
THE CONCEPT OF REDUCTION IN SYSTEMS BIOLOGY

A Project Report

By

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1. INTRODUCTION

1.1. Motivation of the Philosophers

This work is part of a series of studies initiated by Professor Jotun Hein of the Department of Statistics and the Oxford Centre for Gene Function, University of Oxford, and Professor Carsten Wiuf of the Bioinformatics Research Centre, University of Aarhus. Some time ago they selected a number of concepts whose use in modern biology, in particular systems biology, is common, but which they felt gave rise to certain philosophical or methodological questions not always fully addressed in the scientific literature itself. They felt that this lack of explicit and focused attention, along with myriad other factors, had led to difficulties in clarity and even coherence, the current situation being that the precise meaning and correct use of these concepts is left entirely unclear

The concepts that concerned Professors Hein and Wiuf included the following (although of course any such list possesses a certain degree of fluidity): emergence, reduction, levels, function, purpose, disease, dysfunction, and causation.

Two key things about this list are worth noting immediately.

First of all, many of these concepts have a long and storied philosophical history, and while their adoption by the scientific community has been highly considered and the subject of much intelligent discussion and debate, it is not unusual to find published articles which do not clearly refer to any standard definition of the terms they employ. In addition, studies by scientists which address the philosophical issues surrounding the use of these concepts are scattered across many different books and journals, and their inability to achieve a clear consensus view is rivalled only by discussions in the philosophical tradition itself. It was

therefore considered worthwhile to engage the devoted attentions of philosophy graduate students in a series of collaborative summer projects, whose aim (as far as the authors of this report understand) would be to clarify the use of these concepts in science, to provide definitions in harmony with their philosophical history, and to categorise existing literature.

Second of all, it is inevitable that the concepts in any such list form a complex web of interrelations. Certain facets of these interrelations will be immediately obvious, even to those with no knowledge of the area – for example that there must be some connection between function and dysfunction. Certain other facets will come out naturally as the intended series of studies progresses. For example, in the course of last year’s project a certain, tightly circumscribed connection between emergence and causation – specifically, a connection between *strong* or *ontological* emergence and *downwards* causation – was laid bare. Still other facets of the interrelations between the concepts in our list have been made explicit in Professor Hein’s project proposals (see below, section 1.2.). And finally, yet other interrelations between the concepts will be explored more explicitly as the series of studies progresses. Just as next year’s project on disease and dysfunction will draw on the project on function (and purpose) that runs this year in parallel with the present project, the present project will draw on last year’s project on emergence.

In this regard, a small caveat. One year ago, the two authors of this work collaborated on a project entitled “The Concept of Emergence in Systems Biology.”¹ This year we are concerned with the closely connected concept of reduction, and we hope to make connections between the two projects clear as we proceed. During our study of emergence we dared to propose a ‘cluster definition’ of what we called Weak Emergence, our hope being to capture in a single concept the spirit of emergentism as it featured in ground-level biology journals. We started by compiling a list of characteristics ascribed by scientists to emergent properties,

¹ Angela Matthies was the third author.

and claimed that whenever research biologists spoke of an emergent property, they were effectively ascribing to that property a certain combination of characteristics from our list. This meant that we had proposed a definition of emergence which possessed a certain degree of unity, and which we felt did justice to scientists' preoccupations with emergence.² In the case of the current report on reductionism, no such unity will be possible. Questions about reductionism in science are legion. Indeed, their sheer variety have made it difficult for us to know where to concentrate our attentions, and one of the goals of this project will be to provide a catalogue of 'reductionisms' in science and philosophy. Before that, however, let us get a better idea of what the problem is from the scientist's point of view.

1.2. Motivation of the Scientists

System Biology is very much in the vogue. This is partly because full modelling of biological systems is now a possibility. The literature of systems biology has elements that are very well defined, such as the different forms of high throughput data, knowledge of biological structures and dynamical modelling. Moreover, there are concepts at work here like "robustness", "complexity", "redundancy" and "evolvability" that can be used in a sloppy fashion, but can also be defined properly with a little effort. However, this literature is also dominated by concepts that can only be described as elusive and that in many contexts appear unnecessary. Such concepts are "Life", "Function", "Emergence", "Purpose", "Modularity", "Reduction", "Interpretation", "Level", "Analyzability", "Explanation", "Understanding", "Cause" and "Disease/Dysfunction". There are most likely others. These concepts are problematic since they are frequently used by the majority of the bio-science community, but there is no consensus about their definition or even their necessity or irreducibility. We will define a series of projects with the primary aim of clarifying these concepts. (Cautionary

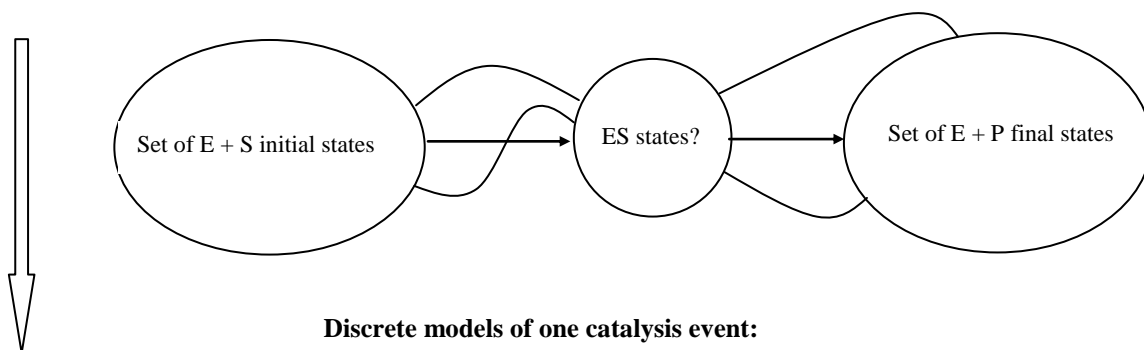
² As philosophers, and not trained scientists, we approach the scientific literature with a degree of humility and wish to thank Jotun and Carsten for the unusual opportunity which these summer projects have provided.

note: The literature on the topic is extensive and the articles often appear in philosophical journals. The articles read should be chosen with serious care to avoid being overwhelmed. Another useful outcome of the projects will be an extensive and usable bibliography.)

1.2.1 Biological Levels and Reductions

Biological concepts are frequently arranged in levels, where the concept at one level (for example, an enzyme) is autonomous in the sense that its behaviour (as described by Michaelis-Mentens' constant, for example) can be summarized with properties that do not need reference to lower levels (for instance its constituent atoms). These concepts and levels are naturally defined during biological research and this process is not part of an explicit meta-scientific program, although these concepts are often central to such debates. For example the distinction between levels is a necessity both for modelling and for understanding. Using kinetics to describe enzyme behaviour instead of molecular dynamics allows an acceleration of more than 8 orders of magnitude in calculations. Using the concept "enzyme" allows a much lower dimensional representation that can be handled intellectually in contrast to a more complete description, in many cases humanly inaccessible.

A molecular dynamics sample path involving one catalysis event:



Discrete models of one catalysis event:

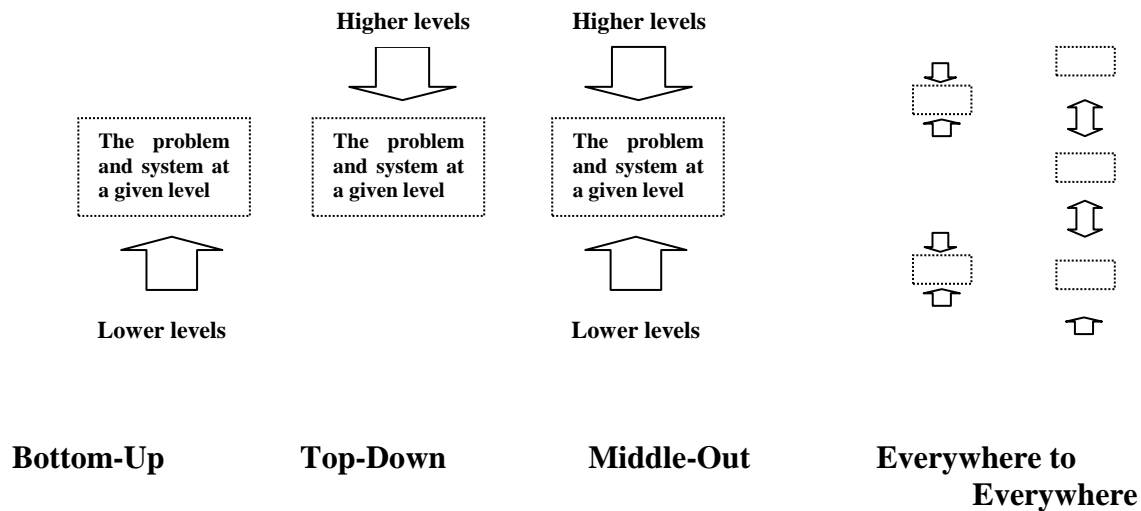


The first models of enzymatic action were published in the first decades of the 20th century by Michaels, Menten, Henry, Haldane and others. These are models with a few states and

interactions and lead to simple equations allowing explicit analysis of their dynamics. It is clear that the real picture is vastly more complicated and has started to be analyzed only in the last decade of the 20th century by molecular dynamics. A naïve MD (Molecular Dynamic) simulation could have 10^3 - 10^4 atomic positions (enzyme, substrate, water and ions) and would in principle be simulated for 10^9 steps of 10^{-15} second duration. Clever techniques such as Transition Path Sampling (Bolhuis et al, 2002) can improve significantly on this and force dynamic trajectory toward a desired end state and still allow rates to be calculated and identification of key interacting groups.

Making discrete approximations have also been applied to other complex molecular events such as protein folding (Fersht, 2004). These are simple illustrations of events and objects formulated at different levels. As computational modelling becomes increasingly dominant in biology, stringent definitions of levels, objects and their dynamics could be increasingly necessary.

Levels are partially ordered since objects in one can consist of many objects from a lower level. This has led to characterisations of the approaches to modelling. *Bottom-up* will start with thorough descriptions of low level and move to higher levels always explaining higher level objects in terms of lower level objects. This approach is also often called reductionism. *Top-down* is used in biology, when the function of an object (for instance a network) is assumed known and lower level (for instance a specific enzyme in the network) is then explained by serving a purpose at the higher level. Sydney Brenner and Denis Noble (Noble, 2006) often describe much practical modelling as *middle-out* in the sense that one starts at the level of interest and refers of lower levels for reductionist explanations and to higher levels to establish purpose.



In systems biology and the analysis of throughput data, there is often a lack of an initial driving question and an emphasis on global modelling where top-down and bottom-down approaches will be applied simultaneously at many levels in an approach that could rather be called from everywhere to everywhere.

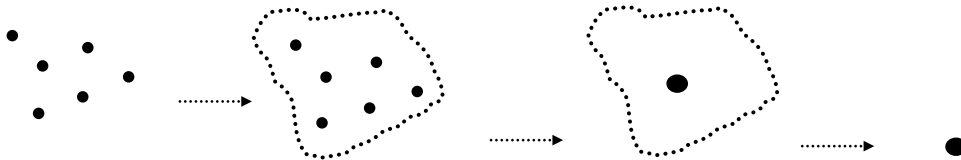
1.2.2. Physical-chemical, Stochastic and Dynamical Modelling Techniques

Due to the size of biological systems modelling is done at many levels: Quantum Mechanical for small sets of atoms involved for instance enzymatic reactions; Classical Force Fields for motions and interactions of molecules involving hundreds to many thousands of atoms; Stochastic Chemical Kinetics for reactions involving tens to a thousand molecules; and Deterministic Kinetics for larger number of molecules. Kinetic Models are often combined to integrate network models used to describe a regulation, metabolic pathways and more. Diffusion Models describe transport and thermal noise in biological systems.

Biological Systems are physical systems, and physics has a hierarchy of models. Berendsen (2007) describes one eleven-level hierarchy starting with relativistic quantum dynamics and ending with steady flow fluid dynamics. There is not easy identification between biological hierarchies and physical hierarchies, although they do intersect and some biological objects

can be identified with naturally defined physical objects. Biological concepts are partially historical constructs, where certain entities have been elevated to the status of “biological object” and its behaviour described and predicted by useful rules and equations.

Defining or recognizing Biological Objects



For computational and conceptual reasons it is convenient to identify a series of objects (for instance atoms or molecules that can be view as a unit with properties that can be defined from the component. Often this is straight forward – a molecule is a set of atoms bound by covalent bonds and a concentration is the number of a specific type of molecule per volume. In other cases it can be harder and the quality of modelling is at risk as when coarse graining in MD simulations.

Since all biological objects are physical a reduction is possible in principle, but can be computationally prohibitive or even detrimental as it would erase central qualities in its biological definition. In modelling biological objects a series of essential decisions has to be made. As systems biology typically involves many levels, models can be mixed and typically are. Useful models arise in a trade-off between tractability and reductive realism, so experience or testing can allow certain aspects to be simplified to, for instance, Boolean networks, if the underlying model is sufficiently switch-like. The complexity of integrated models is no virtue and regaining the simplicity of single-level models is often attempted by observing that the dynamics of different levels occur at very different scales where fast dynamics levels can be assumed to be at equilibrium relative to boundary conditions determined by slow dynamic levels. Recently Ball et al. (2006) have also used multi-level

models for enzymatic reactions, where the stochastic dynamics moves between different for instance Poisson and Diffusion Processes dependent on the number of molecules in the system.³

1.3. Project Goals

- Read key literature, both scientific and philosophical. Provide very brief appraisals of this literature, not in the style of a rigorous and abstruse philosophical essay, but in a style so as to be accessible by and useful to the time-pressured scientist.
- Encourage discussion of the topic between philosophers and scientists. In particular, regular meetings between the students carrying-out the project and the professors instigating it (as often as possible also including interested associates of both parties), and regular presentations to scientists of the progress and results of the philosophers.
- Find examples of reductions in areas of relevance to biology. Find and discuss specific examples of reductions and the size of the systems necessary for them to appear. This will entail an independent critical literature search.
- Produce an extensive bibliographical resource.
- Clarify the concept: ‘reduction’.
- Answer the question: ‘Is the concept of reductions necessary and useful?’

³ Section 1.2 is reproduced from Professor Hein’s initial project proposal. We include it here for two reasons: first, as the title of the section indicates, to evidence the motivation for this project from the scientist’s point of view; and second, because the speculative analysis therein, of systems biology as seeking explanation from ‘everywhere to everywhere’, has proven quite prescient.

2. KINDS OF REDUCTIONISM

It is fair to say that some form of reductionism has been the paradigm under which scientists have laboured since the Renaissance. We may roughly characterise this paradigm as involving the view that complicated systems and entities can be best understood by analysing them into their component parts and showing how the interactions of these simpler entities give rise to more complex phenomena. This approach has been enormously fruitful, no less so in biology than in other branches of science. It is therefore fascinating and highly consequential that there has arisen in modern biology a movement which is (or at least claims to be) vociferously *anti-reductionist*. However, reductionism is not one single unified position; reductionism and its denial represent each a colourful panoply of interconnected views. In this section we categorise some of these varied positions in the hope of clarifying the relevant issues for modern biology. In doing so we aim to show how the anti-reductionism which may or may not be appropriate for modern biology is most likely compatible with the venerable physicalist reductionism which has been so productive since the dawn of modern science. What follows is only a summary, and an extremely brief and selective one at that. For a full, nuanced discussion of these topics, we refer you to the papers and books in the relevant section of the bibliography.

Following Sakar (1992) and Nagel (1998), we think it pertinent to distinguish three principal types of reductionism: ontological, epistemological and methodological. In the subsections below our discussion will focus on these kinds of reductionism as they feature in biology.

2.1. Ontological Reductionism

Ontological reductionism is the view that any biological system or entity is made-up of smaller entities such as molecules, that indeed it is nothing more than a collection of smaller entities and their interactions. This is essentially the reductionist paradigm referred to above, which has directed the efforts of scientists since the Renaissance, and which remains the consensus view among most philosophers and scientists. It is at least closely related to what has been called physicalism or materialism, and some others go so far as to say that ontological reductionism is just another term for these truly venerable -isms. As such, it stands in direct opposition to that outmoded Aristotelian doctrine known as vitalism.

Much can be said about ontological reductionism, but here we will focus on a connection with emergence. To deny ontological reductionism is to sanction strongly emergent properties, the tenability of which we argued against in last year's report, entitled "The Concept of Emergence in Systems Biology." To recapitulate the problem with strong emergence, consider O'Conner's (1994) definition of a strongly emergent property:

P is an emergent property of a object O if and only if P supervenes on properties of O's parts, P is not had by any of O's parts, P is distinct from any structural property of O, and P has a causal influence on the behaviour of O's parts.

What seems to be most central in this definition is the notion of downward causation which is involved. A number of problems with this notion were put forward by Angela Matthies in our earlier report, but Bedau (1997) sums it up most succinctly:

Although strong emergence is logically possible, it is uncomfortably like magic. How does an irreducible but supervenient downward causal power

arise, since by definition it cannot be due to the aggregation of the micro-level potentialities? Such causal powers would be quite unlike anything within our scientific ken. This not only indicates how they will discomfort reasonable forms of materialism. Their mysteriousness will only heighten the traditional worry that emergence entails illegitimately getting something from nothing.

We, the authors of this report, agree with this assessment. Rejection of ontological reductionism is tantamount to accepting the existence of strongly emergent properties, which not only goes against the founding assumptions of science since the Renaissance, but seems unconscionable for almost all scientists and philosophers of the present day.⁴

2.2. Epistemological Reductionism

To sanction epistemological reduction is to affirm that knowledge about one domain of scientific enquiry can be reduced to knowledge about a lower-level domain. Examples of questions which pertain to the theme of epistemological reductionism include how different disciplines within biology are related to each other, and about how biology relates to other scientific domains. For example, one major focus of recent debate has been the question whether classical genetics can be reduced to molecular genetics and biochemistry. Other authors (Beatty 1990, Dupre 1993) have discussed whether evolutionary biology and ecology are reducible to molecular biology. Rosenberg (1997) has further considered whether developmental biology could be reduced to development genetics and molecular biology. And the fundamental question whether biology can be reduced to physics and chemistry is considered by Mayr (2004) and Rosenberg (2006).

⁴ There are, as ever, people who, with varying degrees of force and plausibility, do not adhere to this consensus. We make absolutely no claim to argument here. Our position is philosophically engendered, but is primarily motivated by the aims of this project, which is to explore issues relevant to the practice of current science. See the relevant section of the bibliography for more discussion.

Epistemological reductionism cannot be straightforwardly deduced from ontological reductionism and has – unlike the latter – always been highly controversial. For one thing, it is far more relevant for the day-to-day practice of science. And for another thing, there is the initial question of what it would actually be to reduce one body of scientific knowledge to another. In this regard, attempts can be sorted into two broad categories, models of theory reduction, and models of explanatory reduction.

2.2.1. Theory Reduction

Theory reductionism is basically the view that a ‘higher’ level theory can be logically deduced from a ‘lower’ level theory and is therefore technically redundant. Once again, relevant issues are legion. In order to give a sample picture of the kind of debates that preoccupy the philosophical literature, and to open up further relevant questions, we will focus on two broad models of what theories are and how they function.

2.2.1.1 The Syntactic and Semantic Conceptions of Theories

The debate between proponents of the syntactic and semantic views of theories – both of which views are answers to the question ‘what is a scientific theory?’ – has received much attention recently amongst philosophers of science. In his book *Darwinian Reductionism*, Alex Rosenberg suggests that this debate may have implications for reductionism in biology. By way of introduction, I shall quote Rosenberg (2006: 28-29) at some length:

...reductionism is closely tied to the axiomatic, or so-called syntactic approach to theories, an approach that explicates logical relations among theories by treating them as axiomatic systems expressed in natural or artificial languages. Indeed, closely tied may be an understatement since deduction is a syntactic affair and is a necessary component of reduction. But for a variety of reasons the syntactic approach to theories has given way among many philosophers of biology to the so-called semantic approach to theories. The semantic approach treats theories not as axiomatic systems in artificial languages but as sets of

closely related mathematical models. The attractions to philosophers of biology of the semantic approach must be manifest. For a science like biology, without laws of the sort we meet with in physical science, can hardly display axiomatised theories; and one in which mathematical models figure so centrally in explanations is immediately amenable to analysis from the semantic perspective. But, on the semantic approach, the very possibility of reduction by deductive derivation of the axioms of one theory as theorems of the other became moot. The semantic approach treats theories as families of models, and models as implicit definitions, about which the only empirical question is whether they are applicable to phenomena. For reduction to obtain among theories semantically characterised requires an entirely different conception of reduction. On the semantic view, the reduction of one theory to another is a matter of employing one (or more) model(s) among those that constitute the more fundamental theory to explain why each of the models in the less fundamental theory is a good approximation to some empirical process, showing where and why it fails to be a good approximation in other cases. The models of the more fundamental theory can do this to the degree that they are realised by processes underlying the phenomena realised by the models of the less fundamental or reduced theory. There is little scope in this sort of reduction for satisfying the criteria for postpositivist reduction.

The syntactic conception⁵ of theories – sometimes known as the ‘received view’ (Suppe, 1989) – is the framework within which the Ramsey-sentence method and Russell’s approach to structure are situated. On the syntactic view theories are conceived as linguistic entities, sets of sentences in an axiomatised system, closed under deduction, and expressible in a formal language. The view is characterised as syntactic because elements of the formal

⁵ The label ‘syntactic conception’ is misleading if the alternative is ‘semantic conception’ since this might suggest that on the former view theories do not have semantic interpretations. This is not what proponents of the syntactic conception have in mind; if it were then theories would make no substantive claims about the world. Calling it the received view is also misleading since it suggests wide acceptance. Chakravartty (2001: 325) suggests the ‘the sentential view’ as an alternative label. This is more appropriate, but I will stick with the names by which the account is commonly known.

languages in which theories can be formulated are characterised in terms of their syntactic structure.⁶ As Giere (1988: 47) explains:

Fx , for example, is a one-place predicate function; Rxy a two-place relational function; and $Fa \wedge Fb$, a conjunction of two singular statements, where a and b are the names of particular objects.

In speaking of functions, Giere means that, for example, Fx is a function which could take us from a named object to an attribution of a one-place predicate to that object. Giere imagines a simple first-order language, L . A ‘structure’ for L is defined as a domain of objects plus a function which assigns members of that domain to the one-place predicates of L , and ordered pairs of objects to the two-place predicates, etc. Then a model of a theory, T , is defined as any structure in which the axioms of T are true. Then, for any (consistent) theory there is a set of structures which are models of that theory. On the semantic conception, it is said that we present a theory directly by presenting a set of models without necessarily having recourse to a full axiomatisation of the theory. Theories are not identified with their linguistic formulations, but with what those formulations refer to when given a formal semantic interpretation (Suppe, 1989: 4). A set of models is not dependent on any particular linguistic characterisation of those models, and we can present a set of models in a variety of ways. As Ladyman (1998: 416) notes:

[T]he semantic approach itself contains an emphasis on *structures*. That is, theories are to be thought of as presenting structures or models that may be used to represent systems, rather than as partially interpreted axiomatic systems.

⁶ Giere also notes that on the syntactic conception, certain important logical relationships – including valid inference – are given a purely syntactic characterisation.

Giere suggests that we treat theoretical models as abstract entities having the properties ascribed to them in science textbooks, and writes:

I suggest calling the idealized systems discussed in mechanics texts [for example] “theoretical models,” or if the context is clear, simply “models.” This suggestion fits well with the way scientists themselves use this (perhaps overused) term. Moreover, this terminology even overlaps nicely with the usage of logicians for whom a model of a set of axioms is an object, or a set of objects, that satisfies the axioms. (Giere, 1988: 79)

According to Suppe (1989: 105), the main inspiration for the semantic conception of theories was von Neumann’s (1955) demonstration that two different quantum-mechanic theory formulations described one and the same theory. This fact can be accommodated nicely on the semantic approach, for theories are not identified with their linguistic formulations, but with the models or structures described by various linguistic formulations. The syntactic conception is often criticised on the grounds that by identifying theories with particular linguistic formulations, it implies that a theory cannot be given two different linguistic formulations. As well as conflicting with the von Neumann example, this seems intuitively false. One and the same theory ought to be formulable in different natural or technical languages (Chakravartty, 2001: 326). However, as Chakravartty notes it does not seem that we need to go all the way to the semantic conception of theories in order to avoid this objection. Treating theories as propositions rather than as sets of sentences might be enough, although this depends on one’s understanding of the nature of propositions.⁷

Suppe (1989: 104) complains that the syntactic conception of theories involves correspondence rules which are “a heterogeneous confusion of meaning relationships, experimental design, measurement, and causal relationships, some of which are not properly

⁷ “More specifically, it depends on the extent to which one sees propositions as abstract entities, and free from the shackles of syntax” (Chakravartty, 2001: 326).

parts of theories.” Suppe thinks the semantic conception, according to which such correspondence rules are not properly thought of as part of a theory, is a better way of individuating theories, but it would probably be a mistake if proponents of the semantic conception think that they can avoid committing to linguistic assertions of correspondence between aspects of theoretical models and reality. I will not try to settle the debate between the syntactic and semantic conceptions of theories, but if Rosenberg is right about the implications of this debate for reductionism in biology then this may be an area deserving of further research.

2.2.2. Explanatory Reduction

Explanatory reduction is more concerned with more explicitly anthropocentric issues of understanding and representation. The question is whether elements of scientific study that function at ‘higher’ levels, such as organisms, can be fully explained purely in terms of elements of scientific study that function at ‘lower’ levels. Of course such a question is closely related to the question, mentioned above, of whether *theories* can be reduced (i.e. logically deduced), and many of the same issues arise, albeit on an apparently distinct conceptual axis. Perhaps in parallel with the partial shift in analytic philosophy generally from purely logical, conceptual issues to more grounded experiential issues, current debate focuses more on explanatory reduction. The consensus view is that explanatory reductionism provides a richer and more subtle picture of science than does theory reductionism, since its scope of investigation is wider. Moreover, explanatory reductionism tends to be more explicit about relevant ontological questions and therefore is more explicit with regard to in-practice commitments to ontological reductionism. Still, debates concerned with the variety of epistemological reductionism we are calling explanatory reduction lean toward the abstruse and will not be discussed in detail here. For what the authors of this report consider to be the best contemporary account – which is both itself quite fascinating and unique, in direct

dialogue with the best literature, and in basic confrontation with the surprising so-called anti-reductionist trend in modern biology and philosophy of biology that was mentioned above – see Rosenberg (2006). Brigandt and Love (2008) give an excellent summary of the key elements of Rosenberg’s position in this regard, one which evidences a particular pertinence for this project on reduction in *systems* biology:

Rosenberg’s argument has multiple components. First, nothing less than strict laws (universal, exceptionless, spatio-temporally unrestricted) are required for explanation and the only candidate law in biology is the principle of natural selection. Second, why-necessary explanations are better than how-possible explanations in historical sciences such as biology, but why-necessary explanations are only available at the molecular level because structure becomes decoupled from function above this level. Therefore, all how-possible explanations in ‘functional biology’ (i.e. non-molecular biology), even those invoking the principle of natural selection, and any descriptions from functional biology involving higher levels of organization get explained (why-necessarily) by the principle of natural selection operating on the molecular level (often occurring at some relatively distant point in evolutionary history).

Still, the intricacy and power of Rosenberg’s new approach cannot be done justice to here, and we will now turn to that third kind of reduction that has in fact received relatively little philosophical attention and yet which we intend to focus because of its high importance for the practice of systems biology.

2.3. Methodological Reductionism

2.3.1. The Standard Definition

Brigandt and Love (2008) define methodological reduction in the following way:

...the idea that biological systems are most fruitfully investigated at the lowest possible level, and that experimental studies should be aimed at uncovering molecular and biochemical causes.

This is OK as far as it goes, and it certainly captures something important about methodological reduction. However, we feel it is insufficient in several respects.

2.3.1.1. Two Internal Problems with the Standard Definition

First of all, it does not make explicit the apparent extent of its commitment to ontological reduction. Of course, as we have said above, a certain background presumption of ontological reduction (physicalism, materialism, anti-vitalism, etc.) is not only acceptable but positively required. The problem is that, ideally, at least unless further philosophical reflection accompanies, this presumption should remain highly abstract and should not infringe in such a way as to assume that current best science has already achieved maximal ontological reduction. In other words, the above definition seems to blur, to the detriment of clarity, ontological, epistemic, and methodological domains. For example, what kind of modality is involved in the definition's mention of possibility? For surely, there is *some* sense of possibility – according to the less intrusive presumption of ontological reduction – by which it is *possible* to reduce below the level of molecular and biochemical causes, to the level of exchanges of energy in quantum systems, say. Yet this seems to be overlooked in the definition as it stands above. Does the definition then meant to restrict the kind of modality to some anthropocentric form, to some restricted form of epistemic modality? This sounds right but is not made explicit. Our point for the moment is not that the authors of the above definition of methodological reduction are mistaken, rather it is simply that the above definition is so brief as to be rather unclear.

This unclarity manifests itself in another respect that is also related to ontological reduction, but in opposite fashion. (We take as further testimony to the insufficiency of the standard

definition that it contains two equally internal but *diametrically opposed* problems.) *If one* believes in strongly emergent properties – properties that cannot even in principle be predicted from the bottom up and that cannot even in principle be manifested at lower levels (or that cannot even in principle be decomposed without remainder into properties that can be manifested at lower levels), etc. – *then* the lowest possible level may well be that of the highly complex and organized organism, for example. But if anything is obviously opposed to methodological reduction it is the idea that the proper level of scientific study is a very high one. Once again, we not mean to claim that the authors of the above definition of methodological reduction intended to include such apparent anti-reductionism in the scope of said definition. It is simply that as it stands the definition needs at the very least some elaboration.

2.3.1.2. The Relation of the Standard Definition to Systems Biology

As defined above, the strategy of methodological reduction can well be described as one of ‘decomposition and localization’ (see Bechtel and Richardson (1993)). But in very general terms, the issue of methodological reductionism is simply the issue of to what extent the research project of reductionism in biology is a successful one; it concerns the level of reduction at which it is most useful to consider biological systems. *Prima facie*, then, *systems biology* is antireductionist in this regards, since, as its title suggests, its methodological focus is on systems (wholes) rather than the components (parts) of those systems. Furthermore, it is no coincidence that systems biology is very often a field towards which those who believe in strong emergence gravitate, and conversely, it is no coincidence that those who work in systems biology are not infrequently those who end up defending what they take to be some form of strong emergence. At least this is the standard picture. In last year’s project, however, we argued that strong emergence was much less important to systems biology as it is practiced than many had supposed. Most often, we found, emergence was being used as a

buzz word and in a much weaker sense that is required to deny ontological reduction. For this reason and others that will come out in what follows, things are just not so straightforward.

2.3.2. Groundwork for a Revised Definition – Adding a New Dimension – Reduction To Fundamentality *and* Reduction Of Complexity

To begin with, we think it is useful to designate methodological reduction as best conceived as a sliding-scale, rheostatic, or spectrum concept. The scale or spectrum is to be ordered according to strength, with one extreme denoting what can unequivocally be called *strong* methodological reduction (SMR). This extreme is that which is covered, albeit a little unclearly, by the standard definition: SMR claims that biological systems are most fruitfully investigated at the lowest level possible according to current best knowledge and investigative methods. However, this extreme is just that – an extreme. As one weakens the strength of methodological reduction, and therefore begins to deal with various degrees of *moderate* methodological reduction (MMR), one moves gradually away from the all too restrictive superlative ‘lowest’. So far, then, MMR is to be defined, intentionally equivocally, by the claim that biological systems are most fruitfully investigated by at least taking into account low levels of function in the sense that these levels must remain a bar of consistency and sometimes perform as a real theoretical basis, but that this ‘taking into account’ allows room for the primary investigation of MMR taking place at some non-lowest level.

This may just sound rather vague, but in fact it adds an entirely new dimension of reduction to the definition. Previously, the sole dimension of reduction was that of what we might call *reduction to fundamentality* (RF). What MMR brings into the account, and what is especially pertinent when it comes to systems biology and science as it is practiced in the computer age, is a second, diametrically opposed dimension of reduction that we might call *reduction of complexity* (RC). The idea is that as one moves along the scale of RF, away from the extreme of the lowest level currently possible, one at the same time moves along the scale of RC, *but*

in the opposite direction. For, by the very nature of the kinds of methodological reduction involved, maximizing RF entails minimizing RC, and conversely – the more fundamental one gets, the more complex one gets (in terms of sheer number of variables, if not in terms of covering laws), and the less complex one gets, the less fundamental ones gets.

What we have with MMR, then, is a maximally efficacious compromise between RF and RC – a reduction to fundamentality insofar as it remains compatible with a practical level of complexity. This is the kind of highly context dependent, highly variable reduction, we claim, that systems biology has pioneered. In the next section we explore this rough and programmatic revised definition of methodological reduction by way of a discussion of its various manifestations in selected ground-level research science literature that of interest to systems biology.

3. EXPLORATORY AND EXPLICATORY APPLICATIONS OF THE REVISED DEFINITION OF METHODOLOGICAL REDUCTION

The methodology of systems biology involves an intricate trade-off between two diametrically opposed dimensions of reduction – reduction to fundamentality and reduction of complexity. This is a trade-off between theory and practice, between truth and usefulness. In this section we want to evidence this fascinating trade-off at work.

3.1. Non-Molecular Dynamics Example – Predicting the Properties of Water

3.1.1. Full Paper Reference

Robert Bukowski, Krzysztof Szalewicz, Gerrit C. Groenenboom, Ad van der Avoird, *Predictions of the Properties of Water from First Principles*, SCIENCE Vol. 315, 2007, pp. 1249-1252.

3.1.2. Abstract

‘A force field for water has been developed entirely from first principles, without any fitting to experimental data. It contains both pairwise and many-body interactions. This force field predicts the properties of the water dimer and of liquid water in excellent agreement with experiments, a previously elusive objective. Precise knowledge of the intermolecular interactions in water will facilitate a better understanding of this ubiquitous substance.’

3.1.3. Key Aspects

The paper gives us an excellent example of moderate methodological reduction (MMR). For it is an express purpose of the scientific processes detailed in the paper to both (i) work from a level less fundamental and thereby less complex than the level of quantum mechanical calculation in order to *reduce* computational stress; and yet (ii) work from a level more

fundamental and thereby more complex and comprehensive than the level of empirical data sets in order to *increase* accuracy and generalizability. Both (i) and (ii) can properly be called examples of methodological reduction, although they are kinds of methodological reduction that pull in diametrically opposed directions. The tension that this creates in the methodology of the experiments and calculations detailed in the paper keeps it somewhere inbetween the extreme of a complete reduction to the most fundamental level on the one hand and an epistemologically maximal reduction of complexity on the other hand. Hence *MMR*.

3.1.4. Relevant Background

3.1.4.1. Experimental

Previous work on predicting the properties of water has tended to polarize in terms of methodology, either working from empirical evidence bases and thereby privileging *reduction of complexity*, or working from ‘ab initio’ (literally ‘from the beginning’, i.e. most fundamental according to current best theory) quantum mechanical calculations and thereby privileging *reduction to fundamentality*.

However, both extremes have severe restrictions. On the one hand, predictions of the properties of water from empirical evidence bases have been relatively inaccurate and ungeneralizable to so-called extreme regimes, such as condition supercritical, overcooled, and confined water. On the other hand, while predications from ab initio quantum mechanical calculations are both highly accurate and highly generalizable to such extreme regimes, they are difficult to implement in the sense that they require a huge computational capacity – in effect, they are in principle but not practice highly generalizable.

3.1.4.2. Motivation

The authors of the papers therefore saw adequate motivation to develop a more moderate method of prediction from what we can call mid-level knowledge bases instead of either low-level (fundamental) or high-level (empirical) knowledge bases. This method takes certain

higher level knowledge bases and is at least compatible, consistent, and in some cases derived from the lower, quantum level knowledge bases in order to produce predictions of the properties of water with ‘virtually the same’ (p.1249) accuracy as those from purely lower knowledge bases but with much less demand on computational capacity, which in turn is what enables not only in principle but also in practice generalizability to extreme regimes.

Clearly this paper is not only an extremely apposite example of MMR, but it also makes explicit just how important considerations of efficacy are when it comes to determining choice of methodological reduction. It is therefore not only scientifically moderate but philosophically so too.

3.1.5. A Note on the Title

From what has been said above it is clear that the title of the paper is misleading, for it is an explicit intention to avoid wholesale reduction to fundamentality in order to at the same time reduce to a certain extent complexity of calculation. Surely, then, the paper explicitly does not concern predictions of the properties of water from *first* principles! It might be better to say that it works from *second* principles *that are consistent with and in some cases derived from* first principles, although of course this would not result in a very catchy title.

This character of misleadingness may be dismissed as simply due to carelessness, or even better, in some sense excusable due to those second principles at least being consistent with and in some cases based on first principles. However, it does not seem wholly unreasonable to speculate as to another explanation. Perhaps the title of the paper is supposed to lock on to or even subtly endorse the general reductionist research program that has taken centre stage in philosophical and scientific debates surrounding biology since the discovery of DNA by Watson and Crick (1953).

Of course, the important point as regards the specific methodology of the paper is that molecular dynamics simulation is not used.

3.1.6. The Relevance of Water for Systems Biology

We have, primarily as a tentative working hypothesis, endorsed the presumption that the biological sciences are ‘in principle’ reducible to the physical sciences. In turn, this is primarily on account of the more basic presumption that living biological organisms are ‘in principle’ reducible to their non-living, physical components. (This is intimately connected to our earlier claim that living biological organisms cannot properly be said to exhibit what we have called strongly or ontologically emergent properties. Although at the same time we have allowed that such organisms might well – usefully, accurately, and rigorously – be attributed what we have called weakly or epistemologically emergent properties.)

In a sense, then, we have endorsed the idea that, strictly speaking, the biological sciences have no unique subject matter (although it cannot be emphasised enough that this says nothing as to whether biological idioms provide a useful heuristic). This, however, is highly contentious, and it at least deserves more closely focused and philosophically rigorous attention than we have been able to grant it.

Nevertheless, when it comes to water, things may seem entirely uncontroversial. After all, it is simply a chemical substance, exhibiting none of the characteristics that typify the living organism. Surely, therefore, the study of water surely belongs properly to the physical sciences regardless of one’s more abstract philosophical views. This is of course entirely correct, at least as far as it goes. But it does not go very far. Things are not so simple.

Water, like carbon, is crucial for life as we know it (to put it mildly!), and for that reason it fully deserves a central place among the amorphous kernel of subject matter the study of

which defines the life sciences. So much for the relevance of a paper on water for *biology* generally.

Water can be seen as particularly relevant for *systems* biology specifically in virtue of one undeniable fact: the simplicity of the individual water molecule belies the incredible complexity exhibited by systems of such molecules, as for example constitute pure water in its liquid form and its solid form.

3.1.7. Selected Quotations

3.1.7.1. Implicit Relevance for Systems Biology

‘Water has been extensively studied on account of its ubiquity and importance for so many aspects of human activity. The deceptively simple water molecule forms one of the most complex liquids and solids...’

3.1.7.2. Difficulties with Previous Empirical Level Studies

[i.e. difficulties with reduction of complexity at the expense of reduction to fundamentality] ‘...theoretical analyses of water, all of which require knowledge of the intermolecular potential (the derivatives of this potential give the force field that governs the dynamics). Most such investigations use empirical pair potentials fitted to reproduce certain measured bulk properties in Monte Carlo (MC) or molecular dynamics (MD) simulations of water. These “effective” potentials account for the important many-body interactions in water by (nonphysical) deformations of the true pair potential. The well-known result is that such potentials poorly describe the water dimer, give very inaccurate second virial coefficients, and fail to reproduce experimental spectra of small water clusters. Therefore, studies of molecular-scale properties of water with empirical potentials, such as the molecular jump mechanism of water reorientation, may suffer from an inadequate representation of the force field. Another known drawback of empirical potentials is that the quality of their predictions deteriorates quickly beyond the range of thermodynamic parameters used in the fitting procedure. Moreover, there does not appear to be any systematic method to improve the predictive accuracy of these potentials.’

3.1.7.3. Difficulties with Previous Quantum Level Studies

[i.e. difficulties with reduction to fundamentality at the expense of reduction in of complexity] ‘Another way of obtaining the force fields – which does not require prior knowledge of any experimental data – is by quantum mechanical ab initio calculations. Such an approach can provide the most reliable foundation for an understanding of water and other substances. However, the accuracy of ab initio force fields is limited by unavoidable approximations in the level of theory and incompleteness of basis sets.’

3.1.7.3. Success of Mid-Level Approach

‘The accuracy of the current calculations is virtually the same as that of the most extensive published ab initio work... However, the cited calculations [that is, as are presented in previous papers] have been performed only for a few selected geometries of the dimer, whereas we have obtained the complete six-dimensional potential surface.’

‘The ab initio water pair potential developed in this work recovers well a diverse range of experimental data... These predictions, made entirely from [misleadingly so-called] first principles, are of comparable accuracy to results of simulations with empirical potentials fitted to liquid water experimental data... We believe that the ab initio force field presented here will find numerous applications in predicting the properties of water. It can be used, for example, to resolve the current controversies about the coordination of water molecules in the liquid. The analysis of the temporal structures in MD [i.e. molecular dynamic] simulations should provide the ultimate picture of liquid water. The force field can also be used to investigate the numerous polymorphic forms of ice. Important applications can be made in extreme regimes where empirical potentials fail completely, such as supercritical, overcooled, or confined water. Further improvements in the first-principles predictions for water should take account of the monomer flexibility and of quantum effects in the liquid simulations. For the former case, the first step has recently been attained. Quantum effects in molecular simulations can be

accounted for by either path-integral MC [i.e. Monte Carlo] or centroid MD methods.’

3.2. Molecular Dynamics Examples – Membranes and Lipids

3.2.1. Introducing Molecular Dynamics

3.2.1.1. Full Paper Reference

D.P. Tieleman, S.J. Marrink, H.J.C. Berendsen, *A Computer Perspective of Membranes: Molecular Dynamics Studies of Lipid Bilayer Systems*, BIOCHIMICA ET BIOPHYSICA ACTA 1331, 1997, pp. 235–270.

3.2.1.2. Abridged Introduction

‘Knowledge of the structure and dynamics of membranes has traditionally been fragmentary at the atomic level. This is due partly to the fluid character of membranes under physiological conditions, and partly to the lack of experimental data that are directly interpretable in terms of positions and motions of atoms. In the last decade the availability of powerful computers has opened new ways to study lipid bilayers in atomic detail. Computer simulations now offer a detailed picture of structure and dynamics of membranes...

The important question to ask is: do simulations represent the truth? Is the apparent disorder, compared to most traditional textbook pictures, real? Do simulations have predictive power? What are the possibilities and limitations of these new techniques?

With these questions in mind, we will review simulation studies that use the molecular dynamics technique to study the structure and dynamics of lipid bilayers and molecules that interact with lipid bilayers in atomic detail. This excludes a number of other theoretical approaches...

The molecular dynamics technique has developed over the last decades from a method to study the dynamics of liquids of solid spheres and Lennard–Jones particles to a versatile method to study many different types of systems at atomic resolution. In the field of biophysics a large body of MD studies on proteins in vacuum or in solvents is available... it became clear that MD,

subject to certain limitations, can give detailed insights into the motions of lipids and proteins.

In this review we will focus on the application of MD to biologically relevant lipid and lipid–protein systems. We start with a brief description of the MD technique, its potential for use in simulations of lipid bilayers and its main limitations. Then we proceed to a brief description of experimental data that can be used to validate the results of simulation studies. We review the structure of a pure DPPC liquid crystalline bilayer, the main model system thus far, as it emerges from simulations. Simulations of other phases, lipids, and mixtures of lipids with cholesterol are described. We review a number of current applications of MD, focusing on phenomena of biological importance: transport of small molecules across the bilayer, the connection between lipid structure and the so-called ‘hydration force’, and lipid–protein interactions. We conclude with a brief outlook on future developments.’

3.2.1.3. Key Aspects

This review has many relevant aspects but we will focus on one that is of particular interest for our proposed second dimension of reduction, reduction of complexity (although inevitably, since we have seen they are intertwined, issues regarding reduction to fundamentality will also arise). After the authors’ summary account of molecular dynamic simulation they propose three primary limitations that dog this method. Each is dealt with in turn in what follows:

3.2.1.3.1. Limitation 1 – Classical versus Quantum Treatments

(Warning: essentially, this limitation represents a potentially mammoth philosophical side issue that will not be pursued or even properly explained and expanded on here. Please feel free to skip to the next limitation.) In molecular dynamics simulations all relevant atoms are treated classically. Apparently, there is currently no consequence for simulations of lipid systems, but clearly, as regards a practical principle of consistence-with-reduction-to-fundamentality and a theoretical guiding principle of maximal possible (in terms of efficacy)

reduction to fundamentality, this situation is not ideal. Nevertheless, the explicit classical framework is perhaps the most salient element of molecular dynamics with regard to reduction of complexity. There are some very big questions here, such as: is the trade-off between reduction of complexity and reduction to fundamentality that we have posited constitutes what can be called a contemporary methodological reductionism, really a trade-off, or is it fact merely a poisoning of the truth with practical considerations? This in turn leads us to some very big questions about what we take science to be, what we take its goals and presumptions and methodologies to be and imply, what we take our theories to signify or denote. And then, of course, we are eventually led to questions of what we take our representation of the world to amount to. Here we have long since strayed too far in to the realm of abstruse philosophy, but the logical imperative to follow this line of reasoning bears mention.

3.2.1.3.2. Limitation 2 – Arbitrary Parameter Choice?

The simplification of the model with respect to the ‘real’ situation that it is intended to represent leads to certain problems. Many of the required variables can be derived and accounted for through experiment or quantum mechanical calculation, but other variables that would presumably apply in the ‘real’ situation have been removed in the name of reduction of complexity. While this need not necessarily impact on the accuracy or generalizability (etc.) of the results of the simulation, in order to *ensure* a nonmisleading selection of pertinent parameters has taken place, extensive testing is required. Once again, practically speaking, there must be a trade-off, guided solely by questions of efficacy, between the usefulness of reduction of complexity on the one hand and the irritant of ensuring correctness of procedure on the other hand.

The relevant moral is: while it looks to be acceptable to make a reduction of complexity at the explicit expense of a reduction to fundamentality, this utilitarian compromise must always

be rendered at the very least *consistent with* a total reduction to fundamentality (although it goes without saying that it need not be derived from such a reduction) – in short, it must remain reliable enough to preserve the connection we take our scientific models to have, at whatever level they operate, to the truth.

3.2.1.3.2. Limitation 3 – Timescale (etc.) Restrictions

Due to the limits on computational power – or, which amounts to the same thing practically speaking, due to the fact that reduction of complexity must be moderated at all times by considerations of truth, they must be tempered by a general theoretical principle of reduction to fundamentality – the scope of molecular dynamics is currently quite restricted. For example, take the timescale of a simulation, that is, the duration over which one wishes to observe the changes in some given molecular-scale system. Typically (although there are of course significant deviations, depending on various variables but in particular complexity of model and speed of computer), a supercomputer will take somewhere between one and two weeks to run a model that is intended to simulate the dynamics of a molecular scale system over just a single nanosecond!

One may take this limitation in either of two ways. On the one hand, one may take this current limitation of scope as indicating a limitation to the method of molecular dynamics simulation itself. On the other hand, if one is committed to the idea – really an amorphous research programme – that detailed computer simulations of low-level (i.e. reduction to fundamentality) biologically relevant systems is the way to go, then one may take this current limitation of scope as indicating that efforts at reduction of complexity must be redoubled. Those who favour the latter route have birthed what may well class as an entirely new research programme, namely, one of exploring ways to improve such simulation. Of course there are many ways to pursue this, but one notable and relevant way is by exploring techniques of reduction of complexity. Hence so-called course-graining – see our next two

examples, which both evidence course-graining of molecular dynamics simulations. The next example in particular is aimed specifically at maximizing the timescales that are, realistically, available for molecular dynamics simulation. Millisecond durations are apparently now within reach. In the seven years between these papers (the present one and the one immediately following), this is surely a significant result in favour of the worth of spending time on improving techniques of reduction of complexity, a mainstay methodology of *systems* biology.

3.2.1.4. Selected Quotations

3.2.1.4.1. Limitation 1

‘In a molecular dynamics simulation all atoms in the system under consideration are treated classically’

‘...the classical treatment of the system... makes it impossible to consider chemical reactions without describing at least part of the system quantum mechanically, but is currently of no consequence in simulations of lipid systems’

‘The force field is the description of interactions and the parameter set that belongs to it. There are many choices in the literature... Parameters in different sets are internally consistent, but this is not necessarily true between different sets.’

3.2.1.4.2. Limitation 2

‘The precise form of this potential function is a choice for which there are many options. In particular, different forms for the van der Waals interactions and the dihedrals are in common use and the bonds are often constrained in simulations. However, the form given here is reasonably general and shows the most important assumptions that are made: only pair-additive interactions are taken into account (non-bonded interactions involving three or more atoms are

neglected), atoms are represented as point charges (electronic polarizability is neglected) and simple quadratic forms are used for computational efficiency’

‘The potential function requires a large number of parameters for partial charges, van der Waals interactions, equilibrium values for bonds, angles and dihedrals, and force constants. Many of these values can be obtained from either experiment (spectroscopy) or quantum mechanics, but because of the simplified form of the potential function compared to the ‘real’ function, there is no guarantee that these parameters will give good results. In particular, the omission of atomic polarizability in the commonly used force fields influences the force field parameters such that average effects of polarizability are retained but detailed effects are not properly represented. Additionally, some parameters like the dispersion in the van der Waals interactions and the height of the barriers in the dihedral potentials are difficult to determine. This uncertainty in the parameters makes extensive testing of parameter sets on simple systems, which can be compared to experimental data, necessary. In fact, often parameters are treated as empirical values that can be obtained by fitting models to experimental data, e.g. a water model to experimental data on water’

‘simulation-method details influence the parameters. Therefore, parameters may need to be adjusted when the simulation conditions or algorithms are changed. An example of this is the behavior of a popular water model, TIP3P. Feller et al. found rather drastic changes in the properties of TIP3P water when they used Ewald summation instead of a simple cutoff for electrostatic interactions and concluded that the model needed reparameterization.’

3.2.1.4.3. Limitation 3

‘...the maximum timestep for which the integration of the equations of motion is still stable. A typical value in practice is 2 fs (10^{-15} s). This means that 500 000 computationally expensive integration steps are necessary (taking in the order of one to two weeks on a supercomputer for typical systems) to calculate the dynamics of a system during 1 ns. This limits the lengths of current simulations to the nanosecond time scale. The same practical limit on

computer power dictates that the largest system that currently can be handled is of the order of tens of thousands of particles, corresponding to system sizes of roughly 5–10 nm’

‘...any simulation of a lipid bilayer at the current state of the art will stay relatively close to the initial configuration, since the rotational and translational motion of lipids is too slow to sample in a few nanoseconds. This is not necessarily a problem, but it cannot be expected for instance that phase separation is observed when two different types of lipids are mixed. This is an important consideration in the simulation of the interaction of phospholipids with cholesterol or the interaction between proteins and lipids, to name but two applications. In practice, the size of a model bilayer in a simulation is currently limited to ca. 100–200 lipid molecules; 50–100 lipids is the most popular size. Usually, periodic boundary conditions are used to avoid strong artefacts from the presence of boundary planes, so that effectively a stack of bilayers with infinite dimensions is simulated. In the literature the length of simulations is limited to a few nanoseconds; most simulations are less than a nanosecond. Although many interesting phenomena occur on the nanosecond time scale, processes like phase transitions, phase separation in lipid mixtures, membrane fusion, protein folding or protein insertion into membranes are well out of reach of straightforward molecular dynamics.’

3.2.1.4.4. Key Conclusion

‘...straightforward MD is an excellent method to study the dynamics of tails and individual lipids. This is an important application because MD can give detailed atomic pictures that can be used for the interpretation of, e.g., NMR studies on relaxations and diffraction studies on the rather disordered lipid membranes. It is also possible to study the behavior of solvent molecules in and near bilayers, as well as the differences in behavior of different types of lipids in terms of structure and solvent dynamics.’

3.2.2. Coarse Graining in Molecular Dynamics 1

3.2.2.1. Full Paper Reference

Siewert J. Marrink, Alex H. de Vries, and Alan E. Mark, *Coarse Grained Model for Semiquantitative Lipid Simulations*, J. PHYS. CHEM. B 2004, 108, pp. 750-760

3.2.2.2. Abstract

‘This paper describes the parametrization of a new coarse grained (CG) model for lipid and surfactant systems. Reduction of the number of degrees of freedom together with the use of short range potentials makes it computationally very efficient. Compared to atomistic models a gain of 3-4 orders of magnitude can be achieved. Micrometer length scales or millisecond time scales are therefore within reach. To encourage applications, the model is kept very simple. Only a small number of coarse grained atom types are defined, which interact using a few discrete levels of interaction. Despite the computational speed and the simplistic nature of the model, it proves to be both versatile in its applications and accurate in its predictions. We show that densities of liquid alkanes from decane up to eicosane can be reproduced to within 5%, and the mutual solubilities of alkanes in water and water in alkanes can be reproduced within 0.5 kT of the experimental values. The CG model for dipalmitoylphosphatidylcholine (DPPC) is shown to aggregate spontaneously into a bilayer. Structural properties such as the area per headgroup and the phosphate-phosphate distance match the experimentally measured quantities closely. The same is true for elastic properties such as the bending modulus and the area compressibility, and dynamic properties such as the lipid lateral diffusion coefficient and the water permeation rate. The distribution of the individual lipid components along the bilayer normal is very similar to distributions obtained from atomistic simulations. Phospholipids with different headgroup (ethanolamine) or different tail lengths (lauroyl, stearyl) or unsaturated tails (oleoyl) can also be modelled with the CG force field. The experimental area per headgroup can be reproduced for most lipids within 0.02 nm². Finally, the CG model is applied to nonbilayer phases. Dodecylphosphocholine (DPC) aggregates into small micelles that are structurally very similar to ones modeled atomistically, and DOPE forms an inverted hexagonal phase with structural parameters in agreement with experimental data.’

3.2.2.3. Key Aspects

In a nutshell, the key aspect of this paper is the way it presents a coarse graining model that successfully trades a large reduction of complexity for a small loss of reduction to fundamentality – it makes molecular dynamics modelling more useful without deviating too much from the truth. In particular, to connect this paper explicitly with the potential problems for molecular dynamics that we outlined from the previous example, the coarse grained model presented here enables full millisecond timescales (and micrometer lengths), a possibility that was merely speculated as nearly in reach at the time of the previous paper. This is a substantial, concrete improvement in the ratio of the two dimensions of reduction.

Moreover, whilst the paper does itself go some way towards *applying* the model developed therein, its primary focus is what we might call *metemethodological*, in that it focuses on developing a general technique for improving the efficiency of the trade-off between reduction of complexity and reduction to fundamentality. In a sense, then, this is a scientific research paper, roughly in the area of systems biology, that not only implicitly utilizes consideration regarding methodological reduction but explicitly focuses on them – it is a systems biology paper on methodological reduction understood as involving simultaneously both of the dimensions that we have identified.

3.2.2.4. Selected Quotations

3.2.2.4.1. Maximizing the Trade-Off

‘To improve on the CG models currently available, four aspects are deemed important: speed, accuracy, applicability, and versatility. In the CG model presented in this paper these four aspects are optimized simultaneously: (i) Speed is obtained by including only short-range interactions and by the use of smooth potentials such that large integration steps can be used. (ii) Accuracy is

maximized by matching CG results to atomistic simulations as much as possible, for a variety of components and phases simultaneously. In this process structural and dynamical as well as thermodynamical data are used. (iii) Applicability is enhanced through the simplicity of the force field, the use of standard interaction potentials, and few parameters. Furthermore, the parameters are physically meaningful and used in a consistent manner. (iv) Versatility is implied as the force field leaves enough room to accommodate structural detail of molecules, and because there is no restriction to the phase of the system.’

‘In the introduction four cornerstones for a successful coarse grained model were defined: speed, accuracy, applicability, and versatility. The coarse grained model presented in this paper has been optimized to match these criteria as well as possible. (i) Speed: A speed up factor between 10 and 25 is obtained due to the use of a 50 fs time step instead of 2-5 fs maximum for atomistic simulations. The reduced number of interaction sites allows simulations approximately between 5 (for force field with unified methylene groups) and 10 times faster (for force fields that have explicit hydrogens). Furthermore, the short-range nature of the interactions speeds up the calculations between 3 times (compared to simulations using typical cutoffs of 1.4 nm) and 10 times (when Ewald summation type techniques are used to treat the long-range interactions). The increased dynamics in the CG model results in another effective speed up with a factor of ~ 4 . Together, these factors result in a speed up of 3-4 orders of magnitude with the CG model compared to currently used atomistic simulation techniques. Also compared to the semiquantitative CG model of Shelley et al.¹⁸ the current model is much faster and comparable to the speed obtained with DPD techniques. (ii) Accuracy: The CG model is shown to be accurate at least at a semiquantitative level for structural, elastic, dynamic as well as thermodynamic properties for a range of lipid systems. Structural properties of lipid systems such as the area per headgroup in the lamellar phase or the hexagonal spacing in the inverted hexagonal phase agree well with the available experimental data. Compared to results obtained with atomistic simulations, atom density distributions are very similar in all cases considered. Elastic properties computed for a DPPC bilayer such as the

bending modulus, the line tension or the area compressibility are of the same order as the experimental measurements. The absolute dynamics in the CG model is faster compared to real systems or simulations with atomistic force fields. The relative dynamics, however, appears well preserved. With a time conversion factor of 4 a variety of dynamic properties such as self-diffusion in bulk phases and lipid lateral diffusion, the permeation rate of water across a membrane, or the lipid self-aggregation rate are meaningful at a semiquantitative level. Thermodynamically speaking, the CG model has encouraging properties too. Not only is the mutual solubility of water and alkane well reproduced, but more importantly lipids aggregate into the correct phases whether lamellar, micellar or hexagonal. For DPPC a freezing transition was even observed when the temperature was lowered below the main phase transition temperature. (iii) Applicability: The use of physically meaningful parameters makes the model easy to interpret. Instead of dealing with reduced units that need conversion afterward, it is immediately clear what the state conditions are. The limited number of particle types and interaction levels provide for a small set of building blocks from which related molecules that are expected to perform at the same level of accuracy as the examples given in this paper can be easily constructed. (iv) Versatility: Although optimized mainly for lipid systems in the lamellar phase, the CG model has no built in restrictions as to the phase of the system. The lipids in the CG model are very flexible, free to adapt (almost) any conformation at a reasonable energy cost. Two applications to nonlamellar systems were used to illustrate this versatility.’

3.2.2.4.2. Utility Guided Coarse-Graining in Action

‘A four-to-one mapping is used to represent the molecules in the simplified model; i.e., on average, four atoms are represented by a single interaction center. This rule is not strict, as sometimes it is appropriate to map three, five, or more atoms into one interaction center. Because of their small size and mass, hydrogen atoms are not considered at all.’

‘Realistic masses can be assigned to the particles, but for reasons of computational efficiency, the same masses can be used. In the applications

described here a mass of $m = 72$ amu (corresponding to four water molecules) is assigned to each site unless otherwise stated.’

3.2.2.4.3. Timescale Issues

‘Although the variables of the CG system (densities, length scales, energies, temperature, pressure) keep their physical meaning, this is not strictly true for the time scale. The dynamics are faster because the CG interactions are much smoother compared to atomistic interactions. On the basis of comparison of diffusion constants in the CG model and in atomistic models, the effective time sampled using CG is 3-6 times larger. Note that this factor affects ALL the dynamics present in the system. The relative dynamics present within the system appears to be well preserved (within a factor of 2). When interpreting the simulation results with the CG model, one can to a first approximation simply scale the time axis. The standard conversion factor we use is a factor of 4, which is the effective speed up factor in the diffusional dynamics of CG water compared to real water.’

3.2.2.4.4. Limitations

‘...the CG model as presented in this paper is limited. There will be many applications for which it is not well suited. Further optimizations are possible but as with any CG model its utility is inherent in its simplicity. Any application for which long-range electrostatic forces are important should be considered with care. Fine chemical detail is inaccessible in any coarse grained approach. One should be careful not to overinterpret the results on a quantitative level. The CG model is not a tool to replace atomistic simulations, but rather the two should be used side by side. With the CG model the long time-scale or length-scale properties of the system of interest can be explored, whereas with atomistic models the details can be studied. Results from atomistic simulations should be used as much as possible to judge the quality of the CG force field in the application at hand.’

3.2.3. Coarse Graining in Molecular Dynamics 2

3.2.3.1. Full Paper Reference

E. Jayne Wallace, Mark S. P. Sansom, *Blocking of Carbon Nanotube Based Nanoinjectors by Lipids: A Simulation Study*, NANO LETTERS, Vol. 8-9, 2008, pp. 2751-2756.

3.2.3.2. Abstract

‘Carbon nanotubes (CNTs) are possible nanoinjectors for the introduction of therapeutic agents into cells. To explore their interactions with a lipid bilayer membrane and to model the nanoinjection process, we used coarse-grained molecular dynamics to simulate the penetration of dipalmitoylphosphatidylcholine (DPPC) bilayers by single-walled CNTs. Lipids are extracted from a bilayer during CNT penetration and reside on both the inner and the outer tube surfaces. Lipids that interact with the CNT interior wall spread out and hence can “block” the tube. However, the degree of lipid lining of the inner surface is strongly dependent upon the tube penetration velocity, with fewer lipids extracted from the bilayer at higher rates. There is no apparent effect on bilayer integrity after CNT penetration, with the bilayer able to self-seal. Our findings reveal some of the complexities of the interactions of lipids with CNT nanoinjectors and suggest a need to further characterize the influence of, for example, CNT functionalization and cargo on lipid blocking of CNTs.’

3.2.3.3. Relevant Background

Carbon Nanotubes (CNTs) might enable a way of delivering drugs into cells that proves highly relevant for medicine, among other biologically relevant sciences. However, the nature of the interaction between CNTs and the cell membranes through which they would of necessity deliver their load if they were indeed to provide such a function is not well understood. This is due at least in part to a relative lack of simulation studies of this kind of interaction. Hence the present paper.

3.2.3.4. Key Aspects

The key aspect of this paper for us is its implementation of co-called course-graining techniques applied to molecular dynamics, a form of computer simulation ubiquitous in

systems biology. Coarse grain models represent groups of atoms (of various small sizes) as single interaction sites, which is to say that coarse grain models aim inherently at what we have called reduction of complexity. However, the intention is always to remain consistent with the lower level description and thus to accurately represent whatever phenomena are in question. Moreover, it is the reduction of complexity itself which allows (the potential for) greater generalizability. This is because the simpler the model, the more frequently it can be run, thus generating a high result output (although this in itself does not of course generate high generalizability of prediction etc.).

3.2.3.5. Selected Quotations

3.2.3.5.1. Motivation

‘If CNTs are to be exploited as delivery systems (either experimentally or therapeutically), it is of both fundamental and practical interest to understand the interaction between CNTs and biological membranes. To date, the uptake mechanism of CNTs awaits consensus, with some reports stating that CNTs may enter cells via endocytosis, while others imply that CNTs undergo spontaneous insertion and diffusion across the cell membrane. While molecular dynamics and related simulations have been used quite extensively to study the properties of CNTs and of fullerenes, there are relatively few simulation studies that address the interaction mechanism between CNTs and lipid bilayers. Thus, while Klein and co-workers have performed simulations of hydrophobic nanopores inserting into bilayers, there are currently no simulation studies that examine the entire process of CNT entry into and exit from a lipid bilayer.’

3.2.3.5.2. Course Graining Implementation and Benefits

‘We implement the CG methodology developed by Marrink et al. whereby one particle comprises approximately four heavy (i.e., not hydrogen) atoms... This model leads to an ~100 fold increase in speed with respect to atomistic simulations, therefore, allowing the simulation of large systems for longer timescales. We have recently extended the CG model developed by Marrink to

enable simulation of the self-assembly of CNTs with lysophosphatidylcholine, a detergent which shares a common headgroup with DPPC. This model accurately reproduced experimental data and thus is appropriate to study the interactions between CNTs and phospholipid bilayers.’

3.2.3.5.3. Differences to Experimentation

‘In comparing experiments and simulations, the pulling velocities achievable via CG SMD are ~5 orders of magnitude higher than in experiment... we can expect the maximum forces observed in our SMD simulations to be larger than those in experiments. This is indeed what we see... Therefore, given experimental velocities are smaller than the simulated ones, it seems reasonable to assume that lipid extraction will occur.’

3.2.3.5.4. Differences to Atomistic Simulation

[i.e. differences between course grained and non-course grained simulation; note the select use of ‘smooth’, which relates to the question as to the accuracy of simulation, the question of whether simulations simulate what actually happens, the truth] ‘It is also useful to compare CG and atomistic simulations. A force of ~100 pN is required to pull a single lipid out of a bilayer at $V = 5 \text{ \AA/ns}$ using the CG methodology (see Supporting Information, Figure S2). In an analogous atomistic MD study,³¹ a force ~200 pN was needed to pull a lipid out of a DPPC bilayer at velocities ~20 \AA/ns . As we might expect the CG methodology to “smooth” interactions between lipid molecules relative to atomistic simulations, this is an acceptable level of agreement. Hence, the pulling forces measured for the differing CNT orientations and size may represent lower bounds relative to atomistic simulations.’

4. CONCLUSION – REDUCTION AND LEVELS

In accordance with much of the philosophical and scientific literature on reduction, we have identified and very briefly discussed three different kinds of reduction – ontological, epistemological, and methodological. While all kinds of reduction are to varying degrees intimately connected with one another, and while all certainly deserve serious philosophical attention, we soon found that the latter – methodological reduction – is both the natural focus of a project such as this and also the kind of reduction that has received the least attention from philosophers. On the one hand, ontological reductionism – roughly equated with physicalism and materialism, and opposed to vitalism – is about as philosophically and scientifically uncontroversial as a thesis gets (which is not to say there is universal consensus), and for perhaps this very reason is highly interesting to philosophers. And on the other hand, epistemological reductionism – its nature, its tenability, everything about it – is about as hotly disputed in the philosophical literature as a thesis gets, and of course for this reason is highly interesting to philosophers. Both, however, are rather abstract philosophical topics and have relatively little to do with the day-to-day practice of science. With ontological reduction, this is probably because it has functioned as an absolutely unquestionable assumption of scientific methodology since the modern age – it is less a scientific research programme itself as the foundation of all specific scientific research programmes. This detachment from day-to-day scientific practice is perhaps less the case with epistemological reduction, since discussions surrounding this kind of reduction usually focus on the nature of relations between theories and explanations, both of which no doubt play a major role in day-to-day ground-level research. Nevertheless, despite the fact that discussions of epistemological reduction, more so than those of ontological discussion, concern themselves with specific theories and often require a detailed knowledge of some relevant area of science, it is not so much the case that

in practice some area of science concerns itself overmuch with the shape philosophers think its theory should take – in short, the relationship is rather one-way. We neither assert nor deny that this is as it should be, and we would readily concede that there are probably some notable exceptions – we merely mark a modest observation as part of the complex cause of our primary focus on methodological reduction.

Regarding methodological reduction, we have deviated far more from the standard literature and consensus than in our brief discussions of the other forms of reduction. In particular, we have consciously done far more to align it, or rather make of exemplary relevance for, day-to-day scientific practice, and in particular the practice of systems biology. As such, we identified within the standard definition a single dimension or axis of reduction, that of reduction to fundamentality. Coming from a philosophical background this dimension of reduction is the most obvious candidate because it provides the clearest links with the issues that arise with ontological reduction especially, but also with epistemological reduction – namely, issues regarding fundamental truth and the basic stuff of the universe. However, coming from a less theoretical background, and in particular coming from a practical-level systems biology point of view, we claimed that it becomes equally clear that another, altogether different dimension of reduction needs to be taken into account, namely that of reduction of complexity. A trade-off between these two crucial aspects of scientific practice – in essence a trade-off between theory and practice, between truth and usefulness – best characterises the loosely unifying research methodology that typifies what gets called systems biology. This is something we have started to support with the examples of the previous section. However, there is clearly much more room for support of this kind, and we are sure that time spent on expanding this example base will prove fruitful, although we cannot achieve this in the current project.

To conclude we intend to take a slightly different, tentative but suggestive track. Berendsen (2007), in his excellent book on simulating the physical world with computer models includes a detailed hierarchy of levels of description, along with the various aspects of systems and rules that each of those levels focuses on, what each levels ignores and cannot take into account, and where each levels stands in approximation to other levels (his focus is physical, not biological). The concept of level is one we have not explicitly tackled in this project, although we were notionally mandated to do so in our project proposal. To some extent, much of what can be said about the concept of level can be read directly off what we have said about the two dimensions of reduction involved in our revised working definition of methodological reduction. In a straightforward sense, each step of reduction to fundamentality takes us down a level, just as each step in reduction of complexity takes us up a level. But then there are many troublesome worries to do with the relativity of words such as ‘up’ and ‘down’, just as there are with words such as ‘low’ and ‘high’. Is it best to call a reduction to fundamentality a step down or a step up? Is the most fundamental level of description of the universe the lowest level, or the highest? We have not resolved these rather superficial issues, but much of what is interesting underlying them has been dealt with, at least implicitly, above. Nevertheless, in partial recompense, we offer here a basic diagram of some of the different levels of function, based heavily on Berendsen’s (2007: 9-12) but simplified and with our dimensions of reduction added. What Berendsen says about his levels-hierarchy makes it clear that there is a close connection between it and the trade-off between the two dimensions of reduction upon which we have placed so much emphasis:

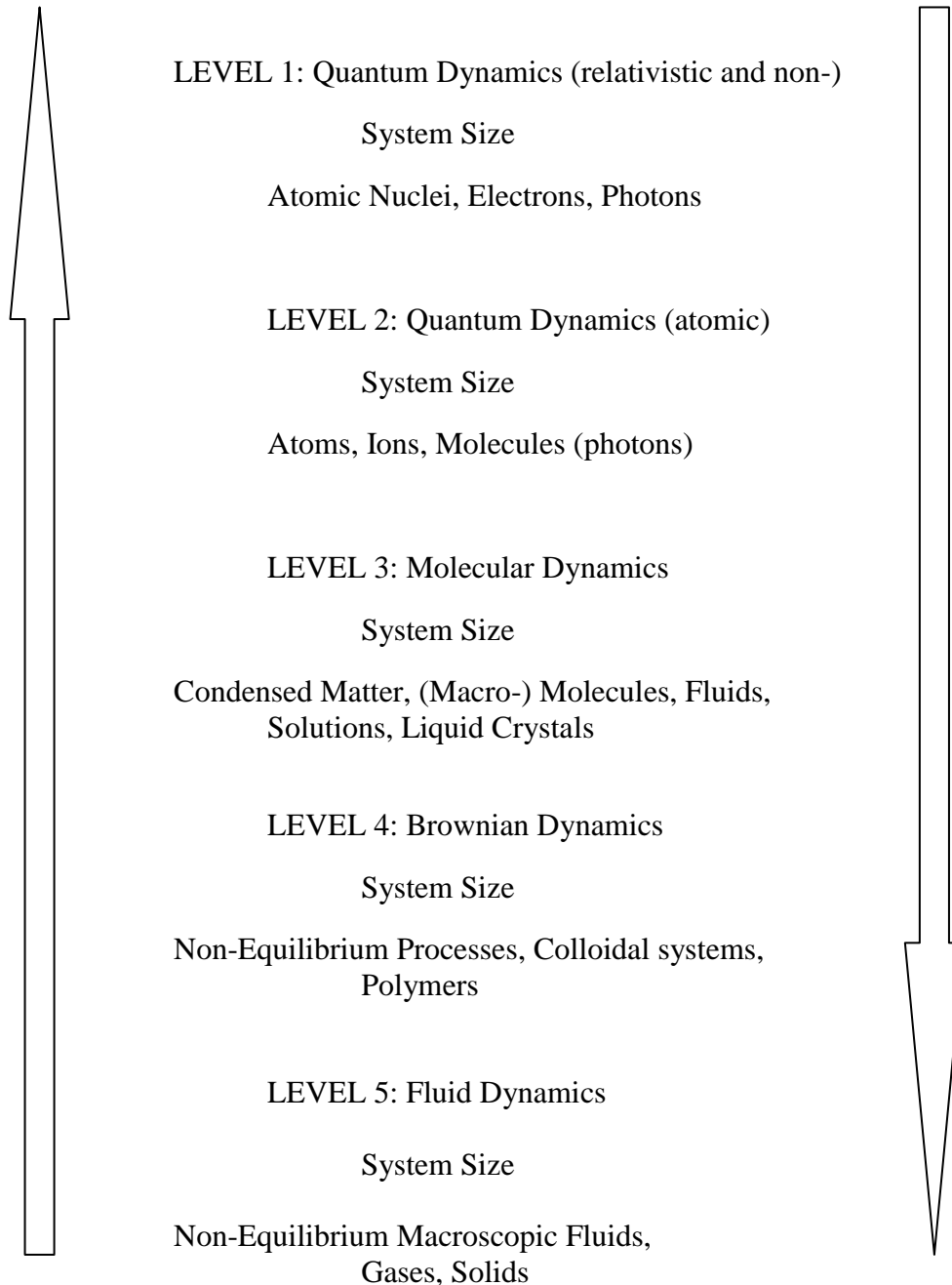
‘Every lower level [level 5 being the ‘lowest’] loses detail and loses applicability or accuracy for a certain class of systems and questions, but gains applicability or efficiency for another class of systems and questions.’

Reduction to Fundamentality

(most fundamental to least)

Reduction of Complexity

(most complex to least)



As we have seen, much successful systems biology currently works around level 3 (see the relevant section of the bibliography for more). This level is ‘normally’ somewhere below the lowest biological level – it is below the lowest system size at which there is life, even with significant coarse-graining; and as computer power increases and the practical need for coarse-graining decreases, we can only expect this level to drop further. For the ideal is total reduction to fundamentality, tempered only by practical limitations (once again, the trade-off on which we have focused is the result of tempering the theoretical ideal with the practical need). Moreover, even though the examples from systems biology that we have discussed function in the middle of the hierarchy, their model of explanation may well be described as ‘from-everywhere-to-everywhere’, rather than as middle-out’, for both quantum equations (bottom-up) and empirical data (top-down) play their role in filling out relevant parameters.

In last year’s project, on emergence, we had an important negative conclusion that we wanted to defend: strong or ontological emergence, was probably not philosophically tenable, and regardless, it is not in fact being put to work in ground-level systems biology research papers. This year, we make no such claims (except in so far as that previous rejection of strong emergence goes hand-in-hand with an acceptance of ontological reductionism, but really we have said very little of this). What is important for systems biology in the concept of methodological reduction at least is simply not amenable to such conclusions. Rather we have contented ourselves with paralleling the other major facet of last year’s project, that it is weak or epistemological emergence (under our cluster definition) that is being put to work in ground-level systems biology research papers. Thus we simply hope to have provided a useful insight into how methodological reduction functions in ground-level systems biology research papers, an insight that can be furthered and deepened with more work on the examples.

Appendix: Bibliographic Resource

One of the primary resource for papers exploring the more purely philosophical aspects of reduction, both in biology and more generally, is the highly regarded and long-standing general philosophy of science journal, *Philosophy of Science*. More specifically, there is also *Biology and Philosophy*. Of course, there are many excellent papers in other journals, not to mention books, but *Philosophy of Science* is the best single source, and it goes all the way back to the original controversies of the 70s and 80s is one is interested in the history of the philosophical literature on these hot topics.

As we have already noted, we found it quite difficult to locate research papers located centrally within systems biology proper that we could both understand and that were useful for exploring and explicating our revised definition of methodological reduction. However, some very useful resources that we do not feel we have had the time investigate thoroughly, are the journals *Bioinformatics*, and the *Current Opinion in Cell Biology*.

And, as ever, for an introductory project such as this, the SEP (Stanford Encyclopedia of Philosophy), REP (Routledge Encyclopedia of Philosophy), and even various Wikipedia articles, have been extremely useful.

What follows is a selected list of both philosophical and scientific literature (just which is often evident from either the title of the paper or that of the journal in which it appears). Unlike last year, there was no single philosophy paper that was the most useful, nor was there as much philosophical material written by scientists, and nor was there as relevant a history worth detailing – these are some of the reasons for the unpartitioned bibliography.

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