It is more difficult to decide how computational post-processing of data affects its status as empirical data. In magnetic resonance imaging, the raw data obtained from the electromagnetic signals emitted by the previously stimulated protons of the body are turned into an image by means of various highly sophisticated computations (Lee and Carroll, 2010). According to our criteria, magnetic resonance imaging falls still into the category of experimental measurement, because the output is an image of the structure of the body, but it is just that structure of the body that determines what the electromagnetic signals (i.e., the raw data) are like. In this sense, the output values are causally responsible for the input values. Simultaneously, both output values and source values lie in the same spatiotemporal region. But not only according to our criteria—intuitively it also makes sense to consider magnetic resonance imaging as a measurement. For it bears a strong similarity to photography. And it can be verified by dissection that the images it produces resemble the object under study and thus are not fabricated by a model.

Simulations are a very popular tool in astronomy. One reason for this is that it is impossible to carry out material experiments with stars and galaxies. However, the fact that it is impossible to study, say, the collision

[11] LHC terminology speaks of "reprocessing" of data. However, since the data is not changed but merely is a subset of data filtered from a larger set of data, we use the term "pre-selection" here to avoid misunderstanding.

of galaxies experimentally does not turn a simulation of the collision of galaxies into an experimental procedure, other than in a purely metaphorical sense of the word "experimental." If we consider such examples, then these are not experimental measurements according to our criteria, because clearly the input data is not empirical, but is model data about hypothetical galaxies (Struck, 1997). In this case, the simulation would not even be classified as a hybrid in the first place.

There are of course other kinds of simulations in astronomy that make heavy use of empirical input data, like the Bolshoi simulation (HIPACC, 2011). The Bolshoi simulation is a simulation by our criteria because the output of the simulation (evolution of the universe or, rather, of regions of the universe) is not a cause of the initial state nor is it located at the same time and place. The classification of the Bolshoi simulation as a simulation and not as an experiment is in agreement with the self-ascription by its creators, and it is intuitively plausible that it is a simulation and not an experiment.

This brief survey of examples indicates that our criteria for distinguishing experimental measurements that involve the computational refinement of data from simulations based on empirical input data can account for many prominent examples of advanced science. This in turn suggests that the criteria articulate at least an implicit standing convention for distinguishing data-based simulations from empirical measurements. It still leaves open the philosophical question whether and how this practice can be justified epistemologically. However, this answer to the problem of hybrids builds on a structural feature that is already present in traditional measurement instruments and that has been described here as the measuring the cause by its effects pattern. Therefore, I conjecture that the problem of justifying it is either exactly the same or very similar to that of justifying traditional measurement or observation methods which rely on this pattern. For example, we say we measure the temperature, when in fact we are measuring the extension of the volume of a liquid in a thermometer and infer the temperature with the help of a scale. Still, we consider the temperature value as empirical data and I believe we do so because the kind of inference we make adheres to the two conditions stated above.

Summary and Open Questions

In this chapter I have argued that experiments and simulations and, by the same token, empirical measurements and theoretical calculations are clearly separate and well-distinguished categories. I have defended this

distinction against what appears to me to be a strong tendency towards the contrary in the newer philosophy of simulation literature. However, the problem of hybrid methods (i.e., methods that combine empirical measurement of data with the computational processing of this data) raises conceptual problems that are not so easily solved. There are different possible approaches to solving these problems. In my opinion, the best way to frame these problems is by asking the question: what distinguishes a computer simulation based on empirical input data from an empirical measurement that involves the computational refinement of data? My answer consisted in transferring a typical of pattern of traditional measurement methods to the case of hybrids.

Several questions remain open, however. First, as the approach proposed by me is not the only possible or promising approach, it can still turn out that other approaches work better. Alternatively, it could turn out that no universal answer can be given, but only different answers for different subject areas. For the area of economic simulations, in particular, the approach proposed by Sebastian Zacharias and Moritz Lenel appears to be the best suited and promising.

However, there are also other open questions. The definition of hybrids that I have used more or less silently assumes that the output data really is computed from the input data and not ignored or dropped or the influence of the empirical component changing over time. However, plausible cases where this does not hold can at least be imagined: imagine, for example, a control device that regulates a machine based on data it receives from sensors. Let us assume that since the sensors tend to be unreliable from time to time, the regulatory device runs a simulation of the machine alongside the sensors. Whenever some kind of plausibility test shows that the sensors have delivered unreliable data, the machine switches to the simulation. Otherwise, it uses the sensor data as input and updates the simulation with the measured state of the machine. While it is not possible to tell whether the data produced by the device is empirical or not, this case turns out to be rather unproblematic upon closer inspection. For lack of another word, we could describe the data produced by this device as *potentially empirical data*. Now regarding the epistemic potential of this data, it is clear that this data can only be used in those contexts where in principle simulation data also would suffice (provided it is accurate enough), but not in those contexts, like empirical theory testing or model validation, where real empirical data is indispensable.

Similarly unproblematic is the case where a switch between empirical and simulation sources of input data does not occur, but where empirical and simulation sources are merged. This case is already covered by the

theory of hybrids proposed here: as long the empirical data source has any significant influence on the computed output, the procedure can be classified as empirical data. In principle, it is suitable for all purposes for which real empirical data is needed. Of course, the details still matter. If a theory is to be tested, then the validity of any model that is required for producing (or better, revealing) the empirical data against which it is to be tested must be independent from the theory. This must of course already be considered in the case of conventional measurements. It does not constitute a novel or singular problem of computationally enhanced measurement techniques.

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CHAPTER FOUR

THE USE OF THE 'MATERIALITY ARGUMENT' IN THE LITERATURE ON COMPUTER SIMULATIONS

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Introduction

Much of the current philosophical interest in computer simulations stems from their extended presence in scientific practice. This interest has centered on studies of the experimental character of computer simulations and, as such, on the differences (and similarities) between computer simulations and laboratory experiments. The philosophical effort, then, has been primarily focused on establishing the basis of this contrast; specifically by means of comparing the epistemic power of a computer simulation with that of a laboratory experiment. The basic intuition has been that if computer simulations resemble laboratory experiments in relevant epistemic respects, then they too can be sanctioned as a means of providing understanding of the world.

The literature on the topic distinguishes computer simulations from laboratory experiments on both ontological and representational grounds. The fact that a computer simulation is an abstract entity, and therefore bears only a formal relation to the system being investigated, contrasts with a laboratory experiment, which typically has a causal connection to the target system. These ontological and representational differences have suggested to some philosophers that establishing external validity is a much more difficult task for computer simulations than for laboratory

experiments. For others, however, it has been a motivation to reconsider experimental practice, and see it as a broader activity that also includes simulations as a new scientific tool. These two approaches, I claim, share a common rationale that imposes restrictions on the epistemological analysis of computer simulations. In this paper I propose to discuss this claim.

The most well-known criterion for distinguishing between computer simulations and laboratory experiments is given by the so-called *materiality argument*. Parker has provided a helpful account of this argument:

> In genuine experiments, the same 'material' causes are at work in the experimental and target systems, while in simulations there is merely formal correspondence between the simulating and target systems [...] inferences about target systems are more justified when experimental and target systems are made of the 'same stuff' than when they are made of different materials (as is the case in computer experiments). (2009, 484)

Two claims are being made here. The first is that computer simulations are abstract entities, whereas experiments share the same material *substratum* as the target system.[1] The second, which is essentially epistemic, is that inferences about empirical target systems are more justified by experiments than by computer simulations due to the material relations that the former bears with the world.

Current literature has combined these two claims into two different proposals: either one accepts both claims and encourages the view that being material better justifies inferences about the target system than being abstract and formal (Guala 2002, Morgan 2005); or one rejects both claims and encourages the view that computer simulations are genuine forms of experimentation and, as such, epistemically on a par with experimental practices (Morrison 2009, Winsberg 2009, Parker 2009). I claim that these two groups of philosophers, that superficially seem to disagree, actually share a common rationale in their argumentation. Concretely, they all argue for ontological commitments that ground their epistemic evaluations on computer simulations. I will refer to this rationale as the *materiality principle*.

[1] Some of the terminology in the literature remains unspecified, such as 'material' causes or 'stuff' (Guala, 2002). I here take them to mean *physical causal relations*, as described, for instance, by Dowe (2000). In the same vein, when I refer to *causes*, *causality*, and similar terms, they should be interpreted in the way here specified.

In order to show that the materiality principle is at work in most of the philosophical literature on computer simulations, I discuss three distinctive viewpoints:

> a) Computer simulations and experiments are ontologically similar (both share the same materiality with the target system); hence, they are epistemically on a par (Parker, 2009);
>
> b) Computer simulations and experiments are ontologically dissimilar. Whereas the former is abstract in nature, the latter shares the same materiality with the phenomenon under study; hence, they are epistemically different (Guala 2002, Giere 2009, Morgan 2003, 2005);
>
> c) Computer simulations and experiments are ontologically similar (both are 'model-shaped'); hence, they are epistemically on a par (Morrison 2009, Winsberg 2009).

With these three viewpoints in mind, the materiality principle can be reframed from another perspective: it is due to the philosophers' commitment to the abstractness (or materiality) of computer simulations that inferences about the target system are more (or less thereof) justified than laboratory experiments.

The principal aim of this paper is to show that philosophers of computer simulations do adhere, in one way or another, to the materiality principle. I am also interested in outlining some of the consequences of adopting this rationale. In particular, I am convinced that grounding the philosophical analysis on the materiality principle, as most of current literature seems to do, places a conceptual corset on the study on the epistemological power of computer simulations. The philosophical study on computer simulations must not be restricted to, not limited by, a priori ontological commitments. By analyzing themes in the literature, then, I show that the materiality principle does not engender a helpful conceptualization of the epistemic power of computer simulations. I will also give some suggestions as to how to circumvent this issue and address the epistemology of computer simulations at face value.

The paper is divided in a way that corresponds to the three uses of the materiality argument listed above. The section entitled 'the identity of the algorithm' discusses option a); the section entitled 'material stuff as criterion' addresses option b), which comes in two versions, the *strong*

version and the *weak version*; and finally option c) is addressed in the section entitled 'models as (total) mediators.'

The Identity of the Algorithm

Wendy Parker's formulation of the materiality argument has a prominent place in the recent literature on computer simulation. Following Hartmann (1995), Parker defines a computer simulation as a time-ordered sequence of states that abstractly represents a set of desired properties of the target system. Experimentation, on the other hand, is the activity of putting the experimental setup into a particular state by means of intervening in it, and studying how certain properties of interest in the setup change as a consequence of that intervention (Parker 2009, 486).[2]

Parker's goal is to show that computer simulations and experiments share the same ontological basis, and to use this basis as justification for the claim that computer simulations and experiments are epistemically on a par. To her mind, the central problem is that current definitions of computer simulation do not qualify as an experiment because they lack the crucial intervening mechanisms. Indeed, it is the abstract character of the model that prevents computer simulations from serving as intervening systems. The solution to this issue consists in construing the notion of *computer simulation studies* as a computer simulation where an intervention is made into the physical computer itself. So defined, a computer simulation study does qualify as an experiment.

> A *computer simulation study* […] consists of the broader activity that includes setting the state of the digital computer from which a simulation will evolve, triggering that evolution by starting the computer program that generates the simulation, and then collecting information regarding how various properties of the computer system, such as the values stored in various locations in its memory or the colors displayed on its monitor, evolve in light of the earlier intervention. (2009, 488)

The notion of *intervention* is now defined as the activity of setting the initial state of the computing system and triggering its subsequent evolution. Thus understood, a computer simulation study is an experiment in a straightforward sense, for now the system intervened is the programmed digital computer (2009, 488). On this basis, Parker claims that there is ontological equivalency between computer simulations and

[2] 'Intervention' is conceived of as the manipulation of physical causal relations in the experimental setup.

experiments, and this in turn allows her to claim an equivalency in their epistemic power.

Notably, she does not explain what it means for a computer simulation study to be epistemically powerful. Instead, she limits the argument to asserting that an epistemology of computer simulations should reflect the fact that it is the observed behavior of the computer system that makes them experiments on a real material system (and therefore epistemically powerful).

The influence of the materiality principle can be made yet more explicit. First, Parker conceives of the digital computer as the 'substratum' for the simulated system, thus claiming ontological equivalence between computer simulation studies and experiments. Since the computer simulation study is the activity of putting the physical computer into an initial state, triggering the evolution of the simulation, and collecting physical data as indicated by prints-outs, screen displays, etc. (2009, 489), then the epistemic value of computer simulation studies also corresponds to that of experiments. The evolution in the behavior of the programmed computer represents material features of the simulated phenomenon. Our understanding of such a phenomenon, then, is justified by this evolution on the physical computer. Computer simulation studies and experiments are, then, ontologically on a par, and so is their epistemological power.

Here I have briefly outline Parker's main claims. The problem is that it is still not clear which are the reasons for considering the materiality of the digital computer as the relevant player in the epistemology of computer simulations. Let me put this concern in other terms. To my mind, Parker's motivations are to subvert the materiality argument by showing that computer simulations and experiments are ontologically on a par (and so is their epistemic power). This move, as I have argued, is grounded on a rationale behind the same materiality argument that she is trying to overthrown. The question, then, is what role does the materiality of the digital computer play in the evaluation of the epistemic power of computer simulation studies? Let me now reconstruct three interpretations of Parker's argument.

First, Parker takes the materiality of the digital computer to play some relevant role in the interpretations of results (2009, 490). Under this interpretation, hardware failure, round-off errors, and analogous sources of miscalculation affect the results of the simulation in different ways. This is true of computers and of computation, and it does not call for any special terminology or treatment. It is then doubtful that Parker is grounding her ontological claim on the fact that a digital computer is prone to errors that might affect the final results.

A second possible interpretation is that the system of interest is the physical computer itself, regardless of the represented empirical system. In this scenario, the researcher runs her simulations as usual, only paying attention to the changes in the behavior of the physical computer. These behavioral changes become the substance of the scientist's inquiry, whereas the target system is only regarded as the initial point of reference for the construction of the simulation model. In this context, the researcher learns first and foremost from collecting information on the properties of the physical computer—the values in its memory and the colors on the monitor (Parker 2009, 488).[3] If this is the correct interpretation, then it is incumbent upon Parker to show that the scientist can cognitively access the various physical states of the computer, something that she fails to do. Philosophers have discussed whether it is possible to access different locations inside a computer—the memory, the processor, the computer bus, etc.—and the general agreement is that these are cognitively inaccessible for the unaided human. There is a guiding principle of epistemic opacity ascribed to computational process which rules out any possibility of cognitively accessing the internal states of the physical computer (see Humphreys 2004, 2009). Moreover, even if scientists could actually access these locations (say, if they were aided by another computer), it is still not clear why accessing these locations would be of any relevance for the understanding the simulated phenomenon.

To my mind, neither of the above interpretations is correct. Rather, Parker should be interpreted as taking the materiality of the digital computer as playing the fundamental role of 'bringing about' the target system (i.e., brings into causal existence the phenomenon simulated). In other words, the behavioral changes that the scientist observes in the physical computer are instantiations of the representations built into the computer simulation.[4] Such representations are, naturally, representations *of* a target system. In this way, the digital computer behaves *as if* it were the empirical phenomenon simulated in the programmed computer. I refer

[3] Eckhart Arnold (this volume, 50) interprets Parker in a similar way. As he puts it: "the data of a simulation usually does not convey any information about the computer on which it was produced, but only information about the simulated system."

[4] Note that appealing purely to the visual behavior of the machine is not enough for claiming that computer simulation studies are ontologically on a par to experiments. Moreover, Parker is clearly thinking of causal relations originating in the machine: "The experimental system in a computer experiment is the programmed digital computer (a physical system made of wire, plastic, etc.)" (2009, 488-489).

to this interpretation metaphorically as the 'phenomenon in the machine.' Let me now explore this possibility a little further.

No Phenomenon in the Machine

Parker's main strategy consists in locating the notion of physical causality in the digital computer, and assuming that the evolution of the simulation (represented by the physical states of the digital computer) corresponds to the physical evolution of the target system. In the same vein, intervention in the computational system corresponds to intervention in the target system. Taking this interpretation to be correct, I will now object that there is a principle of multi-realizability in computer software that prevents us relating the physical states of the computer with the target system simulated. Unlike experiments, where the scientist assumes consistency in the causal relations at work in the phenomenon, the physical states of the computer are not constantly the same; rather, they change with each run and for each type of computer architecture. It follows that the physical computer cannot work as the basis for the target system in the same way as materiality works as the basis of the phenomenon.

Let me begin by pointing out some basic modes of operation of the computer. The physical state of the computer is understood as the electronic configuration that the computer has at a given time. Such a configuration is provided by the state of the memory, the state of the computer bus, the I/O devices, and of every other physical component of the computer. Parker refers to this electronic configuration as the *materiality of the computer*.

Now, Parker's argument requires that a set of sufficiently similar physical states of the digital computer is instantiated by the same computer program. To put the same idea slightly different: a computer program must instantiate sufficiently similar physical configuration of the digital computer over each run of the program. This assumption must be met otherwise Parker has no grounds for claiming for the epistemological value of computer simulations (2009, 489). The misunderstanding from Parker is that the physical states of the digital computer are rarely, if ever, similar between multiple instantiations of the same computer program. Indeed, the simulation is not the only process running on the digital computer for it must share the digital computer with the operating system, the processes in charge of running the physical machine, and other user process. Moreover, with a computer processor switching back and forth among all the processes that are running, the rate at which a process

performs its computation is not uniform, and therefore not reproducible on the same machine (Tanenbaum and Woodhull 2006, 56).

To illustrate this point, consider the unique case of *one* computer program running *once* on the *same* machine. A general setup would be: let P_t be the logical state to which a computer program enters when running at time t. In this sense, P_t could be the *if ... then* clause, a loop, or simply an instruction for printing out some data. Since the computer process is implemented on the physical computer, P_t instantiates the physical state of the computer at time t, let us call it M_t. Now, there is a unique mapping relation from P_t to M_t described by F_t which takes as its argument the state of the computer program at time t and matches it with the physical state of the computer at the same time t (Tanenbaum and Woodhull 2006, 56).

Consider now the situation where the *same* computer program is executed on the *same* machine, although *multiple* times. This situation looks very much like Figure 4-1. Using the previous notation: there exists a P_t such that, for each execution $1 \leq i \leq n$ on M, and for each $F_{i,t}$, there exists an $F_{j,t}$, $1 \leq i \leq n$ and $i \neq j$, such that $F_{i,t} \neq F_{j,t}$ and $M_{i,t} \neq M_{j,t}$. In other words, if we run the same instruction on multiple occasions, the internal behavior of the computer will be to create different mappings to different physical states of the same machine.

If we were to draw an analogy with experiments, we would be envisaging something along the following lines: intervention on the same variables instantiates different causal relationships, despite which we obtain the same set of results. This is an unacceptable consequence, because it shows that it is impossible to identify one set of causal relations that is consistent for a given phenomenon.

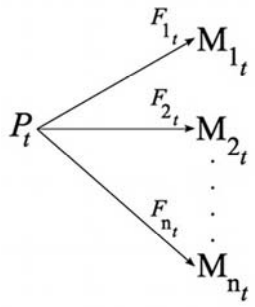

Figure 4-1: Program P at time t running on multiple occasions on the same machine M

Similarly, if the same computer program is run on different physical computers, there are no reasons for thinking that will instantiate the same physical state across the different machines. This situation is illustrated in Figure 4-2.

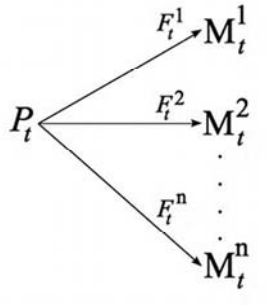

Figure 4-2: Program *P* at time *t* running on multiple machines $M^{1...n}$

In addition, it is a common practice to upgrade hardware by adding new components, or to completely renew the architecture of the computer. For this latter case, take M_t^i as the machine *i* running at time *t*. Then M_t^i differs from M_t^j, for all $1 \leq i, j \leq n$, $i \neq j$ (see Figure 4-2).

With these ideas in mind, any attempt to recreate the 'phenomenon in the machine' is fundamentally flawed for it contradicts basic principles of computer architecture. As I have said, however, this is only an interpretation of Parker's central thesis. Whether correct or not, it should not affect our main claim that her account of computer simulation studies follows the dictates of the materiality principle. This is the case because, as I argued before, Parker takes it that the epistemology of computer simulations is restricted to the conditions imposed by laboratory experiments. The epistemological value of computer simulations is established, therefore, by arguing that the ontology of simulations is equivalent to the ontology of experiments.

Material 'Stuff' as Criterion

The idea of 'material stuff as criterion' is perhaps the most faithful account of the materiality argument.[5] According to this view, there are

[5] There is a generalized and, to my mind, imprudent use of the word 'stuff' in current literature. In this section, however, I use it in the same context and in the same sense as the authors.

fundamental and irreconcilable ontological differences between computer simulations and experiments, the latter being epistemically superior. There are two versions of this account: a *strong version* and a *weak version*.

The strong version holds that the causal relations responsible for bringing about the phenomenon must also be present in the experimental setup. This means that the experiment must replicate the causal relations present in the empirical system. According to the strong version, then, the experiment is a 'piece' of the world.

Take as an example a beam of light used for understanding the nature of the propagation of light. In such a case, the experimental setup is identical to the target system; that is, it simply *is* the empirical system under study. It follows that any manipulation of the experimental setup does address the same causes as the phenomenon, and that an insight into the nature of light can be delivered by our understanding of the controlled experiment (i.e., the beam of light (Guala 2002)).

Applied to computer simulations, the strong version takes it that the merely formal correspondence between the computer and the target system provides a sufficient basis for downplaying their status as epistemic devices. If there are no causal relations acting, then the epistemic power of inferences thereby made about the world is conceptually downgraded.

The weak version, on the other hand, relaxes some of the conditions imposed by the strong version on experimentation. According to this view, a controlled experiment requires only the set of relevant causal relationships that bring the phenomenon about. In this vein, the proponents of the weak version do not commit themselves to a complete reproduction of the phenomenon under study, as the strong version does, but rather to the set of relevant causes that characterize the behavior of the phenomenon.

Let us illustrate the weaker version with a simple example: a ripple-tank can be used as a material representation of light, thus providing insight into its nature as a wave. To the proponent of the weaker version, it is enough to have a representative collection of causal correspondences between the experimental setup and the target system in order for the former to provide some insight into the latter. The relation between the experiment and the real-world phenomenon, then, is one of causal similarity: a cloud chamber detects alpha and beta particles, just as a Geiger counter can measure them. But neither instrument is a 'piece' of the phenomenon under study nor fully interacts with all kinds of particles. It follows that experimental practice, as exemplified by the detection and measurement of particles, depends on a complex system of actual causal relations between the experimental setup and the target system.

Applied to the general evaluation of computer simulations, the weak version presents a more complex and rich picture, which affords of degrees of materiality being ascribed to computer simulations.

Despite these differences, however, both versions share the same viewpoint regarding computer simulations; namely, that they are epistemically inferior to experiments. This claim follows from the ontological conceptualization previously depicted, and stems from the same rationale as underlies the materiality principle. To show this, I discuss arguments provided by two authors.

The Strong Version

Francesco Guala champions the defense of the *strong version*. He assumes from the outset the existence of fundamental differences between computer simulations and experiments grounded on causality.

> The difference lies in the kind of relationship existing between, on the one hand, an *experimental* and its *target* system, and, on the other, a *simulating* and its target system. In the former case, the correspondence holds at a 'deep', 'material' level, whereas in the latter the similarity is admittedly only 'abstract' and 'formal' [...] In a genuine experiment the same 'material' causes as those in the target system are at work; in a simulation they are not, and the correspondence relation (of similarity or analogy) is purely formal in character. (Guala 2002, 66-67)

Guala conceives the experiment as one that reproduces the causal relations present in the phenomenon. The author emphasizes the changes of materiality by appeal to the concepts of 'same' and 'different stuff.' The case of the ripple-tank is paradigmatic in this sense. According to Guala, the media in which the waves travel are made of 'different stuff' (and therefore so are the equations of force): while one medium is water, the other is light. The ripple-tank, then, is a representation of the wave nature of light only because there are similarities in the behavior at a very abstract level (i.e., at the level of Maxwell's equations, D'Alambert's wave equation, and Hook's law). The two systems obey the same laws and can be represented by the same set of equations, despite their being made of 'different stuff.' However, water waves are not light waves (2002, 66), and a difference in the materiality presupposes a difference in the epistemic insight into nature. Indeed, Guala straightforwardly admits that the ontological difference between experiments and simulations grounds epistemological differences (2002, 63). His loyalty to the materiality principle is unquestionable: there is a clear distinction between what we

can learn and understand by direct experimentation and what we can learn by mediated simulation. The epistemic payoff of the latter is less than the former, and this is because, on this view, there is an ontological commitment to causality as epistemically superior that determines the downplaying of the epistemology of computer simulations.

Let me now consider a few objections to Guala's point of view. Parker has objected that his position is too restrictive for experiments, as well as for computer simulations (Parker 2009, 485). I agree with her on this point. Guala's conceptualization of experiments and computer simulations imposes artificial restrictions on both that are difficult to back up with examples in scientific practice. Moreover, and complementary to Parker's objection, I believe that Guala is adopting a perspective that takes both activities as chronologically mutually exclusive: that is, the computer simulation becomes a relevant tool when the experimentation cannot be implemented. STRATAGEM, a computer simulation of stratigraphy, provides us with an example here: when geologists are faced with difficulties in carrying out controlled experiments about strata formation, they appeal to computer simulations as the most efficacious replacement (2002, 68).[6] Such a tendency towards a disjunctive assessment of the two activities is a natural consequence of taking computer simulations to be epistemically inferior to experimentation. In other words, it is a natural consequence of adopting the materiality principle.

The Weak Version

For a proponent of the *weak version*, I turn to the work of Mary Morgan. She has presented the richest and most exhaustive analysis currently to be found in the literature regarding the differences between experiments and computer simulations.

Morgan's primary concern is with so-called *vicarious experiments*, that is:

> Experiments that involve elements of nonmateriality either in their objects or in their interventions and that arise from combining the use of models and experiments, a combination that has created a number of interesting hybrid forms. (2003, 217)

[6] Guala allows that experiments and computer simulations are appropriate research tools, *knowledge-producers* as he calls them, although only for different contexts (2002, 70).

Having thus set out the features of vicarious experiments, she then turns to the question of how they provide an epistemic basis for empirical inference. Briefly, the more 'stuff' is involved in the vicarious experiment, the more epistemically reliable it becomes. In plain words, degrees of materiality determine degrees of reliability. As Morgan comments: "on grounds of inference, experiment remains the preferable mode of enquiry because ontological equivalence provides epistemological power" (2005, 326).

Morgan thus adheres to the weak version, because a vicarious experiment is characterized by different degrees of materiality, as opposed to the strong version that holds that experiments must be a 'piece' of the world. In terms of the materiality principle, however, there are no fundamental differences between the two versions: she also considers ontology to determine the epistemological value of computer simulations. The difference lies, again, in the detailed analysis of the different kinds of experiments involved in scientific practice. Let me now briefly address her account.

As noted above, vicarious experiments can be classified according to their *degree of materiality*; that is, the different degrees to which the materiality of an object is present in the experimental setup. Table 4-1 summarizes four classes of experiments: *Ideal laboratory experiment* (also referred as a *material experiment*), two kinds of *hybrid experiments*, and finally *mathematical model experiment*. As the table indicates, the classification is in terms of the kind of control exerted on the class of experiment, the methods for demonstrating the reliability of the results obtained, the degree of materiality, and the representativeness of each class.

The first and last classes are already well known to us: an example of an ideal laboratory experiment is the beam of light, for it requires effort by the scientist to isolate the system, rigorous attention to the control of the interfering circumstances, and intervention under these conditions of control. An example of the mathematical model experiment, on the other hand, would be the famous mathematical problem of the seven bridges of Königsberg; that is, a class of experiment whose control requirements are achieved by simplifying assumptions, whose demonstration method is via a deductive mathematical/logical method, and one whose materiality is, as expected, inexistent (2003, 218).

Among the number of ways in which these two classes of experiment differ, Morgan emphasizes those constraints imposed naturally via physical causality, and those imposed artificially via assumptions:

> The agency of nature creates boundaries and constraints for the experimenter. There are constraints in the mathematics of the model, too, of course, but the critical point is whether the assumptions that are made there happen to be the same as those of the situation being represented and there is nothing in the mathematics itself to ensure that they are. (2003, 220)

	Ideal lab experiment	**Hybrid experiments**		**Mathematical model experiment**
		Virtually	*Virtual*	
Controls on:				
Inputs	experimental	experimental on	assumed	assumed
Intervention	experimental	inputs; assumed	assumed	assumed
Environment	experimental	on intervention and environment	assumed	assumed
Demonstration method	experimental in laboratory	simulation: experimental/ mathematical using model object		deductive in model
Degree of materiality of:				
Inputs	material	semimaterial	nonmaterial	mathematical
Intervention	material	nonmaterial	nonmaterial	mathematical
Outputs	material	nonmaterial	non- or pseudo-material	mathematical
Representing and Inference Relations	representa*tive of*... ... to same in world; representa*tive for*... ... to similar in world		representa*tion of*... ... back to *other* kinds of things in the world	

Table 4-1: Types of experiment: Ideal laboratory, hybrids, and mathematical models with representing relations (Morgan, 2003, 231)

Hybrid experiments, meanwhile, can be conceived as experiments in-between the other two: they are neither material nor mathematical.[7] The class of *virtually experiments*, then, are understood as those "in which we have nonmaterial experiments on (or with) semimaterial objects," whereas *virtual experiments* are those "in which we have nonmaterial experiments but which may involve some kind of mimicking of material objects"

[7] "By analyzing how these different kinds of hybrid experiments work, we can suggest a taxonomy of hybrid things *in between* that include virtual experiments (entirely nonmaterial in object of study and in intervention but which may involve the mimicking of observations) and virtually experiments (almost a material experiment by virtue of the virtually material object of input)" (2003, 232).

(2003, 216). Table 4-1 again summarizes the properties of all four kinds of vicarious experiments showing their representing and inference relations.

The differences between virtually and virtual experiments can be illustrated with the example of a cow hipbone used as surrogate for the internal structure of human bones. In this context, there are two alternatives: one can use a high-quality 3-D image of the hipbone that creates a detailed map of the bone structure, or, alternatively, a computerized 3-D image of the stylized bone; that is, a computerized 3-D grid representing the structure of the stylized bone. According to Morgan, the 3-D image has a higher degree of verisimilitude to the structure of the real hipbone because it is a more faithful representation of it, as opposed to the mathematization represented by the computerized 3-D grid (2003, 230). The former is referred to as *virtually an experiment*, whereas the latter are called *virtual experiments*.

What are the differences among the kinds of experiment? As expounded in Table 4-1, whereas a virtually experiment is semi- or nonmaterial, an ideal laboratory experiment is strictly material. Also the demonstration methods are also significantly different. The distinction between a virtual experiment and a mathematical model, on the other hand, seems to be located solely in the method of demonstration, which is experimental for the former and deductive for the latter. Morgan also shows how models of stock market prices, despite being mathematical models simulated on a computer, can also be classed as a virtual experiment on account of the input data and the observation of results (2003, 225). The boundaries between all four classes of experiment, however, seem to be unfixed and dependent on factors external to the experiment in question. For instance, if a 3-D grid of the cow bone makes use of real measurements of the cow bone as input data, then what was originally a virtual experiment becomes virtually an experiment.

The epistemological analysis, on the other hand, is a function of the degree of materiality of the class of experiment: "ontological equivalence provides epistemological power" (2005, 326), as Morgan indicates. Back inference to the world from an experimental system can be better justified when the experiment and the target system are of the same material. As Morgan explains: "the ontology matters because it affects the power of inference" (2005, 324). A computer simulation, for instance, cannot test theoretical assumptions of the represented system because it has been designed for delivering results consistent with built-in assumptions. A laboratory experiment, on the other hand, has been explicitly designed for letting the facts about the target system 'talk' by themselves. According to Morgan, then, it is the material substratum underlying an experiment that

is responsible for its epistemic power. Hence, the ideal laboratory experiment is epistemically more powerful than a virtually experiment; in turn, a virtually experiment is more powerful than a virtual experiment, and so on. Since computer simulations can only be conceived as hybrid experiments or as mathematical experiments, it follows that they are always less epistemically powerful than ideal laboratory experiments. To Morgan's mind, therefore, there are *degrees of materiality* that determine the *degrees of epistemic power*.

In this context, Morgan uses the terms *surprise* and *confound* to depict the epistemic states of the scientist regarding the results of a computer simulation and of a material experiment, respectively. Results of a computer simulation can only surprise the scientist because its behavior can be traced back to, and re-explained in terms of, the underlying model. A material experiment, on the other hand, can surprise as well as confound the scientist, for it can bring up new and unexpected patterns of behavior inexplicable from the point of view of current theory (2005, 325; 2003, 219). The materiality of the experiment, then, works as the epistemic guarantee that the results may be novel, as opposed to the simulation, which takes results as capable of being explained in terms of the underlying model.

This shows how Morgan's ideas regarding experiments and computer simulations bear the stamp of the materiality principle. It exhibits the same rationale, putting materiality as the predominant feature for epistemic evaluation. Despite Morgan's strong emphasis on the place that materiality has in the discovery of new phenomena, there are examples of virtual experiments whose epistemic power is clearly superior to any ideal laboratory experiment. Take as a simple example the dynamics of the micro fracture of materials. It is virtually impossible to know anything about micro fractures without the aid of computers. Indeed, only the computational efficiency of finite element methods and multi-scale strong discontinuity can tell us something about the micro fractures of materials (Linder 2012). The lesson is that understanding something about the world do not necessarily comes from material experiments, or from any degree of materiality whatsoever. Neither a field experiment nor a high-definition 3-D image would provide the understanding about the dynamics of micro fractures that can be provided by an accurate mathematical model. The conclusion is that the rationale behind the materiality argument is once more misdirecting us regarding the epistemic power of computer simulations.

Models as (Total) Mediators

The last account in my list is the one I called 'models as (total) mediators.' As the title suggests, this account is directly influenced by Morgan and Morrison's *Models as Mediators* (2009). Briefly, their book is a defense of the mediating role of models in scientific practice. It considers that scientific practice is neither driven by theories, nor is purely about direct manipulation of Nature. Instead, scientific practice needs the mediation of models in order to be successful in achieving its goals. A theory, then, cannot be directly applied to the phenomenon, but only by means of the mediation of a model; similarly, in experimental practice, models render data from measurements and observations in a form that is available for scientific use. In the following, I focus on the mediating role of models in experimental practice, since the proponent of the models as (total) mediators approach is more interested in analyzing computer simulations in the light of experiments. I will thus leave the mediating role of models in the context of theory unanalyzed.

Now, according to the proponent of the models as (total) mediators account, experimental practice consists in obtaining, by manipulation of the phenomenon, data that inform us about certain properties of interest. This data, however, is in such a raw state that it is impossible to consider it reliable or representative of the properties measured or observed. Rather, for these raw data to be of any scientific use, it is necessary to further process it by filtering out noise, correcting values, implementing error-correcting techniques, and so forth. These correcting techniques are conducted by theoretical models and, as such, are responsible for rendering reliable data.

Scientific practice, then, is conceived as strongly mediated by models; and scientific knowledge is no longer obtained uniquely by our intervention into the world, but also by the conceptual mediation that the model–world relation represents. In this vein, the epistemic analysis now concerns the data filtered out, corrected, and refined by models, rather than the raw data collected by directly manipulating Nature.

Computer simulations should easily fit into this new image of scientific practice. One might think that since they are conceived as models implemented on the digital computer, then their results must be data produced by a reliable model in a straightforward sense. Unfortunately this is not what the proponent of models as (total) mediators has in mind. To them, it is correct to say that computer simulations are models running on a digital computer, and it is also correct to say that there is no intervention

into the world in the empiricist's sense.[8] Nevertheless the data obtained by running a simulation are 'raw' in the same sense as the data collected by a scientific instrument.[9] The reason for this is that there are material features of the target system that are being modeled into the simulation, and thus represented in the final simulated data (Morrison 2009, 53). Simulated data, then, need to be post-processed by a further theoretical model, just in the same way as raw data. In other words, simulated data must also be filtered, corrected, and refined by another set of models in order to produce data that can be reliably used in scientific practice. Ontologically speaking, then, there are no differences between data produced by a scientific instrument and data produced by a computer simulation. In addition, the proponent of this approach takes that there are no epistemic differences between these two kinds of data either.

Let me now elaborate on these points by appealing to the work of Margaret Morrison. In 2009, she published a fundamental contribution to the debate on measurement in the context of computer simulations. In that work, she claimed that certain types of computer simulations have the same epistemic status as experimental measurements precisely because both kinds of data are ontologically and epistemically comparable.

To illustrate this point, let us briefly consider her example of measuring the force *g*.[10] In an experimental measurement, Morrison argues, a scientific instrument measures a physical property up to a certain degree of precision, although such measurement will not necessarily reflect an accurate value of that property. The difference between *precision* and *accuracy* is of paramount importance for Morrison here: whereas the former is related to the experimental practice of intervening in nature (or computing the model in the simulation), the latter is related to the mediation of models as rendering reliable data. In this context, a precise measurement consists of a set of results wherein the degree of uncertainty in the estimated value is relatively small (2009, 49); on the other hand, an accurate measurement consists of a set of results that are close to the true value of the measured physical property.[11]

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[8] I am using the term *empiricists* in a rather loose way. Here, I refer only to the epistemic attitude of knowing the world by causally intervening or manipulating it.

[9] In order to keep these two notions of data separate, I will continue referring to data collected by the scientific instrument as 'raw data,' while I will refer to the data obtained by running the computer simulation as 'simulated data.'

[10] Morrison also discusses the more sophisticated example of spin measurement (2009, 51).

[11] The difference between *precision* and *accuracy* is framed by Franklin in the

The distinction between these two concepts constitutes the cornerstone of Morrison's strategy: data collected from experimental instruments only provide precise measurements of *g*, whereas reliable measurements must first and foremost be accurate representations of the value measured. It is in this context that Morrison considers that raw data must be post-processed in the search for accuracy (for the particular case of measuring *g*, Morrison proposes the ideal point pendulum as theoretical model).

From Morrison's perspective, then, the reliability of the measured data is a function of the level of accuracy, which depends on a theoretical model rather than on the scientific instrument or on the computer simulation.

> The calculation generates a large amount of data which requires that they be appropriately modelled in order to render them interpretable. Only by doing that can we say that the computer experiment, like an ordinary experiment, has measured a particular quantity. In both cases models are crucial. And, just as in the pendulum example where we are interested in both the precision and accuracy, similar concerns arise for simulation where the precision of the machine and the behaviour of apparatus is related to the observed properties of the microscopic system. (2009, 53)

Computer simulations, just like scientific instruments, share the same fate of being precise but not accurate—for the latter, it is because of the physical constraints related to manipulating the real world; for the former, it is because of the fact that a computer simulation implements the physical constraints of the target system as well as the physical constraints of the machine itself (e.g., round-off errors, truncation errors, and so forth). The precision/accuracy dichotomy, then, applies to computer simulations just as it does to experimental measurement, making both practices ontologically equal at the level of precise data, and epistemically equal at the level of accurate data. The materiality argument is also present here: equal ontology determines equal epistemology. And this was precisely the intention behind Morrison's analysis: "the connection between models and measurement is what provides the basis for treating certain types of simulations outputs as epistemically on a par with experimental measurements, or indeed as measurements themselves" (2009, 36).

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following example: "a measurement of the speed of light, $c = (2.000000000 \pm 0.000000001) \times 10^{10}$ *cm/s* is *precise* but *inaccurate*, while a measurement $c = (3.0 \pm 0.1) \times 10^{10}$ *cm/s* is more *accurate* but has a lower precision" (Franklin 1981, 367n1).

Thus interpreted, Morrison is applying a philosophy of modeling and experimentation onto a philosophy of computer simulations. This is also a consequence of following the materiality principle; that is, there is no analysis provided of computer simulations in itself, but only in the light of a more familiar philosophy. By making raw data and simulated data ontologically equal, and the post-processing a further epistemic step, Morrison is applying model techniques to computer simulations, regardless of the particularities of the latter. With this move in mind, Morrison also narrows down the class of computer simulations to those that are used as measuring devices; and in doing so, she is narrowing down the epistemic analysis to those simulations.

There is a further concern about Morrison's argument. According to it, simulated data need post-processing. The claim considers simulated data *as if* they were not model data in a straightforward sense, but rather raw data as obtained by experimentation. A computer simulation, however, consists of a series of nested models that produce a final output, and therefore the data produced by a simulation is already accurate as regards the value measured. In this vein, there is no need to postulate any further post-processing step, as Morrison does. However, let us accept for a moment the argument that simulated data needs to be post-processed. If this were the case, Morrison's argument faces another challenge. Given the fact that computer simulations produce vast amounts of data, arguing for a separate correcting process such as post-processing begs the question about a possible 'computer regress'; that is, the need for another computer model capable of processing the initial simulated data. This new computer model would fix some inaccuracies in the original data, but would also introduce new ones, since the same physical constraints apply to this new processing stage. It then seems reasonable to be concerned about a possible infinite regress of post-processing simulated data. To my mind, there are no other motivations for thinking about post-processed simulated data except for Morrison's interest in analyzing computer simulations in the light of scientific experimentation, which is an unnecessary precondition for the epistemological analysis of computer simulations.

Conclusions

I have discussed three different views of how philosophers currently understand the epistemological study of computer simulations. I have shown that all three make use of the same rationale as the guide for their argumentation. I called this rationale *the materiality principle*, and I conceptualize it as the philosophers' commitment to an ontological

account of computer simulations (and experimentation) that determines the evaluation of their epistemic power.

The aim of this paper was to show that the materiality principle is a rationale shared by many philosophers working on the epistemology of computer simulations. It was also the aim of this paper to alert us to the possible consequences of allowing the philosophical discussion to be so diverted. In this vein, I have suggested that adapting our philosophical investigations in line with the materiality principle might be placing a conceptual corset on inquiries regarding the epistemology of computer simulations. In this context, I distinguished three viewpoints that conform to this rationale, and set out the various restrictions that they place on the epistemological analysis of computer simulations.

The first two views were rejected on the grounds that they purport internal inconsistencies in the conceptualizations of experiments and computer simulations. The objection to the 'identity of the algorithm' is that it makes implausible claims regarding the ontology of computing machines; whereas the objection to the strong version of the 'materiality stuff as criterion' is that misplaces the role of computer simulations in scientific practice. I also claimed that the materiality principle is the underlying motive for these inconsistencies. On the other hand, the weak version of the 'materiality stuff as criterion' and the 'models as (total) mediators' views are, to my mind, the most promising interpretations of experimental as well as computational practice. However, as I showed, neither account directly addresses the epistemology of computer simulations. Rather, they reduce it to the epistemology of semi-material experiments (weak version of the 'materiality stuff as criterion'), or to scientific modeling via measurement ('models as (total) mediators').

The conclusion is that philosophers who accept the materiality principle are less likely to recognize what is distinctive about the epistemology of computer simulations than those who do not. Of course, I am not urging the adoption of an entirely new epistemology, enlightened and guided by computer simulation, as Frigg and Reiss have proposed (2009). My conclusion is more modest, and aims to encourage certain changes in the philosophical inquiry on computer simulations. For instance, Barberousse et al. (2009) have made a central contribution to the notion of computer-simulated data, and Humphreys has followed their work by analyzing the notion of data in more detail (this volume). Nevertheless, more work needs to be done and, to my mind, it must begin by reconsidering certain classic topics in the philosophy of science through the lens of computer simulations. In this sense, a review of

traditional notions of *explanation*, *prediction*, *confirmation*, *evidence*, and the like might work as the starting point.

Evidently, there is a way of doing philosophy of science that is strongly grounded on empirical inquiry exemplified by experimentation. The guiding epistemic principle is that the ultimate source of knowledge is given by interaction with and manipulation of the world. However, the continuous success of computer simulations is calling these principles into question: first, there is a growing tendency towards representing rather than intervening into the world; second, computational methods are pushing humans away from the center of the epistemological enterprise (Humphreys 2009, 616). The philosophical inquiry on the epistemological power of computer simulations has thus been misguided, for some philosophers are still maintaining a false dichotomy between experiment and computer simulation while ignoring the fact that scientific practice has already transcended this division.

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CHAPTER FIVE

EXPLORATORY STRATEGIES: EXPERIMENTS AND SIMULATIONS

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Introduction

The use of computer simulations in different scientific activities has increased considerably in the last few years. However, philosophical reflection on computer simulations is rather scarce, partly due to the relative novelty of this type of activity, and partly due to complexity of the subject. What aspects should be taken into account, and what perspectives must be adopted for the investigation are among the most important questions to ask when analyzing computer simulations from a philosophical point of view.

In the present work, we suggest that an analysis based on exploratory strategies can be used to illuminate and characterize epistemic and methodological aspects of computer simulations. Putting the focus on the exploratory strategies implies adopting a perspective that, albeit it is relevant to the experiments and simulation analysis, is not limited to any of these areas. Exploratory strategies can be found in very diverse scientific practices. Notwithstanding, they can be used to underline relevant philosophical aspects of experimental practices and computer simulation practices alike. In this way, our proposal explicitly surpasses the comparison between experiments and simulations, albeit we are convinced that analyzing exploratory strategies in experiments and simulations helps substantially in the elucidation of their methodological and epistemological roles.

The elucidation of the role of the exploratory strategies in computer simulations and experiments would contribute to the philosophy of both

activities. Because the relation between computer simulation and experimentation has been understood in a very different way by the philosophical literature, a brief revision of some of the central issues will be needed. In addition, philosophical literature on exploratory experiments presupposes, although it rarely makes it explicit, an exploration notion that we will briefly address in this article. It is important to note that in their original contexts, both discussions have the pretension of drawing limits between simulations and experiments or between exploratory experiments and other experiments. On the contrary, as we repeatedly say in this paper, instead of stipulating limits for each type of practice, we propose to establish a 'topology' of the ways science tests, searches, and explores.

We organize our work in the following way. First, we will schematically describe the way in which computer simulations are compared with experiments to establish the differences with the perspective defended in this paper. Second, we will address the distinction between exploratory experiments and other types of experiments. We will analyze exploratory strategies in experiments and simulations with the sole purpose of making our argument clearer; it is also important to keep a certain similarity to the way this matter has been questioned in philosophy. However, in most scientific practices, boundaries are not so clear. More than being a difficulty for the chosen cases, this seems to be the way in which contemporary scientific activity is organized. We think this could be an additional advantage of adopting the perspective of exploratory strategies, because it is neither centered on the distinction between experiment and simulation nor restricted only to experimental practices.

Philosophy of Computer Simulations: Experiments and Simulations

Experiments have been compared to simulations taking into account ontological and inferential aspects on one hand, and representative or interventional aspects on the other. So, although there are many ways of implementing a simulation on a computer, they can be characterized as a sequence of time ordered states that represent another sequence of time ordered states (Cfr. (Guala 2002), (Hartmann, 1996), (Parker, 2009)). Representation and imitation seem to be the main concepts. On the other hand, an experiment is usually characterized as an interventional activity.

A main concern in reflections on these subjects is usually the question of the validity of the simulations or, in more general terms, their epistemic credentials. At the same time, the discussion of ontological and epistemic problems usually assumes a basic scheme: simulations are seen as systems

characterized principally by some model that typically refers to another system (usually called target system). In this way, the question about the validity is set forth in terms of the relation between a given system and the target system, as well as the possibility of generalizing these results or connecting them to other systems. Accordingly, Francesco Guala (2002) has proposed that the differences between an experiment and a simulation can be understood by appealing to the type of justification of the inferences that relate the different systems. The inferential link that can relate the experimental result of a system A with the result of another system B can be very strongly justified, according to Guala, if both systems are operating under the same causes. Here one must suppose that there is only an abstract and formal correspondence between a computer simulation and a simulated system, while between an experiment and a target system there usually is a correspondence at a deep level. In this second case, the same causes should be operating in the experiment as well as in the target system.[1] A main concern in reflections on these subjects is usually the question of the validity of the simulations or, in more general terms, their epistemic credentials. At the same time, the discussion of ontological and epistemic problems usually assumes a basic scheme: simulations are seen as systems characterized mainly by some model that typically refers to another system (usually called target system). In this way, the question about the validity is set forth in terms of the relation between a given system and the target system, as well as the possibility of generalizing these results or connecting them to other systems. Accordingly, Francesco Guala (2002) has proposed that the differences between an experiment and a simulation can be understood by appealing to the type of justification of the inferences that relate the different systems. The inferential link that can relate the experimental result of a system A with the result of another system B can be very strongly justified, according to Guala, if both systems are operating under the same causes. Here, one must assume that there is only an abstract and formal correspondence between a computer simulation and a simulated system, whereas between an experiment and a target system there is a correspondence at a deep level. In this second case, the same causes

[1] Parker argues that Guala's proposal is too restrictive in his experimental notion, even though she accepts that Guala doesn't mean to say all material causes are relevant in this case, but only the ones that are 'closer.' Well then, scientists that are trying new drugs on mice are experimenting, even though the results on humans later turn out to be different. Also, Guala's proposal is very restrictive when it refers to simulations, because it is too strong to say that there are 'never' common material causes. (Parker, 2009)

should be operating in the experiment as well as in the target system.[2] Gilbert Troitzsch (1999) also seems to implicitly presuppose the relation between an experimental or computer system, on the one hand, and a target system on the other. Such relation underlines the differences between a simulation and an experiment, although it focuses on purely interventional aspects. These authors point out that in the case of an experiment one is handling a real object, while in a simulation if anything is to be handled it is a model:

> While in an experiment one is controlling the actual object of interest (for example, in a chemistry experiment, the chemicals under investigation), in a simulation one is experimenting with a model rather than the phenomenon itself (Gilbert & Troitzsch, 1999, 14)

It is probable that the same type of intuition that is sustaining the notion of materiality, or the correspondence on a deep level, is operating behind the notion of the real object. Parker (2009) suggests that the notion that must be considered is the one of relevant similarity, instead of the one of materiality. As we have already said above, if a simulation is understood as a representative system, an experiment is characterized as "an investigative activity that involves intervening on a system in order to see how properties of interest of the system change, if at all, in light of that intervention" (Parker, 2009, 487). When a simulation is arranged on a digital device we have a "computer simulation." Although a computer simulation is characterized in terms of representation, a "computer simulation study" can be seen as an interventional activity inasmuch as one requires "setting the state of the digital computer from which a simulation will evolve, and triggering that evolution by starting the computer program that generates the simulation" (Parker, 2009, 488). Parker believes that this way of characterizing a "computer simulation study" allows us to talk of an interventional activity and therefore of an experiment, because the focus is not on the model but on a programmed digital computer. Although Parker's proposal seems interesting because it tries to account for the difference between mere modeling and computer

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simulation, it does not appear that the sole act of pointing out an interventional aspect is enough to qualify a "computer simulation study" as an experiment in a relevant sense.

There are other philosophers, such as Winsberg (2009), that suggest that instead of considering ontological aspects to distinguish experiments from simulations, one must pay attention to the type of inference made and the role taken by the background knowledge. In the case of simulations, this background knowledge allows us to build models that can later be taken as the object of investigation. Consequently:

> When an investigation fundamentally requires, by way of relevant background knowledge, possession of principles deemed reliable for building models of the target systems, and the purported reliability of those principles, such as it is, is used to justify using the object to stand in for the target, when a belief in the adequacy of those principles is used to sanction the external validity of the study, then the activity in question is a simulation. Otherwise, it is an experiment. (Winsberg, 2009, 586)

In an analogous way of thinking, Morgan (2005; 2003) argues not only about the material but also the inferential aspects of simulations. Experiments and simulations should have different "epistemic power": the inferences on experimental systems can be better justified when the experiment and the target system that the experiment refers to are made of the same "stuff." Morgan supposes that traditional experiments have greater epistemic power than simulations because as long as the latter depend completely on a model they cannot confuse or surprise scientists. Here the notion of confusion is not taken in a psychological sense but in an epistemic one: the phenomenon in question is somewhat "surprising" as it cannot be accounted for with the available theoretical resources. Morgan (2003) also points to the material aspect as discriminatory criteria, but now between two types of experiments (material and non-material). Simulations would be among the latter (non-material experiments). In fact, one of the most interesting suggestions from these accounts is that the usual situations in science are "hybrid" scenarios, where a clear distinction between experiments and simulations are not easy to draw.

Taking a different perspective to the one we have quoted up to now, Morrison (2009) emphasizes the functional dimension of simulations and experiments. Somehow, she also tries to clarify the conception of experiment by describing some experimental activities such as measurements. This change in perspective allows her to argue about some ways of creating a model with similar functions to a measuring instrument.

In this sense, and for some cases, we could speak of simulations as experimental measuring instruments.

Typically, by comparing experiments and simulations one tries to build a philosophy of computer simulations based on ontological, inferential, representational, interventional, or functional aspects. They could serve to establish limits between experimental and simulative activities. However, to some extent, ontological aspects could play an important role in the comprehension of simulations. Beyond the intrinsic virtues of this way of approaching simulations, our proposal can be taken as a move from ontological to methodological and epistemological problems through the consideration of exploratory strategies. In this sense, most of the ideas quoted in this section allow us to underline differences with our exploratory strategies proposal.

Considering that the notion of exploration has been mainly used in the philosophy literature on experiments, in the following section we will begin with this discussion to continue later with the notion of exploratory strategy.

From Exploratory Experiments to Exploratory Strategies

The notion of exploration in science has not received a great deal of attention in the philosophical literature. Nevertheless, among the diverse proposals to classify scientific experiments it is possible to find reflections about the role of exploration in science. The category of "exploratory experiment" is quite common among the various experiment classifications. In this way, the attempt to elucidate exploratory experiments presupposes characterizations about exploration (for example, cf. (Burian, 2007); (Elliott, 2007); (Franklin, 2005); (O'Malley, 2007); (Peschard, 2009); (Steinle, 1997, 2002); (Waters, 2007)). Although we will show that the diverse characterizations of exploratory experiments do not achieve adequate discrimination of these experiments, the analysis of the different proposals will allow us to show some of the characteristics of exploration. However, these exploration characteristics would not be useful to do an adequate taxonomy of the experiments; they will be the basis of our characterization of "exploratory strategies." In this sense, it is important to remember that exploratory strategies are not specific to the exploratory experiments, but they do constitute a relevant aspect of the best part of scientific activity, including experimentation and scientific simulation.

It has been suggested that exploratory experiments can be understood based on the contrast with experiments where the relevance of theory is substantive. In most of the classifications, this is a distinctive feature.

Franklin (2005), for instance, holds that exploratory experiments are the ones scientists do without considering a particular theory. This concerns the effects of their intervention on the values they are measuring. In a similar way, Steinle suggests there are experimental designs that are guided by theory (i.e. theory driven) and others which are not, the latter being the exploratory experiments. Thus, exploratory experiments could be characterized by their relative independence to strong theoretical restrictions (Cf. (Franklin, 2005, 888); (Steinle, 1997, S69; 2002, 418)).

In the same sense, Steinle (1997) maintains that the standard perspective on experimentation typically considers those cases that are theory driven as the only type of experimentation. Accordingly, experimental activity is understood in terms of: "a theory that led to expecting a certain effect; the expectation led to designing and conducting an experiment; and the success of experiment counted as support for the theory" (Steinle, 2002, 418). However, from this author's perspective, exploratory experimentation "typically takes place in those periods of scientific development in which – for whatever reasons – no well-formed theory or even no conceptual framework is available or regarded as reliable" (Steinle, 1997, S71). Even those authors that do not explicitly uphold this idea seem to keep this way of understanding exploratory experiments in mind, inasmuch as they choose examples from the initial stages of scientific disciplines.

However, the related literature, which sees the discriminatory criteria in the theoretical guide, also underlines other aspects that are important for characterization, such as the purpose of these experiments, their use or the experimenter's expectations. For example, the variety of epistemic goals present in the exploratory experiments becomes relevant:

> The contrast of exploratory experimentation to the theory-driven type, as understood as the standard view, is not only visible in the different epistemic goals (search for regularities vs. test of expectations), but also in the character of the guidelines of the experimental activity. (Steinle, 2002, 422)

Likewise, we must remark that the exploratory experiments are not circumscribed to a particular historical or theoretical context:

> (…) exploratory experimentation is not so much bound to certain historical periods, fields of research, or scientific traditions, but first and foremost to specific epistemic situations: those situations namely in which, for reasons whatsoever, the very concepts by which a certain field is treated have been destabilized and become open for revision. Situations in which theories and well-formed expectations are tested, in contrast, require a well-

> elaborated conceptualization, a stable language by which the expectation can be expressed in the first place. Exploratory and theory-driven experimentation are connected to different constellations and situations of our knowledge, to different regimes of stability on a conceptual level. (Steinle, 2002, 425–426)

Finally, some philosophers underline the relation between the experimental activity's purposes and its results:

> Roughly speaking, the aim of exploratory experiments is to generate significant findings about phenomena without appealing to a theory about these phenomena for the purpose of focusing experimental attention on a limited range of possible findings. The findings might be significant with respect to a variety of goals ranging from the practical goal to learn how to manipulate a phenomenon to the theoretical goal to develop a conceptual framework that will help focus future experimental attention. (Waters, 2007, 5)

It is important to note that the previous three quotations correspond to authors that defend the theoretical dependency criteria for the distinction of exploratory experiments. However, in all three one can notice that other characteristics are the ones that stand out in this type of experiments.

When exploration is taken as a distinctive characteristic of some experiments, it does not appear to be adequately characterized by its dependency on the theory. In fact, whoever tries to defend this idea should be able to explain the different levels of theory involved in an experiment, and determine which of these levels is or are relevant to the "theoretical guidance."

To say that an experiment is guided by a theory means that the expectations regarding its results are theoretical, or that the design of the experiment depends on a theory, or that the instruments used are theory dependent, etc. It is possible that a large part of the difficulty of the characterization, in terms of theoretical dependence of the exploratory experiments, is due to the lack of a sophisticated notion of theory and of levels of theory involved in the design, execution, and analysis of experimental results.[3] However, the perspective of the dependency to theory, even when attention has been paid to the previous observation, does not reflect important epistemological and methodological aspects of exploration in science.

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[3] A first approach to the different types and levels of theory involved in an experiment can be found in (Hacking, 1992).

In this sense, Steinle himself states that in exploratory experiments we can distinguish the following activities as typical methodological practices:

- Varying a large number of different experimental parameters,
- Determining which of the different experimental conditions are indispensable, which are only modifying,
- Looking for stable empirical rules,
- Finding appropriate representations by means of which those rules can be formulated,
- Forming experimental arrangements that involve only the indispensable conditions, thus presenting the rule in particular clarity. Those experiments are typically characterized as "simple," "elementary," or "pure case" (Steinle, 1997, S70).

One of the activities pointed out as typical in an exploratory experiment is the variation of parameters. This is usually a regular procedure in experiments, not only exploratory but also in general. The variation of parameters can be done with different aims in mind: from the calibration of a measuring instrument to the intention of obtaining some empirical regularity. Now, the purpose of an experiment can turn the variation of parameters into an exploratory experiment even though it is carried out under strong theoretical restrictions. This makes one believe that an exploratory experiment is best characterized by its purpose rather than by its particular relation to theoretical aspects. This relationship with theory can only be understood if no qualification appears as an inadequate characterization.

In addition, emphasizing the aims and the roles of the experiments helps us to distinguish between exploratory strategies that not only form part of exploratory experiments but also of experiments with different purposes, such as hypothesis confirmation. This point seems relevant for different reasons. In the analysis of cases that usually accompanies the characterization of exploratory experiments, there is confusion between what we could call the exploratory experiment typology and the searching and exploring strategies. However, it seems clear that there are exploring strategies belonging to non-exploratory experiments, as they are also part of other non-experimental scientific practices.

Yet, it is necessary to point out that search strategies or exploratory restrictions do not seem to be the defining feature of exploratory experiments. However, their consideration allows a more adequate description of certain aspects of scientific and experimental practices in particular.

Exploratory Strategies in Scientific Practices

We organize this section in the following way: first, we will make explicit what we understand as an exploratory strategy; then we will show some examples that will permit us to contextualize our proposal. Finally, we will analyze some cases regarding exploratory experiments presented by the literature to show the advantages of our proposal. In particular, we will show how adopting the point of view of the exploratory strategy leads to a more direct relationship with computer simulations.

In this paper, we will consider any activity or resource that allows us to do an exploration as an "exploratory strategy." These activities or resources can be very different, but as long as they perform the function of allowing us to question, search, probe, or explore, we will call them "exploratory strategies." It is important not to restrict the notion of a strategy by setting rules or any other structure implying a procedure. The relevance of this point will become evident in the following paragraphs as we present the ways in which exploratory strategies can be instantiated.

A first way of characterizing exploratory strategies is in terms of what they are looking for (what they explore), the way in which they do this operation (how they explore) and to what end they are doing it (what they explore for).

A second way of characterizing exploratory strategies would be paying attention to the structure of the search –or, if you prefer, to the restrictions in the "searcher"– and the structure of the media in which one is searching –the restrictions in the search space. We could have searches with few restrictions – for them to be as adequate as possible – or searches with strongly selective criteria. This way of understanding exploratory strategies can be instantiated as searching rules or heuristics. The structure of the searching rule will let us account for part of the restrictive capacity of the exploratory strategy. We can call this way of understanding exploratory strategies as 'type 1.' We can also explore using judicious construction of an exploration space or by limiting the size of this space. This way of understanding exploratory strategies we will call 'type 2' strategies. We are using, although in an indirect way, the metaphor that distinguishes between the search strategy and the space where the strategy takes place. In the same way that we talk of restrictions in the type 1 strategies, we can suppose that the space structure involves, among other things, graduating the restrictions. One could argue that the distinction between type 1 and type 2 strategies is not genuine because type 2 strategies can be rewritten in terms of type 1. Although in principle it seems possible to do this rewriting task and eventually reduce one type to

the other, this perspective does not look adequate when we are trying to account for epistemic and methodical aspects associated to the description of scientific practices. In this 'reduction' task, the specific ways in which the exploration is being done, within the simulations or the experiments, would not be adequately shown.

Before continuing, let us see some examples that help put our discussion in context. The first case involves the so-called combinatory chemistry and high-throughput screening. Combination chemistry can be described, in very general and schematic terms, by methods associated with combinatory synthesis and high-throughput screening. According to Valerie Gillet, an investigator in this area, combinatory chemistry "refers to the synthesis of large numbers of compounds in parallel where product molecules are formed as combinations of available reagents or buildings blocks" (Andrew R. Leach & Gillet, 2007, 617). High-throughput screening "is an automated process whereby a large number of compounds (104 – 105) are rapidly screened for biological activity" (Andrew R. Leach & Gillet, 2007, 617). This focus on synthesis and screening, more than a new methodology, represents an automation of traditional methods with the help of new instrumental resources. Combinatory synthesis can be seen as a procedure to construct, in different ways and suppositions, a 'search area.' The high-throughput screening can be seen, not only by its design but also by its application, as a 'search strategy.' Let us have a look at these two types of analysis.

Starting with high-throughput screening one can understand the types of search involved here from their historical evolution. During the 80s it was taken as an advantage for this search to be as little restricted as possible, so as to be able to obtain the largest number of candidates for a new drug (leads), by the sole record of the force of automation. Sometimes, this way of search is described as "serendipity" (Cf. García, 2009). With time it became clear, from the poor results obtained, that a more selective search was required. Therefore, restrictions were added to the type of mechanism that was desirable in a drug precursor. Among the restrictions for selecting drugs candidates, we can quote the Lipinski's rule of 5 (Lipinski, 1995) –a set of desirable characteristics in drug, such as solubility or permeability. However, there are also other types of restrictions that may take the form of superposition or adjustment between molecular structures. This way of understanding high-throughput screening is sometimes called "rational" or "design" to mark its differences to a search without too many restrictions.

The increase of restrictions in the search was not the only resource used to improve the performance of these systems. The use of combinatory

chemistry to design libraries of compounds has become more sophisticated since the 90s. This aspect can be seen as an instantiation of the second criteria to classify exploratory strategies. In fact, the construction of libraries of substances seems like a way to restrict or guide the search by means of a rational structuring of the problem's space. This began the discussion about the way one could obtain libraries of substances with a sufficient degree of variation to make the search interesting. This supposes a relevant notion of "variation." Although this notion can be instantiated differently according to the case, the construction of a more general notion has been attempted. A standard way of understanding this notion is to link the concept of "diversity" to that of similarity. In the context of the construction of libraries, what one needs is some codification of the substances in question (molecular descriptors are usually used) to be able to later define a measure that can be taken as a degree of similitude. In this way, one can determine if a sample of substances is more "diverse" than another in terms of some quantifiable criteria (Cf. Bleicher et. al., 2003).

In several of the more interesting stages of work in combinatory chemistry, simulation, experimentation, and exploration strategy practices are involved. This makes it far from simple – and probably inconvenient – to make differences between experiments and simulations when investigation processes are under consideration rather than their constituent parts. For instance, one can take not only the construction but also the search in *virtual libraries* (an approximation sometimes called *in silico*). In this case, libraries of aspects and properties of the substances with relevant descriptions are constructed, and the search is done in these virtual spaces. Thus "in silico" screening "refers to the use of computational techniques to select compounds, either from existing libraries…or from virtual libraries that represent the compounds that could potentially be made via combinatorial synthesis" (Andrew R. Leach & Gillet, 2007, 618). If what interests the researchers involves the known links ("ligands") for a compound with a certain "target," then you can build a "pharmacophore" model to account for the compounds structural aspects. It is important to point out that "a pharmacophore does not represent a real molecule or a real association of functional groups, but a purely abstract concept that accounts for the common molecular interaction capacities of a group of compounds towards their target structure" (IUPAC Recommendation cited by A. R Leach, et. al., 2010, 539). For this reason, this type of model is usually used for virtual searches (virtual screening) and predictive "docking" models in general; that is, rational design models that in some way allow to have expectations on candidate ligand receptors (Andrew R. Leach & Gillet, 2007, 166ff).

One way to systematize the virtual search types is to consider the amount of structural information and biological activity available (Andrew R. Leach & Gillet, 2007, 158ff).

First, if what is known is only a single active molecule, virtual search will generally be based on the possibility of binding. Second, if there are various active molecules, you can build a pharmacophore model and then search using 3D properties. Third, a neural network can be used when there is sufficient information about active and inactive structures. Finally, when the 3D structure of a protein is known, "protein-ligand docking can be employed" in the search (Andrew R. Leach & Gillet, 2007, 160). Thus, the virtual search involved in this type of computer simulation depends on the type and the amount of information available on the chemical compound's space. Any results that may be of interest can become part of experiments in real libraries.

The virtual library search can hardly be seen as an exploratory experiment; in this case, however, it is clear that exploratory strategies are used. Moreover, it is possible that similar strategies are used in both the virtual and real experimental spaces. Considering the discussion in the previous section, here we would have experiments using exploratory and search strategies in contexts where the goals can be confirmatory. An example of this would be the search process that is triggered when it is estimated an achieved precursor or a more or less reliable candidate for a drug. The process in this scenario is a type of search, although for confirming a promising result. This is a good example of situations that Morrison called "hybrid," which are so common in current scientific practices.

Shown in this schematic presentation are some of the advantages of our proposed characterizations. However, it is clear that such characterizations require a more careful elucidation. Returning to the first characterization of exploratory strategies, it could be endorsed that the functional aspects of these strategies are only linked with the third item (what they explore for) of the first characterization. However, to account properly for the functional aspects requires an explanation of the ways in which the exploration is performed and certainly of its goal. In turn, the first aspect of the first characterization of exploratory strategies (what are they looking for?) could be understood as referring to the particular scientific discipline in which they are used – chemical, physical, or otherwise – or the main purpose of the experiment or activity performed. Yet, this does not seem to be its primary meaning. If an experimental design uses a variation of parameters in order to calibrate an instrument, then the alleged exploratory strategy here seems to be aimed at the

instrument itself (or at least at some relevant contexts to increase the precision or accuracy of the instrument). From this point of view, we can see that exploration activities are also involved in the different aspects of design and execution of an experiment or other scientific activities. Among the latter, we can point out the situation in which models are explored; that is, we explore the limits of a model, the empirical approximation of a model, the adjustment of a model to other models, etc. This aspect of exploratory strategies can also have a more sophisticated network. For example, when we consider the field of computer simulations, we have, and typically this is the case, exploratory strategies at different levels, in this sense, the question about what these strategies look for, has a different response at each of these levels. The scientists have general goals that characterize the computer simulation's main objective. However, this central goal does not invalidate the aims of other strategies at lower levels. Thus, we can have a computer simulation whose main objective is to explore a model in a certain way, but which also has different exploratory strategies in its "lower" levels. This complexity is not necessarily a difficulty, since it allows us to explain the relative independence – at least in a certain sense – between each of these exploration strategies. Depending on the type of problem in which we are interested, we can distinguish different strategies at different levels.

Regarding the second aspect of the first characterization of exploratory strategies – how to perform the exploration – here one can consider different types of search, exploration and inquiry. Virtually all we have considered in type 1 and 2 strategies could come into this point, taking into account the restrictions on the search and the structuring of the space where the search is made. Either way, it is possible that this approach can be developed in the future by checking other aspects through which the types of search can be seen, or by specifying the types of restrictions that are taken into account. For example, returning to the case of high-throughput screening, one could take into account the differences between the exploration based on structural aspects (such as "host-based coupling") and those based on properties. The latter could include the aforementioned rule of Lipinski. A compound can have "drug-likeness" if it has certain properties, such as absorption or permeability (which is unlikely if the compound in question has a molecular weight greater than 500). While what we might call structural searches also have the goal of finding compounds that may be plausible candidates for a new drug, the type of restriction that guides the search is very different. The methods called "molecular docking" would fall into this category. In general, what is intended to be found in the "docking" experiments is the 3D structure

resulting from two or more molecules. Computational methods involved here are concentrated on two tasks: exploring the space of possible "protein-ligand geometries" (Andrew R. Leach & Gillet, 2007, p. 161) and the weighted evaluation of these geometries to enable them to "identify the most likely binding model for each compound and to assign a priority order to the molecules." (Andrew R. Leach & Gillet, 2007, p. 161). To a large extent, the difficulty of this task lies in the degrees of freedom in rotation and translation of molecules – in relation to other molecules – which affect their geometrical configuration. For this reason, the biggest effort is often in the design and implementation of algorithms that account for this problem.

The third aspect of the first characterization of exploratory strategies (what is the exploration performed for?) is important because it allows us to highlight another angle of the relationship between exploratory strategies and other scientific activities and experiments. One might suppose that this appearance coincides with the one that allowed us to distinguish between exploratory experiments and confirmatory experiments. However, as we saw above, the goal of an overall activity is not the reason for the exploratory strategies involved. Continuing with the aforementioned example we mentioned above, we might have an experiment whose design or calibration assumed exploratory strategies, but whose ultimate goal is to test or confirm a given hypothesis. At least in principle, given the complexity of current experimental designs and the different levels sometimes involved, there may be exploratory strategies at an execution level, although the aim of the experiment itself is another.

From this characterization, taking some cases from the literature on exploratory experiments, exploratory strategies can be analyzed in a new light. As noted in the previous section, the concern about drawing a line between exploratory experiments and other interventional practices has left in the background other interesting aspects of these scientific practices. In order to show the advantages of our proposal we discuss some of these examples. In our analysis, we will focus on what we called type 2 strategies that is in the form in which the exploration space is selected and configured. In a complementary way, we highlight the importance of instruments in these cases. Franklin (2005) noted that the adoption of certain instruments is often accompanied by an increase in experimental "exploratory practices." The impact of the instruments is similarly highlighted by several of the philosophers who analyze exploratory experiments. However, it can be argued that not only are there methodological strategies associated with the mere adoption of an instrument to carry out a task, but also with its configuration and use.

Moreover, the notion of instrument, understood from the methodological resources, can serve to understand the role of computer simulations. O'Malley (2007) presents a case within the scope of what is often called "metagenomics." This case is related to the discovery of proteorhodopsin in marine bacteria gene (in the Monterey Bay). Metagenomics can be characterized by the manner in which the samples to be examined are selected. Under the assumption that genomic diversity is not sufficiently represented by the crop cloning methods used to sequence the genetic information, samples taken from some "natural" environment that is relevant to the investigation are used. In this way of selecting the samples, we can see a first sense of exploration linked to the selection of the space where the investigation is to be performed. This consideration is reinforced when comparing the sample "area" to the cultivated samples space where experimental protocols tend to favor their "isolation." O'Malley also highlights this aspect, as it allows him to describe a form of exploratory experiment. However, beyond this first exploratory direction presented by O'Malley, one might suggest a second direction associated with the sequencing of the samples.[4] For several years, a parallel sequencing technique ("shotgun" Sanger sequencing or massively parallel pyrosequencing) is being used, and is often seen as a suitable complement to the objectives of metagenomics. It seems clear that there is a sense of exploration involved in the parallelism in this type of method (Eisen, 2007).

Franklin quotes another case in the literature on exploratory experiments, which concerns the use of what is called "microarrays" (DNA chips). Franklin underlines the use of this tool in the investigation of the role of certain proteins in the cell cycle. This instrument consists of a "plate" of a material that can serve as a "grid" for samples to be analyzed. These plates must be constructed of a material that allows DNA binding. Due to the parallel nature of this technique, it is often used to investigate "the differential expression of the genes." The level of gene expression is measured by a "probe," which is added to the sample to be investigated and that has been "marked" (with a fluorescent or radioactive tracer). These marks are analyzed in an image that indicates the level of gene expression. The differential aspect of gene expression can be investigated by changing the conditions in cells (with or without a particular alteration). The first exploratory aspect that can be noted in this context has to do with the configuration of the space in which the

[4] The use of shotgun sequencing is quoted in O'Malley´s work, although its methodological importance isn´t highlighted in terms of exploratory strategies.

sequencing will be done. This point becomes clearer when comparing this technique with that which gave rise to it: Northern and Southern blot. In principle, the only difference between the two techniques is that the latter only allows the study of genes "one at a time." Yet there is another aspect of the exploration that can be pointed out here, related to the design of the configuration of the DNA chip samples. Because of the amount of samples available, the design of these early stages is usually done with the help of specialized software that allows putting into practice strategies that are considered appropriate for the exploration. Thus, one can take any diversity criterion – for example, by homology – and apply it to construct a sample. In this sense, it seems that there is a relationship between sample design and the ways to explore.

Final Words

We have tried to explain how an insight into exploratory strategies allows us to show different methodological and epistemological aspects of computer simulations in science and scientific experimentation. Our intention has been to collaborate in the construction of theoretical tools that help to analyze and highlight the epistemological and methodological richness of certain aspects of these practices that have been overlooked in philosophical research. In this sense, we believe that the activities of exploring and searching have not received sufficient attention in the field of the philosophy of science.

The analysis of exploratory strategies has allowed us, through the presentation of some cases, to show the different levels at which exploration is relevant in scientific practices. However, this is only a first approach to the characterization of a concept that we believe is promising for the task of understanding, from a philosophical point of view, the role of computer simulation and scientific experimentation in scientific practices.

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PART II:

PRACTICE

CHAPTER SIX

MODEL SYSTEMS IN COMPUTATIONAL SYSTEMS BIOLOGY

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Systems Biology is gaining momentum in a wide sphere of biological sciences, although the exact meaning of the term has not yet been universally agreed upon.[1] Although there is agreement that systems biology involves a shift of focus from individual components to the inter-relations between components and levels in biological processes, with the potential of illuminating non-linear causality and phenomena of emergence, there are important differences between those who hold that it is a methodological approach, such as Kohl and Noble (2009), and those instead who claim that the enterprise of systems biology is a far more theoretical one, aimed at arriving at biological laws (Westerhoff et al., 2010). It is also closely related and sometimes indistinguishable from its apparently more pragmatic partners, such as synthetic biology, and from other research for pragmatic purposes such as drug development, or medical diagnosis and treatment (for example, Byrne, 2006; Rodriguez et al., 2010). There are also differences between the use computational technologies in systems biology, with one mode of systems biology being closely related to data-intensive research, and the search for statistical

[1] See Breitling (2010), Boogerd et al. (2007), Gunawardena (2010), Kupiec (2009), Kohl et al. (2010), Lesne (2009), O'Malley and Dupré, (2005), Sage et al. (2009) for an array of definitions offered by scientists and philosophers of science. See Powell et al. (2007) for the origins of the term.

correlations between genomic, proteomic, and metabolomic datasets (Boogerd et al., 2007; Kitano, 2002; Calvert and Fujimara, 2011), and another mode being more closely related to the use of computational modelling and simulations with the aim of investigating underlying physiological processes (See Sage et al. 2009; Kohl and Noble, 2009). In this article, we make no attempt to encompass all of systems biology, but discuss only computational systems biology of the latter type. The methodology of computational modelling and simulation with a view to mimicking the mechanisms of physiological processes viewed as complex systems is challenging and difficult, and has not received as much attention as other forms of modelling in systems biology in the philosophical literature. The possible benefits of this methodology are scientific (since, in principle, they could enable greater understanding of complex biological systems and processes which are difficult to understand experimentally), pragmatic (since, again in principle, they could allow for experiments that are difficult or impossible to carry out in laboratories with existing techniques and equipment), and increasingly important, ethical (since, once again in principle they could replace experiments carried out on animals or humans). Some of the most advanced uses of computational modelling and simulations in systems biology settings are multi-scale models, which integrate data from different aspects of a biological system relevant to the understanding of specific processes, thus allowing for an understanding of the interactions and feedback loops between different levels.

Even though the words 'model' and 'modelling' are used in the practice of computational systems biology research, it is not at all clear that they mean, in their everyday use, the same as what is meant by these words in other sciences, such as physics, or in the philosophy of modelling. In his overview of models in biology, Odenbaugh (2008) mentions computational models, but does not consider them as a specific category of models in biology. This also holds for Darden, in her treatment of the role of models in understanding biological mechanisms, and ends her essay on mechanisms with mention of mathematical and computational models (Darden, 2007). In their overview of systems biology, O'Malley and Dupré point out the importance of computational methods, and call for philosophical scrutiny of the modelling tools used by systems biologists (2005, 1272). Bechtel and Abrahamsen (2010) give a detailed account of computational modelling of circadian rhythms and possible applications of this approach in cognitive sciences. The case that we consider is an integrative multi-scale model, which brings complexities that have not yet been considered. It is partly to the opening of this

blackbox of modelling tools and techniques that this paper aims to contribute.

As in many other scientific contexts, it is common for the type of models that are used for computational modelling and simulations to be described as representations among systems biologists.[2] At least it is common that the word is used, while less clear are the understandings of what constitutes representation. That is, answers to the question what is the relationship between a model and its target, such that the model can be said to represent its target, are less forthcoming and when they are, they are often inconsistent. Our combined experience and fieldwork in the field of systems biology show that there is great variation regarding the need for models to be complete in order to be considered representational, while others are satisfied with a more instrumental and heuristic view of models.[3] The fact that this is a relatively less prevalent voiced attitude to models may be due to the fact that the term 'representation' is sometimes used as shorthand for what is in practice much closer to an instrumentalist approach. The focus of scientific publications is not on the conceptual framework of the methodology used, and they are likely simply to use the term that others use. Moreover, what exactly it is in the whole computational process of modelling that is being described as a representation, replica, or instrument is not clear, particularly when there is the added factor of the relation between mathematical models, simulations, and experiments. There is a large literature on the philosophy of models, which rarely finds its way into the practice of scientific modelling. Recently, philosophers have turned their attention to simulations. A selection of recent work shows a great deal of variation: some claim that simulations are merely models in another guise (Frigg and Reiss, 2009), whereas others claim that simulations bring about a quantum difference in the scientific method as well as in the philosophical conception of models (Humphreys, 2004). There is also controversy over whether the physical form of the computational system makes a difference to the role of simulations in scientific research (Barberousse et al., 2008), and what exactly is the relationship between model and simulation (Humphreys, 2004, Varenne, 2007). As is to be expected from such a wide variety of views regarding the nature of simulations, there is also controversy over the epistemology of simulations, with some claiming that when it comes to an account of the epistemic warrant of simulations, a deferential attitude to

[2] One example is Kohl and Noble (2010), but this is widespread in publications, in workshops, and in daily discourse.

[3] See for example the discussion transcribed in Carusi, Rodriguez, Wakefield et al. (2009).

the beliefs that scientists bring to the simulating process might be necessary (Winsberg, 2009) and others instead taking a more sceptical attitude (Parker, 2009). If there is one thing that is clear, it is that there is a great deal of uncertainty surrounding this methodology, which is to an important extent shared by philosophers and scientists alike.

Thus, the questions relating to computational modelling and simulation in systems biology are of interest both for debates on systems biology and for debates in the philosophy of modelling, and the challenges on the two fronts need to be confronted at the same time, and optimally, in the very practice of science. As both systems biology and its methodology are unfolding programmes of research, one finds that the philosophical questions are being posed within scientific practice all the time. There is no standard practice and there are no ready answers, and scientists' philosophical conception of the domains they are studying is being stretched to its limit. On the side of philosophy of modelling, it is not clear that we can apply tried and tested conceptual frameworks for understanding the role of models to this new domain.

In *Models as Mediators*, Morgan and Morrison (1999) point out that if attention is paid to the actual construction of models and their uses in science, it becomes evident that models are partially autonomous both of theory and of reality, and that they have a variety of roles: instrumental, representational, and as learning enablers. We take our queue from this approach, and in this paper, focus on the construction of a particular type of model in systems biology. From this detailed account, we outline some of the main implications for an understanding of the pragmatics of modelling and simulation in systems biology.

The models that we describe are multiscale models of cardiac electrophysiology. In part, our choice is motivated by our own expertise as authors of this paper (Rodriguez is a specialist in cardiac modelling, and Burrage is a specialist in the mathematical techniques used in computational biology). However, it is also motivated by the fact that cardiac electrophysiology is one of the most mature areas where computational methods and a systems approach have been used, and is perhaps the most advanced area of computational physiology. Fifty years ago, Denis Noble (1962) published the first mathematical model of the electrical excitation in a single cardiac cell. Noble's work showed that the work by Hodgkin and Huxley could be extended to other areas of physiology and provided the foundation for the emergence of mathematical modelling and simulation in physiology. Since then there have been many advances and a developing refinement in mathematical models and simulation tools used in physiology, and in particular in

cardiac electrophysiology. Cardiac modelling and simulation are extensively used in basic science investigations and have been crucial to improving the understanding of the mechanisms of arrhythmias, electrotherapy, and the electrocardiogram. Over forty mathematical models of the electrical excitation and excitation-contraction coupling in single cardiac cells are now available for different cell types and animal species (see CellML repository at www.cellml.org). Anatomical models of the ventricles and the atria have also been constructed based on a variety of imaging modalities applied to hearts of different animal species (Seemann et al., 2006; Potse et al., 2006; TenTusscher, 2007; Vadakkumpadan et al., 2010; Bordas et al. 2011; Bishop et al., 2010). Sophisticated software has been developed using advanced computational and software engineering techniques to simulate propagation of the electrical excitation through cardiac tissue often using high performance computing facilities. Using those tools, it is now possible to perform computationally-expensive multiscale simulations of the effect of mutations and drugs at the ion channel level on the electrical activity of the human ventricles (Potse et al., 2006; TenTusscher, 2007; Zemzemi et al., 2011). In great contrast with the sole authorship of Noble in his first paper, modelling and simulation in electrophysiology now seem to have entered the 'big science' era, with large interdisciplinary teams involved in research.

Using these models as our exemplar of modelling in systems biology therefore means that we are considering models at an advanced stage of development and are less likely to be side-tracked by questions which arise at less mature stages. While they do have a long line of development, the programme of research in which the models are embedded are also meeting new interlinked challenges: first, relating to the very possibility of constructing integrative multi-scale models; and second, relating to the possibility of validating these models against the domains which they claim to represent.

The challenge of these models starts out right at the outset, before the question how they are related to – how they represent, or are an instrument for probing – the domain of cardiac electrophysiology. Indeed, it begins with the question: what, exactly is the model, and what does it comprise? This question is introduced in the first section of this paper ("What is the model?") in order to set the scene for the following sections, in which we describe the construction of the models, and consider what is the source (section "The construction of the model"), target (section "The target") and the relationship between the two (section "The source-target relation"). In these sections we build a case for a systems understanding of the

computational models used in systems biology. Just as systems biology is a systems approach, so must the models used in this approach be viewed as systems rather than as discrete atomistic entities. We propose that the model-simulation-experiment system or MSE system is the basic unit of analysis when considering questions of the validation and epistemic warrant of computational methods in systems biology (section "Validation"), while the relationship to theory is considered in the section titled "Theory."

What is the Model?

In this section we consider the question of what, in the array of epistemic tools and other items (including theories, principles, laws, etc.) at the disposal of computational systems biology, is a model.

Leaving aside for the moment the question of how a model relates to theory, generally a model is seen as consisting of three main parts: the source, the target, and the relationship between them. Among many possibilities, the most well-known accounts of what the relationship consists in are possibly a relation of isomorphism (van Fraassen, 1994), of analogy (Hesse, 1967), of exemplification (Goodman, 1976).

However, the question we are starting with is what is the source? In the domain of cardiac modelling – and many other domains – the word 'model' used by scientists might refer to the mathematical formulations, in the form of ordinary and partial differential equations, which are solved through the simulation. In this case, when the 'validation of the model' is spoken of, it seems that what is at issue is only the equations, in a kind of face-off between suitably solved equations and reality. However, this skews the actual practice of validation, as well as the epistemological account of the whole process of modelling and simulating. To reduce the model to the equations is of course a caricature, and in fact, often the word 'model' is shorthand for something far more complex, although the details and possible inconsistencies are often hidden from sight behind tacit expectations of consensus. In the philosophical literature, the work of Eric Winsberg and Paul Humphreys among others has done much to extend traditional accounts of models to a consideration of computational modelling and simulation. Humphreys (2004) offers an extremely useful breakdown of the component parts of a computational model, which according to him consists of 1) a computational template (consisting of a

set of equations)[4]; 2) construction assumptions; 3) a correction set (understanding of how the model can be adjusted); 4) an interpretation (relating the model to a specific domain); 5) the initial justification of the template; 6) an output representation (2004, 102-3). Thus, Humphreys' view already broadens out the understanding of what a model is. We follow his approach to computational models in spirit if not in the detail. We shall return to the main differences between our account and that of Humphreys in the section titled "The source-target relation."

Before going on to an account of the construction of the models, however, it is useful to recall the asymmetrical relation between the source and the target. Sources represent targets, and not vice versa. This fits in with the view that models are classified with other intentional items, which have meaning in terms of their being *about* other items, and this *aboutness* is a major determinant of the meaning of the model source. The intentional relation is key here, as has been pointed out by Suarez (2003) and Giere (2002) in the context of philosophy of modelling, but this is not an unfamiliar position in semiotically inspired theories such as those of Charles Peirce, Nelson Goodman, and Umberto Eco. This is a conceptual point with a bearing on accounts of intentionality generally, but it is also one which it is worth emphasizing in this context of scientific practice, where the targeting is very active indeed, and which serves to illuminate a central aspect of these models: that is, that they certainly do bear all the hallmarks of active construction in an iterated process of refining the targeting of a domain.[5]

We now turn to the construction of the model source in the next section.

The Construction of the Model

The models we consider in this paper are multi-scale models relating to cardiac electrophysiology, from the sub-cellular level to the level of the whole organ. The aim is to gain an understanding of the mechanisms of electrical propagation across the heart. A wide array of techniques goes into constructing these models: experimental (wetlab), imaging,

[4] The template equations are not identifiable with a model since a model is more specific than a template, according to Humphreys.

[5] There is a convergence between these non-naturalistic, pragmatic views of the ways in which models represent, and Humphreys' insistence that computational models ought not to be separated from their intended interpretations. For his criticism of the 'detachable interpretation' and of the 'no-ownership' view, see Humphreys (2004, 80).

mathematical, numerical, computational techniques are all used, and there are many subdivisions to be made within those broad categories. There are three main parts to be considered: the equations, parameter values obtained from experiments, and the simulations; but these have intermediary and bridging stages too, such as the construction of the mesh, and the use of simulations for multiple purposes. After a discussion of each of these and the inter-relationships between them,[6] we will conclude that the model source is the whole system of model-simulation-experiment, or what we have called, the MSE system.

Equations

In cardiac electrophysiology, electrical propagation in ventricular tissue is often simulated using bidomain equations. Two fundamental laws are used to derive the bidomain equations: the Ohm law (to relate electrical potential to flow of transmembrane, intracellular and extracellular currents) and the Kirchhoff law for conservation of charges (Keener & Sneyd, 1998). The equations describe electrical propagation in an electrical model of cardiac tissue, which include three main types of mechanisms: ion channels, exchangers, and pumps. Equations are based on knowledge of the biophysical processes underlying ionic transport. However, uncertainty in the understanding of those biophysical processes means that often several mathematical formulations could be used in the models. In those cases, often the equation that allows best fit between simulation results and experimental data with similar conditions imposed is chosen. In view of the complexity of measuring and modelling the biophysical detail of ionic currents, simplified phenomenological models are sometimes also used.

Parameter Values

Whereas the mathematical framework described above is generic for cardiac tissue, the models aim at being specific; for example, of a particular animal species or spatial location within the heart (i.e. dog versus rabbit, atria versus ventricles). Data obtained from wetlab experiments are the second input into models, and are the means whereby the generic and abstract mathematical equations are related to specific and particular cardiac physiological features and processes. Parameter values in the models are obtained directly from experimental measurements

[6] For a more detailed discussion, please see Carusi, Burrage and Rodriguez (2012).

(when possible) or indirectly by minimizing the difference between simulated and mean experimental behaviour using similar conditions in both cases. Two factors are to be noted: first, parameter values can come from a wide variety of data sets; second, parameter values need to be interpreted against the background context of which model organisms were used, including for example, gender and age, and which experimental techniques were used. For example, cells used in experiments using a voltage clamp protocol are isolated, and in the process, are damaged. For modelling purposes, it is assumed that the dynamics of ion channels is not affected by the isolating procedure. Further information for the models relates to the fibre architecture and to conductivity values.

The initial stage of the mathematical formulation for membrane kinetics is determined by background assumptions, existing knowledge and hypotheses about the biophysical functioning of ion channels such as the existence of voltage or concentration-dependent mechanisms of channel opening, closing or inactivation, or possible states of the protein) and also assumptions about best fit between experimental data and simulation results under similar conditions and how to achieve correspondence between mathematical formulations and biological processes (for example, related to ion channel kinetics). At this stage, there is an abstraction, in that only the functioning of ion channels is selected, excluding other processes, such as mechanics, metabolism, genetics and so on. Importantly in a multi-scale model, experimental data recorded in *different* cells and hearts are integrated in the model, from the ionic to the whole organ level: that is, from the sub-cellular, cellular, tissue, and organ levels. The equations and parameter values allow simulation of electrophysiological function in cardiac tissue. The spatial characteristics of the tissue (such as its geometry) are defined by the mesh, which is discussed in the next section.

Mesh

In order for the simulation to be carried out, it is necessary to ensure that a further relation to actual cardiac physiology is forged; that is, to the anatomy and geometry of the cardiac tissue. In the case of whole-organ level models, this is carried out in the construction of anatomically-based meshes, and in the case of cardiac electrophysiological activity, this will concentrate on the anatomy of the upper or lower chambers of the heart (i.e. whole-atria or whole-ventricles models). The process for arriving at the mesh is itself a complex one, originating in the wetlab procedures of histology and MRI. Computational segmentation techniques are used in

order to obtain a binary image that defines the boundaries of the ventricular wall, abstracting it from the surrounding media (see for example, Plotkowiak et al., 2008; Plank et al., 2009; Vadakkumpadan et al., 2010). The 2D binary image is then used to generate a 3D volumetric mesh by applying a discretisation process in space. This anatomically-based 3D volumetric mesh comprises the elements or points in the cardiac domain over which the solution to the bidomain equation discussed above is calculated. The volumetric mesh is therefore defined by the image-based anatomy and the numerical method used in the simulations to solve the bidomain equations. This means that the mesh is then also part of the model and an important component in determining simulation output.

The mesh can be seen as a bridge point between the models (in the form of parameterized equations) and simulations. It also acts as a mediator between these two stages of the whole process, since it also is the means whereby there is interplay between them as each is adjusted to the other. It is important to note that there is no universal mesh, since meshes need to be constructed in terms of specific research questions embedded in specific models.

The mesh also allows for the *visual* representation of the model and simulation results in spatial and temporal terms – these have a crucial role in the whole modelling and simulating processes (Winsberg, 1999; Humphreys, 2004; Hartmann, 1996; Carusi, 2011) with important consequences for how representation is understood in the domain as a whole and for model validation, which has not yet been well understood.

Simulations

The parameterized equations are solved through the simulations. However, this statement of their relationship to the model in the form of a parameterized equation (the 'computational model' in Humphreys' terminology) makes it appear as an entirely separate process from the modelling process, and obscures its other roles in the overall process. In our example of models of cardiac electrophysiology, simulations have three roles:

(i) To build the models themselves and determine equations and parameter values by minimizing the difference between simulations and experimental data;
(ii) For model validation purposes by comparing simulation results with independent experimental datasets (that are not used in model construction);

(iii) To investigate the electrophysiological phenomena under study.

It is important to note that there is an interplay between the simulations and the parameterized equations as described in (i). In addition, the numerical techniques used in the simulations also determine key features of the anatomically-based mesh, as the spatial discretization is performed by breaking the tissue geometry into smaller spatial steps using finite difference, finite elements or finite volumes. The aim is to obtain a numerical solution of the bidomain equations at every node of the mesh. However, the nodes of the mesh are determined by the need to achieve a convergence of numerical algorithms and has no relationship with the size of the cells. The entire myocardium consists of about 10^10 cells and it is not computationally feasible to simulate, in a bottom up fashion, the electrical propagation through this number of cells. Instead, the bidomain model represents a middle out approach, which arises by assuming a homogenization principle in which the smallest unit is a block of cells.

Thus, the underlying model is a discrete one, which is turned into a continuous model through the homogenization principle. However, computational simulation requires that the bidomain equations be turned back into a discrete model via a discretization process based on the numerical technique.

Depending on the questions being addressed, parallel computers or supercomputers may be necessary to deal with the sheer size of the model and the data that they generate. Simulation complexity is addressed in various ways, all of which involve a trade off between efficiency, robustness, and accuracy within the numerical routines. There are subtle interplays between the spatial resolutions and temporal resolutions and these interplays are different from method to method and mesh to mesh.

The simulation techniques are essentially a three-way negotiation between the equations, computational tractability, and existing knowledge of the domain to be modelled, involving adjustments between these, including, it must be stressed, between the equations and the numerical techniques. There is therefore a feedback from the simulation back to the equations. The results of these techniques need to be *interpreted*, in the strong sense of the word: there is not a single way in which they can be read, and their background and context need to be taken into account. As mentioned, the visualization of the simulation plays a crucial role in this process of interpretation.

Any diagrammatic illustration of this whole process will tend to isolate each stage that we have described, and even the device of bidirectional arrows does not show the extent to which they are interconnected. The

different aspects of this process are not chronologically distinct, and they are not distinct entities, in that they are shaped in answer to each other. Indeed, we could say that these models display at the level of methodology some of the features of biological phenomena as understood by systems biology, in that the process of modelling and simulation occurs in a system where local and global properties inter-inform each other, and distinctions – between stages or levels – are fairly artificial.

Back to the Question: What is the Model Source?

Returning now to the question of what is the model source in the case of multi-scale models of cardiac electrophysiology, we conclude that it is not possible to identify the model with the equations alone, since there is not a principled way in which they can be distinguished from the experimental data, the mesh, the simulation, and the visualization. In this domain, models are constructed not to remain at the formal mathematical level, but in order to gain traction on a physical domain, by incorporating data from the physical domain. The word 'incorporate' is meant literally here, in that what is important about the process we have described in the previous system is that the parameterized model is simulated on a physical entity, the computer, with a physical qualitative and quantitative output. This does not imply that there need be a relation of isomorphism between the physical computer and the model results,[7] yet the physicality of the computer does make a difference; for example to computational tractability, and to the computational input and output. In her analysis of the Repressilator, a synthetic model incorporating mathematical model and cellular structures, Loettgers writes that these 'can be best described as hybrid systems, consisting of models and experiments' (2007,121). The systems we are discussing here are similar to these hybrid systems, except that the matter in which the mathematical model and the experiment are hybridized is *in silico* rather than *in vivo*. As a way of keeping the hybrid and complex nature of the model system in the forefront, we suggest that in computational physiology research using modelling and simulation, the model source should be identified with the Model-Simulation-Experiment-System, or the MSE-system.

This brings us to the next component part of all models, the target.

[7] A view rightly criticised by Barberousse, Franceschelli and Imbert (2008).

The Target

The target of the MSE system is constructed at the same time as the source. First of all, because of the E in MSE system, the target is already in the source. In this respect, the MSE system as a model source shares features with its target.[8] However, there is also a great deal about the target domain that is unknown, and the point of these models is to try to construct a system which, when probed, will provide answers to questions about unknown or currently little understood aspects of the target domain.[9] It is in this sense, at least initially, that the MSE system represents the target: that is, in probing the MSE system, one learns something about its target. In the practice of cardiac modelling, what this means is that a 'match' is sought between source and target. This is clear from the earliest use of the computational modelling method in cardiac electrophysiology, by Denis Noble who wrote in the paper which can be seen as an important initiator of this research programme: "It can be seen that the general shape of the action potential (A) corresponds very closely to that observed experimentally in Purkinje fibres" and "Nevertheless, the sensitivity of the computed pacemaker potential to changes in ionic conductance has been shown to correspond quite well with the experimental information available" (Noble, 1962). Since that time, the programme can be seen as a way of deepening the understanding of what such correspondence consists in. The correspondence referred to by Noble was a qualitative one, judged through observation of trends and visual outputs. Although there is a drive to quantitative matches (discussed further in the section titled "Validation"), the source and the target are not comparable independently of constructing both in such a way that comparisons can be drawn between them. This is what it means for the target domain to be co-constructed with the model source: before two things can be compared there must be some ground of comparison between them. Thus, an appropriate target domain for the model, understood as the MSE system, emerges at the same time as the MSE system is constructed. For example, the target is constructed as an abstracted cell/tissue/organ containing only those features relevant to electrophysiology, building on the electrical model of cells as consisting of ion channels, exchangers, and pumps that are used for the bidomain equations. From this point onwards, there is an adequation between the model and the target domain. Consider, for example, the correspondence

[8] It is (partially) the type of model that Harré identified as a homoemorph, by abstraction (see Rothbart, 2004, 6).

[9] And in this respect they are more like Harré's paramorphic models (Rothbart, 2004, 8).

posited between each node of the mesh and cell size. In the previous section, we saw that the spatial granularity of the mesh does not correspond to actual cell size, but depends on the numerical techniques used. In this step – taken for a number of reasons – the target is similarly constructed as a domain where cell size is, to some extent, not a priority for electrophysiological activity, in the sense that it will not affect the interpretation of whether there is a match with the target domain. The target domain is not the reality of electrophysiological activity in physical or in vivo hearts, but it is a construct where some features – in this example, cell size – are put in the background, and others – ion channels – are put in the foreground. Which features should be in the foreground and which can be relegated to the background can shift and change, depending on, for example, changes in research question, in computational power, or in the understanding of the underlying processes. Because there is not comparability between the MSE system and reality in and of itself, what is occurring in this process – which is fundamental for the validation of the MSE system – is the construction of a target domain, which is comparable to the MSE system. The grounds for comparability between the MSE system and the target domain are at the same time the grounds for understanding the MSE system as a representation, and the grounds of the validation of the MSE system as a model system.

The Source-Target Relation

The process of constructing the MSE system as a model system for a particular domain – in our case, the domain of cardiac electrophysiology – is a process of constructing the grounds for comparability between the MSE system and that domain. Such a process must occur before it is possible to say that the MSE system is a representation of the target domain. The grounds of comparability fix the criteria for judging whether an MSE system is a representation of the target domain. These grounds of comparability are not a pre-established fact. It is precisely for this reason that this is a research programme, not a *fait accompli*.

A comparison with the account of computational models by Paul Humphreys' (2004) will clarify this point.

As we have already mentioned, our approach has much in common with Humphreys' definition of what a computational model comprises, except for two main differences: first, Humphreys sees a more linear progression between simulation and computational model, and does not take into account the active role of simulation and experiment in constructing the computational model. Second, while Humphreys' account

accentuates the fact that computational models must be seen from the standpoint of the process-of-construction rather than that of the context-of-discovery, he goes too far in the direction of divorcing the process of construction from the context of discovery towards which it is geared (at least in the case of the kind of models we are considering here). For example, Humphreys includes in the computational model 'an interpretation,' which connects the [functions of an] equation with specific properties or specific contexts of the target domain (he gives the example of the function *u(x,t)* representing the temperature gradient in a perfectly insulated cylindrical conductor for a diffusion equation (2004, 80)). As we discussed in the previous section, in the models we are considering, there is an interpretation that connects the bidomain equations with specific properties of cells, understood in terms of an electrical model. Even though this interpretation provides a frame for the rest of the MSE system, it underdetermines it. This underdetermination occurs because the MSE system is still in a process of construction, and it is possible for new discoveries about the relation between source and target still to make an input into it and change the interpretation relating to the MSE system as a whole. Thus, we would say that discovery is not entirely separate from the process of construction and the justifications for idealizations, approximations, and principles cannot always be had by considering the computational model (in Humphreys' terms) or MSE system (in ours) as autonomous systems.

On our account, the relation between source and target is one of searching for and building up grounds of comparability, which are at the same time the grounds for being able to say that the MSE system is a representation of the target domain. The target domain is a combination of research questions and area of investigation. It can be either experimentally or clinically defined; are either of these 'real' electrophysiology? We would argue that this question is badly posed, for reasons that will become clearer at the end of the next section on validation.

Before moving on to this section, we make one further point: what is meant by representation in the practice of modelling and simulation can still be relatively indeterminate, or can vary in determinacy across the different modalities that are integrated in the MSE system. For example, it is rather unproblematic to say that the equations represent physical laws relating to electrical currents. However, these equations represent the physics of electrical currents and not the full picture of the physiology of electrical currents in the heart, where multiple ionic mechanisms comprise multiple feedback loops between the molecular level, and the cell, whole-organ, and organism levels. Thus to the extent that we can say that the

equations are representations in advance of the modelling and simulating process, they are not representations of anything specifically biological or physiological. Whether they are representations *of electrophysiology* (in the target domain or in the 'real') depends on establishing the extent to which there is a match between the MSE system as an instantiation of specific cases of electrical current in the heart; for example, whether the modelling and simulation of an arrhythmia matches what occurs in actual *relevantly similar* arrhythmias. In the use of modelling and simulation in cardiac modelling (as one example among many in computational science), the aim of modelling and simulating –that is, the aim of the MSE system in our terms – is to construct a source system that represents its target. Whether it does or not cannot be declared, but has to be evaluated. 'Representation' here is a success term, and one cannot say in advance of evaluation that the model is a representation. Representation and validation, the prime tool of evaluation, are for this reason conceptually connected.

This brings in the role of validation, which we consider in the next section.

Validation

In the previous sections we have stressed the fact that MSE systems are constructed in an iterative process between each of their component parts, and crucially this involves incorporating experimental data sets. New experiments to probe different aspects of the target domain in virtue of research questions thrown up by the developing MSE system are conducted, and data are gathered from other sources and integrated.

Validation is an ongoing process and not one discrete event. However, experiments specifically geared at validation occur when the output of the MSE system is compared with independent experimental data that have not been used in the construction of the system. This is done in two ways (and often a combination of both): quantitative, by checking that the value for a specific electro-physiological property (such as action potential duration) in simulations is within the range reported in experiments (see for example, Romero et al., 2009), or qualitatively, by observing the visual outcome of simulations (Xie et al., 2004). However, qualitative and quantitative matches are relative to the grounds of comparability discussed above. In the case of multiscale systems, such as the one we are considering in this paper, the data sets for construction and for validation have been acquired at different functional levels from ionic to whole organ, in different preparations and using different techniques (Pueyo et

al., 2010; Rodriguez et al., 2005). Each of the datasets provides complementary information to compose the mosaic of knowledge required to construct the ventricular model. However, it must also be remembered that each experimental technique also involves a modification of the preparation with respect to its *in vivo* state (e.g. isolation procedure), and also introduces artifacts that are due to the recording procedure (e.g. insertion of microelectrodes, photon scattering in optical mapping experiments).

At various points, we have mentioned the importance of visualizations to the process of interpreting the computational model and simulation. The visualizations and other qualitative outputs, such as graphs showing trends, also play a role in validation, albeit a contested one. It is often expected that 'real' validation can only be achieved quantitatively, but this is an object of an ongoing research, and it is also questionable to what extent it is appropriate to expect numerical validation (see Sage et. al. (2009) for an example of the use of qualitative validation). This is not a topic that can be fully explored here, but clearly, there is a need to get a better understanding of the relation between qualitative and quantitative validation – and that is, what is the significance of a qualitative or quantitative match (or lack thereof).

Lastly, and most importantly, the pervasive variability of biological systems must be taken into account. Variability is a huge challenge for modelling and simulating of biological systems, and makes further demands on the comparability between the experimental data for model construction and for model validation. MSE systems need to refer to specific targets that are as similar as possible, both with respect to preparation and techniques. However, even aiming at identical targets, stochastic events would rule out arriving at precisely identical targets in every respect. This needs to be considered in the definition of the validation criteria (for example, in the definition of error tolerances[10]) and the interpretation of the validation output.

In view of the above, it is a question what a match of experimental and simulation outputs actually means in terms of the validation of the MSE system. If there is a match, *it is possible* that the MSE system has captured the relevant features of the target, at least for one possible scenario of the target system. The lack of a match cannot be interpreted as a failure of the MSE system as a whole. Instead, the lack of a match normally sets in motion a further round of iterations and refinements. However, in both cases, both false positives and false negatives are possible, given the factors that we have already mentioned. The context against which

[10] Which Humphreys refers to as the 'correction set' (2004, 78-9).

validation results are judged includes a variety of factors, including the following:

1) Appropriate comparability between the *experimental ensemble* that has informed the construction of the MSE system and the target against which it is validated. Even differences in the age of the animals from which the data are obtained, or in the experimental techniques or preparations used can affect comparability.

2) Appropriate comparability between the *integration* of the data from different data sets, and at different functional levels in the MSE system in the target system.

3) The *variability* in biological systems, referred to above, means that MSE system and target system need to be in the similar scenario states.

4) The *numerical techniques* and *software* for simulations must be validated for the whole MSE system in which they participate to be validated.

5) The *error margins* must be set correctly, not too stringent and not too broad. A quantitative match is evaluated using error tolerances (e.g. the maximum difference between simulation and experimental results) defined by the end user and therefore varying error tolerances might provide different outcomes for the validation. Error tolerances in validation need to be related to the variability observed in the experimental results.

6) The description of the model itself can be too broad – that is, what the model is a model of –, encompassing different scenarios that the target could instantiate. For example, the fact that there are different models described as 'rabbit action potential models' raises questions regarding the reasons why they are so different (yet described in the same terms), and why different models describe specific instances of the target better. It may well be the case that different models are actually of different aspects of the broad category 'rabbit action potential.'

Thus, even though validation experiments use independent data that have not been used for model construction, these data need to be comparable with the MSE system in the same way as the data used for experiment construction. All of points 1-6 above are ways of checking whether the data are indeed comparable, and without these checks it

becomes almost impossible to arrive at a proper interpretation of the validation experiment. While the validation experiment *is* independent, it must still cohere with the MSE system, at least to the extent of being commensurable with it. Moreover, validation experiments become absorbed into the MSE system through the further iterations that they set off.

This also holds for validation experiments that use data gathered from *in vivo* electrophysiology of actual human hearts. However, these data are also gathered using one or other intervention method, in specific types of context (healthy hearts or already diseased hearts, in hospital or other contexts, and so on). To the extent that the data obtained from these interventions are even comparable to the MSE system, they need to be rendered commensurable with it, and therefore must be on the same terms as the MSE system. To this extent, even this form of target domain is co-constructed with the MSE system.

Clearly, the process of validation needs to consider the MSE system against the background of its construction, in order to be able to interpret the results of the attempted validation and in order to evaluate those results. In many respects, this is no different from wetlab experimental biology and physiology where the interpretation of experiment results depends on a precise knowledge and often first-hand familiarity with the entire history of the samples, starting from the choice of animal model to all the techniques used for producing and experimenting on samples.

There is another way in which the multi-scale systems that we are considering are continuous with other modes of experimental science, while also constituting a departure from them. In the case of multi-scale systems integrating experimental data from different functional levels and from disparate sources, what can constitute adequate grounds of comparability has the added complexity that a match must be sought against experimental data which do not come in an integrated form – or at least not in the construct that is the initial target system of the MSE system (validation against 'real' hearts in non-invasive non-experimental circumstances is the ultimate aim, but is not as yet on the cards). Of course, experimental and clinical electrophysiologists have traditionally carried out this integration of knowledge intuitively, using diagrams and other visual aids. The novelty and usefulness of these multi-scale MSE systems is that they allow for this integration in a form that lends itself to active interaction on the part of the scientist who can run simulations any number of times, and stop and examine them at specific points, change parameters, and otherwise manipulate them. The multi-scale MSE system also probes and explores the target system in different ways, with a view

to an integrated, systems view. As Morgan and Morrison (1999, 10-12) point out, models can and do function as both interventions and representations. The models we have been describing intervene in order to construct a representation of a domain, actively probing and targeting that domain. In addition, they are highly manipulable themselves, allowing for a high degree of interaction. It is this manipulability that, in the terms of Morgan and Morrison, makes it possible 'for us to learn how and why our interventions work' (Morgan and Morrison, 1999, 12).

Finally, what kind of epistemology does this picture of computational modelling and simulating call for? This is an important question, both philosophically and pragmatically, though it is not always a question on which the philosophy and the practice of modelling converge. The way in which the term 'validation' is generally (although not exclusively) used among scientists is captured in this definition:

> Validation: The process of determining the degree to which a model is an accurate representation of the real world from the perspective of the intended uses of the model.[11]

That this definition is quoted in a recent report commissioned by the National Research Council in the US on *Assessing the Reliability of Complex Models: Mathematical and Statistical Foundations of Verification, Validation, and Uncertainty Quantification* (2012) is an indication of how entrenched this meaning of the term is in the scientific community. Yet, this term is far more problematic for many philosophers. For example:

> "[…] the term validation is used even more misleadingly to suggest that the model is an accurate representation of physical reality. The implication is that validated models tell us how the world really is" (Oreskes et al, 642)

Oreskes et al go on to give reasons that most philosophers of science will recognize and find non-contentious. First: validity is a question of well formedness, internal consistency, and the absence of detectable flaws, but with arguments as beset with implicit assumptions and possibly hidden auxiliary hypotheses as modelling, none of these conditions can be known to have been met. Second: models are underdetermined by data and therefore more than one model could match a physical system. Third: the

[11] Quoting American Institute for Aeronautics and Astronautics. 1998. *Guide for the Verification and Validation of Computational Fluid Dynamics Simulations*. Reston, Va.: American Institute for Aeronautics and Astronautics.

well-known fallacy of affirming the consequent occurs on a hypothetico-deductive construal of scientific experiments, where the hypothesis is that the model is correct and the test implications are that a match with experimental data will occur. Their conclusion is that 'the establishment that a model accurately represents the "actual processes occurring in a real system[12]" is not even a theoretical possibility' (642), and go on to suggest that the more appropriate term for (positive) results of tests of the accuracy of models as representations of physical reality is confirmation, probabilistically expressed.

However, we would like to suggest that there is a way in which the notion of validation does hold of models considered as MSE Systems. Oreskes et al. make a normative recommendation about how terms should and definitely should not be used. However, it is unlikely to result in the term 'validation' being dropped by scientists in modelling communities, for a number of reasons, not least of which is that it is by now firmly entrenched. As Peter Galison has pointed out, from the start of the use of the Monte Carlo simulations in physics, the mathematicians in the research teams were still striving to achieve the gold standard of deductive validation even when other scientists more used to dealing with experimental science in the lab did not hold it to be appropriate (Galison, 2006). The field of computational electrophysiology has many similarities with the situation described by Galison, and there are still disagreements among scientists from multiple disciplinary backgrounds who collaborate in modelling and simulating projects, concerning whether deductive validity is the right way to think of validation.

A further approach is to consider how the terms of traditional epistemology do apply but in different and unexpected ways. For philosophers, validity normally indicates a virtue relating to internal consistency and a lack of flaws such as contradiction, incoherence, or irrelevance. Validity – admittedly a slightly looser sense than strict logical validity governed by rules of deduction – has to do with the ways in which the premises and conclusions of an argument are internally related.

Now we see that there is, after all, a way in which this understanding of the term 'validation' does hold of computational models and simulations understood as an MSE System. As a system of inter-related parts, validation can be thought of not as a face-off between the model and external reality in a single event, but as an ongoing process with the objective of attaining maximal coherence between models, simulations,

[12] Quoting "Radioactive waste management glossary," IAEA-TECDOC-264 (International Atomic Energy Agency, Vienna, 1982).

and experiments. That is, a coherentist epistemology of models, rather than a correspondence epistemology of models.[13]

Earlier, we described the process of validation as a process of 'looking for a match,' and elsewhere we have described the process as seeking a 'stability of matches' (Carusi, Burrage, and Rodriguez, 2012), and we have discussed matches in the terms of resemblances and iconicity, and pointed out the necessity of understanding what these actually could mean in quantitative or qualitative terms. However, we have also stressed the importance of making the quantitative and qualitative outputs along the whole cycle of the process of modelling and simulating comparable; that is, of building up grounds of comparison between them. This is not a matter of correspondence between two externally related items, but a matter of seeing them as coherent and consistent. This occurs between each of the stages of the MSE System, but also at points of validation experiments that aim to show a coherence between MSE System and experiment output. Like Winsberg's notion of 'reliability without truth,' this understanding of validation allows scientists to get on with most of the epistemic and pragmatic tasks that are related to modelling and simulation.[14]

Theory

The models discussed in this paper are not derived from biological theory, in the way that models in physics may be derived from theory of physics. They are far closer to being experimental models than theoretical models, and are developed mostly with an eye to applications, such as for testing of drugs or other clinical interventions. However, models such as these are central to the domain of systems biology and what their theoretical import might be is still an open question. Not only is there an absence of a clear pre-existing biological theory from which the model is derived deductively, particularly in terms of formal theories, but also systems theory is seeking new forms of theories that may emerge from the use of modelling and simulating. In the models we have considered in this paper, there is a core of formal models that are derived from theory, but from physics, not physiology. In models of cardiac electrophysiology, it is crucially the cell structure in its interactions across the system, which

[13] This position cannot be worked out in detail here, but it has affinities with Joseph Rouse's notion of laboratory fictions (Rouse, 2009).

[14] A comparison between this understanding of validation and the reliability without truth advocated by Winsberg (2006) to account for the epistemology of simulations will be undertaken elsewhere.

introduces a physiological level. Modelling these interactions across levels and function requires a step-change in the nature of models and the computational algorithms to solve them. The philosopher Franck Varenne provides an illuminating discussion of the role of theories in systems biology (Varenne, 2010) and suggests that contemporary systems biologists are following three main routes: turning to probabilistic formalizations (J-J Kupiec), neutralizing conceptual imports from models in physics (Lesne), or contesting them through conceptually audacious and creative mathematics (Bailly and Longo). However, he also notes that the aim of much research in this domain is not to construct theoretical models, nor even primarily to mathematize biological processes. Computational simulations for Varenne are not simple numerical solvers of equations that cannot be solved analytically. They are 'machines for interlacing, at different levels and from different points of view, sub-models of a global phenomenon which does not have a formal homogeneity' (2010, 350), for which trying out and honing concepts is the primary aim (2010, 347). As we have tried to bring to the fore in this paper, it is this combinatory and integrative aspect of MSE systems that are their central characterizing feature.

Conclusion

This paper has considered the question 'what is the model?' in a specific example of the use of computational modelling and simulation in systems biology, multi-scale models of cardiac electrophysiology. A detailed account of the construction of the computational models and simulations in these contexts shows that the modelling and simulating process is itself better understood as a hybrid and dynamic system of interacting models (in equation form), simulations and experiments, or what we have called the MSE system. That is, the MSE system is a system both as model source and with respect to the biological systems that they target.

We have argued that the process of constructing the MSE system as a model system is a process of constructing the grounds for comparability between the MSE system and the target domain. The 'systems' nature of the MSE system is foregrounded by validation experiments, which demand consideration of the whole system in order to be interpreted. Like other models, the MSE system has interconnected instrumental and representational roles, fulfilling its role as an instrument through a representational modality, and what it represents is determined in a holistic fashion through the relationships within the MSE system and through

validation experiments (which themselves may come to be incorporated in it). We have also proposed that validation is a process rather than a result, and that it consists in seeking maximal coherence and consistency within the MSE system, and across it and validation experimental outputs. In addition, these models invert the relationship between theory and model that holds on traditional views of models in science, according to which models are derived from theory, and seek to derive theory from models.

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CHAPTER SEVEN

COMPUTER SIMULATION AND THE GROWTH OF NANOSCALE RESEARCH IN BIOLOGY[1]

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Introduction

This chapter explores three links between simulation and nanobiology research. First, the massive growth of nano-related biology publications of the early 1990's strongly coincides with the incorporation of simulation practices. To some extent, availability of simulation algorithms, skills, and hardware promoted nano research. Simulation operates on a par with metrological instruments. They often function in tandem and together comprise a powerful combination. The computational instrumentation of simulation has become as important as metrological instrumentation. Second computational based research contributes to the cognition of nanobiology through the creation, organization, and consultation of databases. An additional important input to learning lies in the categories and the amount of information that simulation provides, particularly concerning morphology and sequencing. Finally, simulation molecular graphics generate images that are informational and analytically rich and that offer a fundamental input into novel forms of epistemology.

What is Nanobiology?

Nanoscale research in biology is defined by a scale, and by dint of this to a specific set of materials, to their structures, functions and dynamical

[1] We wish to thank Alexandra Frenod (GEMASS-CNRS) for editorial contribution to this text.

processes, and to the control over the relevant range of bio substances. Six parameters, and the relations between them, effectively delimit and characterize the interests and much of the laboratory work of scientists associated with nanobiology. Research in nano-related bio fields has grown amazingly over the past twenty years, due partly to an instrumentation revolution in metrological devices and to the generalized introduction of computational-based research in the form of simulation. Characteristic of bio nano research is the investigation at the level of a single bio molecule versus a smaller scale such as the atom, or to larger scale objects such as cells, membranes etc. Nanoscale bio investigation nevertheless contributes to the understanding of such larger objects through examining them in terms of molecular components.

Nano-bio research can be regarded as an extension of molecular biology, which dates back to the 1940s and even before. Despite the fact that nanobiology explores the same objects as molecular biology, some of the questions asked, the way that they are investigated, the fashion that objects are handled, and the importance of control, are all different.

The biological objects most central to contemporary research are by dint of their very scale a privileged terrain of nanoscale research. DNA measures 2.5 nm in width, and the average length of a pair of bases in DNA is 0.33 nm. Amino acids that constitute the components of proteins and peptides are also nanometric.

Questions which are associated with the origins, evolution and functioning of life routinely include objects and forces situated at the nanoscale. The famous chemist Linus Pauling (1901-1994, Nobel Prize in chemistry 1954) who worked on hemoglobin in the 1930's and 40's, acknowledged the necessity to reflect in terms of a reduced biological scale that for some purposes extended from ten to the minus seven meters down to the angstrom. At this reduced scale, it is possible to determine by calculation the angles formed between two atoms in a molecule, and thus to predict the configuration and shape of molecules. The study of form in nano research goes further by identifying details inside an object, and then presenting a synthetic overview of a landscape by revealing relations, and sometimes the dynamics inside the biological material. In biology, nano-based information thus provides synthesis and fine resolution through technologies of integration.

In biological research, the structures of DNA and proteins are today often depicted and understood in terms of form. Issues of biological control and manipulation of the shape and function of molecules are today central, and have been so, particularly since the 1990's. Nanoscale control is emblematically expressed in work on protein design and engineering, in

the building of scaffolding with DNA or proteins, and in the development of entirely new biological structures. Control and manipulation as well as enhanced power of description of molecules are in large part the outgrowth of the development of a range of new metrological and numerical instruments.

Investigations carried out in biology on the nanoscale essentially deal with two large categories of objects: proteins and enzymes or fragments of proteins (peptides) and their amino acids on the one hand, and nucleic acids (DNA and RNA) on the other. Biological objects such as the cell, membranes, organelles (ribosome, mitochondria, endoplasmic reticulum, Golgi bodies...), are studied at the nanoscale uniquely with reference to their components. In the nanoscale perspective, they are observed, manipulated, and discussed in terms of architecture, form, and function.

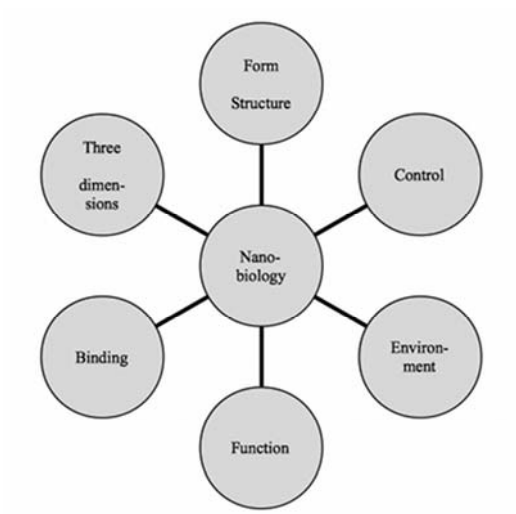
We suggest that the presence, convergence, and intertwining of six specific elements characterize nanoscale research in biology: 1. Form / structure; 2. Three dimensionality; 3. Binding; 4. Function; 5. Environment; and 6. Control.

1. Form and structure refer to the scaffolding and the architecture of the object on the molecular level, and to the external surface topology and internal structures. 2. The three dimensional representations provide invaluable spatial information of objects, which can then be studied in terms of their volume and of the room that they occupy in the space. Volume necessitates taking into account the spatial constraints linked to it. These three dimensions also serve as a point of departure for reasoning where calculations derived from three-dimensional coordinates elucidate intrinsic dynamical forces and interactions. 3. Binding refers to the capacity of two different biological molecules to connect with one another, or alternatively, for one molecule to change shape as one internal element connects to another. This is referred to as folding. Both categories of binding are constrained by structure and form, and they are also directed by forces of different categories such as Van Der Waals forces, or hydrogen bindings. 4. Function refers to the specific actions of a biological substance in connection with the system (be it the set of molecules in which it is integrated or a more complex unit) in which it operates. 5. Binding and function are affected by characteristics (electronic, chemical, thermodynamic, hydrometric) of the surroundings of the biological molecular substance. 6. Nanoscale research in biology entails the capacity of scientists to control the substances, structure, form, binding, and environment.

Simulation constitutes one major motor that drives the research subsumed in these six elements. Even the results of metrological

experimentations often serve the needs of simulation and help it to improve research programs. One can argue that the multiple foci of these six nanobiology parameters are today available to researchers, thanks to the development of new categories of technologies and their powerful combination with older devices.

Connections between the six aforementioned parameters are often acute and decisive. It is the linkages and interactions between the six that allow us to speak of an integrated nanobiology hexagon that finds expression in much nanoscale investigation. It is not the presence of a particular set of elements in the hexagon that proves decisive: it is instead their co-appearance and notably their collective interaction.



Nanobiology Hexagon

For example, protein binding is governed by three-dimensional properties of materials and by the characteristics of the environment such as thermal values, acidity, humidity, and packing conditions. The combined considerations of three dimensionality and binding govern the conformation of the molecule and therefore its function. Through controlling molecular conformation, it becomes possible to control bindings that affect their function.

Control is particularly important. What distinguishes nanobiology from other contemporary biological research is the association and integration of the six above indicated points. While questions of function and binding

have been explored since the 1930's and even before, and three-dimensional models arose in the 1940's, 50's and 1960's, it is only in the framework of nanoscale research that all of the elements are combined. The essential ingredient is the capacity to study processes at the molecular level, to "see" the molecules, to predict their configurations, and behaviors, and to control outcomes. By defining nanoscale research in biology in these terms, we emphasize two characteristics; namely, the combination of resources in research, and their expression as synergies resulting in constant expansion and acceleration.

Post 1990 Discontinuities: Parallel Growth in Nanobio and Simulation Publication

A remarkable discontinuity in the quantity of biology publications on molecular objects occurred circa 1991. Between 1991 and 2010, the amount of annually published articles related to many biological substances has grown up to one hundred full. To imply that all of this expansion represents the level of research activity in nanobiology would be misleading. Nevertheless, nanobiology does comprise an important stream in the flow. Since 2000 a large part of the Feynman Nanotechnology Prizes, established in 1993 (Marcovich and Shinn 2010a, 2010b), has been accorded to individuals whose work involved biological questions and biomaterials. As will be suggested below, the overall increase in biology research funding explains much in the field's research output. Long standing participants in nanobiology benefited from the largesse. Equally important, general budgetary creation and money coming specifically from the U.S. Nano Initiative attracted biologists to the nano paradigm of biological inquiry. Again in the U.S., DARPA programs have proven active in support of nanobiology.[2] The international genome project was launched in 1988, principally by the American National Institute of Health and the Department of Energy. Funding of biology related research rocketed in the USA. Spending stood at $ 27.9 million in 1988, at $ 86.7 million in 1990, rising to $ 134.8 million in 1991, and to $ 437million in 2003, the year when the human genome code was totally identified. Finance in Canada, Japan, the UK, France, Sweden, China, Korea, Australia followed. In 2000, global spending attained $ 1,805,325,883.[3] The launching of the U.S. National Nano Initiative in 2000 provided

[2] Interview of Homme Hellinga at Duke University by Anne Marcovich and Terry Shinn 20 June 2010.

[3] http://www.stanford.edu/class/siw198q/websites/genomics/entry.htm

funding specifically for nano research, and not least of all for biology. The overall budget in 2009 stood at $1.5 billion. Again in the United States, the National Science Foundation similarly earmarked money for nanobiology exploration. The ascending trajectory of nanobiology research is connected to the conjunction of two additional elements. During the mid to late 1980's, many families of new metrological instruments became available that directly or indirectly suited biological research. Some nano instruments were specifically conceived, designed and commercialized for nanobiological work. In parallel, computational research has developed both in terms of hardware and software. The following tables show the extent of the expansion of nanoscale research related biology work. The topics are selected in the light of the six features represented in the hexagon.

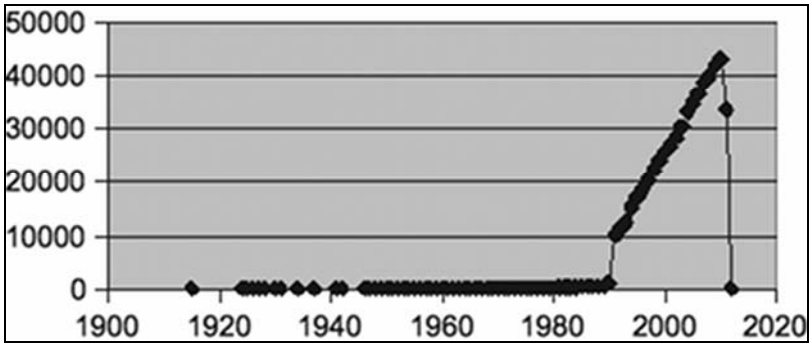
The values in Table 7-1 document the importance of protein in molecular research, and more particularly the growing interest for their conformational structures and dynamics, as well as the significance of aspects linked to control. It signals the recently acquired possibility to detect regions of folding and to characterize them. Note that the discontinuity in publications between 1990 and 1991 is a four-fold increase.

Since the origins of biochemistry in the early twentieth century, proteins have been studied with reference to their chemical composition and function (Debru 1983; Kay 1993). However, the possibility to analyze precisely their internal activity in terms of physical operations, properties, and morphology is recent and overlaps with the birth and rise of nanobiology. The emergence of nanoscale technology has allowed the study of relationships between protein function and their active sites. It similarly elucidates some relationships between function and environment.

The large number of publications can also be explained by huge protein data banks whose complexities and possibilities can be systematically explored using computational instruments. This, in itself, assumes an industrial scale.

Table 7-1: Topics: protein* and function*: 768 711 items[4]

2010	43072
2000	25644
1992	11160
1991	10000
1990	1159
1989	414

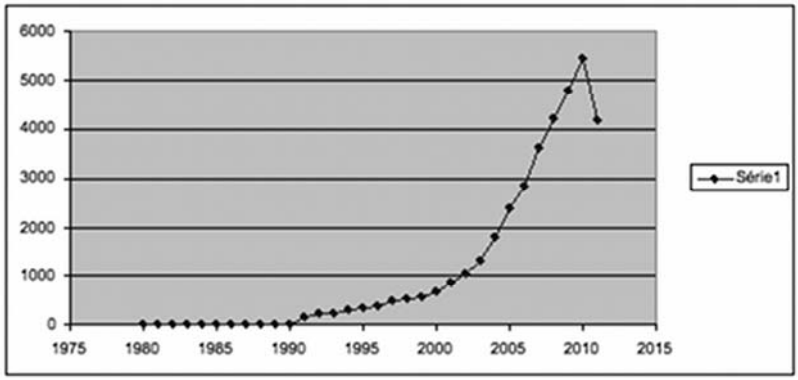


It is necessary to identify precisely the contributions of nanoscale research to the broader wave of molecular biology related investigations. Specifically, nano inquiry can naturally be related to the scale of observation, to the presence of methodological materials such as quantum dots, nano particles, or nanotubes, and to use of certain combinations of metrological or computational devices.

[4] ISI Web of Science (26/10/2011)

Table 7-2: Topics: nano* and protein*: 36 543 items[5]

2010	5454
2005	2417
2002	1065
1995	341
1990	12

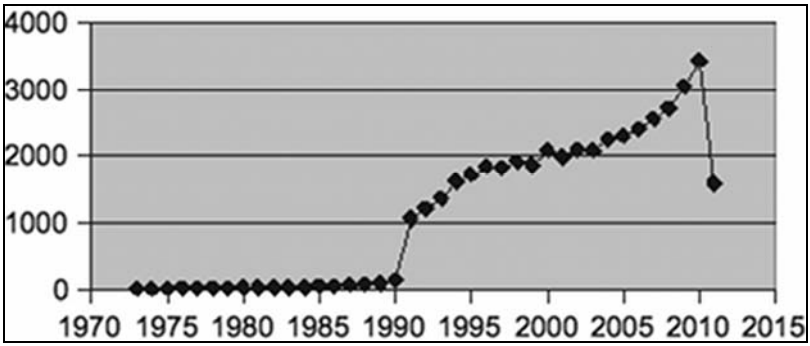


As suggested above, the dramatic growth of DNA sequencing between 1990 and 1991 is in large measure attributable to the financing associated with the international human genome project. Sequencing constituted the very heart of this project (Gilbert 1980; Garcia-Sancho unpublished). The studies on the human genome were accompanied by studies of non-human species and led to the creation of unprecedented huge databases.

[5] ISI Web of Science 26/09/2011

Table 7-3. Topics: DNA* and sequencing*: 43 341 items[6]

2010	3430
2000	2080
1992	1204
1991	1061
1990	134
1989	76



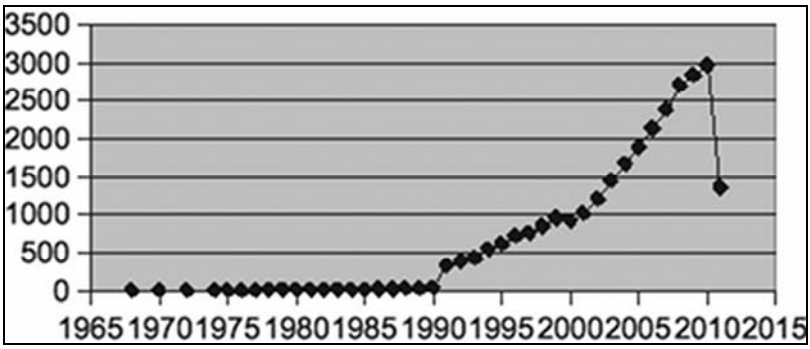
Computational instruments that produce simulation of physical and biological phenomena and therewith description and prediction of properties and dynamics, have operated as an additional motor to the dramatic acceleration of biological research during the 1990's and beyond. The place of simulation is shown in tables 7-4 and 7-5.

One can reasonably assume that many of the articles counted in Table 7-2 on protein and nano also figure in the articles indicated in Table 7-4 on simulation and protein. The explosion in the number of simulations in biology depends on the development of a critical mass of information on the one hand, and on the development of advanced computational technologies on the other, including algorithms.

[6] ISI Web of Science 23.06.2011

Table 7-4: Topics: protein* and simulation*: 29 678 items[7]

2010	2961
2000	922
1991	325
1989	21



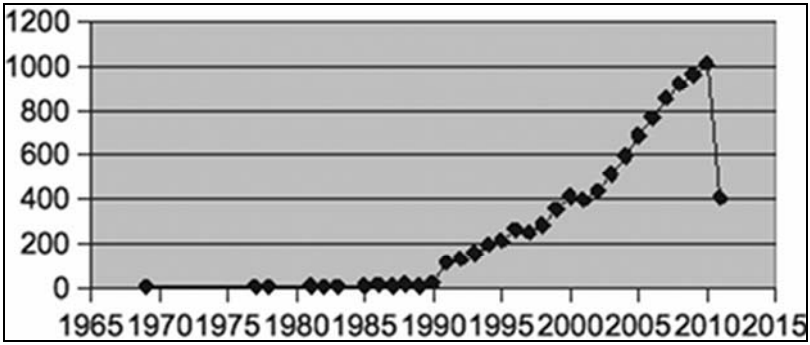
Note that the form of the curves in Tables 7-4 and 7-5 are almost identical. After the discontinuity of around 1990, the curve follows the same slope. When one compares the amount of articles on proteins entailing simulation with publications on proteins based on the Atomic Force Microscope technology, the power of simulation becomes manifest. As shown in Table 4 simulation appears in 29 678 protein related pieces versus 4 406 for the AFM.[8]

The dramatic post 1990 acceleration in molecule centered research in biology is a product of synergies between different fields of investigation and combinatorial between program orientations, new instruments and methods, and new ways of seeing the molecules. In the pages that follow, we examine the profusion of novel instruments that have contributed to metrological, experimental results and to computational biology and simulation.

[7] ISI Web of Science 23.06.2011
[8] ISI Web of Science: topics: AFM* and protein*, 9/05/2012.

Table 7-5: DNA* and Simulation* : 10 390[9]

2010	1010
2000	409
1991	114
1990	20
1989	6



Instrumentations

What has allowed the rapid post-1990 rise of nanobiology? The introduction of much improved or novel families of metrological and computational, simulation instrumentation proved essential. Computational and metrological devices often operate in tandem, and this gives rise to a form of synergy that contributes to the expansion of research expectations, the contraction of frustrating temporality and acceleration of discoveries.

Metrological Instrumentation

The aforementioned dramatic rise in publications after 1990 of nanoscale research is attributable to an instrumentation revolution of the

[9] ISI Web of Science : 22.06.2011

1980's, and to the combination resulting from integration of new instruments with previous generations of devices. The capability to measure objects at this scale in an aqueous milieu is very important because it corresponds to the quasi totality of biological conditions. This is an advantage over other instruments such as the Electron Microscope that often requires destructive sample preparation, notably by drying them and by placing them in a vacuum.

The Atomic Force Microscope (AFM), invented in 1986, offers important possibilities for the investigation of DNA condensates. It is capable of viewing the structure of the delivery vehicle in its hydrated state, as it occurs in cells. Based on AFM nanoscale resolution, one can image the DNA strands and see how they react and connect to a particular other polymer. Among other applications, the AFM can be used as a gene delivery vehicle. The AFM can observe in real time nanoscale processes in vivo. This possibility is recent in biological research, and particularly pronounced in the capability of measurement of nanoscale apparatus and research findings.

Three additional instruments developed circa 1990, are also prevalent in nanobiology work. Near Field Optical Microscopy capable of nanometric, measurements of biological materials in their natural environment arose during the same period. Using near-field optical techniques, researchers currently resolve features in the order of tens of nanometers in size. This makes it possible to study large macromolecules and assemblies of molecules. Nevertheless, intramolecular observations remain restricted. On a different register, a new form of mass spectroscopy was developed. A novel nano sensitive spectroscopy system was invented at the Japanese instrumentation firm "Shimadzu Corporation" by Koichi Tanaka, 2002 Nobel Prize winner in physics, specifically for biology research that was viewed as the wave of the future. Tanaka's project Metric Assisted Laser Desorption Ion Time of Light Spectroscopy (MALDITOF) began in 1987 and was commercialized in 1993. It constitutes a cornerstone of today's nanobio instrumentation revolution (Tanaka, 2002).

The conclusion that developments in entirely novel metrological instrumentation, and in the emergence of new instrument combinations for the rise of nanobiology, is inescapable. It is through such devices that single molecule observation and analysis has become possible during the last twenty years. It is the recent capacity to see inside molecules and to explore dynamical processes, such as folding, which is constitutive of nano in the life sciences.

Although the post 1990 acceleration in bio related research is built on the combinatorial of metrological devices developed during the instrument revolution of the 1980's, we will see below that acceleration also revolves around a second instrument combinatorial consisting of both metrological apparatus and computational instruments. Operating alone, the metrological devices of the revolution would neither suffice to explain the massive increase in nano-related bio molecular investigation, nor would it take into account the richness of nanobiology, its complexities, and analytic possibilities. Perhaps most central, as it will be shown, the conjunction of computational and metrological instrumentations yields a central component of research epistemology, which proved to be particularly significant and potent in nano research.

Computational Instruments

Historically, the emergence of simulation was linked to the Manhattan project and the study of nuclear detonation dynamics, and to the introduction of electronic tube computers (Galison, 1997; Casti, 1996; Lenhard, Küppers and Shinn, 2006). Advanced computational modeling in the domains of the physical and life sciences, expanded in the 1970's, 80's and 90's with the advent of three principal conditions: 1. The invention of the microprocessor and development of enhanced electronic memory beginning in the 1970's and 80's (Lécuyer and Brock). 2. Creation of *ab initio* methods and Density Functional Theory (DFT) between the 1960's and 80's permitting the prediction of physical properties through mathematically driven deductive influences based on the atomic number of elements appearing in the Mendeleyev table (Lenhard unpublished). 3. The massive diffusion of low cost, user-friendly, powerful desktop computers and specialized computer programs in science research laboratories requiring no specialist learning. Simulation of bio molecules allows the calculation and prediction of energy levels and other physical characteristics, which in turn affect the internal organization of molecules sometimes expressed in their structure and form. This is a key signature of nanoscale research especially in biology. Based on some equations and semi empirical evidence, simulations can predict the features and dynamics of biological molecules.

Among the simulation tools used in bio simulation, algorithms are of foremost importance. The number of simulation algorithms multiplied during the 1990's and subsequently, and their capacity for manifold parameter analysis and precision expanded in a variety of biological domains. This evolution was built on a virtuous circle where informatics-

organized data is collected in coherent databanks, and on the basis of these databanks, simulations are performed whose results in turn extend the databanks.

This dynamic is exemplified by the Basic Local Alignment Search Tool (BLAST), created in 1990, on the eve of the vast dilation of bio nanoscale research (Altschul et al, 1990). BLAST is a frequently employed algorithm that enables comparison of primary biological sequence information, like amino-acid sequences of different proteins or the nucleotides of DNA sequences. Another possibility offered by BLAST permits a researcher to compare a query sequence with a library or databank of sequences, and thus to identify library sequences that resemble the query sequence above a certain probability threshold. Different types of BLASTs are available according to the query sequences. For example, following the discovery of a previously unknown gene in the mouse, a scientist will typically perform a BLAST search of the human genome to see whether humans carry a similar gene; BLAST will identify sequences in the human genome that resemble the mouse gene based on similarity of sequence. While BLAST is mainly a databank construction and search device, it is nevertheless clear that it is inextricably associated with more strictly simulation work.

Finally, the Rosetta simulation program offers a second example of the operation of computation in bioresearch and its immense importance. It was developed specifically with nanobiology investigations in mind. Rosetta was created for the prediction and design of protein sequences, and to anticipate the native structures of various proteins, using spatial computer protein structure prediction algorithms. Introduced in 1995 by David Baker at the University of Washington, in 1999 it was used by only three nanobiologists for single molecule nano protein studies. In 2009, Rosetta was being employed by over one hundred nanobiology practitioners. The nano research algorithm is presently freeware on the Internet. Since relations inside proteins are so very complex, an empirical, semi trial and error approach remains productive. The many permutations offered by Rosetta permit taking into account in a very systematic and rigorous way, a huge amount of parameters. Non-biologists in the broad public are invited to use Rosetta to try to find protein pathways through modifying protein forms in a myriad of ways that are consistent with internal molecular forces and changing internal physical environments, but that are so complex that they are not necessarily covered by even the best existing algorithm.

At the core of Rosetta are potential functions for computing the energies of interactions within and between biomacromolecules. One of

the principal aims of Rosetta is the identification of the lowest energy structure for a protein sequence. Simulation feedback from the prediction and design tests is used continually to improve the potential functions and the search for new algorithms (see the text below, and the text located in next section).

> Brian Kuhlman's research on nanoprotein design is emblematic of nanoscale investigations. Kuhlman is co-laureate with David Baker of the 2004 Feynman Nanotechnology Prize.[10] Dr David Baker and Dr. Brian Kuhlman, professor at the University of North Carolina, (Department of Biochemistry and Biophysics), received the theory prize for their development of the afore mentioned Rosetta Design program. This program has a high success rate for the design of stable protein structures with a specified backbone folding profile. Kuhlman and Baker's goal is the design of new forms of proteins.
>
> "These proteins we make are very complicated things. They're a hundred amino acids that we want to fold into a particular shape (…). Folding is not simply a question of directly sticking together two components of an object. It implies to take into account the cumbrances that must be overcome in order to ensure that the components to converge spatially, and this may entail twisting pathways. It is also a problem of matching physical interfaces. This is one aspect of the problem of appropriate atomic and molecular packing. For all of these reasons folding is observed in terms of forms, and needless to say, as three dimensional form. We have projects where we're just trying to build a certain shape. That's kind of like learning how to build a bridge before I even care about what the bridge is going to connect".[11]
>
> This introduces one notion of control which focuses on the mastery of understanding. Here, control does not refer to achieving some wanted effect – some intended output. In the following passage, control assumes a second form. It consists of generating wanted material effects.
>
> "We go experimentally, we make the protein, and it doesn't fold into that shape, or it does something bad, like it aggregates, which means it just clumps together and falls out of solution. Unfortunately, it's very difficult from that failed experiment to know exactly what was wrong with your computational sequence. Actually, a little disappointing for me, as most of the feedback for improving our simulations doesn't come necessarily from the limited number of experiments we do, but rather it comes from -well, maybe this isn't disappointing- what we do is we gather all the experimental data that's out there, from all the labs, and we use that to train our software. And if our own experiments aren't working, we then say, "oh

[10] http://www.foresight.org/FI/2004Feynman.html#2004Winners

[11] Interview of B. Kuhlman by A.Marcovich and T.Shinn University of North Carolina Chapel Hill. 17 June 2010.

> we need to train our software more, with more data that's out there". So that's the process we use. I guess, what we use our experimental results for is kind of knocking ourselves on the head and saying, "we really need to be doing more training of our software. We need to be doing more testing of our software compared to all the data that's out there, not just ours."
>
> This final passage expresses two related fundamental orientations. First, empirical information is employed to train future simulation programs. Second, the activities of bio informatics as expressed in databanks merge with simulation programming and results.

Beyond BLAST and Rosetta, there exists a host of additional simulation programs in nano biology. Among them, the Lamarckian algorithm (1998) analyzes the docking mechanisms of protein-ligand complexes. The Genetic Algorithm for protein Design (EGAD)[12] is an algorithm for the simulation of mutation effects on protein folding stabilities and binding affinities. EGAD can also calculate multiple structures for designing specific binding proteins or locking proteins into specific conformational states simultaneously. Note that many of these nanobiology simulation instruments are intended to promote understandings and practices where molecular prediction, design, and engineering comprise the foremost concern. As argued above, these algorithms are one of the key aspects and aspirations of nanobiology research. Precise examples of this as work strategy and operations inside laboratories will be described below.

Computational experiments and metrological experiments exhibit two different logics, which are mutually reinforcing. Results from simulation research based on models subsequently nourish a databank that then inputs into another set of models. The computational system thus consists of cycling between model conception and application, the constant enrichment of databases, and the genesis of new models. In the case of metrological instruments, it is the object of study and its corresponding problematic that temporarily underpin the gathering of different, otherwise independent, instruments. In the case of computational devices, it is the logic of each system (algorithm, model…) that fuels them. Through developing more and more descriptive and analytic possibilities, the understandings of biological objects in terms of systems expand and encompass other systems in an ascending spiral. The outcome of this is a constant acceleration in the pace of research and the growth of knowledge.

In conclusion, the instrumentation revolutions of the 1980's and 1990's have produced a series of devices that today permit the investigation of

[12] http://egad.ucsd.edu/EGAD_manual/index.htm

new biological parameters that can be observed and understood in novel terms. The new devices allow scientists to see and analyze objects on the nanoscale and in some instances to control them.

Some Impacts of Simulation on Nanobiology Research?

In the 1980's and 90's, computational biology developed two different roles. First, computation based research in nanobiology entails the creation, organization, and consultation of databases, algorithms, computational and statistical techniques and theory to solve formal and practical problems arising from the management and analysis of vast quantities of biological data. The domain of bioinformatics matured with the institutionalization of the human genome program. Along with metrological experiments, bioinformatics computer programs made it possible to stock, manage, and manipulate a huge amount of DNA sequence-related data. Major research efforts in bioinformatics include sequence alignment, gene finding, genome assembly, drugs design, drug discovery, protein structure, protein prediction, prediction of gene expression, and protein-protein interactions, genome-wide association studies and the modeling of evolution. Related to this, computational research in nanobiology focuses on the representation and analysis of various types of data, including nucleotide and amino acid sequences, protein domains,[13] and protein structures. One aim consists of engineering and manufacturing de novo nucleic acids as well as proteins. This requires precise control at the molecular level which often entails simulation (see insert 2 below).

> The 2005 Feynman Nanotechnology Prize laureate, Christian Schafmeister, professor at Temple University in biochemistry, works on "universal scaffolding" of artificial proteins synthesized through building blocks that are intended to create specific functionalities in these proteins. In his work two types of control, control for understanding and control for effects are interlaced. Schafmeister constructs an universal scaffolding from crystals. This technique is present in medicine but is not so frequent in nanoscale research. The protein here remains stable even when

[13] A domain is a physical biological object consisting of a protein unit that resides inside protein polymers and that has its own autonomous specific structure and function that contribute to the determination of the properties of the macromolecule. A specific domain may be present in a host of proteins that induce similar characteristics. Domains figure in data banks where they are classified in terms of their functions and are used in the engineering and fabrication of de novo proteins.

additional components are introduced. Structural instability is the habitual condition of proteins under changing conditions. Schafmeister's objective is the production of a designed function. For Schafmeister, the form of the protein remains central, but it is a means to an end. It is not a target of investigation per se. Otherwise stated, he does not want to understand form. Schafmeister simply changes form to achieve function.[14] To these scaffolds are attached a number of specific amino acids. Depending on their relative position on the scaffold (this expressed in three dimensional space), they generate particular function such as those induced by acidity or hydrogen bonds.

"Actually, what we're trying to do is, we know what these groups, amino acid side chains, do by themselves. We know a lot about how they can catalyze reactions by acting as acids, acting as bases, acting as hydrogen bonding groups. We know how they can coordinate with metals and metals can activate things. What we're trying to do is put these functions together so they can work simultaneously and act in concert, get a synergy, get an additive greater than the sum of their parts. If you have a group here that's acting as a base, while over here there's a group that's acting as an acid, and over here you have something activating by hydrogen bonding, and they're all held in the right constellation, then when the molecule diffuses in there, it'll be like it's completing a circuit. The electrons will flow, and atoms will move and outcome the products. That's our hypothesis."

This citation draws attention to the systemic character of Schafmeister's macromolecular construction. The functions of the system result from the relations between its components and their environment. The stability that he can impose on his constructions gives these systems the possibility to have dynamical interactions with their environment.

The scaffold can adopt a variety of forms, which also depend on the function of the whole molecular construction. Here the most relevant unit of form is the relationship between elements. For Schafmeister an important part of the work consists of writing simulation codes that will allow him to design the protein and then to adapt it in the light of experimental observations with Nuclear Magnetic Resonance and X-ray diffraction. Schafmeister produces control in the sense of pure understanding of biological objects by handling molecules; he obtains control in the sense of effects (outputs) by producing new functionalities, which are created through a triangular system of structure, form and function.

A second highly important bio-computation domain consists of visual molecular dynamics often referred to as molecular graphics. Computational graphics have allowed biologists to express as visual representations the

[14] Interview of Christian Schafmeister by Anne Marcovich and Terry Shinn at Temple University 15 June 2010.

structures and dynamics proposed by the above discussed molecular simulation. Advanced graphics enable researchers to manipulate their representations (rotate them, change the angle of their axis, obtain an alternative angle of observation, penetrate beneath the surface of a molecule in order to better observe packing etc.) in innumerable ways. Through computer graphics, they can also modify the morphology exhibited in the representations to determine the extent to which such modifications are compatible with the molecules' internal organization and forces. This activity is summarized in the expression of interactive molecular graphics and is highly represented in studies on protein structure and design, or on DNA conformations.

Reflections on Images

Simulation images yield an exceptionally precise, rich, and complex landscape. The DNA simulation image presented below (see figure 7-1) contains four sets of information: 1. The double spiral of DNA is clearly composed of strands (in medium gray and dark gray). 2. The atoms and their intermeshing relations as well as their organization that constitutes the strands, are clearly given. This image does not indicate the relative size of the atoms of different elements such as hydrogen versus carbon. A key feature of simulation images is that by opting for a particular algorithm and by setting appropriate values, the scientist selects the particular object to be represented. 3. It is suggested that the DNA spiral is enveloped in a sheath (proteins), composed of highly organized layers of atoms (in bright gray). This is projected as a longitudinal section of a tube. 4. The environment of the DNA strand and of the protein is indicated by the presence of suspension (brighter and darker gray spheres near the DNA).

As in simulation images, in metrology-based images at the nanoscale, objects can be "seen" atom by atom, molecule by molecule. But compared to simulation images, in the latter case, this makes it very difficult to isolate, identify, and hierarchize the different items included in the image. Atoms, molecules, or bigger parts of each entity can appear in such a mixed, jumbled way that the edges and contours of these units are indistinct and fuzzy (see figure 7-2).

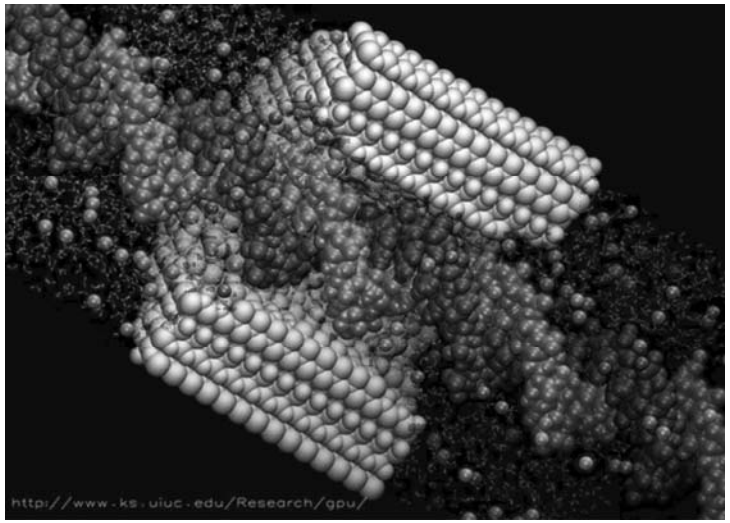


Figure 7-1[15]

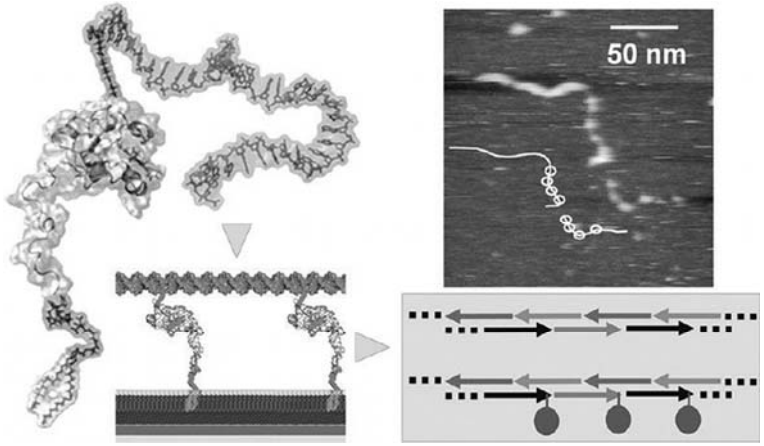


Figure 7-2[16]

[15] Image by the Theoretical and Computational Biophysics Group from NIH Center for Macromolecular Modeling & Bioinformatics of the University of Illinois at Urbana-Champaign, http://www.ks.uiuc.edu/Research/gpu/. (Original image is colored.)

[16] Reprinted (adapted) with permission from (A.Laisne, M.Ewald, T.Ando, E.Lesniewska, D.Pompon " Self-Assembly Properties and Dynamics of Synthetic

The gathering of diversified data available through simulation images often surpasses what is usually achieved by metrology-based images, and this introduces two powerful potentials:

1. Research sometimes entails comparison of metrological images and simulation images where the ideal is a perfect match or at least strong overlapping items across two pictures. The relationship between metrological and computational images is reciprocal testing, correcting, and, eventually, validating. This is an iterative process in which concepts and algorithmic models are fuelled by experimental data and where experiments can be piloted by simulation findings.

2. Simulation images are an integration of the experimental information, originating in metrology research an immense variety and quantity of information (sometimes entailing millions of calculation operations) in the guise of position and relation that is deduced from the simulation algorithms. Computational representations introduce features, forces, relations, and environments that are not necessarily accessible to metrological investigations. They assemble a broad landscape of parameters that conceive the object as a complex integrated component specific whole (electric field, magnetic charge, valence forces, acidity, the

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Proteo_Nucleic Building Blocks in Solution and on Surfaces" *Bioconjugate Chem*., 22 (2011): 1824–1834). Copyright (2012) American Chemical Society. Original image is colored. The following abstract explains the image:
ABSTRACT: Synthetic proteo_nucleic structures (PDNAs) encompassing a single-stranded DNA sequence covalently attached to a redox protein domain able to interact with surface or matrix were designed and characterized. They constitute versatile building blocks alternative to regular DNA for creating scaffolds with optical, electrical, or catalytic properties. PDNAs self-assemble in the presence of complementary oligonucleotides, to form a network of protein domains linked by double-stranded DNA segments. Electrophoretic and hydrodynamic behaviors of PDNAs and corresponding DNA were compared under electrophoresis and gel filtration conditions. Hybridization rates between small and large assemblies were characterized by rapidmixing experiments. Results showed that the protein part significantly contributes to hydrodynamic behaviors of structures but marginally affects the conformation and hybridization properties of the nucleic domain. PDNA metal-mediated complexes with nitriloacetate-modified phospholipids can diffuse and interact at the surface of vesicles or supported membranes. Surface plasmon resonance analysis of membrane_PDNA interactions indicated that two protein units are required to allow stable surface association and that surface occupancy constrains assembly sizes. High-speed atomic force microscopy illustrated rapid lateral diffusion of assemblies on mica, revealing transient association between noncomplementary PDNA extremities and frequent trapping by surface defects. Regularly organized protein domains were visualized using a larger DNA framework.

degree of acquiesces, distance between elements, relations between the interior of a molecule and its surface, chemical bonding properties etc.). All these items thus introduce new information in order to explore the probability of alternative scenarios and their material consequences. These calculations sometimes depict changing states in a biological system. The quantities of temporality are particularly depicted in simulation imagery. The images are sometimes so exact and densely informative that they are referred to as "realistic simulation images," and such images are often viewed as more realistic than many metrological representations. The difference between the two categories is sometimes difficult to establish, particularly for a none-expert. The interesting question is not "reality" but is instead the effectiveness of the representation in the ongoing work of research. Here, simulation images are sometimes viewed as most informative even by metrology instrument practitioners.

Epistemology

Three-dimensional images provide a powerful observational window into the structure of bio molecules, and they offer a stimulating epistemological platform. Structure can be thought of in terms of quantities, different categories of objects, and relations between classes; the structures exhibited in three-dimensional images directly or indirectly convey all of these categories of information, and with reference to very specific and relevant entities. The entities in these images can be grasped on one level at single glance, and on another level, can be disaggregated into units whose interactions can be gauged. Three dimensionality enables the observer to see more detail, to see things from alternative or even contradictory perspectives, to see local and general configurations and the links between the local and the general, and to see connections between internal components and external shapes. The relationship between structure, function, and effects in terms of temporality is sometimes present in images. Today, images are a particularly growing feature of simulation where they are rendered in a three-dimensional perspective and sometimes exhibited as a film.

It is similarly possible to select some regional components of the molecule and to change simply with a computer click some of its relations with the environment or neighboring components. The shape of the molecule can be modified (played with), through the game of possibilities of binding, mostly depending on the energy levels involved in the bindings.

Why are images so important to epistemology? Images can be considered not only as one of the final products of a scientific investigation, but perhaps even more so as a point of departure of reasoning, and an indispensable resource to which one constantly returns that is enriched and adjusted in the process of scientific work. At the nanoscale, form is privileged as a device for understanding. Form is central because it supplies direct information about position, size, and geometry. The form is the image. It constitutes one of the primary vehicles of physical information, and it dominates the description and the discussion. Changes in the form of an object provide information about the intensity and nature of forces acting on or within objects. Finally, through the observation of form, scientists can determine the kind and the nature of perturbation that connects the force and the form. The form of the objects under study (for example protein molecules and the way they fold) fully participates in the explanation. The notion of form is then an assembling concept that permits framing of questions related to structure, dynamics, and function. The alignment of these orientations lies at the heart of calculating and representations of simulation.

Conclusion

Our study of simulation and nanobiology invites some general reflections. We have shown that the importance of computation-based experimentation is constantly accelerating in nanobiology, and it is interesting to ask whether this is true for fields like chemistry, physics, and beyond. In nanobiology, it is notable that the rate of acceleration is still on the rise. To what is this attributable? Is it due to the progress of knowledge, to instrument innovation, or to simply to changing practices in publication strategy?

On another register, metrological and computational instrumentation often operate in tandem in nanobiology. The connection between the two is circular: there exists a type of synergistic relations where one nourishes the other. Simulation and metrological devices both generate images. These images are frequently complementary. Simulation selects and emphasizes intended features of a phenomenon that allows an alternative perspective to the more detailed, often encumbered and inclusive observations offered by metrological instrumentation. The first insists on structure, whereas the second privileges exhaustive depiction. It is equally true that simulation generates results that are not expressed as images. In this case, how tight is the linkage and what is the nature of the relation between simulation and metrology results?

Finally, we ask whether simulation and its relations with metrology do not introduce a novel epistemological ingredient. One thing is certain: simulation is frequently accompanied by prediction to a much greater extent than metrology based experimentation. This is rendered possible by two elements. First, simulation can take into account many experimental findings and thereby, it can attempt to determine which information is most decisive. Second, simulation can inexpensively and swiftly investigate a vast number of permutations and possibilities. This facilitates the task of suggesting which undiscovered outcomes are latent in the presence of specific physical constraints. This is the essence of prediction. The validation of prediction is frequently contingent on metrological findings. Here is another instance of simulation / metrology circularity.

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CHAPTER EIGHT

COMPUTER SIMULATIONS IN A COSMOLOGICAL CONTEXT

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Introduction

Physical cosmology refers to the branch of astrophysics focused on the study of the Universe on a large scale or, more precisely, on the largest scales we can handle. It deals fundamentally with the universe structure, analyzing the distribution of matter and celestial objects, and considering the processes that shaped this specific configuration. This makes structure formation and cosmic evolution key subjects in physical cosmology.

The study of these topics is not a recent phenomenon. Ideas on the origin and development of the Universe also played an important role in other periods of our history. Past notions differ in many aspects from current theories, but they share essential questions and, sometimes, similar answers. In fact, these questions and answers are intrinsic to the Western worldview. In the incipient emergence of science in ancient Greece, natural philosophers like Thales of Miletus attempted to shape a scientific explanation of the primordial matter that constituted the cosmos, while trying to identify its visible effects on certain contemporary physical phenomena. He saw the cosmos as emerging from fluid matter, and it is this primeval fluidity that sheds light on the physical constitution of the world we live in. Whereas mythology attributed the origins of the cosmos to the actions and affairs of gods, Thales initiated the theoretical trend of attributing them to scientific principles. Since then, these two paths, the mythological or religious and the scientific, have run in parallel, sometimes mixing their arguments and conclusions and sometimes clashing.

Medieval Europe pushed the origin of the Universe to the forefront of theological concerns, since the book of Genesis was crucial in defining the principles of the Judeo-Christian worldview. Besides the theoretical debates, as part of the religious propaganda many artists were commissioned to visualize each stage in the world's formation according to the Biblical account of creation. As a result, a number of reliefs in cathedrals and churches and miniatures in illustrated manuscripts reveal how the creation, evolution, and formation of the Universe were visually conceived at that time.

With the emergence of the modern era, scientific arguments regained a dominant position in terms of explaining cosmic origins. One of the triggers of the new impulse of cosmology during this period was the French philosopher and theoretical physicist René Descartes. In *Le Monde* (1989) and *Principia philosophiae* (1644), he described in detail how the universe evolved from a dense, compressed primordial matter to its current, transitory state. We will come back to Descartes's ideas in the section "The necessity of Simulations," which is devoted to the significance of simulations in cosmology. For now, it is important to remember that he gave the first influential cosmological account in modern science, exerting a direct influence on later authors who were consequently also interested in the physical origins of the Universe.

During the eighteenth and nineteenth centuries, the main hypotheses in this context mostly relied on the cosmogonical explanations of the Swedish scientist and theologian Emanuel Swedenborg and their later re-elaboration by the Frenchman Pierre-Simon Laplace. He refined Swedenborg's ideas and shaped the nebular hypothesis for planetary system formation in modern terms.

Cosmology was revived once more in the first decades of the twentieth century, culminating in the Big Bang theory and the idea of an expanding universe in the global framework of general relativity. The term physical cosmology usually refers to this new phase in cosmological theories, when the contemporary worldview started to be consolidated in the 1900s. Since the 1980s cosmology has undergone a new revolution, this time strongly determined by the introduction of simulation techniques as research tools. The following pages deal with this latest attempt at a reasonable physical explanation of the formation and evolution of the Universe on a large scale.

Significance of Simulations in Physical Cosmology

In the context of physical cosmology, simulations are unique if we compare them with other branches of science. They actually represent a special case in contemporary science. Their most remarkable aspect is the essential function they perform in shaping theories, owing to the lack of feasible experiments. This section reflects on the relevance of simulations in cosmology ("The necessity for simulations") and describes their most striking effects on the development of science today ("Simulations and the rise of dark fluid skies").

The Necessity for Simulations

Physics and astronomy have historically dealt consistently with the large-scale structure of the observable Universe available at the time. This task of analyzing and comprehending the cosmos in its largest configuration involves difficult problems when approached in a scientific context. Many of these difficulties arise owing to a general and obvious feature: the incommensurability of the object of study. This factor challenged astronomers in the past and is still challenging them today, though in a very different way. Historically, the problem consisted in not being able to observe the entire existing space, but only the tiny portion perceived by the naked eye or revealed by optical telescopes. Scientists were aware of the immense dimensions of the Universe, but their observational tools were unable to take measurements that offered even tentative proof of the general structure. Space remained mostly incommensurable.

Nowadays, astronomy has apparently overcome many of the previous obstacles. Observational techniques have considerably improved their scope of measurement, so that the produced data give an account of very remote confines of the Universe. In particular, larger sets of observational data reveal how the Universe looks like beyond the boundaries of our own galaxy. The problem of incommensurability has paradoxically emerged again, however, owing to the improvements in observation methods. Contemporary astrophysicists and astronomers are faced with an enormous amount of gathered data, which they must scrutinize. Whereas the problem originally constituted gathering data from an immense space, today the main difficulty consists in processing the huge amount of information provided by sophisticated telescopes. The information we receive from cosmic space remains incommensurable. Regarding cosmology in a scientific context, humankind finds limitations again and again. In the past, they were of a perceptual nature (the impossibility of

observing the entirety of space) whereas, at present, they are operational (the impossibility of fully exploring large amounts of observational data).

Cosmology has always faced the problems mentioned above, which seem to be an intrinsic and insurmountable part of the field itself. Notwithstanding these obstacles, science does not shrink from the search for physical laws, which define theoretical models of the Universe in terms of its structure, formation, and evolution. The main challenge for contemporary cosmology consists in developing alternative research strategies within a realm excluded by definition from traditional ways of experimentation. We should remember that the task is to provide general laws working on a cosmic scale in such a way that the 'object' of study is the entire Universe. Traditionally, science elaborates a hypothesis whose principles are tested by means of experiments, and simulations can be used as additional aids to support or challenge the results obtained in these experiments. In cosmology, the conventional process for proving the theories cannot be applied, since experiments are completely excluded from it as they are impossible to realize in this context. The reason is obvious: one cannot accommodate the whole Universe in the lab to conduct an experiment. In this situation, when the subject of study is totally beyond our grasp, simulation techniques provide the only available solution for testing the theories against available observations. The large-scale structure *must* be simulated if we want to apply more than a purely abstract approach.

Given the long history of cosmological concerns, neither this problem nor its solution is completely new. Several aspects of the current investigations into the large-scale structure of the Universe were also investigated in the past, obviously not in exactly the same way as they are tackled today, but still determined by the corresponding temporal context. One of the most significant examples in this regard was Descartes's physics, set out first in *Le Monde* (Descartes, 1989). In this text, which was guided by his scientific thoughts and free from religious pressure,[1]

[1] It was written between 1629 and 1633 but not published until 1644, since he decided to postpone its public release because of his anxiety about the trouble Galileo was having with the Inquisition. When decades later he developed his physical theories in an extended, "politically correct" version, many allusions to the role of God, as well as many arguments compatible with Roman Catholic ideology, were introduced. This updated, more acceptable, version was published under the title *Principia Philosophiae* in 1644. Nevertheless, Descartes did have Roman Catholic convictions, although he seemed to differentiate them from his scientific theories. He accepted the idea of God, which influenced his philosophical ideas. In the first version of his physical model in *Le Monde*, God was almost totally excluded from the explanations, apart from being the creator of

Descartes expounded his hypotheses regarding the physical principles explaining the formation and evolution of the Universe. Before going to the heart of the question, he warned the reader:

> For a short time, then, allow your thought to wander beyond this world to view another, wholly new one, which I shall cause to unfold before it in imaginary spaces (Descartes, 1989, 99).

In order to present his physical model, the French philosopher put into practice an epistemological strategy: to explain and test his ideas in "imaginary spaces" instead of directly acting upon the actual world. He insisted on this starting-point as a precondition for approaching the subject he wanted to discuss, specifying that

> ... my plan is not to set out (as they –the philosophers or scientists– do) the things that are in fact in the true world, but only to make up as I please from [this matter] a [world] in which there is nothing that the densest minds are not capable of conceiving, and which nevertheless could be created exactly the way I have made it up (1989, 107).[2]

Descartes probably avoided dealing directly with the "true" world in part because of the risk of being censored by the religious authorities, a far from trivial threat, as the case of Galileo demonstrated just after the completion of *Le Monde* when the Italian astronomer was prosecuted. Besides, the specific socio-political context, the intrinsic difficulties of the subject itself could also have led him to apply for this epistemological strategy. Viewed through the lens of the history of cosmology, Descartes's modus operandi can be compared with current simulations to a certain extent, since both of them resort to other simulated worlds to test their hypotheses on a large scale.[3] Descartes's method can be summarized as follows:

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primordial matter and the cause of the first motion at the beginning of the Universe. Once matter was created and put into motion by Him, it continued evolving owing to physical laws acting autonomously, without any divine interference.

[2] Translations based on the text by Michael S. Mahoney. See http://www.princeton.edu/~hos/Mahoney/

[3] For a more detailed comparison between Descartes's theory of vortices and current cosmological simulations, see Ayala and Forero-Romero (2011). Descartes's method of testing hypotheses is usually known as *thought experiment*.

Step 1 Defining an "imaginary space" as the scenario for unfolding his physical model.

Step 2 Setting out the initial conditions (a certain type of matter) and preconditions (concrete physical laws acting on it) that would generate a new universe independent of the actual world.

Step 3 Letting this new universe evolve according to the parameters above.

Step 4 Observing, describing, and analyzing the different stages in the formation and evolution of the universe resulting from these processes.

Step 5 Finally, comparing it with the "true" world to verify how they actually coincide. Descartes considered his hypothesis as valid if the imagined and true world are alike.

The way in which Descartes presented his cosmological hypotheses is comparable with contemporary computational astrophysics in certain basic aspects. In both cases, the cosmological models are tested by means of theoretical tools and not by experiments. Be it in the internal logic of the philosopher's reasoning, or in the internal logic of computers and programmers, a series of physical principles is activated in order to generate astronomical phenomena whose status of reality remains within a purely theoretical realm. This does not hinder the production of "true" results, as the successful comparison with the observed world demonstrates. Descartes did not simulate the universe in the current sense of producing a computer model, but he did operate following a similar logic. The epistemological difference between Descartes's methodology and contemporary simulations is more a question of degree than essential divergences. Whereas Descartes used his mind as a tool for developing the process, today we use computers as external tools to help us to perform the calculations that our minds are unable to do with such efficiency.

By stressing this resemblance, we do not expect to obtain a facile anachronistic identification of these two historical moments since, obviously, they belong to different contexts each characterized by particular scientific and cultural backgrounds. It is, however, important to note the continuities underlying the study of the large-scale structure of the Universe in the last centuries. As we mentioned before, this field has its own intrinsic difficulties, and it is not surprising that in different epochs similar or comparable solutions appeared. Testing scientific hypothesis in

the specific realm of cosmological theories about the Universe on a large scale demands simulation strategies as a sine qua non condition. Although this necessity was envisioned in the past, nowadays it has become a clear requirement of this field.

Simulations and the Rise of Dark Fluid Skies

Simulations have been determinant in the recent development of physical cosmology to such an extent that they have become the trigger for the latest cosmological theories. Our current picture of the large-scale structure of the Universe was shaped in the light of the results of computer simulations in the early 1980s. Consequently, large-scale structure studies have entered a new historical paradigm.

The starting-point of contemporary physical cosmology is Albert Einstein's theory of general relativity. Its relevance in this context is essentially its provision of the best description of gravity so far, meaning that it passes the most stringent observational tests on a wide range of physical scales. Einstein's theory of gravity is linked to two key entities: space-time and matter-energy. According to Newtonian gravity, the movement of a planet around a star is owed to gravitational force; however, from the Einsteinian point of view, this phenomenon is an unperturbed path in the space-time continuum that has been deformed by the matter-energy contents of the star.

The cosmos is now described as an expanding accelerating universe mostly composed of dark matter and dark energy. Theories around dark matter are especially important in this context, since simulations have been the leading factor defining them. Dark matter was first conjectured by the Swiss astronomer Fritz Zwicky in 1933, when he concluded that the total mass of the Coma galaxy cluster should be much greater than the mass directly derived from its luminosity. Otherwise, individual galaxies within the cluster would fly apart, since they are moving very fast. Yet, no galaxy escaped from the cluster, so he inferred the necessity of the presence of "a vast and large density of dark matter," which would bind the galaxies together. He found the "surprising result ... that dark matter should exist in a much larger density than luminous matter" (1933, 125).[4]

Years later, in the 1970s, the US astronomer Vera Rubin made the first measurements of the dynamics of disk galaxies, finding that regions far from the center were moving at the same speed regardless of their distances from the center (Rubin and Ford, 1970). This discovery was

[4] "...würde sich also das überraschende Resultat ergeben, dass dunkle Materie in sehr viel grösserer Dichte vorhanden ist als leuchtende Materie."

surprising, since at that time it was assumed that the distribution of mass in a galaxy would correspond to the distribution of light. In other words, the brighter area in the center of a galaxy should have more mass and, consequently, there should be a decrease as we observe regions even more distant from the center. Rubin's measurements proved the opposite: all the regions were moving at a constant speed. Consequently, Rubin arrived at similar conclusions to Zwicky: there must be additional, non-visible matter holding up the galaxy in one piece.

Besides these first evidences of the necessity for a new kind of non-visible matter, the seminal breakthrough came when theorists dared to speculate about the structure of the Universe on very large scales. In a solitary endeavor, the Canadian theoretical astrophysicist Jim Peebles developed in the 1970s a theoretical framework according to which structures in the Universe could evolve as an aggregation of smaller structures, with dark matter as the driving element.[5]

The definitive shift took place between the end of that decade and the beginning of the 1980s, when a handful of theorists started to realize that numerical computations could be used to trace the evolution of the density field in the Universe. Two notable pioneers in the early 1980s were the Russian astrophysicists Anatoly Klypin and Sergei Shandarin who performed, during the Cold War era, one of the first computer-assisted calculations for the evolution of a three-dimensional matter distribution on a cosmological scale (Klypin and Shandarin, 1983). Their simulation clearly showed a filamentary structure. Almost simultaneously, Marc Davis and collaborators at the Center for Astrophysics at Harvard University published the results of their observations measuring the distances to galaxies listed in a catalog compiled by Zwicky. The catalog included galaxies with an average receding velocity of 5000 km/s, the deepest available data at that time (Davis et. al., 1982). This was the first conclusive observational evidence of the distribution of galaxies around us. For the first time in the history of humankind, we were able to explore a large part of space, considerably improving what had been achieved by thousands of years of astronomical observation. The data from these observations were revolutionary, not only because of their historical significance, but also because of the information they provided. To the astonishment of many theoreticians who expected a homogeneous distribution, the observations reported a network of filaments, the same result expected by the analytical calculations and simulations of the Russian School. After these conclusive evidences, the filamentary

[5] For a complete set of references, see the Introduction in (White and Frenk, 1991).

distribution of galaxies, now dubbed the *cosmic web*, was generally accepted.

In a historic paper published in 1984, Marc Davis teamed up with the astrophysicists George Efstathiou, Carlos Frenk and Simon White to tackle the same problem as Klypin and Shandarin earlier, but this time using improved numerical techniques (Davis et. al., 1985). They had the additional advantage of having the latest observational data from Davis, which allowed comparison with the results of their simulations. The initial conditions in their simulations implicitly contained elements that described cold dark matter, which is physically conceptualized as a non-collisional fluid that only interacts through gravity, and they found that it provided the best match with the observations. In parallel, other astrophysicists adduced powerful analytical arguments for the need for density fluctuations provided by dark matter to explain observational data (Peebles, 1984; Blumenthal et. al., 1984).

After the favorable outcomes of these pioneering simulations, which matched the data from observations, cold dark matter started to be considered as one of the main components of the Universe. This paved the way for the general paradigm still valid today. An additional consequence of these scientific endeavors, perhaps as important as the actual discovery, was the cultural change that they implied. Thanks to these successful investigations, numerical simulations were accepted as one of the most effective workhorses for astrophysics, since they proved their usefulness in moving theories forward.

Motivated by these achievements, the field of computational cosmology started to attract attention during the rest of the 1980s. The algorithms were improved and the computing power increased. However, the scientific advances were not as impressive as the first ones owing to the lack of new observational data. Therefore, at that time there were too many different kinds of universes that were allowed by the available observations. As a consequence, the work by theoreticians did not manage to appeal to the observers: the discussions seemed too theoretical with no bearing on observations. Scientists understood that any further progress had to come from new observational data, since better observational constraints could narrow down the different kinds of universes dreamt up by theoreticians, making the work more interesting for observers. This lack of empirical data had a stagnating effect on the relevance of a dark matter universe paradigm.

In the early 1990s, two events completely changed the scene by making galaxy evolution an observational science. First and foremost, the emergence of charge-coupled devices (CCDs) allowed astronomers to take

detailed images of the sky. As a consequence of their precision in gathering data, the quality of the spectra of distant galaxies was considerably improved. As a result, CCDs started to give accurate information about the matter distribution of the Universe on larger scales. The second groundbreaking event, also related to the introduction of CCD techniques, was the launch of the Hubble Space Telescope (HST) in 1990, which significantly enhanced the scope of observations. Five years later, it was possible to observe very distant galaxies and to see the evolution of their properties.

The usefulness of the HST was not limited to observing new galaxies. The telescope also helped in the determination of cosmological parameters, which were one of the largest impediments to theoretical progress. For instance, by 2001 the data taken with the HST helped to resolve a 70-year-old dispute on the value of the Hubble constant, which quantifies the expansion of the Universe. This constant relates the observed receding velocity of galaxies to their distance from us. Fixing its observational value had a bearing on the inferred age of the Universe and the allowed range of other cosmological parameters (Freedman et. al., 2001).

The first decade of the year 2000 saw an explosion in the number of observational campaigns that helped to improve the characterization of galaxy populations, and to determine very precisely the cosmological parameters needed to define the matter-energy contents of the Universe we live in. A key role in this process was played by the Wilkinson Microwave Anisotropy Probe (WMAP)[6], the spacecraft that measures the tiny differences in the cosmic microwave background (CMB) radiation, which is thought to be the remnant radiation from the Big Bang. Data from WMAP helped to establish the standard model of cosmology, in which the energy contents of the Universe are dominated by dark energy, and the matter content is dominated by dark matter.

Another milestone in the study of the Universe on large scales was achieved by the Sloan Digital Sky Survey (SDSS). This project used a dedicated 2.5 meter telescope in New Mexico, which started collecting data in 2000 and is still active, to image a quarter of the sky. The SDSS also took spectra of nearly one million objects in the sky, allowing the distribution of matter on large scales to be mapped with unprecedented accuracy. Another key feature of this project is its promise to make all the

[6] The spacecraft was launched in 2001 and it is still taking data. The scientists working on the Cosmic Background Explorer (COBE), the predecessor of WMAP in 1989, received the 2006 Nobel Prize in physics "for their discovery of the blackbody form and anisotropy of the cosmic microwave background radiation."

gathered data available. The latest public data release of SDSS, which was the ninth release (DR9), took place on July 31, 2012.

This steady improvement in observations forced the theorists to develop new tools able to produce at least the same kind and amount of data as the one provided – or expected to be provided – by telescopes. This demand represented a huge theoretical barrier, however, since optical observations detect light, whereas theoretical (i.e. computational) astrophysics at that time relied on dark matter, which does not emit photons. To bypass this problem, it was developed a semi-analytic approach for modeling the properties of large numbers of galaxies. The next section explains the most important features of this technique.

Today, the majority of astronomers and physicists have embraced the idea of dark matter as the underlying reason for the evolution of galaxies. Many observational astronomers have become avid consumers of the results of simulations of dark matter-dominated universes. This has had the interesting effect of pressing theorists to make the data public in open databases (following the example set by SDSS), which encourages their usability by a wider community. As a result, public databases have become a common prerequisite if a group of computational astrophysicists want to be noticed by the scientific community (Riebe et. al., 2011). This event has, however, been widely criticized because of a negative spin-off: many users blindly use the data without really reflecting on their limitations and range of validity and, therefore, they risk misinterpreting the results.

The consolidation of the current model of our Universe was made possible thanks to the implementation of simulations as a reliable scientific tool. Dark matter still lacks a conclusive description in terms of fundamental particle physics, however. Its effects can only be inferred by its gravitational effects since it is postulated that it does not interact with electromagnetic waves (i.e. light). Discovering the physical nature of this collision-less fluid of dark matter confronts physics with one of the biggest puzzles of the twenty-first century.

The Simulation Process: Computation, Verification and Visualization

In this section, we focus on two kinds of simulations that are central to the contemporary work on physical cosmology: N-body simulations and semi-analytic models. In both cases, three main steps are needed to produce scientific results: (1) defining the initial conditions and the relevant parameters that describe the model universe, (2) verifying that the codes produce reliable results within the range of parameters already

chosen, and (3) visualizing the simulated data in order to process them and draw conclusions.

N-Body and Semi-Analytic Simulations

N-body simulations and semi-analytic models (SAMs) are radically different, though complementary, techniques to simulate the universe. N-body simulations resolve the fundamental physical equations that describe the gravitational interaction in an expanding universe. On the other hand, SAMs describe the interaction of different physical processes (i.e. gas dynamics, star formation, black hole formation) through very simple analytical prescriptions; they are based on observations and good feeling, without any ambition to address equations solving fundamental physical laws.

In N-body simulations the relevant differential equations are integrated in the computing through a process of discretization of space, mass, and time. Therefore, achieving a solution as accurate as possible requires a good capacity to carry out this discretization. In other words, it requires a large number of points to sample the spatial and temporal dimensions, which are only possible with the aid of substantial computational resources. In the case of large-scale structure studies, N-body simulations aim ideally at representing larger patches of the universe by means of a large number of points that sample the underlying matter distribution. In other words, the goal is to simulate larger volumes of the universe with as much spatial detail as possible. In the case of cosmological simulations including only a dark matter component, this level of detail depends on the number of particles participating in the calculations: the more particles we include in the computation, the more accurate the results we obtain. Consequently, increasing the number of particles in the computations has been one of the most important challenges in the classical cold dark matter simulations (Klypin et. al., 1999). In fact, it has generated a race among scientists to achieve even more powerful calculations; that is, to obtain even more detailed representations of larger volumes of the universe. Whereas in the 1980s only a few thousand particles could be included in the computations, at the end of the last century their number increased to billions. This competition was largely impelled by the growth in computing power, improved super-computer architectures and more efficient algorithms (Klypin et. al., 2011).

Notwithstanding the relevance of the number of computed particles, N-body simulations can only provide partial information. In the case of dark-matter-only simulations, they present the spatial distribution of matter

produced under the action of gravity, but they do not reveal the properties of the numerical galaxies that could form in this specific matter distribution. This would imply introducing gas and stars as key factors of the simulations, which involve tackling hydrodynamics and the reciprocal influence of radiation and matter. The algorithms required to perform these calculations would be extremely complex and consequently very expensive. Furthermore, a huge amount of time and energy would be required for computing physical details that are irrelevant in view of the general processes taking place. For these reasons, semi-analytic models are used as a complementary method of computing. These models avoid deriving a physical description from fundamental laws and instead are based on phenomenological approximations: they assume certain observed facts without trying to perform a detailed computation (Baugh, 2006).

At first glance, SAMs appear as a deceptive, simple, and rough approach to complex problems, since they do not try rigorously to describe physical processes from fundamental considerations. They introduce free parameters; that is, certain values that do not immediately correspond to fundamental physical quantities, but that assume the results of a process as given. Thanks to this strategy, SAMs make feasible the simulation of complex processes that otherwise would be excluded from computational astrophysics, since fundamental laws are not enough to predict their results; N-body simulations including hydrodynamics and other processes would be insufficient to achieve any satisfactory result. Without SAMs, the effects of key galaxy formation processes could not be calculated through simulations. As a result, SAMs open new possibilities in theoretical astrophysics. For instance, to model the effect of a supernova exploding in a galaxy, SAMs simplify the problem with a handful of free parameters describing the final outcome, whereas N-body simulations would try to solve each relevant equation of hydrodynamics and chemical reactions, making the calculation impracticable owing to its complexity and, in any case, unattainable owing to the high computational costs (Scannapieco et. al., 2012).

A crucial achievement of SAMs is that they made possible statistical comparison between simulated and observed galaxies, therefore constituting a fundamental tool for studying the evolution of galaxies in cold dark matter universes. These models can predict observable properties of galaxy populations, which essentially mean predicting the total amount of light emitted by every single galaxy. Since these simulations are based on light values, it is possible immediately to contrast their results with data obtained in actual observations. In the case of a disadvantageous comparison, different sets of free parameters can be

corrected until they match the observed values. Consequently, these comparisons result in the refinement of the theoretical grounds defining the model. Even though the parameters cannot be interpreted in physical terms, this kind of reasoning has pushed the development of important theories in cosmology. An example especially relevant in this context is the role of supermassive black holes in the evolution of galaxies. The results of SAMs that include the alleged effect of black holes on galaxy evolution provide a much better match with observational data than models without that effect (Croton et. al., 2006).

Protocols for Verifying Simulations

Verifying cosmological simulations of large-scale structure involves two different stages. First, the scientist has to be sure that the code accurately solves the equations it was designed for. This accuracy can be quantified by comparing the numerical solutions with the results calculated through analytical considerations used in very simplified configurations. In the specific case of simulations that only include dark matter, this first step in the verification process means ensuring that the code accurately calculates gravitational forces. To this end, several techniques have recently been developed, each algorithm having a different degree of accuracy for a given computational cost. Among them, the most popular are the Particle-Mesh (PM), the Tree algorithm, and the hybrid Tree Particle-Mesh (TreePM).[7]

In a second stage, the results of the code are tested for numerical convergence. This involves making sure that the computation does not depend on the particular numerical implementation of the model, but only on the basic physics that is expected to drive the results. Such differentiation between computation/physics is not as clear-cut as one might think. In many cases, the numerical implementation and the physical model are strongly connected. For instance, in the case of N-body simulations there is a trade-off between the volume of universe patch that can be simulated and the minimum mass used to discretize the matter distribution in the computational volume. Both the volume and the minimum discretization mass are computational parameters, which nevertheless are related to physical quantities. A convergence test in this case implies running a simulation of the same volume, but with the matter distribution discretized in a larger number of discrete mass elements

[7] Section 3 in Springel (2005) provides a good account of the kind of convergence tests that can be performed on a code aiming at describing gravitational interaction for the purposes of cosmological simulations.

(called particles). One would expect the results for the higher resolution simulation (larger number of particles) to be compatible with the lower resolution computation (lower number of particles). Only the properties that are the same in the two simulations are considered robust and reliable. These two steps in the verification process are also performed in other kinds of simulations that include computations of the fundamental equations describing hydrodynamics, gravity, and the interaction of radiation with matter.

Albeit some recent exceptions exist (Benson et. al., 2012), SAMs are usually not verified. This circumstance is partially owed to the lack of significant analytical expressions to describe the result of a SAM simulation, but mostly because there is no standard way to implement a SAM model. A consequence of this peculiarity of SAMs is its neglect by some of the astrophysical community who regard these codes as opaque tools that do not provide any physical insight into the problem of galaxy formation. In spite of this, the results obtained by SAMs are widely used both by observers and by theorists.[8]

The Role of Visualizations

Be they N-body simulations or semi-analytic models, all the results of a simulation *must* be visualized: astronomy is essentially a visual science dominated by observation. An important traditional research method in astronomy consists in analyzing images; that is, observing them to gain information. With the introduction of the telescope astronomers ceased to look at the sky directly with their naked eyes. They no longer look at the sky but at images containing information about it – information that can be provided by telescopes or, more recently, by simulations. In any case, nowadays the daily work of many astronomers largely consists of looking at the screen of their computers. Even if they are observational astronomers, instead of being seated at the telescope looking through the eyepiece, they are more commonly seated at a desk working with digital

[8] In 2008 there was a workshop called "Semi-analytic models – are we kidding ourselves?" (http://www.sr.bham.ac.uk/workshop/2008/) with the following scientific rationale: "This semi-analytic approach allows baryon physics to be incorporated in a way which, compared to hydrodynamical simulations, is fast, transparent, and easily modified, and arguably provides greater physical insight into the results. The contrary view is that semi-analytic models contain so many adjustable features that their optimization constitutes little more than an underdetermined fitting operation, resulting in models, which are non-unique and have little predictive power."

data and digital images received from the device. Under these circumstances, it is not surprising that data from simulations are *naturally* visualized so that the information can be processed.

Another reason for the necessity of visualizing simulations is its usefulness. Comparison of different simulated results is easily done, as a first approximation, by "direct inspection" of visualizations. Nevertheless, comparing raw data requires the design of an appropriate mathematical tool to quantify a given effect. Looking at images guides the development of such tools. Consequently, visualization is still a practical step in cosmological simulations to analyze and interpret data, although quantitative analysis has an increasing role in the comparison of different models.

In general, images are especially useful in this field because in most cases the simulated processes and phenomena cannot be observed in the physical world. For instance, the gradual collision of galaxies, the early stages of the Universe, or its large-scale structure become visible to us only by means of simulations. Since the first attempts in the modern era to define the large-scale structure and the processes that took place at this level, scientists have indeed made use of images to support their theories and hypotheses. The special case of Descartes mentioned above is not an exception. In his scientific books, he took special care to include a rich number of images associated with each important explanation.[9] Following the internal logic of his epistemological strategy, the images of *Le Monde* and the *Principia* can be seen as screenshots of the sort of simulation (the "imaginary spaces") he proposes. Only through these woodcuts and engravings, the process of formation of the large-scale structure of the universe becomes visible. In a similar way, contemporary simulations also offer the opportunity to analyze the large scale by using images that otherwise would be impossible to achieve. As in the case of Descartes, today it is not the whole simulation process that is visualized, but only certain selected moments. In both cases, what we obtain is a kind of sample image of a more complex process that largely remains on a theoretical (non-visualized) level.

In contemporary simulations, the quality of the visualizations is correlated with the degree of detail of the conclusions drawn from them. As mentioned before, in the 1980s only a few thousand particles were computed. Consequently, at the beginning of the simulation era the images

[9] The artist and mathematician Frans van Schooten the Younger was commissioned to make the images of Descartes's *Principia Philosophiae*. The philosopher worked closely with him to achieve images as faithful to his ideas as possible (see Zittel, 2009).

obtained from the computations were very rough, only consisting of a small number of dots. The computing power progressively increased with the passing of time and, with it, the complexity of the resulting images. Whereas earlier visualizations only showed a very simple dot distribution, currently they give much more detailed information, making visible textures, and nuances previously impossible to achieve. As a result, today's simulations provide much more information about the Universe, also because we understand better than ever before how to program the code and how to interpret the resulting data. Notwithstanding the refinement of visualizations derived from the general improvements in the field, the fundamental physical effects were already present in the early examples.

Limitations of Simulations

Simulations are used as tools to explore the consequences of a theory. Therefore, they are only as convenient and informative about the Universe as the theoretical concepts included in the model. If a simulation successfully reproduces some feature of the observed Universe, one can only see this result as circumstantial evidence proving the relevance of a given theoretical component in the description of the Universe. This limitation of simulations is often forgotten by routine and convention.

A second limitation is their physicality: time, data storage, and data transfer rates are restricted. There is an upper limit to the amount of time a simulation can run, since they do not run for years in a row. The runtime of a simulation is largely restricted by the short lifetime of the machines themselves, which is in the order of just a few years. Another aspect of physicality consists of the space that can be allocated to store the simulation results: hard disks are limited in terms of both number and capacity. Finally, nowadays, in the era of networked science, there is an additional limitation: the transfer rate of data around the globe is not unlimited. If an international collaboration wants to have access to the same results, there is a minimum non-negligible time lapse in the transfer of the data. All these limitations are taken into account in the design of a code and a simulation.

Eventually, these physical limitations produce a digital divide that clearly defines the kind of science that different groups can make. At one end of the spectrum is science based on large amounts of data, with powerful supercomputers, and fast network connections; at the other end are groups aiming at exploiting the complexity of the algorithms and the novelty of the physics to be probed, with codes that can run on modest

computers and produce results that can be instantaneously shared with colleagues around the world.

Finally, in relation to the fast pace of scientific collaboration, there is another physical limitation: the amount of time a human can invest in analyzing the data. The rhythm of scientific research funded by large institutions (universities, companies, and scientific foundations) imposes a quick turnover of ideas and people. The results must be obtained and published in the literature as quickly as possible. This is seen by many as the real bottleneck in progress in computational cosmology, since tasks have to be finished on timescales of a few months or years, providing little motivation to do long-term work such as finding new algorithms, rewriting codes to improve computational efficiency or even trying out new ideas.

Simulating the Right Universe

We have seen how N-body simulations of structure formation in a dark-matter-dominated universe have played a central role in the emergence of a standard cosmological model. The main factors for the construction of such a robust computational framework were the refinement of numerical models and their comparison against observations that were developed during more than three decades. However, this development does not imply conclusive proof that the Universe is indeed well represented by the physics commonly included in the simulations; namely, general relativity and dark matter.

In 2010, during a debate over the existence of dark matter, Simon White – one of the early proponents of the concept of cold dark matter – was confronted with the following question: what observational or experimental result would convince him to change his mind about cold dark matter? He answered that only a theoretical model providing a better match with observations could persuade him to ignore cold dark matter.[10] Purely observational or experimental evidence alone is no longer decisive in terms of discarding or accepting a model in physical cosmology. A hypothetical competing model has to reach the same degree of sophistication as cold dark matter, with accurate N-body simulations and flexible semi-analytic models, to be able to stand comparison with a wealth of observational data. This position reveals the particular state of affairs in contemporary large-scale structure studies.

[10] The debate took place on November 18, 2010, at the Physikalisches Institut in Bonn. This debate can be viewed here:
http://www.uni-bonn.tv/podcasts/20101201_Bethe_Debate.mp4/view.
The question is asked around 29 minutes and 34 seconds into the video.

The current standard model that explains the emergence of structure in the Universe has two unsettling elements: dark matter and dark energy. To make advances in the nature of dark energy, the astrophysical community has agreed that we require measurements that are accurate within a fraction of a few percent, which has served to coin the term *precision cosmology*. It means that we are looking for effects that are small deviations from the results derived by simulations in the standard model. If such precision is achieved, it also implies that it will be possible to look for small deviations beyond general relativity and the standard cosmological model. This realization has motivated the study of computational models beyond the standard cold dark matter model.

Such deviations from the mainstream of research, in spite of being minority tendencies, are progressively gaining attention. In fact, some of the current simulations are based on different kinds of gravity or different kinds of dark matter. This wide range of possibilities is affecting confidence in our own picture of the cosmos: we do not know whether we are simulating the right universe! We can only wait until these new theories find their way into computational models and, in parallel, until observational probes diversify and improve their precision. In the next decades, we expect renewed interplay between simulations and observations to solve these questions at least partially.

Coda

Studies of the large-scale structure of the Universe have three main components; namely, theory, observations, and simulations. They are interconnected and mutually influenced: new theories trigger new observational strategies, simulations are essential for refining theoretical concepts and, at the same time, they are also essential for interpreting observations.

Each of these epistemic genres can act as a solution when the others reach their limits. This is the case with simulations able to explore beyond the boundaries of observations. Some simulations therefore acquire such complexity that it becomes impossible to manage all the data produced. At this stage, scientists, in an attempt to find new valuable information, start to observe the simulations themselves.

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CHAPTER NINE

EXPERIMENTATION AND SIMULATIONS IN THE PHARMACEUTICAL INDUSTRY

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Introduction

Computers have revolutionized the past century in terms of social interaction, knowledge, and especially science. Several scientific areas have evolved to the point that now they can solve previously unsolvable theoretical problems, mainly because of the increase in computational power, combined with necessary model simplifications. In other areas, the technological development has enabled scientific disciplines to work together in defining new approaches to gaining knowledge of the world. Models are implemented on computers, which execute the calculations and have thus become an important instrument. One field where models have gained ground and are used for simulations is the pharmaceutical industry.

In this paper, the focus will be on some of the different kinds of models that are used in simulations with different purposes. Some of them are more mechanistic and related to the physiology of the body incorporating empirical constants, while others serve a more instrumental purpose such as optimizing clinical trials with regard to a chosen dosing regimen. Both types of models are based on what are called 'pharmacokinetic'[1]/'pharmacodynamic'[2] (PK/PD) models, but with a different detailed relation to the human body.

[1] Pharmacokinetics is the study of what the body does to a drug in terms of degradation.

The physiological models are more detailed and incorporate mechanisms that are relevant for the developed drug. The more instrumental and simpler models are known as 'compartment' models and these mathematical models, combined with statistics, give rise to a novel scientific area known as 'pharmacometrics.' This is a combination of PK and PD models, which involves modern graphical methods, stochastic simulations, and computer programming. These models aid in understanding the impact of varying dosing strategies, and patient selection criteria, improve population dosing strategies, and are useful when customization of patients' dosing strategy is needed through therapeutic drug monitoring (Rowland, 2009).

Before going into the role of the models and their relation to experimentation, I will introduce the pharmaceutical industry and elucidate the regulations and historical background of the current drug development process.

The Pharmaceutical Industry

In the pharmaceutical industry, it is crucial to develop new drugs that are effective and safe. In order to get a drug on the market it has to be approved by the national agency in the country where approval is sought. One of the heavyweights in the world of agencies is the Food and Drug Administration (FDA) in the US. The US is a very large market for many companies and the FDA has issued many guidelines that clarify current expectations for areas in the development process.

Some of the key elements for drug approval from the agencies' perspective are: ensuring the safety and efficacy of a drug, assessment of whether the drug candidate is safe and effective for human testing, and eventually assessment of the quality of the drug when manufactured on a large scale. In recent years, there has been an increased focus on better prognostic tools to improve the efficiency and cost in developing safe and efficacious drugs. The FDA has identified model-based drug development, simulation of clinical trials and assessment of variability by pharmacometrics as some of those tools and issued guidelines or regulations to ensure a minimum level of research, reliability, and ethics.

There are different stages of drug development; I will try to sketch the process in the following, although depending on accessibility of data for a given drug in development there can be certain variations in the course of

[2] Pharmacodynamics is the study of what a drug does to the body in terms of physiological effects.

events; however, the description still gives an insight into the realm of drug development. On average, it takes a drug 7-12 years before it is ready for the market and the cost is between 0.802 and 1.7 billion dollars (Ette and Williams, 2007).

The first stage is the 'discovery', where different compounds are synthesized, targeted for a disease. Prior knowledge about the disease mechanism is useful (often necessary) for the development of a new drug. The different compounds are tested on animals to exclude the toxic candidates; this is also known as the 'preclinical phase.' *In vitro* testing is also of great importance as it can contribute to the understanding of drug mechanisms. After that, there are phase 1 clinical trials in healthy volunteers, phase 2 clinical trials with a larger number of participants, and finally phase 3 trials in patients. Phase 1 studies identify well-tolerated doses, and sometimes the maximum tolerated dose. The PK is studied for single doses and multiple doses (accumulation taken into account) to gain initial knowledge of the exposure-response relationship. Food and gender effects on the PK can sometimes be determined.

Phase 2 focuses on the 'proof of concept' that the drug is capable of being effective. These phases also aim to define the most likely safe and effective dosage regimen for phase 3 trials by determining the maximum tolerated dose if this has not already been done. Phase 2 also provides mechanistic information, and identifies and quantifies the magnitude and causes of variability in pharmacokinetics. In many cases, phase 3 trials evaluate several doses to define benefits and risks further, and, more specifically, dose-response relations are investigated. This is the pivotal phase for the registration of a drug.

Figure 9-1: Drug Development

As mentioned, a drug is approved by a national medicinal agency before it is launched on the market. Agencies examine the produced data thoroughly and, in the case of deficiencies, they can demand further investigations. After the approval, the drug is still monitored, as there can be adverse effects that take years to develop and caution is therefore needed. There is communication between agencies and the pharmaceutical companies during the whole development process in which feedback is given to the companies.

Not long ago, regulatory agencies were not part of this process and pharmaceutical companies had full autonomy to conduct research as they wished. The need for such agencies was evoked by several historical tragedies, which I will go through to give an idea of the risks associated with drug development.

Historical Perspective on Experimentation and Agency

The establishment of agencies as we know them today is rooted in accumulated historical mishaps that led to the more formal institutions and current rules in force. The origins of the FDA can be traced back to 1848; however, it was not known by its present name until 1930, and the modern regulatory function of the FDA began with the passing of the 1906 Pure Food and Drug Act. In 1937, 107 people died in the US of diethylene glycol poisoning due to the consumption of sulfanilamide elixir used as a chemical solvent without safety testing. This led to the Federal Food, Drug, and Cosmetic Act in 1938 (Lembit Rägo, 2008; FDA, 2010). The law authorized the FDA to demand evidence of the safety of new drugs, issue standards for food and to conduct factory inspections.

Some of the key features for clinical testing[3] include informed consent and a required research protocol, which have to be approved by an ethical committee before the study begins. The informed consent discussion gained momentum after the Second World War when prisoners in Nazi concentration camps were used for medical experimentation by German physicians (Shuster, 1997). The justification of the doctors conducting the trials was that they served the state by developing medication to save the lives of German fliers and soldiers. This led to the emergence of the Nuremberg Code in 1947 which, among other principles, introduced the principle of the informed consent of human research subjects before participation in a clinical trial through which a protection of human research subjects was ensured by focusing on their human rights instead of than focusing on the consequences or a greater good.

Another drug disaster that had a severe impact on regulations concerned Thalidomide, which was approved in the late 1950s in Europe as a sedative and against nausea during pregnancy. The FDA did not approve it in the US, and it was tested on animals and gave to patients without this approval and without obtaining informed consent. Thalidomide was approved as a racemic blend, meaning that it was

[3] This is, experimenting with dosing of a drug on human subjects in specifically designed trials.

approved as containing both left- (S) and right- (R) handed isomers[4] in equal amounts. The R enantiomer[5] was effective against nausea whereas the S enantiomer was a teratogenic agent, meaning that it disturbed the development of the embryo or fetus. It was estimated that more than 10,000 children have been born with Thalidomide-related deformities in the world. If the drug had been tested on pregnant animals it would never have been approved as the teratogenic effects would have emerged as they did subsequently; however, Shuster argued that scientists did know and tested whether the drug could cross the placenta, but this is not the opinion found in the majority of the available literature (Shuster, 1997).

The difficulty with Thalidomide is that it does not cause the same types of deformity across animal species, and in general, they are different from the effects seen in human subjects. The types of deformity, which would have been observed if testing had been done on pregnant mice, are not necessarily as severe as in humans due to differences in hepatic metabolism. Thalidomide is broken down into many different molecules in the body and some metabolites can be toxic as well, so metabolic differences can have severe implications for toxicity. It was found that the drug had a much shorter half-life in mice than in humans. However, there is no doubt that given the complications, fetus research across species would have prevented the catastrophe as the development would have been stopped due to some observed deformities, albeit not as severe as in humans, as it would have raised some red flags.

This disaster had a great impact in the pharmaceutical world and together with many other events led to the formation of the Helsinki Declaration in 1964. This was established by the World Medical Association (WMA) and emphasized the respect for and autonomy of human research subjects and the obligation of physicians to the patients. Though it is not a legally binding document, most regulatory agencies or national laws consider it when regulating research practices. The document is still revised from time to time in order to meet developing trends within medical research.

As mentioned earlier, all sorts of guidelines and regulations exist today to ensure the safety and efficacy of new drugs, ranging from the preclinical and clinical development to manufacturing. The historical perspective brings to light the importance of experimentation and observations in drug development, and it is inescapable as the human body

[4] Compounds with the same molecular but different structural formulas.
[5] The two mirror images of a chiral molecule.

is complex and the risk of adverse events is high due to the complexity and relatively scarce knowledge of physiological mechanisms.

Even today, drug disasters take place, but mostly this is because the knowledge gathered from experimentation is ignored or downplayed. A relatively recent major drug disaster is the case of the anti-inflammatory and pain-relieving drug Vioxx developed by Merck (Houlton, 2007). The company pulled it from the market in 2004 as they discovered an increased risk of adverse cardiovascular events such as strokes and heart attacks. The FDA approved it in 1999, and Merck initiated post-approval clinical testing. This study showed that the risk of adverse effects was greater for Vioxx than from the older drug Naproxen. Some of the study results were omitted and Merck was accused of hiding the side effects, though the company claimed it was because they were seen after the trial cut-off date. The FDA was also accused of not acting on behalf of public health but on behalf of corporate interests (Pai, 2005).

Such drug disasters are wake-up calls for regulators to be more vigilant when it comes to drug safety. Knowledge of how the drug works in the human body is crucial to make sure it is approved and stays on the market. However, knowledge in itself is not enough; it is important, but it is even more important to be aware of what we do with the knowledge gained. In the Vioxx example the knowledge was there as study results had indicated the higher risk of cardiovascular events, but Merck chose not to act upon the knowledge gained.

There is a great deal of unpredictability, and to minimize that it is, and always will be, necessary to test new molecular entities on human subjects. Drugs are not like ordinary consumer products such as shampoo, iPhones etc., as consumers in the case of drugs are in a risk zone if they take matters into their own hands and decide when and how to take the drugs, and they do not have the knowledge to weigh the benefits against the risks of different possible uses. With ordinary consumer products, desires and needs were dominant, and the personal freedom is larger than with drugs since, in the latter case, the implications of wrong use can be severe.

Normative elements are associated with drugs as professional advice from experts with specific knowledge of the drug is a necessity to use the drug correctly and without causing harm to oneself (from a patient perspective). As some put it in studies of technology, there is a use form attached to the drug, a prescription telling the patient how to use the drug, but more importantly the side effects that might occur. Such knowledge is largely gathered from experimentation, which in the past was the only

approach to acquire the knowledge; combined with a more reckless attitude towards patients it resulted in many drug disasters.

However, the obligation to act upon the knowledge is still crucial and this depends on the experts who are the pharmaceutical companies in this case. For now, the focus will be on the approach to knowledge gathering, where simulations play an increasingly important role. Before the age of simulations in the pharmaceutical industry, the approach to dose selection only took a point of departure in experiments where the highest tolerable dose was determined. A typical study could consist of a parallel-dose clinical trial where two groups are given two different doses, the outcomes are compared, and the dose with the most favorable outcomes is chosen for further investigation (Bonate, 2007). The patient groups in such studies are often homogenous in terms of demographics, age, disease progression etc. and only a few outcomes are recorded and observed, often at the beginning or end of a trial. The analysis of the observations is traditional hypothesis testing with a null hypothesis claiming no difference between the two dosing regimens. In this way, the dosing regimen determined is the one resulting in the best outcomes, which are minimum toxicity and maximum effect.

However, as the starting point is the highest tolerable dose, the dose selection is often too high. Sheiner et al. (2001) point to a survey conducted on 354 evaluable drug labels out of 499 drugs approved in the US in the period 1980-1999, and the fact that 25% of the formal labeling for doses was changed (80% was a reduction) for new chemical entities suggests that it surely is the case that excessive doses are settled upon. The need for a better approach to dose selection was evoked by leading scientists such as Lewis B. Sheiner and they had a great impact on introducing PK/PD modeling and statistics as a more effective and safe means of dose selection in the industry. In the following, it will be elaborated how specific types of models are used for simulations to gather crucial information in deciding on the normative aspects of drug use.

The models and their role - the current state

The types of model that are the focus of this article are known as ‘compartment’ models and they are combined with statistical methods to account for the variability in responses to drugs and the kinetic properties of the drug that is seen in patients. The differences can be due to specific genetic dispositions or varying capacities of the liver or other organs to metabolize the drug; weight and age are also of great importance. However, the compartment modeling approach is used to model drug

passage in the human body by representing it by one or several (mostly two or three) compartments (see Appendix A for more details). These models enable modelers to predict the drug passage (kinetic properties) for different dosing regimens and they are known as pharmacokinetic (PK) compartment models. Another type of model is the pharmacodynamic (PD) model. PD is concerned with what the drug does to the body, the responses it elicits: for instance, a drug could have an agonistic[6] or antagonistic[7] effect on cell receptors, triggering or inhibiting a certain response. Data from trials consist of both, measurement of drug concentration in the blood plasma to determine the kinetic properties of the drug and of measurement of other factors to determine the body's response to the drug. There is a great variation in individual pharmacokinetics due to age, genetics, gender, weight (prognostic factors) etc. Pharmacodynamics is determined by kinetics, as response depends on the drug exposure, which results in a similar variation in PD; all in all, variation gives rise to noisy data. When the two model types are combined, a relationship between dose and response is established, which Sheiner argued was a key method of turning noisy data into a signal. For instance, if the combined model is based on data from a study where patients have been given 200mg of a drug every 6 hours and responses are observed, the final model could be used to simulate what the drug-response profile would look like if 400mg were to be given every 12 hours.

The models are used in two different ways during the drug development in the different phases, either in a learning, or a confirming mode. The statistical approaches to analysis of clinical data, the goals and the study design, combined with the structural PK/PD model, differ between the learning and confirming mode as will be described in the following. The goal of learning is to estimate the benefits, regimen, and prognostic factors resulting in variation. The more the knowledge of a drug that is gained, the more capable the company is of controlling sources of variation; and the latter is important – as it results in stability, reliability, and less unpredictability, it is often associated with less risk. The analysis mode of data from clinical trials is probabilistic, often Bayesian, where prior knowledge (for instance, knowing a two-compartment model is suitable, or a certain mathematical relation between clearance and age) is incorporated when updating beliefs with current data from trials. Many different regimens are chosen, and the study design is not necessarily

[6] Activates or stimulates a response.
[7] Inhibits a response.

symmetrical. An asymmetrical design means that the number of patients assigned to different dosing regimens need not be the same, and the reason for this is that learning is achieved best when diversity is explored. The types of patient included in the learning design are heterogeneous in terms of age, sex, demographics etc. because this allows the variation in dose response to be discovered. To get a grasp of drug exposure, plasma concentration as a function of time is of interest. Therefore, compliance (individual PK and drug-taking behavior) is taken into account, as the goal is to correctly attribute response differences to variation in actual regimens.

Contrary to learning, the goal of the confirming phase is to falsify that treatment efficacy is absent or more generally that there is no difference between two dosing regimens.[8] Because the goal is more specific, the statistical analysis is traditional hypothesis testing and the selected patient group is homogenous and specified with regard to prognostic factors. The study designs are more symmetrical in the sense that a typical confirmation design could be a randomization of patients into two equally large treatment groups, which could be the test and the control group (often placebo). The test group (not placebo) is often assigned as high a dose as possible, a dose that is unlikely to induce toxicity, which makes sense as the goal is to show that there is a drug-related benefit which is more likely the higher the doses that are given (falsification of null hypothesis). In the confirmation study, the assigned treatment is taken into account and not the actual adherence to the assigned treatment. It is assumed that all patients have taken the assigned doses. The observational strategy (outcomes) is often restricted to one or two clinical measures.[9] However, a confirmation design study can easily be used for learning analysis if a few additional extra measurements are taken into account in the observation strategy. When developing a drug, there are alternate cycles of learning and confirming in the development process (see figure 9-1). After a learning trial, a confirmation trial is initiated, possibly with learning elements to confirm what has been learned and to learn new things. This is also why this paradigm is called the 'learn-confirm-learn' paradigm, because learning is still possible for confirmatory studies and examples of this are given in literature (Sheiner, 1997).

As outlined above, the models can differ in complexity and be used in different ways. There are empirical models that are data-driven and simply

[8] Each of these could be taken to be the null hypothesis in statistical hypothesis testing.

[9] If the confirmatory trial is conducted with respect to toxicity, a large number of toxicity outcomes are observed and the analysis itself will be a learning analysis where toxicity is understood better.

describe the data at hand, which is the case with compartment models. Then there are mechanistic models that incorporate mechanisms known to be relevant for the system – these could be blood flow, saturable protein binding etc. The kind of model chosen depends on the questions that the company seeks answers for; for instance, sometimes the purpose is to characterize data in terms of a few kinetic parameters (volume of distribution, clearance etc.[10]) for individuals from the drug concentration-time profile. If the goal is to understand the factors affecting drug efficiency (genetics, renal or hepatic impairment, concurrent diseases etc.), models that are more mechanistic are useful. To account for the variability, which can be due to individual PK differences, random statistical methods are combined with the models. In the next section, different ways of using these models for simulations will be covered.

Simulations

The models are used for simulations. Most of the cost in drug development is related to clinical trials, and so successful trials are a key to keeping the costs down. If the models are used alone without statistical methods, they are what it is called 'deterministic of nature.' It could be that a model is developed based on a single-dose trial and used to simulate the concentration-time profile for a repeated multiple dosing scheme to assess the steady-state[11] concentration in the body. However, these kinds of simulations do not play a large role in the effectiveness of drug development; rather it is the type that simulates the costly clinical trials what has great value. These simulations protect the company from failed clinical trials where no learning or confirming is gained, which is why they have great value. The simulations could be stochastic, where error is introduced into the structural model as a randomly draw from the statistical probability distribution or statistical model. Such simulations are also used in other scientific areas and go under the name 'Monte Carlo simulations.' They can be used to estimate the percentage of patients experiencing an adverse effect by defining an adverse effect cut-off in a fixed dosing regimen, and depending on such results, the dose can be adjusted. One cannot be certain of the estimates, as there is some measure of imprecision in their values. A possibility for accounting for such imprecision is to use Bayesian simulation where an additional level of

[10] For further information, see Appendix A.
[11] The rates of drug administration and drug elimination are equal.

uncertainty is introduced; however for now the statistical details will be left out (further reading (Bonate, 2007)).

Simulations consist of an input-output (could be a PK model linked to a PD model) model and a covariate model coupled to a trial-execution model. A covariate model relates kinetic parameters to covariates such as age, weight etc. A trial-execution model is part of the input-output model in the sense that it defines how the clinical trial is conducted (dosing regimen). The trial can now be simulated either once or several times iteratively. It is recommended that the simulation has a few replicate runs to confirm that it is working before letting it run many times, as stochastic simulations can be quite time-consuming and this ensures that problems are detected early. One of the challenges with stochastic simulations is to know how many iterations run or how long to run the whole simulation, and this depends very much on the goal of the simulation. If an estimation of average outcomes is sought, relatively few iterations (in the order of fifty or so) could be sufficient, but if the goal is to observe rare events, a large number of iterations are necessary to detect them.[12] These simulations provide guidance for future clinical trials, allowing the modeler to 'test' a clinical study design before conducting it. This simulation is of the type called 'computer-assisted trial designs' (CATDs). It could be that two different dosing regimens for an approved drug show the same efficacy, which can be confirmed by one trial resulting in a label change. Another type of simulation is 'computer-simulated clinical trials' (CSCTs), used to determine the clinical trial outcomes without ever having to conduct the study and serve as a justification for not doing such a trial. An example could be that it is simulated that no change in exposure occurs due to 50% decreased metabolic capacity and thus a study in patients with such a deficiency is argued to be unnecessary from a company perspective.

In the philosophy of science, a discussion on the nature of computer simulations has raged in recent years. There are many opinions between two extreme poles claiming that they are a completely new method in science or that simulations contain no philosophical novelties (Humphreys, 2009; Frigg and Reiss, 2008; Lenhard, 2007). Humphreys claims that computational science is a *sui generis* activity that gives rise to new philosophical issues and requires a non-anthropocentric epistemology and a new account of how theories and models are applied. Moreover, he says (Humphreys, 2009):

[12] These are ad hoc rules based on statistical theorems and inequalities (Bonate, 2007).

> […] computer simulations often use elements of theories in constructing the underlying computational models and they can be used in ways that are analogous to experiments.

The simulation types outlined above are related to experimentation in different ways. CATD simulations exist in interplay with traditional experimentation. Part of the underlying model is constructed based on data from clinical trials together with elements from pharmacokinetics or pharmacodynamics (could be both), and the model is then applied to a scenario where initial conditions are changed to simulate a possible future trial. The changing of initial conditions to simulate future trials is a kind of theoretical experiment, where outcomes are predicted and form the basis for deciding upon design choices in clinical trials. Theoretical experiments differ from classical experiments, as the element of measuring or physically observing is not present. In these experiments, the observations are on a computer, where the parameters typically measured or physically observed are estimated based on a theoretical model.

These two kinds of simulations, CATD and CSCT, are related to traditional experimentation in completely different ways. In CATD simulations the theoretical observations are followed up by traditional experiments, so-called 'confirmation trials', which confirm the simulated results, or perhaps the trials reveal a need for adjusting the model in case a good match between theoretical and observed results is not obtained. Such semi-theoretical simulations I call 'cooperative simulations' as these gain credibility through the relationship to traditional experimentation. They are thus intertwined with empirical work. They are evaluated, and gain validity by fulfilling certain criteria ensuring goodness of fit to data. Such things are sometimes specified in guidelines: for instance, the FDA has issued guidelines on population modeling where such criteria are specified (FDA Guidance for Industry Population Pharmacokinetics). The purpose of simulations is very often to make better, more informed decisions on traditional experimentation designs and they serve as a pre-evaluation, which is later, confirmed by experiments. It could be that a new dosage is simulated in human subjects, and because it shows promising results, it is decided to run a clinical trial with that particular dose. Results from that trial can then confirm the simulation.

CSCT simulations are more theoretical as they are not followed up by traditional experimentation because the purpose of these theoretical experiments is to avoid the traditional approach. These simulations detached from traditional experimentation are called 'non-cooperative simulations.' Here credibility is not needed in the same way as the simulated results in these cases are outside the region of desired results

and thus give reason to avoid the investment in experimentation as a confirmation of undesirable results is a waste of money. These simulations thus create distances to experimentation in the sense that they are grounds for not performing experiments. They do not serve the purpose of being an evaluation prior to experiments; rather these simulations are substitutions for the scenario that is simulated as no confirmation is sought. Without a doubt one could say that both types of simulation have contributed to new aspects in the pharmaceutical industry, so to say that there is no philosophical novelty related to them would be to undermine the effects and purpose of them. They have brought novelties to the industry when it comes to optimizing experimentation and, in general, to understanding drug effects, and thus simulations are truly *sui generis* in a Humphreyan sense, requiring a new epistemology also from an agency perspective.

Future Simulations

With the increasing computational power, the possibilities for complex underlying models are enabling simulations of even more complex phenomena. One of the more complex approaches within the field of PK and PD is the physiologically based pharmacokinetic approach (PBPK), where the body is represented mathematically in a way that is closer to reality. The number of compartments here is larger as all the organs important for the drug mechanism, and different biochemical and physiological processes are included. These models can enable simulations across species or extrapolation to other conditions, for instance change of dose. Recently, an entire book has been launched which is dedicated to PBPK modeling (Peters, 2012) and this shows an increasing interest in this more complicated approach, which accompanies the technological advances.

It is a difficult process to develop such models as they often require PK data and parameters that are beyond the realm of available procedures, for instance extensive tissue sampling, which can be problematic for patients enrolled in trials. *In vitro*[13] testing is important when trying to determine specific parameters as binding coefficients. In a way, this simulation method requires more experimentation, and so the bond between simulations and experiments grows stronger as this tendency gains inertia. When dealing with drugs, I believe that simulations will never become completely independent from experimentation; also due to the many

[13] In vitro testing is outside a living organism. Cells are isolated and testing is done in the laboratory.

uncertainties related to human physiology. The historical mishaps have also scared the industry and affected the trust in drug development. Traditional experimentation will be difficult to evade and the need for clinical and laboratory testing will very likely remain in the future despite the propagated use of simulations.

The increasing complexity of simulations does not come without troubling implications. Computers that are more powerful can be problematic in the sense that there are always hardware faults, and the number of hardware failures is proportional to the number of components, which increases with computational power. The development within computers shows that there has been an exponential increase in the number of components in computers in recent decades. This is briefly touched upon to elucidate the possible challenges of future simulations, and this very big subject deserves a complete paper of its own, but for now this will do.

Hardware can give rise to different kinds of errors, which can either result in crashes or be silent and pass undetected. The latter are potentially more harmful as the effects of such errors are unknown, whereas a crash is detected and corrected. The impact of such errors on simulation results remains unexplored, and thus caution is needed when evaluating results from simulations where powerful computers are used, especially when the outcomes have a high societal impact as with drug development. However, this is something that the industry as a whole must face, whether it be companies, agencies, or the particular modeler working with this. A systematic approach to error detection and an awareness of possible effects on results is needed. As these results are closely linked to experimentation design it is important not to undermine the optimizing aspects of simulations by a naive belief in results when they fulfill defined criteria. How the pharmaceutical realm will face the challenges of increasing computational power and validity of results remains to be seen.

Appendix A

A typical model could be a two-compartment model with intravenous administration where the body is represented by two compartments, one central, and one peripheral. In the following this model will be elaborated (Rowland, 2009; Peters, 2012).

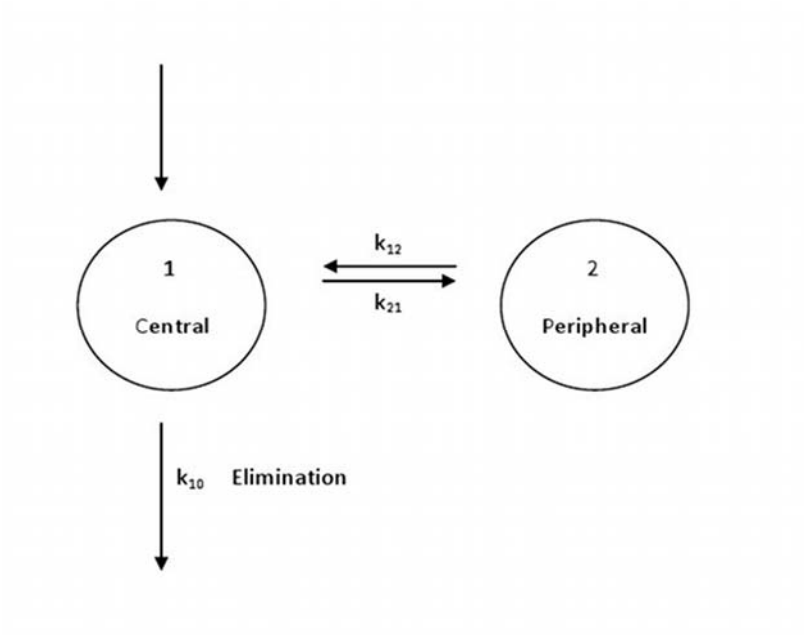

Figure 9-2: 2-compartment representation; k_{12} and k_{21} can be determined in the 2-compartment model.

Mathematically differential equations describing the change in the amount of drug in each compartment are solved to get the 2-compartment model.

$$C(t) = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \quad (1)$$

The exponents[14] are expressed in terms of the rate constants in the following way:

$$\lambda_1 = \frac{1}{2}[(k_{12} + k_{21} + k_{10}) + \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4k_{21}k_{10}}] \quad (2)$$

$$\lambda_2 = \frac{1}{2}[(k_{12} + k_{21} + k_{10}) - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4k_{21}k_{10}}] \quad (3)$$

In this model there is an initial volume of distribution which is obtained by setting $t = 0$ and isolating V_1 (Rowland, 2009).

$$C(0) = \frac{Dose}{V_1} = C_1 + C_2 \quad (4)$$

The initial volume of distribution does not sufficiently describe the distribution as the plasma concentration declines more rapidly in the initial phase in the body, and as the drug distributes into the slowly equilibrating tissues, equilibrium is established slowing down the elimination. The effective volume of distribution increases with time, and when the equilibrium is reached, which is the case in the terminal phase (the decline in tissue is parallel with that in plasma), a volume of distribution can be calculated. This is why the volume of distribution in the two-compartment case is defined from the terminal phase.

Amount of drug in the body, terminal phase =

$$V \cdot C = V \cdot C_2 \cdot e^{-\lambda_2 \cdot t} \quad (5)$$

Extrapolating to time zero and matching the amount $V \cdot C_2$ by an equal amount eliminated given as the product of clearance and area (C_2 / λ_2) it follows that

[14] The unit is time^{-1} (hours or min)

$$V = \frac{C\,L}{\lambda_2} \tag{6}$$

for the two-compartment intravenous case. A quick reflection on the units confirms the accuracy of the relation as:

$$\text{Liter} = \frac{\dfrac{\text{Liter}}{\text{hr}}}{\dfrac{1}{\text{hr}}} = \frac{\text{Liter}}{\text{hr}} \cdot \text{hr} \tag{7}$$

The Cl is:

$$C\,L = \frac{Dose}{\left(\dfrac{C_1}{\lambda_1} + \dfrac{C_2}{\lambda_2}\right)} \tag{8}$$

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PART III:

HISTORY

CHAPTER TEN

DESIGNING THE MEMBRANE ROOF OF THE MUNICH OLYMPIC STADIUM USING SUPERCOMPUTERS

WOLFGANG BRAND
UNIVERSITY OF STUTTGART

Prologue

After the 1936 Summer and Winter Olympic Games in Berlin and Garmisch-Parten kirchen, respectively, Germany was selected to host the Olympic Games for a second time in the 20th century. In 1966, Munich was named host of the XXth Summer Olympic Games in 1972. Not only most of the public, but also the architects, were eagerly expecting this epochal event. It provided the opportunity to open a showcase of German culture and architecture to the world. While the 1936 Olympic Games were overshadowed by the repressions of the Nazi regime, the 1972 Olympic Games were meant to represent the new liberal, democratic, and open-minded postwar West German spirit. The official motto, *The Happy Games*, reflected this new attitude and was to be complemented by a novel and natural architecture. However, on the openness and happiness of the 1972 Olympic Games fell the dark shadow of the assault on the Israeli team, claiming many lives. Nevertheless, the constructions of the Munich Olympic Park proved to be landmark architecture of their time in the same way as, for example, the *Atomium* in Brussels, which was erected for the *Expo '58* world exhibition in 1958 (Diem, 1937; Fort, 1936; N.N., 1972*a*; Schiller and Young, 2010).

The Olympic Stadium, the multipurpose Olympic Hall, the Olympic Swimming Hall, and the home of the athletes – the Olympic Village – are all situated in a wide and open park surrounded by a lot of water and greenery. The objective of the design by the head architect Günther Behnisch was to present Munich and Germany as open and easy-going. The Spiritus Rector of this novel architecture of natural constructions was Frei Otto, one of the most influential architects of the 20th century. The

roofs of the Olympic Stadium, resembling the Alps, visible from Munich on clear days, and the Olympic Swimming Hall were designed to provide the impression of a natural lightness. In particular, the tent-shaped membrane roof of the Olympic Stadium, made of acrylic glass overlays on a metal cable net and hanging solely from a few pillars, still impresses visitors to Munich with its airiness (Jaeger, 2005; Luce, 2009; N.N., 1972*b*).

Impressive and lasting architecture means teamwork. Many different disciplines contribute to a lasting building. One of these disciplines is civil engineering. Without the ability to compute the statics of constructions, no design idea can be put into reality. One of the experts, well known for many innovative constructions, was Jörg Schlaich who was the main civil engineer for the Olympic Site in Munich and professor of civil engineering at the University of Stuttgart. Among other things, he and his group were in charge of doing all the calculations to determine the shape and layout of the roof of the Olympic Stadium. However, it turned out that this task required additional expertise and resources not available to them at that time. Never before had such large-scale light-weight structures been designed and therefore no methods to do the calculations were readily available. To minimize the risk of failure and to guarantee timely delivery of the required results, this task was assigned to two groups led by John H. Argyris and Klaus Linkwitz, respectively. Both were also professors at the University of Stuttgart. By training, John H. Argyris was a civil engineer and, since 1959, director of the Institute of Statics and Dynamics of Aerospace Structures (ISD), and Klaus Linkwitz who represented geodesy, was the head of the Institute for the Applications of Geodesy in Civil Engineering (IAGB). The collaboration between the parties involved was facilitated by the fact that the architects, Frei Otto and Günther Behnisch, were also professors at the University of Stuttgart. They and their working groups formed a network, which enabled the easy interchange of information and data to comply with the tight temporal constraints.

The following sections of this article tell the story of how the first supercomputer available, the Control Data CDC 6600, made the design of the tent-shaped roof of the Munich Olympic Stadium feasible. The focus will be on the group of Klaus Linkwitz, where least-square error and curve fitting methods were applied to determine the shape of the pre-stressed cable nets that are at the core of the roof's construction. Starting from this 'ansatz', the Force Density Method was developed, which offered an even more elegant way to do the required calculations. It is shown what obstacles had to be overcome and in which environment these events unfolded. That period in architecture marks the transition period from

building physical models to determine properties of constructions to more computational, computer-based approaches. This contribution argues that the period of the 1960s marks the point of transformation where the usage of high-performance computers altered the architectural design processes. Computing technology had reached a level where model building was no longer necessary.

Architecture in the 1960s

Architecture is the art of transforming fleeting mental images and ideas of form and shape into real things. It is also a visual art and science, where sketches and drawings are iteratively refined until a final visual representation is obtained. This process is often augmented by the construction of physical models. These are not only means to provide a three-dimensional impression of the buildings to be erected, but serve also as tools to support the design process and to study the complex behavior of various construction materials under realistic conditions. Depending on their purpose, models are made of paper, wood, metal, or even textiles. They are also used to determine the static of constructions and to collect data under changing conditions, such as wind or snow load, earthquakes, or vibrations. Another area where building models is employed is "form finding." The impact of gravity on the shape of flexible and lightweight structures is highly non-linear and complex. Before computers became available, the only means available to architects and civil engineers to design such constructions were rough calculations using slide rules, tables, diagrams, and electromechanical calculators. Many models of different sizes had to be built to study different effects, which resulted in a lengthy and expensive process with many iterations and dead ends. Under these circumstances, the design of complex shapes like canopy roofs or cable nets where the construction materials are continually under stress was nearly impossible (Gründig, 2011; Gründig et al., 2000; Luce, 2009).

In the decade after the Second World War, computers slowly started to penetrate new application areas such as architecture. In the early 1960s, the first Computer Aided Architectural Design (CAAD) systems became available. The first systems did no more good than to draw simple objects and construction plans, and many architects and designers felt more comfortable with their traditional drawing boards. A lot of civil engineers and architects also had the impression that numerical calculations and simulations on digital computers, where there was a loss of information due to their discrete nature, could not properly represent the many-layered and complex behavior of constructions under real conditions. Back in

those days, physical models still seemed to be an integral part of all stages of the architectural design process. When the first high-performance computers became available, new computational methods and their implementation in sophisticated software packages shifted physical model building to the early stages of the design process. Physical models were being substituted by software models and simulations. The trust in computer-based calculations and simulations began to grow, and physical models were reduced to material representations of architectural design ideas, such as drawings and sketches (Gründig, 2011; Streich and Weisgerber, 1996).

Computer Technology after the Second World War

Even in ancient times, humans tried to simplify the tedious work of counting and calculating. The abacus is one of the first witnesses of the attempt to mechanize numerical calculations. Employing machines not only increases the speed of calculations, but also reduces dramatically the chance of miscalculations. This proved not only attractive to merchants, but also to scientists. In the 16th and 17th centuries, Pascal, Napier, Leibniz, and Schickardt made the first attempts to mechanize logic and calculation. They did not stop at theoretical musings and started to build, more or less successfully, the first mechanical calculation machines. These devices were often quite expensive, of limited use, and lacked the most important property of today's computers; that is, programmability. Using tables containing pre-calculated results such as logarithms or trigonometric function values to reduce the burden of calculation remained the only feasible alternative for most scientists for the next few centuries (Friedewald, 2009; Wurster, 2002).

When the scientific progress during the 19th century revealed the nature of electromagnetism, and the formulas of James Clerk Maxwell allowed for a quantitative description of effects; the emerging discipline of electrical engineering offered new ways to implement calculation devices. The failure of Charles Babbage to build a programmable mechanical computer clearly demonstrated the need for a new technology. The road to computers, as we know them today, started with electromechanical designs. By the early 20th century, technology had advanced to electronic components such as vacuum tubes. The invention of the transistor in 1947 and the integrated circuit (IC) in 1958 increased the capabilities of the first computers dramatically. At the same time, theoretical insights gained by Turing, Church, von Neumann, and others during the 1930s and 40s created the architecture of computer systems as we know them today.

Computers were no longer solely used for the purpose of doing numerical calculations. They developed into universal machines ranging from tiny embedded devices to large-scale solitary number crunchers performing numerical computations at a speed never heard of before. The *computers* of the 1920s and 30s, mostly female operators of electromechanical calculators, transformed into the freely programmable tools most people take for granted today (Aspray, 1990; Friedewald, 2009; Hodges, 1994; Wurster, 2002; Zuse, 1993).

Newly emerging technologies usually produce a quickly increasing number of commercial entities, which are keen to take advantage of new market opportunities. After the end of the Second World War, and with the advent of the Cold War, a large number of computer manufacturers were founded. Although most of them were located in the United States, some European firms also tried to build computers. Examples are Ferranti in the UK and Zuse in Germany. By far the most successful was IBM, the International Business Machines Corp. of Armonk, New York, focusing on the market of commercial computers with applications such as inventory management, record keeping, and databases. During the 1950s, IBM managed to dominate the market of mainframe computers on a global basis. However, such a success story also attracted potential competitors. During the final years of the 1950s, Control Data Corporation (CDC) of Minneapolis, USA, entered the market. While IBM's computer designs were based on an extensive and universal instruction set to cover all possible application areas, the chief designer of Control Data, Seymour Roger Cray, later to be known as the *Father of Supercomputers*, decided to focus on systems for numerical and scientific applications. The numerical capabilities of his CDC 6XXX line of machines were far superior to IBM's, and so Control Data swiftly gained a dominating market share in scientific computing. Later attempts by Control Data to challenge IBM in the market segment of commercial computers resulted in a legal battle with IBM over anti-trust regulations and proved to be a landmark legal case. Finally, these developments led to the decline of Control Data into obsolescence (Lutz, 1966; Murray, 1997; Zuse, 1993).

Today, when people talk about computers, they are talking about digital computers based on the canonical Byte and Word design introduced by IBM in the System 360. In the early days of computing, there was not only competition between different manufacturers but also between digital and analog computers. Already the first computing aids could be grouped into either digital (for example, Napier's bones) or analog (slide rules) devices. The technological advances in the form of vacuum tubes, transistors, and integrated circuits enabled both digital and analog

computers. Using the newly invented operational amplifier, able to multiply, subtract, and add signals, electrical engineers could build analog computers to solve complex and coupled differential equations in a quite efficient manner. These machines were used for special calculations right into the early 1980s. The main disadvantage of such devices was the way that they were programmed. Each new program was implemented by rewiring parts of the machine and this took quite some time. Eventually, the increasing speed and memory capacity of digital computers and their versatile programmability with high-level programming languages brought this era to an end (Ammon, 1966; Zuse, 1993).

The Emergence of High-Performance Computers

Most scientific problems can be expressed in the form of equations or systems thereof. However, only the simplest problems have analytical solutions (i.e. the solution can be expressed as a formula). In nearly all realistic scenarios, numerical calculations are the only way to obtain a solution. Therefore, powerful numerical computers proved to be essential for progress in science and engineering. Each new and enhanced generation of computers stimulated the demand of the users for even more advanced computing machines. Over the years, a new breed of computers appeared: the *supercomputer* (Aspray, 1990; Hodges, 1994; Murray, 1997; Zuse, 1993).

Control Data Corporation (CDC) of Minneapolis, USA, started to develop computers for military purposes in the 1950s. One of their most talented designers was Seymour Roger Cray, who, by 1957, would start to create a completely new family of high-performance computers, dubbed the CDC 6XXX series. In particular, the model CDC 6600, regarded by many as the world's first true supercomputer, and later on the numerous Cray machines, made him the undisputed *Father of Supercomputers*. Supercomputers, or high-performance computers, are designed to dedicate substantial amounts of computing power to one specific task on a continuous basis. This ability opens the gate to new classes of problems which cannot be handled by just combining the computing power of a group of less powerful machines. The main design decision made by Cray was to reduce the instruction set and tailor the remaining instructions to numerical computing. He also used the latest developments in hardware, such as silicon transistors and integrated circuits, to increase the speed of his machines. New elements of computer architecture such as vector or parallel data handling resulted in a substantial increase in performance. When Control Data presented, in 1964, their new flagship model CDC

6600, they offered a 50-fold increase in calculation speed over all other machines available in the market (Murray, 1997).

In the second half of the 1960s, Control Data was able to sell over one hundred copies of the CDC 6600, a history of success that triggered the corporate management of Control Data to attack new commercial market segments and eventually led to the demise of the whole company. The decline of Control Data was accelerated by the fact that the chief engineer, Seymour Roger Cray, had left the firm over a dispute on the next generation of computer systems and had set up his own company, Cray Research, Inc., to build even more powerful number-crunching computers. As a technical artifact, the CDC 6600 proved to be one of the most innovative designs. It was equipped with two core memories having a capacity of 128,000 and 500,000 words, respectively. Each word was sixty bits wide and ten integrated peripheral units would address a dozen communication channels independently. The system had a modular and extendible layout. The customers could choose between plotters, printers, high-speed card readers and punchers, magnetic tape stations, and one of the first hard disk storage devices. The system was designed to provide interactive user sessions, which displayed their output on cathode ray tube monitors. Access for remote users was provided via telephone and dedicated data lines. Approximately one million floating-point operations per second (MFLOPS) catapulted the CDC 6600 to the top of the performance list in the 1960s (Almond, 1970; Murray, 1997).

The term *supercomputer* is a relative measure that fades away very quickly over time when new, more powerful, systems enter the arena of competition. Pushing memory size, the speed of data buses and processing speed to the limits of technology provide not only a quantitative increase, but also qualitative enhancements. Graphical or even animated output in real time is more attractive to humans than long columns of figures. Higher computing power also means more user-friendliness and an increase in epistemic power.

Soon, not only scientists and engineers would be users of such devices, but also new user groups took advantage of these machines to widen the limits of their disciplines. Sketches, drawings, and graphics being essential tools of their trade, architects became attracted quite early to the possibilities that high-performance computers had to offer. For architects, powerful computers offered a new way of model building and manipulation. Virtual models, existing only as bits and bytes in a computer memory, were more flexible, less expensive, and considerably reduced the time needed for finishing a design. Over time, the growing confidence in the capabilities of computers and simulation software reduced the number of

physical models being built considerably. Today, it is a rare event to see any physical models being built (Murray, 1997; Streich and Weisgerber, 1996).

Designing the Home of the Olympic Games

On 13th October 1967, the chairman of the jury, Egon Eiermann, declared the architects Behnisch & Partner to be the winners of the first prize of the competition to design the Olympic buildings of the 1972 Olympic Games in Munich. Günther Behnisch had prevailed over one hundred one other submissions, and yet, at that point in time, the jury had not reached a final verdict on the design of the membrane roofs for the three main sports facilities. Encouraged by Frei Otto, the mastermind behind *natural constructions*, Behnisch had decided to equip the buildings with lightweight membrane roofs. Eventually, when the contracts to the architects –still without the roofs– were awarded on 1st March 1968, "(…) no one from the jury actually believed that the proposed design of the lightweight structure, covering an area of 75,000 m^2, could be realized" (Phocas, 2005, 99), and the decision on the roofs was further delayed until 21st June 1968. Nearly one year of intensive discussions had not been able to silence the critics, and as late as 18th August 1968, the board of directors of the Olympia Baugesellschaft (the company set up to erect the Olympic Site) discussed what kind of roof should be built. However, at that point, it was too late to change directions, and it was decided to give the ambitious plans of Behnisch a try. These delays required the construction process to be started in parallel with the design works and later on led to many problems for all parties involved (Gründig, 2011; Linkwitz, 1971, 1).

Advised by Günther Behnisch, the Olympia Baugesellschaft commissioned the task to design the roofs to two groups headed by John H. Argyris and Klaus Linkwitz, respectively. Both were experienced in managing large projects under time pressure and had the necessary expertise to do the structural engineering calculations. The actual computations would be done on a Control Data CDC 6600, the most powerful computer available around 1970. Two years earlier, John H. Argyris had bought a CDC 6600 machine for his Regionales Rechenzentrum (Regional Computing Centre) at the University of Stuttgart. Splitting the design contract between two different groups helped to reduce the risk of failure and provided the potential to regain some of the time lost during the lengthy discussions following the architectural design competition. Both teams had to use the same infrastructure to do their computations and were based at the

University of Stuttgart, where the group leaders were professors. John H. Argyris, the co-inventor of the Finite Element Method (FEM), modified his method to cope with the non-linear aspects of the membrane roofs, whereas Klaus Linkwitz and his team relied on proven algorithms for surface and curve fitting from geodesy. Lothar Gründig, who had a diploma in geodesy, adapted these methods for the form-finding process in structural analysis and wrote most of the programs to perform the calculations. Hans-Jörg Schek, a mathematician and member of the Linkwitz group, would develop the Force Density Method (FDM) to design lightweight structures, while working on the Olympia project (Gründig, 2011; Phocas, 2005).

Figure 10-1: Building of Frei Otto's institute at the University of Stuttgart in Stuttgart-Vaihingen. This construction served as a test case for the German pavilion for the Expo 67 in Montral (photography taken by the author in August 2012).

The tent-shaped roof of the Olympic Stadium consisted of a covered pre-stressed cable net with a total length of 210 kilometers hanging from masts rising up to 80 meters. The first ideas of the architects centered around using a shell made of timber or covering a cable net with timber and perlite concrete. Neither material was flexible enough to withstand movements and vibrations caused by the wind, hence a cover of acrylic

glass was selected. The acrylic tiles measured 2.9 meters in each direction and were separated by continuous neoprene joints to allow for a buffered connection to the cables (Fang, 2009; Gründig, 1976, 2011; Linkwitz, 1971; Phocas, 2005).

The group around Linkwitz started using the same methods as in the design of the German pavilion for the Expo 67 in Montreal. The starting point was the construction of tulle models of the roof. Tulle is a flexible, semi-transparent fabric, which allowed the architects and civil engineers to find an optimal shape for the roof by experimenting. This was a design process typical of Frei Otto, who had mastered finding the form of lightweight structures by deploying physical models. In a second step, models made of piano wire (mostly scaled 1:125) were built. They were referred to as *measuring models*. Piano strings had roughly the same properties as the actual cables to be used. It was intended to collect the necessary data for the construction of the cable nets from these models and to simply scale them up. The models were measured for the first time using high-resolution photogrammetry to avoid perturbing the structures. The measurement errors were well below 1 millimeter, but still too large to be used for cutting the cable segments. Structures under stress and exposed to heavy wind and snow loads are vulnerable to internal tensions, and deviations of several centimeters in the final construction would have been fatal. Adding additional parts, such as masts, and their locations on the construction site, the models were used by the architects and civil engineers to generate the first estimates of the static properties of the buildings. These preliminary data were also utilized by the construction companies to order construction materials (Linkwitz, 1971, 1–3).

The third round of model building by Frei Otto produced physical models, which resembled the cable nets with their varying mesh sizes as accurately as possible. These models served as *pattern models*. The most critical part of the design problem was to determine the exact cutting pattern of the cable segments, because the interior sections of the cable nets consisted of an equally spaced mesh, whereas the outer parts used cable segments of differing length. To reduce the level of complexity in the models, only every fourth cable was modeled, resulting in a mesh width of 24 mm or 3 m in reality. To obtain the coordinates of the left-out cables for the required 75 cm spacing of the mesh, interpolation algorithms had to be developed (Gründig, 2011; Linkwitz, 1971, 2–3).

Again, the positions of the intersection points of the cable nets were collected from the pattern models by photogrammetric measurements. This time the Linkwitz group relied mainly on a Zeiss comparator PSK, an optical precision instrument for survey photography in minute detail. The

photogrammetrically registered co-ordinates of the intersection points were used as starting values for the calculations to obtain correct cutting patterns. It soon turned out that the precision of these final models was also not sufficient to determine the pattern without further processing of the data. To arrive at the final virtual model of the cable nets the erroneous data had to be corrected. At that stage, the errors were treated like errors in geodesy. The aim of the data processing was to obtain an "ideal theoretical model" (Linkwitz, 1971, 4). However, the problem was that this ideal model was not known in advance. It had to be found by modifying the co-ordinates using "geometric and plausibility criteria" (Linkwitz, 1971, 4). The first step was to produce an equally meshed net in the interior area of the roof using an adjustment program called *Äquidistanz*. In a second step, the cables at the edges were smoothed to produce a concave curvature between the cable's end-points connected to the supporting masts. The next step included a three-dimensional interpolation of the data points to get a 75 cm cable net. This mesh was then projected onto a plane and plotted using a Kingmatic drafting machine. The area close to an edge cable usually consisted of 8 to 10 individual printouts (Gründig, 2011; Linkwitz, 1971, 3–4).

However, Linkwitz had to accept that this heuristic, geometric-mathematical method to compute the patterns was not sufficient to produce an exact net. The noisy measurements could not be improved by plausibility arguments alone. What was needed were "mathematic-static computational methods" (Linkwitz, 1971, 4).

From a mathematical point of view, the main characteristic of this kind of structure is the combination of concave and convex curvatures in one surface structure. The vertical cable net segments form a concave line in three-dimensional space, while the horizontal segments show a convex curvature. All interconnection points of the cable segments had to be in equilibrium. Each interconnection point could be described by three non-linear equilibrium conditions. The number of equations to be solved was, therefore, triple the number of interconnection points. After linearizing the equations, a curve finding algorithm using least-squares fitting was applied to the problem (Linkwitz, 1971, 4–5).

The implementation of this algorithm was programmed in FORTRAN IV to run on the CDC 6600 of the Regional Computing Center at Stuttgart. The linear equation systems had a size of up to 8,000 variables. All nine roof sections of the stadium and their connecting intermediate roof sections were computed in this way. The results were documented on approximately 3800 square meters of construction drawings (scaled 1:10)

for the construction companies in Munich (Gründig, 2011; Linkwitz, 1971, 5).

Figure 10-2: The Munich Olympic Stadium of 1972. The roof resembles the Bavarian Alps and is supported by just a few pillars. The two smaller inserts cover details of the construction of the glass-covered cable-net structures (photography taken by the author in November 2012).

Deploying the more traditional methods that civil engineers and architects were accustomed to around 1970 would not have been sufficient to accomplish this major construction task at all, let alone in this tight time frame. Model building and experimentation, rather simple calculations using slide rules, logarithmic tables, and small electronic computers did not suffice anymore for a construction project of this proportion. Only the most powerful computer of those days, the CDC 6600, provided enough computational power to enhance and refine the available measurement data to draft the ideal model to build the real roof in Munich. In any case, building the 1972 Olympic Games Site in Munich was an endeavor stretching the boundaries in many aspects. The calculated construction costs rose from an estimated amount of 17 million German Marks to 190 million German Marks. However, most Germans welcomed the Olympic

Games and all relevant social and political groups supported the project (Gründig, 1976, 2011; Phocas, 2005).

John Hadji Argyris, the Finite Element Method, and the Supercomputer

John H. Argyris was born on 19th August 1913 in the small Greek port town of Volos, located approximately 300 kilometers north of Athens. His parents were members of the Greek Orthodox Church and traced their ancestry back to ancient times. His mother's family had ancient Byzantine roots, his father was the descendant of a Greek independence fighter, and many of his relatives had been poets, scientists, and politicians – ambitions also inherited by John Argyris. However, his main field of interest soon became mathematics, in which he showed an extraordinary talent. Perhaps his talent was inherited from his uncle, Constantin Carathéodory, who was a famous professor of mathematics in Munich.

The Argyris family relocated in 1919 to Athens, where he attended a classical high school. After graduating from high school, he started training as a civil engineer at the National Technical University of Athens. Two years into his studies, he moved to the Technical University of Munich where, in 1936, he completed his education with a diploma in civil engineering and the degree of Diplom-Ingenieur. Argyris had passed all his exams with distinction and could expect a brilliant and smooth academic career. However, his destination was to lead an unsettled and restless life with varying positions over half of Europe. At the Imperial College London, he would meet his second wife, Inga-Lisa, a Swede, and would have a son with her (Hughes, Oden and Papadrakakis, 2004, 3764, 3766; Phocas, 2005, 97; Universitätsarchiv, 1991).

Argyris' first position after graduating from the university was with a German company by the name of J. Gollnow & Sohn in Stettin (now Szczecin in Poland). J. Gollnow & Sohn had a long tradition in steel construction and engineering. Founded in 1833, they had built numerous bridges and towers made of various metals, and Argyris was able to collect his first hands-on experience in the design of complex metal structures. Between 1937 and 1939, he worked as a project leader and was involved in the construction of a tall radio antenna mast 320 meters high. During this period, he earned a reputation for being the man for unsolvable problems (Doltsinis, 2004, 665; ZEIT, 1950).

In 1939, Argyris joined the Technical University of Berlin to earn a doctorate but was soon arrested because of his opposition to the Nazi regime. He managed to escape from prison and fled to Switzerland,

crossing the river Rhine during a nightly allied bomb raid holding his passport in his teeth (see the dramatic report by Hughes, Oden and Papadrakakis, 2004, 3764). He continued his studies at the ETH Zürich in 1941/42 (Kurrer, 2008, 713), but soon moved on to England to work as a *technical officer* at the *Royal Aeronautical Society* in London. Beginning in May 1943, he studied the stiffness of airplane wings and fuselages for civil and military aircraft. He stayed at this institution until 1949. His work was at the boundary of theory and applications and inspired him to do preliminary work on the Finite Element Method, which would earn him later on so much reputation (Universitätsarchiv, 1991).

During 1949, Argyris was a *senior lecturer* at the *Imperial College of Science and Technology*. The next year brought him a promotion to *reader in the Theory of Aeronautical Structures*, and in 1955 he became *professor of Aeronautical Structures* (Doltsinis, 2004, 665; Phocas, 2005, 97). Argyris proved to be a talented member of the faculty who knew how to get his way. He managed to establish a nearly independent sub-department but remained as demanding as ever. Already in 1957, he had asked for a *Ferranti Pegasus* computer whose price tag was well beyond the budget of the university. At this time, he had already recognized the potential in the deployment of high-speed computers in aerospace engineering. After joining the then Technische Hochschule Stuttgart in 1959 as director of the Institute of Statics and Dynamics of Aerospace Structures (ISD), he stayed at the Imperial College until he became emeritus in 1975. This led to a sometimes fruitful exchange between the two universities (Gay, 2007, 331–332).

In the early years after the Second World War, the Technische Hochschule Stuttgart tried to reposition itself. The aerospace department was restructured to reflect the latest technological developments. Starting in 1954, John Argyris had made a name for himself by publishing a series of research articles on the application of the Finite Element Method to aerospace engineering (Doltsinis, 2004, 666). Both the State Government of Baden-Württemberg and the Technische Hochschule Stuttgart identified Argyris as a potential candidate for a chair in aeronautical engineering. After the negotiations with the State of Baden-Württemberg had lasted for quite some time, the *Große Senat* (Great Senate) of the Technische Hochschule Stuttgart discussed his status during its session on 24th July 1957. The Senate accepted the condition of John Argyris to retain a maximum of independence and agreed to keep all negotiations confidential to avoid weakening John Argyris' position in London (Universitätsarchiv, 1956–57, 29). It took another two years until John Argyris finally came as director of the Institute of Statics and Dynamics of Aerospace Structures

(ISD) to Stuttgart. He held this position until 1984 and then became the director of the Institute of Computer Applications (ICA) for the next 10 years (Phocas, 2005, 98).

The Finite Element Method

Having its earliest roots in the 19th century, the Finite Element Method (FEM) is a numerical algorithm to calculate solutions for a wide range of problems. Complex structural elements, such as bridges, airplane wings, or fuselages, can all be modeled using (systems of) differential equations. Usually, these equations have no analytical solution; that is, there is no solution that can be expressed using standard functions. The only way to solve these equations is by numerical computation, and this requires powerful computers (Huebner et al., 2001, 3–16).

The Finite Element Method models complex structural elements with irregular shape by dividing them into interconnected simpler elements possessing a regular shape. The behavior of a complex object can be approximated by a large number of combined simple elements and their interactions. Points within the elements or the boundary (vertices) can be modeled by analytical functions. Combing the geometry of these elements and the functions, one describes the whole problem. The combination of partial solutions yields the complete solution (Kaiser, 2008).

Starting in 1954, John H. Argyris published a series of papers offering efficient methods for the computation of solutions using the matrix calculus (matrix displacement method). Computers manipulated matrices very efficiently, and were therefore the ideal tools to automate the processing of Finite Element calculations deploying high-level programming languages like FORTRAN (FORmula TRANslation). The bigger the problems modeled by the Finite Element Method, the bigger the computers to manipulate them had to be and vice versa. Ray Clough, another co-inventor of the Finite Element Method, named it, in one of his publications, instead of the Finite Element Method, the "Argyris Method" (Hughes, Oden and Papadrakakis, 2004, 3766). In 1964, when the CDC 6600 supercomputer became available, the first commercially marketed Finite Element software package also emerged. This triggered a spiral of ever-increasing performance that is still active today (Huebner et al., 2001, 3–16).

The First Supercomputer in Stuttgart

John H. Argyris worked not only on theoretical aspects of the Finite Element Method but also on the solution of practical problems. One of his preconditions to accept the chair in Stuttgart was the availability of sufficient computing power at his institute. Since 1963, the Technische Hochschule Stuttgart had had a UNIVAC 1107 which could no longer fulfill all user requirements. His institute was the largest user of this machine, and he saw the necessity to expand the computing capacities at Stuttgart. John Argyris was very enthusiastic about the latest developments in high-performance computing, and in 1968 he managed to buy a CDC 6600. This made him the founding father of high-performance computing in Stuttgart (Grieger, 2004; Murray, 1997; N.N., 1971).

Besides using the computers for extensive calculations, Argyris and the members of his institute worked on system programs and new programming languages for their machines. This convinced Control Data to deliver the CDC 6600 to Stuttgart at a huge discount. Argyris' institute received a 50 percent discount on the list price and an additional five years of free maintenance. The overall value of this package amounted to five million German Marks (Universitätsarchiv, 1965–68). After serving the Stuttgart scientific community from 1968 to 1984, the CDC 6600 was finally decommissioned. The successor was a Cray 1 made by Cray Research, Inc., building the second element in a yet unbroken chain of supercomputers in Stuttgart (Rühle, 2011).

In honor of his contributions, John Argyris received numerous awards during his lifetime. He had over 400 publications to his credit and was at the center of a closely knit network of scholars always ready to defend and promote their scientific ideas to the world (Universitätsarchiv, 1991).

John H. Argyris passed away on 2nd April 2004, aged 91, at Stuttgart. He was laid to rest at the Sankt Jörgens Cemetery in Varberg, approximately 60 kilometers south of Gothenburg, Sweden (Hughes, Oden and Papadrakakis, 2004, 3763).

Klaus Linkwitz and the Force Density Method

Klaus Linkwitz was born on 3rd July 1927 in Bad Oeynhausen/Westfalia, in the north of Germany. He graduated from high school in 1947 after having served in the Second World War. After high school, he studied geodesy from 1948 to 1952 in Stuttgart and Munich. His next career step brought him to the construction company C. Baresel AG in Stuttgart for whom he worked from 1953 to 1959 as a civil engineer in Afghanistan and

India. In 1960, he became partner in an engineering company in Munich where he planned and supervised various road construction projects in Lebanon, Iran, Saudi Arabia, and Cameroon. Beginning in 1959, he was working in parallel on his doctoral thesis at the Technische Hochschule Munich where he got his Dr.-Ingenieur in 1961. For his thesis, he studied curve-fitting methods on networks, which formed a preliminary work on the Force Density Method developed in the late 1960s.

In 1964, he became director of the Institute for the Applications of Geodesy in Civil Engineering (IAGB). He combined his hands-on experience collected in many projects with the results he had obtained in his thesis and tried to refine and improve the methods he had developed. In the mid 1960s, there were two major technological changes underway in geodesy. The first laser systems appeared and brought a substantial enhancement to measurement precision, and computers altered the way in which data were handled and processed. Yet, they were not powerful enough to deal with substantial amounts of data. This would change with the appearance of the CDC 6600 at the University of Stuttgart in 1968.

Like John Argyris, Klaus Linkwitz was looking into ways to handle complex non-linear calculational problems in an efficient way based on sound theoretical foundations. His field of expertise was geodesy, where straight lines and right angles are rarely found, and he wanted to apply his results to sophisticated civil engineering problems. With this background, it became quite natural that he and his institute were commissioned by Günther Behnisch to work on the 1972 Olympic Games project.

However, his ideas were not yet so established and fully developed as to be readily applicable. Two young and ambitious graduate students who had joined his institute in the late 1960s came to his rescue: Hans-Jörg Schek, a mathematician who later became professor for geospatial databases at the ETH Zürich, and Lothar Gründig who became head of the geodesy department at the Technical University of Berlin. They were very open to the new possibilities that fast computers would provide for their work.

In 1971, Linkwitz and Schek developed the Force Density Method, which offered a new and computationally more efficient way to determine the equilibrium of forces necessary at connecting points in pre-stressed cable nets. In the meantime, Lothar Gründig was successfully applying his method to the shape finding of pre-stressed cable nets and membranes using least-square error or curve fitting methods. Although he had the most powerful computer of his time at hand, he was forced to develop sophisticated methods and software to handle real-world problems such as finding the form of the membrane roof of the Munich Olympic Stadium.

Klaus Linkwitz became emeritus in 1995 and is still active both as a lecturer at the university and as a consulting engineer. In the meantime, Hans-Jörg Schek and Lothar Gründig are also retired (Albertz et al., 2002; Gründig, 2011; Gründig et al., 2000, 270).

All Roads Lead to Rome

After the two groups headed by John Argyris and Klaus Linkwitz were commissioned for the shape finding and design of disjunct parts of the pre-stressed cable net-supported membrane roof of the Munich Olympic Stadium, both groups worked largely independently from each other and in parallel.

The route taken by each group clearly reflects the background and training of their leaders. The trained geodesist Linkwitz was accustomed to starting with a terrain where measurements could be taken. Due to the limited accuracy of the available measuring instruments, it was necessary to eliminate measurement errors to obtain a (nearly perfect) representation of the real world. The models provided by Frei Otto were a perfect fit for this approach. The sensitivity and fragility of the fabric and wire constructs made it necessary to use a contactless photogrammetric measurement procedure – an approach not uncommon in geodesy with the exception that the size of the object was considerably smaller than usual. The shape was already there. The only thing to be done was to measure and refine it (Gründig, 2011; Gründig et al., 2000).

With his strong mathematical background, John Argyris was used to taking another route. He could even start with a flat and shapeless cable net without any measurements and models –an object far from its final shape; the same way as an aeronautical engineer starts designing an aircraft, an empty piece of paper in front of him ready to see how things will evolve. Although aeronautical engineers deploy models, they are usually introduced at a later stage in the design process. The Finite Element Method was modified by the Argyris group in such a way that an iterative process was developed in which the supports of the roof were (virtually) moved, and the resulting equilibrium recalculated until the final shape of the roof was found (Argyris, Angelopoulos and Bichat, 1974; Phocas, 2005).

The methods applied by the Linkwitz group tried to refine an already existing solution: the model. The modified Finite Element Method of Argyris created a new (virtual) structure. Both methods were able to solve the task, which not only consisted in designing the membrane roof resting on groups of parallel and each other crossing pre-stressed cable segments,

but also demanded solutions ready for production under very restrictive conditions.

To facilitate the construction of the building, both groups had to deliver detailed lists specifying the length of the cable segments and their positions in the net. It was desirable to have as many cable segments of equal length as possible to reduce assembling complexity, decrease the complexity of the logistical processes on the construction site, allow for easy prefabrication, reduce costs, and improve aesthetics.

All these boundary conditions could be handled by the methods and the software packages that implemented them. Essentially, both approaches delivered on their promises and could be used interchangeably. This provided a comforting redundancy regarding potential failures or delays. The fact that core parts of the programs are still in use today demonstrates their quality and performance.

The only non-redundant element, which both groups had to rely on, was the computing resources provided by the CDC 6600 at the University of Stuttgart. Both teams used the same infrastructure and had to compete for resources such as runtime or storage capacity.

The programming was done using FORTRAN IV, and to achieve this level of performance the code was tailored to the architecture of this specific machine. The software stretched the capabilities of the computer to the limit and allowed the processing of nets with up to 10,000 nodes where each node had three degrees of spatial freedom.

The real bottleneck in this project was the available runtime on the computer. Had this machine failed or had there not been enough memory, the whole project might have collapsed. In those days, computers were not as reliable as today. After a few days, a maintenance shift was necessary where technicians tried to fix minor problems. The typical runtime of programs started at 200–300 seconds and larger nets took several hours to compute.

When the machine became unavailable because of a longer downtime, the Linkwitz group tried to secure runtime on a CDC 6600 in The Netherlands. The importance of this project, and the pressure under which the work was performed, is also demonstrated by another event. Early versions of the programs produced suboptimal solutions. Instead of improving the programs and rerunning the calculations, Linkwitz managed to organize a group of soldiers from the German Army (Bundeswehr) who would select the useful results and discard the useless ones by hand (Gründig, 2011; Linkwitz, 1970).

However, when asked about the self-perception of the work that had been performed, one of the participants expressed the feeling that there

were just more and better calculations using newer tools, but not a new quality of scientific achievements (for these paragraphs, Gründig, 2011).

Conclusions

This historical case study unfolded the events behind the design of the Munich Olympic Stadium membrane roof for the 1972 Olympic Games and demonstrated how two groups with different approaches successfully completed the task to design their assigned segments of the roof. Both groups gave their best in order to transform the ideas of Frei Otto into glass and steel and prevailed.

The group headed by Klaus Linkwitz started with a physical model of the roof provided by Frei Otto. By modifying and transferring methods and concepts from one discipline (geodesy) to another (civil engineering and architecture) they developed the Force Density Method, a new way to efficiently design membrane roofs.

John H. Argyris' group developed a modified Finite Element Method and started with a purely mathematical model. They showed that physical model building was no longer necessary, even for designs with such a high degree of complexity.

Both examples also show how the professional background and training influenced the mode of work. One group tried to refine an already existing solution: the model. The other group created a new structure.

In the end, both methods proved to be more or less equivalent in power and demanded approximately the same amount of computing resources.

Neither of these two attempts would have been possible without the first supercomputer: the CDC 6600. The advent of high-performance computing capabilities drew a new line. Using models might still be useful but was no longer necessary. If required, all modeling could be done on the computer. The decade of the 1960s also marked the diffusion of high-performance computing capabilities into non-traditional application areas, such as architecture and design –a still ongoing process.

When asked, participants of these developments regarded the novel approach based on extensive numerical calculations merely as a more intensive computational process without new epistemic aspects. This is an interesting result, which could be the starting point for further investigations.

The case study also showed how progress in this area rested on a combination of new mathematical methods, advanced technology and the willingness of society and politics to provide the necessary funding to facilitate change within such a short time frame.

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CHAPTER ELEVEN

WHAT'S THE RESULT? THOUGHTS OF A CENTER DIRECTOR ON SIMULATIONS

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Introduction

Simulation has become a widespread tool not only in science but also beyond. The performance of high-performance computing systems drags the performance of smaller systems and provides simulation power to the average human being. The questions that arise for a practitioner –as the director of a supercomputing center– are manifold. In this article, I address some of them. I look at the workflow of a simulation and try to connect it to some philosophical aspects of simulation. I present a prototypical workflow and compare it to a concept recently introduced by Eric Winsberg. Our focus is on the practical aspects of simulation. Therefore, I also address the issue of interpretation – though this is limited to the technical possibilities of interpretation, leaving out the epistemological issues.

Before getting into the core of our subject, I admit that this article and our work in the field of philosophical examinations of the process of simulation are heavily influenced by some recent and some not so recent work. Educated as a mathematician, I very much rely on Ludwig Wittgenstein's understanding of mathematics and hope to extract some understanding of simulation from this. Furthermore, I am influenced by the most recent discussions about simulation and philosophy as expressed in the works of Winsberg (2010), Gramelsberger (2010), Greco (2011), Elgin (2011), and others. In general, I follow a concept of information that is inspired by Vilem Flusser (1999) and Peter Janich (2006). Both state that "information" cannot only be defined in terms of a communication

theory as described by Shannon and Weaver (1963) and then be transferred to other fields. Flusser explicitly traces the term "information" back to its Latin roots and emphasizes the aspect of "formation" or "putting form into something." Janich emphasizes the technical origin of the term "information" and argues against its "naturalization."

Finally, I have to note that I make use of the language of my original field, which is mathematics, computer science, and engineering. Language forms our thoughts, and our thoughts form language. The reader should keep this in mind.

What is Simulation?

Simulation is not a well-defined term. It is even used in different ways in the scientific community. It can mean the mathematical description and computing of a physical phenomenon in order to understand a process. It can, however, also mean an attempt to create a virtual reality environment (simulate reality) in order to train pilots or drivers. I have therefore undertaken to find some definitions of the term "simulation" that may help to better understand the phenomenon.

Thomas Junker –a well-known evolutionary biologist– gives a clear and simple link between thought and simulation by saying:

Denn was ist Denken anderes als Simulation?[1]

In this sense, simulation is not a special technique that humans have developed but rather it is what actually defines the status of a human being. I think, therefore, I simulate. Keeping this in mind, one might have to distinguish between an explicit simulation (or for that matter a technical one) and an implicit one – which according to Junker has become second nature for us. This paper will focus on the explicit type of simulation but will keep in mind that thinking and simulating are close relatives.

Sigmund Freud is another source of inspiration when it comes to simulation as he states that simulation is

> *…probeweises Handeln mit kleinen Energiemengen, ähnlich wie die Verschiebung kleiner Figuren auf der Landkarte, ehe der Feldherr seine Truppenmassen in Bewegung setzt.*[2]

[1] "For what is thinking other than simulation?" (Junker, 2006)

[2] "… acting on trial with small energy quanta, like the relocation of tin soldiers on a map, before the general sets his troops in motion" (Freud, 1933, 96).

At this point, we might note the similarities between Junker and Freud. It remains to be investigated what Junker means by "*Denken*" (thinking), and whether this coincides with what Freud calls "*probeweises Handeln*" (acting on trial). For the purpose of this paper, it is enough to state that simulation is a process that at least starts with thinking and is part of human nature.

Nevertheless, I continue the investigation by looking up the term "simulation" in dictionaries – without trying to be comprehensive but rather aiming at a number of facets of the term "simulation" that may help to better understand what we as scientists are doing. As little as dictionaries may have to do with philosophy, they reflect the common understanding of terms in their respective language community. We find for an English definition of simulation:

Produce a computer model of a process[3]

This brings in the computer as a tool to use for simulation, and it introduces the term "model" into our discussion. In this sense, we first look at the computer as a tool to extend our thinking. The focus now is clearly on the machine as a tool and on a "process" that is handled by the simulation. Taking a look at an Italian dictionary we find:

> *Analisi di un fenomeno, di un processo, o di un sistema effettuata attraverso la costruzione di un modello matematico che lo simuli*[4]

This definition brings back the notion of analysis, which can be found in Junker and Freud. However, it combines it with the mathematical model and it states – which is interesting to note – that the mathematical model simulates the process or system. This emphasis on mathematics is to be found later on in other concepts and already shows that simulation is very often taken to be applied to mathematics only.

From all of the above suggestions and my own work I deduce the following concept for simulation through asking questions to myself and providing technical answers:

[3] Concise Oxford Dictionary, 8th Ed., 1990.

[4] "The analysis of a phenomenon, a process or a system that is accomplished by constructing a mathematical model that simulates it" (Dizionari Garzanti – Italiano, Prima edizione, 1994).

What is our purpose?

We would like to understand a **natural/technical process** in order to **predict** the behavior of **a system** AND to take measures to **optimize** the result of such a process.

What do we mean by prediction?

The intention is not to exactly predict the future but to get a better understanding of the behavior of a system both quantitatively and qualitatively.

What do we mean by system?

A system is a structure that is too complex to be easily understood.

What do we mean by optimizing?

Optimization is the process of minimizing or maximizing a given set of qualities under certain boundary conditions.

What do we mean by simulation?

Simulation **describes** natural/technical processes in a computer program and **computes** the results.

This is a technical approach that serves its purpose for teaching classes on simulation. It remains to be discussed whether it is enough to fully grasp the extent to which simulation is part of our technical and natural life.

Simulation Failures

In order to better understand a concept, I tend to look at its failures. The history of simulation is full of success stories, and as the director of a national high-performance computing center, I am inclined to add a few of our own success stories to this. However, it helps more to look at the failures.

Financial Markets

The simulation of financial markets is based on the assumption of rational behavior and on the necessity for quick decisions. It comes as no surprise that making quick decisions requires rapid processing of available data, fast simulation of future scenarios and immediate decision-making. All of this can be achieved by using high-performance computers that are

fed with all the necessary data. They, then, simulate a number of scenarios and make buying or selling decisions within microseconds. Banks and insurance companies have thus become big players in high-performance computing and networking in recent years. The models that had been used were sophisticated in nature, and mathematically they were certainly state of the art. However, when the financial crisis hit the markets in 2008, all of these models failed to foresee the unforeseeable.

One may resort to the basic fact that human beings do not always behave rationally, or, as the Austrian author Peter Handke put it:

> *Was unter Menschen geschehen wird, die, wie man sagt, ihre Taten nicht nach den Naturgesetzen einrichten, ist nicht berechenbar.*[5]

Technical Simulations

However, we are also facing problems in technical simulations where we tend to believe that simulation is able to predict material behavior. I point to the fatigue cracks in the Airbus 380 engines and wings (NYT Feb. 8th, 2012; ATSB, 2010) and a Boeing fuselage (NTSB, 2011) detected recently. In both cases, it seems to be obvious that simulations were carried out. Increasingly, also, technical simulation is turning from an "a posteriori" analysis to an "a priori" analysis. Technical processes and design increasingly rely on the validity of simulation. Verification and validation also become ethically and economically important issues.

Verification & Validation

Simulations are always viewed as some sort of representation of the real world. However, they require an understanding of whether the representation is adequate. In simulation technology, the two concepts of verification and validation have been established over the years. I follow Eric Winsberg here in defining verification as follows:

> **Verification** … *is the process of determining whether or not the output of the simulation approximates the true solutions to the differential equations of the original model* (Winsberg, 2010, 19-20).

While Winsberg has a focus on the mathematical side of this definition, I will later show that it has to be extended also to the computational side.

[5] "What is going to happen among people who, as it is said, do not direct their deeds to natural laws, cannot be calculated" (Handke, 1977, 230).

Nevertheless, verification seems to be the part of the process that is open to notions like "proof" and it seems to be the technical part of any simulation.

> **Validation** *is the process of determining whether or not the chosen model is a good enough representation of the real-world system for the purpose of the simulation* (Winsberg, 2010, 19-20).

It becomes immediately obvious that by asking for a "good enough representation" we require a definition of "good." Validation is obviously the more difficult part of the two concepts, as it requires a comparison to be made between the real world and the simulated world. This is typically done using pictures and movies or extracting significantly computed data that are then compared to measured data. The role of pictures and movies is far from being well understood yet. However, it is not further discussed here. The interested reader is pointed to Vilem Flusser (1999) who provides an interesting concept for technical pictures.

A Simulation Framework

In order to work out a simulation framework I provide two different approaches. Both lead to the same concept of simulation, but both also give a different angle of view. I first look at a schematic view of simulation. This approach states that simulation is a series of transformations, each of which brings us closer to the understanding of reality. I compare my own approach with a concept from Eric Winsberg to show the difference in understanding simulation between a technical and a philosophical approach.

For a better understanding I have a more detailed look at my own scheme. It all starts with reality and a perception of reality. I leave out all the discussion about perception and reality and, for the sake of focusing on the simulation aspect, assume that we can actually somehow understand and measure what happens in reality. From this I derive a physical model, which is a description of the interaction that takes place in reality. From this physical model, I move on to a mathematical model. One may argue that the mathematical model is but a mathematical description of the physical model. However, any mathematical description is a very exact description and what we typically do when we move from physical data to mathematical models is to find a best fit – but usually not an exact fit. So I think that the distinction between a physical and a mathematical model is not only valid but also important.

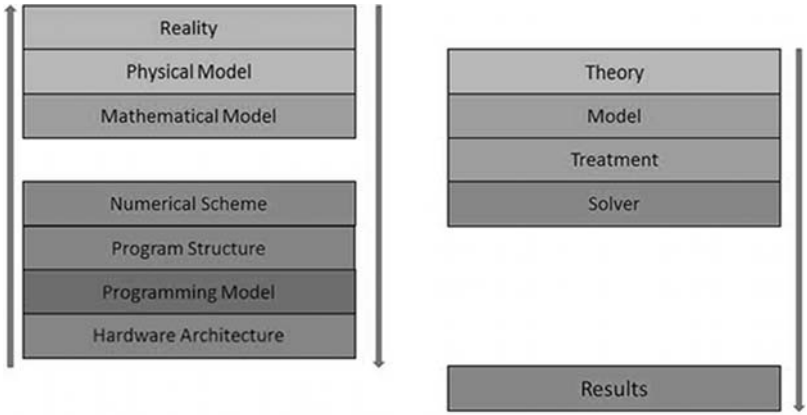
Once I have a mathematical model, I have to find a solution for that model. The simulation typically comes into play when I cannot find an exact mathematical solution for the problem. In that case, I need a numerical scheme and a computer. Having defined the numerical scheme, I have to translate into a program structure. This means that I translate the numerical scheme into a logical computer-readable scheme. It is obvious that this cannot be done by a simple translation that would keep all the properties of the numerical scheme. Issues like computer accuracy and order of execution of numerical operations come into play. The name "FORTRAN" (Formula Translation) for one of the first programming languages in that sense was completely misleading. In the next step, I turn to what I call the programming model. Having moved from classical John von Neumann machines with a single processor and a single memory to massively parallel machines, I have to find a way to map the computational work on these massively parallel architectures. Only after that have I successfully mapped whatever I perceive to be real onto whatever kind of hardware architecture I am using.

Three things are immediately obvious. First, my own schematic view ignores what Winsberg calls "treatment." According to Winsberg, this includes the setting of mathematical boundary conditions and further mathematical groundwork. This could be thought to be hidden in my numerical scheme. Nevertheless, the omission makes clear the neglect of mathematical boundary conditions in my very much computer science-driven view. Second, the concept of Winsberg takes the computation as a given thing, and hence does not put any emphasis on the issues of programming. This may reflect the more logical and mathematical approach of a philosopher. A combination of both approaches should come closer to a realistic description of a schematic simulation view. Finally, it is noteworthy that Winsberg indicates a direction of development that goes from the theory towards the results, and gives no indications of getting back to the initial assumptions. Pointing at both directions in my approach, on the other hand, indicates the possibility of also working in both directions.

In simulations, we also see the approach of starting with a given hardware and then looking for adequate models that could fit to the hardware. This is not a very common approach today. Starting from reality and successively mapping models until one has found a mapping to the existing hardware is a historically more "natural" approach. We saw mathematical models before we developed numerical methods. We had numerical methods before we had computers and computer programs. The reverse order of mapping might, however, make sense. It is sometimes

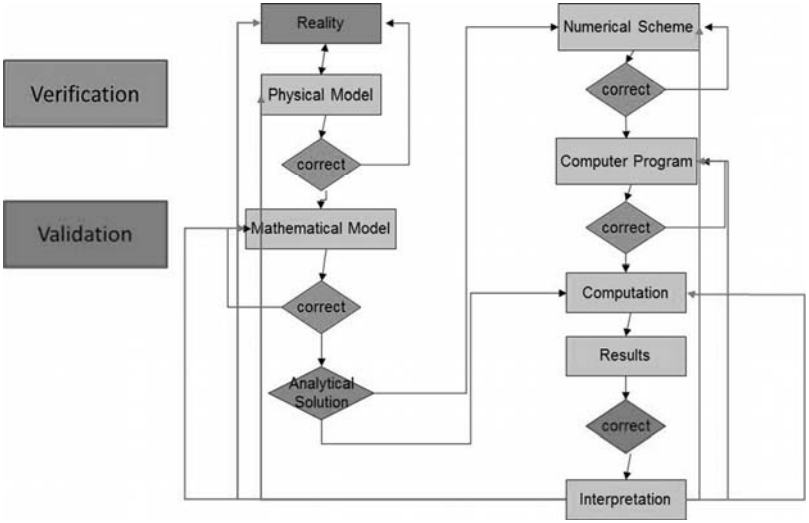
used as an escape from reality when large-scale systems grow out of programmability, and national centers are desperately looking for codes that might fit the architecture and hence justify the investment. Such an a posteriori justification of supercomputer investments is becoming common but is not recommended. The large investments in supercomputers (about 250 million US dollars for the Blue Waters system in the US and about 600 million Euro for the most recent Japanese supercomputer) should be justified by a preparatory analysis of existing problems and a search for the right hardware solution.

Figure 11-1: On the right, an approach following E. Winsberg; on the left, the author's approach.



However, starting from hardware is scientifically interesting. Following that approach, one would first analyze very carefully the potential of the hardware and identify programming models and programming structures that best fit the architecture. One would then look for numerical schemes to make best use of the programming models and structures. This would lead us to mathematical models that best fit the numerical scheme, and finally to physical models that best fit the selected mathematical approaches. The final issue is: how do the physical models that we derive from this synchronize with reality? It seems to be a fruitful approach to work through these models and mapping operations both directions at a time in order to find a best fit that best brings together the computer and reality.

Figure 11.2: Process driven approach simulation



Thinking about the notion of "direction" of workflow in simulation, a second way of looking at simulation is through a process-driven approach. Figure 11-2 describes such a process-driven flow. It indicates that going through the various steps in a simulation we repeatedly have to go through a verification phase. At each of these steps of verification, we need to be able to jump back to a previous modeling step in order to correct errors. Furthermore, the proposed process model indicates that once we have gone through a validation process we need to be able to restart the simulation process at every intermediate step. This highlights that errors can occur at any given intermediate step.

Finally, we need to discuss the errors that may occur during the "computation" step. We typically assume that computers do not make mistakes. This is not the case. The most famous case is a bug that was found in 1994 in the Intel Pentium processor (Cipra, 1995). The Pentium processor was estimated to make one error for every 9,000,000,000 calculations. Methods to test and check hardware have improved since then and we can estimate that the error rate is a factor of 10–100 better now. However, the increase in operations may lead to problems here. If we assume that in the year 2020 the error rate for a single processor will be about 1 error for every trillion operations (10^{12} operations), we can make a simple calculation to understand the problem. In 2020, we expect systems that are able to perform one Exaflop – this translates to 10^{18} operations per

second. As a result, we would have to expect about one million errors per second. To make the estimation more realistic we can assume that such systems will actually only deliver between 1% and 10% of their peak performance. For a sustained performance of 1%, we would still have to expect about 10,000 errors per second. For an eight-hour simulation, this would result in about 300 million errors for such a simulation. Modern microprocessors do have error correction detection and correction methods. However, the huge numbers will be a problem and will have to be considered when it comes to checking the results of a large-scale simulation.

Simulation Results & Interpretation

When looking at the results of a simulation we have to go back to the start of the simulation. Which questions did we ask the simulation? Which input data did we provide? Which model did we use? All of these questions are at the core of an interpretation of the results. After all, the results of a simulation are functions of the answers to these questions.

Interpreting the results that we receive requires looking at the "hard" results of a simulation. Usually these are data. In order to make these data comprehensible for human beings we have developed a variety of technologies. The most typical ones are:

- Number
- Diagrams
- Pictures
- Movies
- Virtual Reality
- Mixed Reality

This is not the place to discuss in detail all of the above-mentioned representations of information. However, I would like to note two things here that seem to be relevant for practical purposes in a simulation environment.

The first issue that I consider important is well described by the "Thomas theorem." Although developed for sociological analysis it can be applied to the interpretation of results as well. The Thomas theorem states:

> *If men define situations as real, they are real in their consequences* (Thomas & Thomas, 1928).

Taking this concept for the visualization of simulation results, we understand that when we visualize simulation results we typically create "realities" for the non-experienced users. The visualization defines truth by making things visible and making them look real.

Catherine Elgin proposes the second concept that I consider very relevant:

> *Understanding is often* couched *in and conveyed by symbols that are not, and do not purport to be, true. Where such symbols are sentential, I call them felicitous falsehoods* (Elgin, 2004).

The concept of felicitous falsehoods may be fruitful for the interpretation of simulation results if we are able to understand the meaning of such falsehoods and if we know how to integrate them into our interpretation of simulation results. It remains to be seen how such concepts can be discussed in the purely technical context in which simulation typically resides.

Furthermore, we have to consider a number of cases in which our process model of simulation with its concepts of verification and validation through experiments or comparison with the real world either fail to work or partially do not fit the underlying simulation concepts. Such cases are simulations where the problems…

- … are too small to be validated by experiments (e.g. nanotechnology)
- … are too big to be validated by experiments (e.g. world climate)
- … last too long to be validated by experiments (e.g. black hole collision)
- … last too short to be validated by experiments (particle collision)
- … are too dangerous to be validated by experiments (e.g. Tchernobyl-type experiments)
- … are too expensive to be validated by experiments (e.g. plane crashes)

For all these cases we need to reconsider the notion of "validation" and will have to work with concepts that rely entirely on verification. Usually that means that we have to accept uncertainty. It would go too far for this paper to discuss this special topic.

Open Questions

While scientific papers in the field of simulation technology usually come up with some conclusions, I will rather point at some of the questions that I consider relevant in the discussion between philosophy and simulation technology.

The Simulation Act

The key question is: What do we (human beings) do when we simulate? Following the models presented here, some of the follow-on questions are: How do we go through a modeling chain? What are the consequences of such a modeling chain? Does it make sense to simulate what can never be validated? Does it make sense to talk about "numerical experiments"?

By following a model that assumes a chain of steps, we give simulation a certain framework in which we operate. It is an open question whether such an approach actually describes the mental –scientific– process that happens in simulation. It seems to be worthwhile to rethink our technical activities considering further options for simulation frameworks. It furthermore seems to be worthwhile to get a philosophical and a technical view on simulation frameworks and to work out how the different views can fruitfully be employed to allow both sides a better understanding. The rather critical problem is the lack of validation for the many kinds of simulation that increasingly fill our supercomputing systems. Science has always worked with unproven assumptions but –as we see later– simulation has left the premises of science and we have to understand what a lack of validation can mean in this context. Finally, we need to better understand the meaning of the notion of "numerical experiment." The wording has been used a lot over time without specifying exactly what we mean by it.

The Interpretation of Simulation Results

The next question is: What happens when we interpret simulation results? The follow-on questions are many, but two of them seem to be very important here. First, we should be able to understand what the physiological reaction to visualization is. Visualization of simulation results goes beyond the classical perception of the real world. We are able to "add" information and to "highlight" information and the human being is exposed to what is often called "virtual reality." We need to better

understand the consequences of this exposure. Furthermore, we need to look at the framework in which we interpret visualized results. So far, this framework has been very much a scientific one and there is little work about the framework of interpretation for simulation results. In the future, simulation will be more pervasive in society –which brings us to the third set of questions.

The Public Understanding of Simulations

The final issue is: What happens when technical simulation becomes "public"? Simulation has by now already become part of the work of a variety of people who are not involved in the production process of simulation. This is already a problem, as many end-users do not understand the meaning of a simulation. The problem will become more difficult once we move from "experts" to "laypeople." At this point, a simulation will become –and is already gradually becoming today – part of the work and entertainment of people who are consumers. Among the many issues that will arise, "truth" is a very important one. What is the "truth" of a simulation? When can we say/discover/judge that a simulation is true or not true? Finally, we will come to the point –which we have already partially reached in the climate change discussion –where we disagree. If our discussions are based on simulation results, we will have to find ways to handle disagreement.

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