

**Validation and Variability:
Dual Challenges on the Path from Systems Biology to Systems Medicine**

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Abstract

Systems biology is currently making a bid to show that it is able to make an important contribution to personalised or precision medicine. In order to do so, systems biologists need to find a way of tackling the pervasive variability of biological systems that is manifested in the medical domain as inter-subject variability. This need is simultaneously social and epistemic: social as systems biologists attempt to engage with the interests and concerns of clinicians and others in applied medical research; epistemic as they attempt to develop new strategies to cope with variability in the validation of the computational models typical of systems biology. This paper describes one attempt to develop such a strategy: a trial with a population of models approach in the context of cardiac electrophysiology. I discuss the development of this approach against the background of ongoing tensions between mathematically and experimentally inclined modellers on one hand, and attempts to forge new collaborations with medical scientists on the other. Apart from the scientific interest of the population of models approach for tackling variability, the trial also offers a good illustration of the epistemology of experiment-facing modelling. I claim that it shows the extent to which experiment-facing modelling and validation require the establishment of criteria for comparing models and experiments that enable them to be linked together. These 'grounds of comparability' are the broad framework in which validation experiments are interpreted and evaluated by all the disciplines in the collaboration, or being persuaded to participate in it. I claim that following the process of construction of the grounds of comparability allows us to see the establishment of epistemic norms for judging validation results, through a process of 'normative intra-action' (Rouse 2007) that shape the social and epistemic evolution of systems approaches to biomedicine.

[p.28]

Systems biologists frequently promote their field as a form of biomedical rather than pure biological research.¹ Currently, the position pieces and manifesto statements in this field express the potential to develop medical applications from systems biology in terms of personalised medicine, translational medicine, network medicine or systems medicine (for example, Auffray, Charron, & Hood, 2010; Auffray, Chen, & Hood, 2009; Hood & Flores, 2012; Hunter et al., 2013; Wolkenhauer, Auffray, Jaster, Steinhoff, & Dammann, 2013). By their very nature,

¹ Systems biology is a form of biological research that typically uses mathematical and computational means to investigate inter-relationships among components and levels from the sub-cellular to the whole organism level, and to illuminate non-linear causality in biological causality. See for example Boogerd et al. (2007) and Kitano (2002).

such pieces show the extent to which the medical applications of systems biology are still aspirational rather than actual. Even though progress is still at early stages, the shift to a medical paradigm brings new challenges to systems biology, or makes existing challenges more acute. This article discusses a challenge with both an old and a new face as systems biology attempts to forge its way into medical applications: that of model validation. The old face of this challenge is that [p.29] of interdisciplinary collaboration. Even though close-knit interdisciplinary groups of modellers and experimentalists are increasingly common in systems biology, this is still not the norm. This becomes an issue as systems biology tries to cross a new interdisciplinary threshold into applied medical clinical and pharmacological contexts. The new face of this challenge is variability, which is not new in itself, given how pervasive variability is in biology, but which makes new demands on systems biology in applied medical contexts. Systems biology claims to be particularly well suited to fulfilling the aim of tailoring diagnosis and treatment to individuals. However, the fulfilment of this promise depends on how systems biology handles the variability inherent in biological processes and in individuals' responses to drugs and other treatments. This paper discusses validation and variability as joint challenges of the bid to transform systems biology into systems medicine. The first section revisits the issue of the interdisciplinarity of systems biology, discussing the ongoing tensions and perceptions of systems biology as a domain dominated by mathematics and computer science, despite the many counterexamples that are emerging and developing into mature research collaborations. The second section focuses on validation as a topic on which these tensions converge, and the third considers one attempt to address the validation of models in the face of variability. The resultant new approach to validation is a bid to alleviate some of the reservations of clinical researchers and others in the applied medical field. New approaches to modelling specifically geared towards validation in biomedical contexts are opportunities to observe the process of what Joseph Rouse has called 'normative intra-action' between modelling and experimenting (Rouse, 2002). I claim that this occurs through the constitution of epistemic norms that underlie the validation process through the construction of the grounds of comparability between models and experiments. The example comes primarily from systems cardiac electrophysiology, that is, the development of multi-scale models of the electrical activity in the heart. Empirical research for the paper draws upon 1) participative research with a cardiac modelling group, and in particular on a suite of documents including draft research papers, peer review, funding proposals and their reviews, and workshop notes; 2) broader literature reviews of cardiac electrophysiology focussing upon validation methodologies. A secondary site of fieldwork is with a systems biology group working on cell biology of the liver, with an eye to possible future applications in the treatment of liver cancer.

1. Interdisciplinarity revisited

Systems biology offers the science studies scholar an interesting combination of sociological and philosophical problems. The technologies it deploys, and the shifting disciplinary boundaries that characterise it have social, institutional and epistemological aspects that commentators and analysts have not been slow to

take up (for example Boogerd, Bruggeman, Hofmeyr, & Westerhoff, 2007; Breitling, 2010; Brigandt, 2013; Bruggeman & Westerhoff, 2007; Calvert & Fujimura, 2011; Carusi, 2011; Carusi, Burrage, & Rodriguez, 2013; Green, 2013; MacLeod & Nersessian 2013a; Macleod & Nersessian 2013b; O'Malley, Calvert, & Dupré, 2007; O'Malley and Dupré, 2005; Vermeulen, 2009; Vermeulen, Parker, & Penders, 2013; Bechtel (2013) and Gross (2011) focus on specifically medical applications of systems biology).² It has been noted that there is often resistance on the part of experimental biologists to collaborate in systems biology research, which they often perceive as being overly theoretical, mathematical and not sufficiently biological. This can be seen as a continuation of resistance to mathematics and physics described by Keller (2002). However, lately the picture of systems biology in the philosophical literature has started to shift, and there are now several examples of the close collaborations between the different disciplinary groupings that go to make up mature systems biology research. This is a matter of epistemological as well as sociological significance: if systems biology genuinely presents a new mode of knowledge, this can be analysed and evaluated fully only in instantiations of systems biology where the traditional disciplinary boundaries have been overcome. A hallmark of these cases is that modelling and experimenting are brought into close interrelationship (Green, 2013), either through interdisciplinarity being embodied in individuals able to do both modelling and experiments (Macleod & Nersessian, 2013b), or through teamwork and collaboration, when the nature of experiments does not allow for this (Carusi et al., 2013). The relationship between modelling and experimenting is a central feature of the epistemology of systems biology, since it defines in what kind of relationship the models typical of systems biology stand to the biological field investigated, what epistemic criteria they should meet and what kind of epistemic warrant these models have. It is a relationship that is particularly emphasised as systems biology makes inroads into applied medical research.

As has been mentioned, there are increasing numbers of close knit interdisciplinary systems biology groups. Although there has been a rapprochement between mathematicians, computer scientists and biologists in many systems biology teams in recent years, deep disciplinary differences and disagreements persist in many domains of systems biology. There is also a lingering perception that systems biology is primarily oriented to mathematics, engineering and computer science. As systems biology targets medical applications more vigorously, new rifts emerge, together with new pockets of scepticism about whether systems biology can deliver on its promises. This was clearly evident in the reviews of a fellowship proposal for research to develop computational modelling as a resource for clinical and pharmacological applications. Although for reasons of confidentiality, it is not possible to know with certainty which disciplines were represented in the review panels, there was clearly hostility on the part of some reviewers at what was perceived as the presumption of computational modellers to be able to come to the assistance of

² Although there are close affinities between systems biology and other forms of new biology, such as synthetic biology, this article considers only systems biology.

clinicians. From the perspective of clinicians and others involved in medical science research, the computational modelling approaches typical of systems biology are still relative outliers. Evidence of this can also be gleaned from an overview of publications in this field using the Pubmed platform that scientists themselves are likely to use for literature searches. Considering only the case of cardiac electrophysiology, a typical search for literature reporting or including a systems computational approach does not present a picture of uniformly integrated modelling and experimenting. For example, in the proceedings (published in 2012) of a workshop held in 2011 on Computer Simulation and Experimental Assessment of Cardiac Function, only three out of 17 papers reported experiments carried out in their methods,³ and only one out of six sessions was devoted to studies that comprised both computational and experimental research. A search of articles published in 2012 and early 2013 found that just over a third of the articles included experiments in [p.30] the study, though in less than a quarter of cases, did the validation methodology include conducting experiments.⁴ The relative dearth of papers that report experimenting for validation of models is particularly telling for this area. To medical scientists such as clinicians or pharmacologists, this reveals an approach to systems biology that is still more interested in developing mathematical and computational techniques than in getting to grips with biological processes.

As discussed elsewhere (Carusi et al., 2013), cardiac electrophysiological modelling is one of the earliest examples of the use of computational science in physiology, beginning with the publication in 1962 of the first mathematical model of the electrical excitation in a single cardiac cell (Noble, 1962). At this early stage, it was quite possible for Denis Noble, a scientist trained in physiology, to acquire sufficient mathematical and computational knowledge to conduct the experiments, modelling and simulations himself⁵; however since then the complexity of the domain has entailed a division of labour, and demanded a high level of specialisation both for the mathematical complexity and for the physiological experiments across the range of ion channels, cells,

³ 'The TRM Forum on Computer Simulation and Experimental Assessment of Cardiac Function' http://europace.oxfordjournals.org/content/14/suppl_5/v1.full).

⁴ The search was conducted on Pubmed, using the MeshTerms: atrial fibrillation; atrial fibrillations; arrhythmia; models, cardiovascular; and computer simulations, and limiting the search to Jan 2012 to July 2013. The search returned 31 useable results (that is, results that were not reviews, not already included in the Proceedings of the Workshop referred to in footnote 5, and that reported on appropriately similar simulation studies); 13 included conducting experiments in the methods section (rather than relying on published data), and of these 7 included a validation process that included experiments. For each listing, the methods section was checked to see whether data had been procured especially for the research, or whether pre-existing data were relied upon. A search including the term 'systems biology' for the same period yielded one publication which had been mislabelled, and another using a genomic approach to systems biology, rather than the computational science approach being investigated here. Yet, systems biology is a term frequently used of the methodology centred upon computational simulations for the investigation of cardiac electrophysiology to judge by the use of the term as a keyword in scientific articles. A systematic investigation is needed of which terms are used where and for which audiences, and which methodologies are included.

⁵ As described in Noble, Chen, Auffray, & Werner (2012).

tissues and whole organs that are required. For this reason, systems biology is characterised by a team approach.⁶ However, interdisciplinarity has not been driven purely by a recognition of the complexity of research, but by a wide variety of factors, including funding sources. As with other domains of systems biology, two important sources of funding for the systems approach to cardiac electrophysiology have traditionally been engineering funders on one hand, and medical research funders on the other. In the UK, a major source of funding was the EPSRC (Engineering and Physical Sciences Research Council) who have been keen to develop the burgeoning area of computational science (or e-science); in the European Commission FP7 funding programme, major funding came from sources dedicated to developing ICT for science (a major example of which is the 'Virtual Physiological Human'). The development of computational methods is an extremely strong theme in systems biology, and many systems biology groups are predominantly mathematical or computational, and most often in the area between the two, computational mathematicians. People with these skills are central for the development of computational techniques capable of solving the ordinary and partial differential equations of the mathematical models. It is extremely difficult to be a specialist both in experimental methods and in these mathematical/ computational techniques, particularly in multi-scale modelling. Moreover, the academic careers of people employed in these projects depends on their producing publications that recognisably fall under the remit of the funding body (Darch et al., 2010, Section 3.1). This leads to the crucial issue of how model validation is conceptualised in the area.

2. Validation

In this setting, the very term 'validation' gives rise to disciplinary misunderstanding and disagreement. In computational science (of which systems biology is a form), simulations solve the equations of a mathematical model that cannot be solved analytically. Verification is a test of whether the numerical techniques and algorithms correctly solve the equations of the mathematical model, and is an internal relationship between these elements of the model. Validation instead is a test of whether the model is a model of the domain in question, and is an external relationship.⁷ In computational science, there can be disciplinary disagreements even with respect to the former steps. In his study of the introduction of Monte Carlo simulations in physics, Peter Galison points out that at the inception of this method there was resistance from mathematicians, who gave a higher epistemic value to mathematical proof than to the 'messy' solutions of numerical analysis (Galison, 1996). Even though this distinction is made, the two processes, verification and validation, are in practice very closely connected. The most frequent form of validation test is conducted

⁶ Thus, this particular field of systems biology started off with the bimodal approach embodied in one interdisciplinary individual as described in [Macleod & Nersessian \(2013b\)](#), but has since become more socially complex as well as physiologically complex.

⁷ See Humphreys (2004: 101e113) for a detailed explanation of the different steps in computational modelling and simulation; and National Research Council (2012) for a concerted effort to distinguish between verification and validation in a way that makes sense for computational science.

through prediction against the data used in the construction of the model (as we saw in the previous section, often acquired from existing literature or datasets). The interpretation of the results of these tests depend on how much weight is given to the techniques of model construction, as opposed to the results of prediction. Frequently, in practice, validation remains a relatively internal affair, with a focus on the development of numerical techniques and algorithms for the construction of simulations rather than on experimenting.⁸ Often this is because computational science is particularly useful in domains where experiments are hard to conduct for practical, ethical or financial reasons (Humphreys, 2004: 106). Despite the fact that this is not the case in systems biology, this attitude still prevails more than one would expect. Frequently, it is researchers who identify themselves primarily as mathematicians, engineers and computer scientists who are responsible for model construction. Even if a lot of tweaking goes into the process of modelling and simulation, still the ultimate outcome is to produce a simulation that is evaluated on the grounds of the techniques used to construct it. Scientists with these interests are not used to thinking in the terms of hypothesis and discovery in an open system that characterises experimental biology and physiology. This is reflected in the relative dearth of modelling that is actually coupled with experimenting, as discussed in the previous section.⁹ As mentioned, the [p.31] examples of systems biology to which philosophers have paid more attention have been those where modelling and experimenting are closely coupled (especially Carusi et al., 2013; Green, 2013; Macleod & Nersessian, 2013b). These have shown that models and experiments are inter-related throughout the model construction process, but most importantly 1) experiments are required for the data to parameterise the models, and 2) for testing the models. These two roles are not always clearly distinguished. Because it is taken for granted as the 'modus operandi' in the context studied, the need for the distinction may not emerge. Working in a context where there are different attitudes towards validation, and therefore the choice of validation approach is reflected upon and defended, Carusi, Burrage, and Rodriguez (2012, 2013) call attention to the role of validation experiments as distinct from model construction experiments. This is not an absolute distinction, since obviously the results of validation experiments do feed back into model construction. Model validation experiments, that is, experiments conducted specifically with a view to testing models generate independent data that were not initially used for the construction of the model being tested. These validation experiments involve an interpretation process that is geared towards the comparison of model outputs and experiment outputs, as scientists 'look for

⁸ This tendency to disconnect validation from experiments is also reflected in the philosophy of computational modelling. For example, Eric Winsberg (2009a) claims that the external validity of a computational model (that is, the extent to which it is accepted as standing in for a target) depends on the scientists' trust in their model building techniques rather than on experimentation. The epistemic warrant of models has a relatively inward looking basis, and is regarded by Winsberg as being autonomous of experiment (2009b: 836). The distinction between simulations and experiments is discussed and critiqued by Parker (2009).

⁹ As Krohs points out for the case of top-down Systems Biology, often coupling with experiments is in the form of convenience experiments, which "only allows for gathering data that match the demands of the program" and do not foster the epistemic attitude of exploration (Krohs, 2012: 56).

a match' between the two. The terms 'correspondence', 'similarity' and 'match' are very common in systems biology publications, but it is not always clear how these terms are 'cached out'. These are terms that are interpreted in the process of comparison, against the background of questions about whether there is appropriate comparability between the model and experiments (Carusi et al., 2013: 135). To be sure, there are always questions of appropriate comparability when comparing experiments relating to the same process or components, even in wetlab, for example, when the experiments involve different model organisms, or different techniques. To some extent, the same set of issues arises in the computational modelling domain, with particular force for three main reasons: 1) the computational model and simulation has a greater degree of difference to the wetlab experiment, through being made of different matter (in silico vs organic); 2) it employs entirely different techniques (mathematical and computational vs wetlab laboratory); 3) there is an asymmetry between the computational model and simulation on one hand and experiment on the other, as the former is tested against the latter.¹⁰ These issues emerge most sharply in the case of multi-scale modelling, which integrates processes across sub-cellular, cellular, tissue, and whole organ levels, by combining models. The possibility of multi-scale integration is a great advantage of systems biology, since its computational technologies and techniques allow for an investigation of complexity that is out of reach for wet lab experimentation. However it is also an extremely challenging aspect of the validation of these systems, because the multi-scale model is not validated against a multi-scale experiment. As we shall see in the case discussed below, even in an experiment at two scales (cellular and sub-cellular) there is no self-evident way of comparing models and experiments. A number of philosophical and social studies of systems biology raise the issue of comparability between models and experiments. For example, Green (2013) describes modelling of transcriptional data in a network model as a process of 'constructing, manipulating and comparing representations in a spiral-like fashion where a whole body of models interact' (Green, 2013:170). She points out that the role of some of these models is to provide a background for comparison (Green, 2013, Table 1). Carusi et al. (2012, 2013) describe a computational science based approach to investigating the kinetic aspects of a physiological process (the propagation of electrical current across the heart). On their account, in order to be geared towards validation, model construction needs to incorporate the construction of the grounds of comparability that allow for comparisons between the model system and validation experiments to be made. O'Malley and Soyer (2012) point out that making different data sets comparable is a central challenge of the data integration that is characteristic of systems biology. Chandrasekharan and Nersessian (2011) discuss the ways in which the fit of a model with experimental data is not a 'point-for-point replication' but rather something that starts off being rather fluid, but 'coagulates' during the model building process, as it becomes more and more constrained (271e2). Macleod and Nersessian (2013b) focus on the cognitive

¹⁰ For all of these reasons, there can be an epistemic privileging of wetlab experiment against computational model and simulation. See Morgan (2005). For ongoing debate on this issue in the context of systems biology, see Leonelli & Ankeny (2012).

strategies deployed by modellers to adapt models and experiments. The present paper focuses on comparability as underlying the epistemic warrant that is at issue during validation procedures. In particular, it considers the way in which the modelling process includes setting up the criteria for comparison between models and experiments. The example described in detail in the next section is taken from a new direction of research that is currently under development, and directly responds to demands made on modelling by the shift into medical applications.

3. Validation and variability in medical contexts

Medical applications obviously bring with them the priorities of safe and effective treatment, as well as a different range of interdisciplinary relations with clinicians and others whose goals are not pure but applied science. Therefore as systems biology approaches medical applications, there is greater emphasis on methods of validation as against experiments, or pharmacologically and clinically acquired data.¹¹ An example of this is an in house workshop organised by a world leading drug regulation body to explore the possibility of using these approaches for drug safety testing.¹² Validation was a prominent theme of the workshop, and a follow up questionnaire invited participants to give in-depth answers to questions in three topics: data sources, validation, and sharing. The questions on validation included questions on the relation between models and data sets, and whether goodness-of-fit, robustness or predictiveness could be used as measures for evaluating models. We can also see a closer scrutiny of the validation of models in the clinical context, by clinicians who both do clinical research and treat patients. A feature of both of these contexts of drug regulation and clinic is the need to understand the wide range of variability that occurs in biological systems, giving rise to variability between individual patients, and the extent to which this variability makes a difference to treatment, for example, in the form of dosage or drug type. Variability occurs at all levels of organisation in living organisms (Claridge, 2010: 91); variability between patients is something that doctors and clinicians [p.32] every day (Montgomery, 2006).¹³ In the context of cardiac electrophysiology at the cellular level, there are three important kinds of variability: the sub-cellular variability in the opening

¹¹ In this article, I have focused on a particular mode of systems biology, computational modelling and simulation of physiological processes, and have not broached the challenges of other forms of systems biology. Data intensive modes of systems medicine bring other challenges, such as relating modelling to medical and clinical datasets, and to biobanks.

¹² The workshop was invitation only, and not made public. My knowledge of the workshop was obtained through fieldwork interviews and correspondence.

¹³ It remains to be explored what types of medically relevant variability systems biology may be able to illuminate. Variability in the evolutionary sense plays an important role in the conception of disease (for an early formulation and criticism of this view, see for example Canguilhem, 1991); and this can be unpacked further in terms of, for example, the variability in gene mutations. However, the way that variability was explored in the trial discussed here did not take these aspects of gene mutation into account although in principle, it could be enlarged to include them.

and closing of ion channels and the movement of ions¹⁴; cellular variability between the same type of cells that are spatially colocated; variability between the same type of cells that are not spatially co-located. For the scientists, understanding variability entails understanding the mechanisms for each type of variability, as well as understanding the ways in which they interact with each other.¹⁵ In the context of the clinic or of drug regulation, grasping variability at these levels would make a huge contribution to the project of personalised medicine. Even if complete personalisation remains out of reach, the stratification of variability, finetuning it into different groupings and ranges, would be extremely useful. Systems biology, with its integrated models, promises to attain this goal. However, the issue of variability is difficult to get to grips with for many reasons having to do with biology and with scientific discourse and practice, and the fact that they do not always cohere. Variability between individuals comes up much more in the practice of clinicians and medical practitioners generally than it does in published findings, where it tends to be washed out. That is, in experimental set ups, one of the aims is to decrease variability; this is important for the reporting of the experiment, and for the way publications are reviewed. Thus a further reason why relying on data from published results is problematic for modelling and simulation of biological or physiological processes is that variability is not reflected in experimental results. Even where systems biologists do obtain experimental data sets directly for themselves, or through collaboration, the common practice is to work with averages of data values: for example, in the broad domain of electrophysiology, sometimes scientists choose the fastest and largest current conductances, and sometimes the mean (Marder & Taylor, 2011, 134). These are both idealisations of models; however, as with any form of idealisation, these choices need to be weighed up against what is potentially lost. Both of these choices for parameter fitting wash out variability, with the consequence of losing sight of the underlying interactions between mechanisms (Marder & Taylor, 2011, 135). Variability also makes it extremely difficult to interpret and compare experimental and computational results. I have already mentioned that this is particularly true of the results of integrated models, which are precisely the strength of computational modelling and simulation over experimental methods. Even as computational modelling allows for greater integration, the possible sources of variability increase, since each scale or level comes with its own variability, and there is further variability in the way the scales or levels interact with each other. In addition, since there is not only one way to integrate a multi-scale model, the variability associated with the integration of the model muddies the waters even further. For clinical researchers, who are also often practicing clinicians, the variability of biological

¹⁴ Electrical activity in cells occurs through the flow of ions (such as potassium and sodium) through ion channels in the cell membrane.

¹⁵ However it is unclear what the appropriate notion of mechanism is, or what pressure variability places on extant understandings of mechanism. Gross (2011) has considered the way in which systems biology's incursion into the medical domain may require different conceptions of mechanism and therefore may point to a different conception of disease. While Gross discusses variability, his account focuses on systems that exhibit stability rather than variability (2011:484). See also Bechtel & Abrahamsen (2012).

processes is a key issue to whether modelling and simulation could really be of use to them. In their eyes, it does not help to develop an integrated model which is built according to modelling techniques and computational tricks trusted by the modellers, if in so doing the model has no way of dealing with the variability they encounter in their real world applications, or offers no better way of dealing with it than the techniques they already have available to them. Thus tackling the problem of variability is a way of showing clinicians that their problems are taken seriously. It is both an epistemological and a socio-interdisciplinary endeavour. Once modelling and simulation become more attuned to biology and to the research needs of biologists working in biomedical contexts, validation begins to shift in focus from being thought of in mathematical and computational terms, to being thought of in experimental terms. As this occurs, the emphasis is no longer on producing one model of a process that is perfectly mathematically or computationally validated; as one of my informants (a biochemist researching cancer in the liver working closely with mathematical modelling) put it: 'I think that solutions [to variability] must be sought in the direction where modellers are prepared to produce many different variants of their model (conceptually, i.e. in its logic/ topologic structure) to accommodate and respond to the experimentaliststinking interrelation with the biological system.'¹⁶ On this suggestion, variability is addressed not by washing it out of the experiments, but by taking a pluralist attitude to models, and producing many versions of a model or of a model system rather than a single model. That is, rather than forcing invariability on experiments (and thereby on the target domain), it is a technique that absorbs some of the variability into modelling and simulation. The populations of models approach is an emerging methodology for modelling variability (Britton et al., 2013; Marder & Taylor, 2011; Sarkar, Christini, & Sobie, 2012).¹⁷ In this paper, I shall limit myself to the description of one attempt to develop the population of models approach to address the issues of variability with which medical scientists and practitioners are faced in the context of cardiac electrophysiology. This trial stands out because of the way it combines the aim of addressing variability and experiment facing validation. It does so on the sub-cellular level of ion-channels and cellular level of Purkinje fibres; and is therefore trying to establish a way that variability could be tackled for these levels to start off with, and it shows this with respect to the type of experiments of interest to clinicians and pharmaceutical bodies: the drug test or drug assay to test the effect of a drug on ionic channels, which, as has already noted, are highly variable. Intra- and inter-cellular variability of ionic channels ultimately manifests as inter-subject variability in the side effects and toxicity of drugs. The trial is interesting for both social and epistemic reasons. Its social interest resides in the fact that this approach was developed in order to try to meet the challenge of clinicians to modellers regarding validation generally and specifically, validation in the face of variability; and was a focal point for forging

¹⁶ Email correspondence, 17 June 2013.

¹⁷ This approach was first developed in the neurophysiology domain by Marder & Taylor (2011). In climate modelling, a related approach is the ensemble of models approach, but this differs from the biomedical context because it has a radically different relation to experiment

new collaborations in the face of [p.33] much scepticism on the part of clinicians. Its epistemic interest resides in what it shows about the process of devising a modelling approach geared at validation. The approach consists in producing a population of models in two stages: first the team generated 10 000 models by randomly varying parameter values on the initial data set of a base model (a set of equations and parameters relating to Action Potential Duration (APD) in Purkinje Fibres¹⁸ for a generic action potential model). They then calibrated the 10 000 models with experimental ranges of six biomarker values of particular interest in cardiac electrophysiology and drug safety testing. Those models with a range of variability that did not fall within the biological range (indicated by these experimental data) were excluded. When questioned by one of the reviewers on the use of the term 'calibration', the authors specified that: 'We use calibration to refer to the process performed on the entire population, in the sense that the population is adjusted so as to bring the range of behaviour seen within it in line with experimental data.'¹⁹ This process itself required a way of attuning the population of models with the initial data set: that is, of establishing ranges of values for the calibration. The problem is the paucity of experimental data sets relative to the size of the population of models. Given the standard number of experiments used for drug safety assays (that is, five), it is not possible to establish the range of biomarker values for the calibration statistically. The authors go on to describe their method of establishing ranges as follows:

We therefore chose to use the upper and lower values of each biomarker as observed in our experimental data to guarantee our estimates of variability were within biological range for each of the three pacing frequencies. At each frequency and for each preparation, biomarker values were calculated by taking their median from a continuous train of at least 100 APs at steady state conditions. For each biomarker, at each frequency, the maximum and minimum values of that biomarker found across all preparations were used to set the range of acceptable biomarker values for model calibration (Britton et al., 2013, 5).

This is an important step for establishing the experiment-facing nature of this modelling process. In the wider setting where this trial took place, there was not universal acceptance of calibration by excluding models outside of the physiological range. Mathematicians argued that this made the model mathematically biased. This is one of the points where we see very different attitudes towards validation coming to the fore. For example, despite the reservations of mathematicians, reviewers of a previous version of the paper

¹⁸ Purkinje fibres are cells in the ventricular walls of the heart, particularly able to conduct cardiac action potentials. Action potential is the change of voltage on the inside and outside of a cell membrane, due to an imbalance of positively and negatively charged ions on each side of the membrane. The action potential duration (APD) is a measurement of the time it takes for the voltage to rise and fall, and is represented by a curve.

¹⁹ Correspondence, 27 July 2013 and 11 September 2013.

reporting the study and its results appreciated this first calibration step, and even suggested further ways in which the fit to experimental data might be fine-tuned (e.g. by ranking the models according to how much they deviated from the experimental mean). This process of calibration left 213 models forming the population of models. (See Fig. 1). The team used the remaining 213 models to explore the range of inter-subject variability, through establishing correlations between the six biomarkers²⁰ and parameter values relating to ionic properties. The aim of this correlation process is to make hypotheses regarding the mechanisms for variability via these correlations, and to find which ionic properties are involved in which aspects of variability. This is further extended and tested by making quantitative predictions concerning the response of Purkinje fibres to a particular drug in new experiments specifically aiming to validate the population of models and the correlations of biomarkers and parameters, couched in the language of prediction and test. The new experiments carried out by the team took the form of a typical drug assay, that is 5 experiments involving microelectrode recordings of Purkinje fibres as affected by a different concentrations of a drug (dofetilide). The team used the range of variability in the population of models, and the correlations between biomarkers and parameters to make predictions about these features in the new experimental data set generated for the purpose. However, what would count as correlations that could be observed and compared between modelling and experimenting did not pre-exist the trial. The criteria for these correlations between which biomarkers, and in which parameter ranges were themselves established in the trial, starting off with the first calibration step. In many respects it is an ongoing process of calibration, both of the population of models with previously obtained experimental results and with the newly produced experimental data set. The entire process was geared towards establishing comparability between the variability in the population of models, and that in the experimental dataset. The ongoing calibration and finetuning process builds up a picture of how a whole population of models (rather than one model at a time) can be compared to experimental data, establishing which parameter ranges can be used to interpret the variability across the datasets. At crucial points, it is literally the picture that counts, since the visual means of depicting the relationship between the models and experiments were as important as the textual description of the methodology, and the figures went through several modifications alongside the text. Thus, the results of the trial are as much about how to make variability in electrophysiology interpretable as they are about how to deal with variability across models, simulations and experiments.

This early trial in the population approach found that there is a very wide range of combinations of parameter values that produce models that are within the range of experimental variability. The issue is to narrow that range down further, by introducing further constraints and additional biomarkers, in order to make finer discriminations in the calibration process. The calibration process,

²⁰ The biomarkers are those commonly used in cardiac electrophysiology, that is, specific points along the curve of the Action Potential Duration: for example, the peak or the dome.

therefore, is not limited to this one trial, but is an ongoing process as further populations of models and further experimental datasets are produced. This is a methodology that is at early stages of development, but the approach it exemplifies marks an important shift in the way in which modelling and simulation are undertaken in systems biology. By shifting the focus from one model in isolation to the behaviour of a population of models, validation shifts from being about how one model matches up to experiment (with all the concomitant problems of interpretation of the results when variability is blackboxed) to how the range of variability in an experimentally calibrated population of models maps onto the range of variability in an experimental data set. In this case, variability is incorporated into the model-simulation-experiment system, rather than being blackboxed.

The trial described here positions the population of models between experiments at two stages, 1) for producing the population and 2) for investigating patterns of correlation between biomarkers and parameters relating to ionic properties in a newly produced experimental data set (See Fig. 1). There is no straightforward comparison in this process, no straightforward matching or checking for correspondences in a 'face-off' between models on one hand and experiments on the other to determine when models [p.34] can be considered validated. Rather, it is a process of establishing what could count as criteria of comparison, match or correspondence, through (for example) setting the criteria for including and excluding models from the population, for dividing the population into sub-populations, for quantifying correlations so that they can be used for comparison and so on.²¹ The criteria are further developed in the ongoing cycle of iterations with experiments. There is not an ultimate validation, rather its test is that it holds for long enough to make the next iteration worthwhile, and will gain in robustness as it goes along. If a meaningful cycle of model-simulation-experiment iterations succeeds, which experiments are conducted (including experimental design and the specific type of data obtained, for example, on which ion channels and pumps) is also changed.

²¹ There is a large literature on the relationship between model source and target. The claim that comparability is established through the ongoing process of modelling the population of models (or other forms of models) is resonant with Weisberg's position on the 'feature set'. This is a selection of features with respect to which similarity between model and target is judged; for example he writes that '[t]here is no context-free answer to this question, but part of the answer lies in the modeler's intended scope. The modeler's intended scope takes into account the research question of interest, the context of research, and the community's prior practice (Kitcher, 1993). These elements of the modeler's intended scope, in turn, determine the contents of the feature set' (2013: 150). However, it is clear from the discussion in Section 4, that our accounts also differ. See also footnote 24.

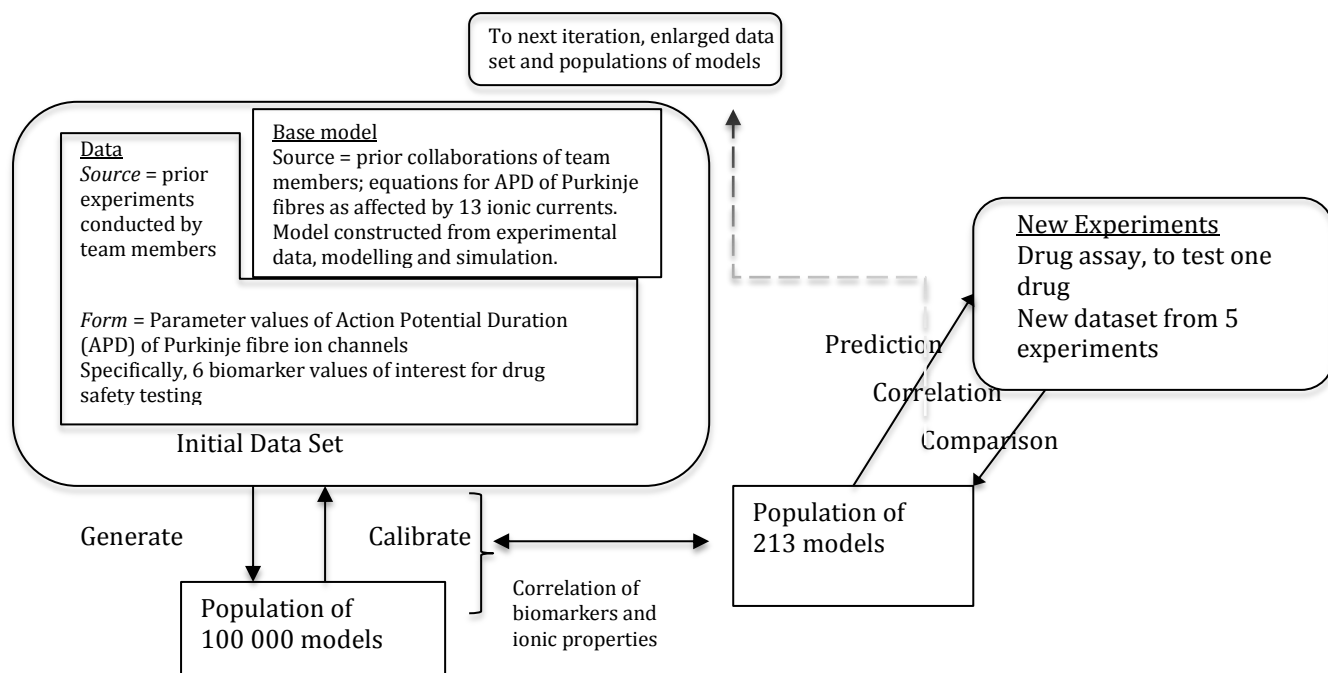


Figure 1: The relationships between experimental data sets, the initial and calibrated population of models, and new experiments in the population of models approach to variability. Solid lines: processes in this trial; dashed lines: processes towards future trials.

The population of models trial I discuss is not a final validation but an argument for further iterations, addressed to the broader community. If it is convincing it will also bring about changes in the broader community as these modellers put the case that in order to further develop this joint approach to validation and variability, there should be separate data sets for calibration and validation, and much more extensive data sets to be made available by drug companies. In fact, so far, it seems that the argument is being successfully made with new clinical collaborations forged and drug companies showing interest. In making the argument and in the response to it, it is clear the extent to which the modelling and experimenting processes change in response to each other. Validation as being an inward looking process concerned with the relation between equations and simulation falls away. Instead, a new process of validation starts to establish itself, one where validation is negotiated in the relationship between modelling and experimenting, and where emphasis shifts from a 'one model at a time' approach to a multiple models approach. This process of negotiation between modelling and experimenting is simultaneously epistemological and social, as it institutes new relationships between modellers and researchers and their respective communities in medical settings, be they clinical or pharmaceutical. In the next section, I suggest that it is fruitful to see the interrelationship between modelling and experimenting as one of 'normative intra-action'.

4. Discussion

The validation of computational models has closely inter-related social and epistemological aspects in systems biology. What counts as validating a model can be controversial in the communities of scientists conducting different forms of systems biology. The funding structures of systems biology mean there are many systems biology projects that are still funded primarily by mathematical and computational science funding bodies, with the concomitant research and publication demands to focus on mathematical and computational aspects of modelling and to approach validation from these perspectives. The domain of systems biology is still uneven regarding collaboration between modellers and experimentalists. The push for systems biology to move towards medical applications brings this to the fore yet again, since it requires a new set of collaborations, this time with clinicians or pharmaceutical companies. This in turn places further demands on validation: some are a more pressing version of existing demands, in view of the practical use to be made of the modelling techniques and approaches typical of systems biology; some instead are rather different demands, such as the demand to tackle validation in the face of variability. Variability is always a feature of medical contexts, but even more so when there is a predominant discourse of personalised or precision medicine as the goal of translation from systems biology into systems medicine. Both socially and epistemologically, the practicalities to be managed in bringing about systems medicine revolve around bringing modelling and experimenting into closer inter-relationships, [p.35] not only for model construction, but even more importantly, for validation. The examination of the construction of a population of models so that it explicitly engages with experimental data sets, foregrounds aspects of the epistemology of experiment-facing model construction. The epistemic goal of validation is 1) normally conceptualised in terms of similarity, correspondence and match, which are achieved through qualitative or quantitative comparison between model and simulation outputs and experimental data sets; 2) normative in that it establishes criteria for epistemic warrant. The relation between models (and populations of models) and experiments for validation might be thought of in two ways: as external or as internal. On the view that they are externally related, comparison occurs between two independently constituted outputs, that of the model and simulation (or population of models as in the case discussed here) and that of the validation experiments. Considering the different material forms of models and experiments, an analogy from the art world might help to illustrate this point: comparing externally related entities is akin to comparing two art forms in two different material modalities, such as a film and a novel about the same real world event, that however are produced completely independently of each other, and seeing what are the correspondences between them. In this case, interpreters draw the norms for the criteria of comparison from either one or the other, or from a context which is sufficiently analogous with both, or believed to be so. On the view that model (or population of models) and validating experiments are internally related the two outputs will instead be seen as co-constituted rather than independently constituted. This means that they are defined as the models and experiments that they are, that is with the specific features that they have (for example, which models are included and excluded,

which parameters considered, which ranges are correlated, which research questions asked), in response to each other or in terms of a 'dialogue' with each other. These features are not chosen from the vantage point of modelling or experimenting, but in terms of the inter-relationship between them). To continue the art world metaphor, this is not analogous to a film version of a novel; rather, it is more akin to films and novels of the same event being produced in response to each other, often in quite long stretches of repetition and iteration.²² In this case, the very fact that some features emerge as shared by both films and novels, and thus as comparable, is due to this responsiveness to each other. On the conception of the validation relation as an internal one, models and experiments are produced in this form of ongoing mutual responsiveness to each other, which produces important features of each at the same time as it lays down the grounds for their being compared at all. In this case, the norms for the criteria of comparison are drawn from the relationship between modelling and experimenting. Considering the extent to which modelling and experiments are responsive to each other in establishing a common ground for comparison between them, it seems that analysing the validation process in terms of internally related models and validation experiments would be fruitful. Joseph Rouse (2002) has described a similar relation between theory and experiment as one of normative intra-action. Intra-action is a term introduced by Karen Barad (2007), signifying the way in which the entities or in Barad's terms, the causal processes are defined within the process. Rouse argues that in the relations between theory and experiments or more broadly still, science and the natural world intra-action is also normative, since it brings about not only actants with specified bounds and features, but also the criteria whereby scientific claims can be evaluated and judged. Rouse refers to this as the 'domain constituting' aspect of experimental systems, the practices of which 'help constitute the fields of possible judgment and the conceptual norms that allow [conceptualizable] features to show themselves intelligibly' (Rouse, 2009, 51). Importantly, however, the word 'constitution' here does not imply a stipulation (Rouse, 2009, 52). In the example discussed in this paper, the range of variability of models and experiments is articulated into a system defining what ranges in the population of models might be considered equivalent to what ranges in the experiments. This can be seen as a system of equivalences²³ between models and experiments through the calibration process, defining the borders of ranges. This system gives significance to the patterns of data output between models and experiments, so that they can both function as a framework for making comparisons, and as criteria for evaluating the extent to which models succeed in grasping the salient features of experimental datasets. That is, it defines what counts as points of comparison on the basis of which a match between the outputs of modelling on one hand, and experimenting on the other, can be perceived. But this system of equivalences that articulates model and experiment

²² For example, De Lillo's novel *Libra* (1988), Oliver Stone's film *JFK* (1991), and Stephen King's novel *11/22/63* (2011) all deal with the assassination of John F. Kennedy, in response to each other, and potentially other films and novels to which they intertextually refer or which refer to them.

²³ The term 'system of equivalences' is adapted from the philosophy of Maurice Merleau-Ponty, for example in his essay on the algorithm in *Prose of the World* (1973).

and co-defines them is a modifiable framework, one that can be more finely articulated, or modified. It does have normative import, but this is tentative; if and how it will be developed depends on the ongoing iterations. Whether it 'takes' as a norm depends on both social and epistemological factors. In order to become entrenched as a norm, it needs social acceptance, but this it can find only among those who are prepared to try to see comparisons between models and experiments according to it.²⁴ Therefore, the continued iterations between modelling and experimenting, using experiments that are geared towards the very processes that clinicians and others are concerned with (such as the safety and side effects of particular drugs) are social at the very same time as they are epistemological. The 'dialogue' between models and experiments enacts a dialogue between modellers and medical, clinical and pharmaceutical experimentalists across their communities.

5. Conclusion

As systems biology approaches medical applications, the relationship between modelling and experimenting comes under scrutiny once again. The question of how models are validated is central to this scrutiny, and divisions that exist in systems biology communities account for residual scepticism and resistance in medical communities. Overcoming this scepticism requires systems biology to lose the last vestiges of being a science that is more about mathematics and computation than about biology, and to [p.36] find ways to ensure a (relatively) external validation process. However, here, a further challenge that emerges more urgently in medical contexts is that of variability, among individual patients, and in biological processes. Validation and variability are interconnected challenges, since one reason that validation experiments are difficult to interpret is the variability that there exists both in the biological processes, and in the modes of integration of the models typical of systems biology. Variability is always an issue in medical and clinical contexts, but even more so if the aim is personalised or precision medicine. Epistemologically, tackling the variability of physiological processes through modelling is at the same time to tackle the variability in the very relationship between modelling, simulating and experimenting. The philosophy of systems biology has given us many examples of the extent to which systems biology challenges any clear demarcation between the source and target of a model, and instead defines a new epistemology of hybrid model systems. The example discussed in this article

²⁴ This idea has resonances with Evelyn Fox Keller's proposals regarding the ways in which models as metaphors become literalised in a 'conceptual-material' convergence between the metaphors used in model building and processes and goals in laboratories and other contexts of application. For example, the 'genetic computer' "is no longer just a metaphor or even just a model: in two quite different domains, on the one hand, in the designing of new kinds of computers and on the other, of new kinds of organisms, the 'genetic computer' has begun to acquire something resembling literal truth [...] the convergence is simultaneously material and conceptual, and there is no residually literal sense in which any of the referents remain fixed. (2000:S84). Similarly, if a system of equivalences is taken on board and iterated, 'it' may come to be entrenched in the scientific domain (of practices and realities), but 'it' will also have been modified in that process of entrenchment through iteration: the system is not first conceptually fixed and then entrenched.

is taken from this renewed push of systems biology into the medical domain, and it shows up something that does not always come out clearly in these tightly knit social and epistemic groupings: that is, the extent to which the epistemic evaluation of the models is itself a target of modelling. Rather than epistemic evaluation consisting primarily in 'looking for a match' between models and experiments, these modelling processes also establish the conditions for identifying a match and build them into the models, through laying down the grounds of comparability between them. The representational force of the models is predicated upon these grounds, without which it is impossible even to ask the question whether a model represents its target, or what its validation might consist in. Drawing attention to these grounds as a form of normative intra-action invites attention to the specific ways in which they are built up in different modes of doing systems medicine, both epistemologically and socially. In particular, in the process of achieving personalised medicine informed by systems biology, the articulation, management and modelling of variability will ultimately play an important role in defining emerging systems notions at stake in personalised medicine. These include the notion of disease and ultimately, of the person.

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References

- Auffray, C., Charron, D., & Hood, L. (2010). Predictive, preventive, personalized and participatory medicine: Back to the future. *Genome Medicine*, 2(57). Also available at doi [10.1186/gm178](https://doi.org/10.1186/gm178).
- Auffray, C., Chen, Z., & Hood, L. (2009). Systems medicine: The future of medical genomics and healthcare. *Genome Medicine*, 1(1), 2. Also available at doi [10.1186/gm2](https://doi.org/10.1186/gm2).
- Barad, K. (2007). *Meeting the universe halfway: Quantum physics and the entanglement of matter and meaning*. Durham, N.C. & London: Duke University Press.
- Bechtel, W. (2013). From molecules to behavior and the clinic: Integration in chronobiology. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 44(4), 493e502.
- Bechtel, W., & Abrahamsen, A. A. (2012). Thinking dynamically about biological mechanisms: Networks of coupled oscillators. *Foundations of Science*, 18, 707e723.
- Boogerd, F., Bruggeman, F. J., Hofmeyr, J.-H. S., & Westerhoff, H. V. (2007). *Systems biology: Philosophical foundations*. Amsterdam: Elsevier.
- Breitling, R. (2010). What is systems biology? *Frontiers in Physiology*, 1(9). Also available at doi [10.3389/fphys.2010.00009](https://doi.org/10.3389/fphys.2010.00009).
- Brigandt, I. (2013). Systems biology and the integration of mechanistic explanation and mathematical explanation. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 44(3), 477e492.
- Britton, O. J., Bueno-Orovio, A., Van Ammel, K., Lu, H. R., Towart, R., Gallacher, D. J.,

- et al. (2013). Experimentally calibrated population of models predicts and explains intersubject variability in cardiac cellular electrophysiology. *Proceedings of the National Academy of Sciences of the United States of America*, 110(23), E2098eE2105.
- Bruggeman, F. J., & Westerhoff, H. V. (2007). The nature of systems biology. *Trends in Microbiology*, 15(1), 45e50.
- Calvert, J., & Fujimura, J. H. (2011). Calculating life? Duelling discourses in interdisciplinary systems biology. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 42(2), 155e163.
- Canguilhem, G. (1991). *The normal and the pathological* (Carolyn R. Fawcett, Trans.). New York: Zone Books (Translation of *Le Normal et Le Pathologique*, Presses Universitaires de France, 1966)
- Carusi, A. (2011). Computational biology and the limits of shared vision. *Perspectives on Science*, 19(3), 300e336.
- Carusi, A., Burrage, K., & Rodriguez, B. (2012). Bridging experiments, models and simulations: An integrative approach to validation in computational cardiac electrophysiology. *American Journal of Physiology e Heart and Circulatory Physiology*, 303(2), H144eH155.
- Carusi, A., Burrage, K., & Rodriguez, B. (2013). Model systems in computational systems biology. In J. Duran, & E. Arnold (Eds.), *Computer simulations and the changing face of scientific experimentation*. Cambridge Scholars Publishing.
- Chandrasekharan, S., & Nersessian, N. J. (2011). Building cognition: The construction of external representations for discover. *Cognitive Science Conference Proceedings*, Boston, Massachusetts.
- Claridge, M. E. (2010). Species are real biological entities. In F. Ayala, & R. Arp (Eds.), *Contemporary debates in philosophy of biology* (pp. 91e109). Malden, MA, Oxford and Chichester: Blackwell Publishing Ltd.
- Darch, P., Carusi, A., Lloyd, S., Jirotko, M., De La Flor, G., Schroeder, R., et al. (2010). Shared understanding in e-Science projects. A Report from the EPSRC funded Embedding e-Science Applications Project. Available at http://www.oerc.ox.ac.uk/sites/default/files/uploads/ProjectFiles/FLESSR/HiPerDNO/embedding/Shared_Understanding%2030%20June.pdf Accessed 16.06.14.
- Galison, P. (1996). Computer simulations and the trading zone. In P. Galison, & D. J. Stump (Eds.), *The disunity of science: Boundaries, contexts, and power* (pp. 118e157). Stanford, California: Stanford University Press.
- Green, S. (2013). When one model is not enough: Combining epistemic tools in systems biology. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 44(2), 170e180.
- Gross, F. (2011). What systems biology can tell us about disease. *History and Philosophy of the Life Sciences*, 33, 477e496.
- Hood, L., & Flores, M. (2012). A personal view on systems medicine and the emergence of proactive P4 medicine: Predictive, preventive, personalized and participatory. *New Biotechnology*, 29(6), 613e624.
- Humphreys, P. (2004). *Extending ourselves: Computational science, empiricism, and scientific method*. Oxford: Oxford University Press.
- Hunter, P., Chapman, T., Coveney, P., De Bono, B., Diaz, V., Fenner, J., et al. (2013). A vision and strategy for the virtual physiological human: 2012 update. *Interface Focus*, 3(20130004), 1e10.
- Keller, E. F. (2000). Models of and models for: Theory and practice in contemporary biology. *Philosophy of Science*, 67, 72e86.
- Keller, E. F. (2002). *Making sense of life: Explaining biological development with models, metaphors and machines*. Cambridge, Mass. & London, England: Harvard University Press.
- Kitano, H. (2002). Systems biology: The genome, legome and beyond. *Science*, 295, 1662e1664.
- Kitcher, P. (1993). *The advancement of science*. Oxford: Oxford University Press.
- Krohs, U. (2012). Convenience experimentation. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 43(1), 52e57.
- Leonelli, S., & Ankeny, R. A. (2012). Re-thinking organisms: The impact of databases

on model organism biology. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 43(1), 29e36.

MacLeod, M., & Nersessian, N. J. (2013a). The creative industry of integrative systems biology. *Mind & Society*, 12(1). Also available at doi 10.1007/s11299-013-0119-3.

Macleod, M., & Nersessian, N. J. (2013b). Coupling simulation and experiment: The bimodal strategy in integrative systems biology. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 44(4), 572e584.

Marder, E., & Taylor, A. L. (2011). Multiple models to capture the variability in biological neurons and networks. *Nature Neuroscience*, 14(2), 133e138.

Merleau-Ponty, M. (1973). *The prose of the world* (John O'Niell, Trans.). Evanston, Illinois: Northwestern University Press

Montgomery, K. (2006). *How doctors think: Clinical judgement and the practice of medicine*. Oxford & New York: Oxford University Press.

Morgan, M. S. (2005). Experiments versus models: New phenomena, inference and surprise. *Journal of Economic Methodology*, 12(2), 317e329.

National Research Council. (2012). *Assessing the reliability of complex models:*

Mathematical and statistical foundations of verification, validation, and

A. Carusi 36 / Studies in History and Philosophy of Biological and Biomedical Sciences 48 (2014) 28e37

uncertainty quantification. Washington D.C. http://www.nap.edu/catalog.php?record_id1/413395

Noble, D. (1962). A modification of the Hodgkin-Huxley equations applicable to Purkinje fibre action and pacemaker potentials. *Journal of Physiology*, 160, 317e352.

Noble, D., Chen, Z., Auffray, C., & Werner, E. (Eds.). (2012). *The selected papers of Denis Noble: A journey in physiology towards enlightenment (Vol. 2)* London: Imperial College University Press.

O'Malley, M. A., Calvert, J., & Dupré, J. (2007). The study of socioethical issues in systems biology. *American Journal of Bioethics*, 7(4), 67e78.

O'Malley, M. A., & Dupré, J. (2005). Fundamental issues in systems biology. *BioEssays : News and Reviews in Molecular, Cellular and Developmental Biology*, 27(12), 1270e1276.

O'Malley, M. A., & Soyer, O. S. (2012). The roles of integration in molecular systems biology. *Studies in History and Philosophy of Biological and Biomedical Sciences*, 43(1), 58e68.

Parker, W. (2009). Does matter really matter? Computer simulations, experiments, and materiality. *Synthese*, 169(3), 483e496.

Rouse, J. (2002). *How scientific practices matter: Reclaiming philosophical naturalism*. Chicago and London: University of Chicago Press.

Rouse, J. (2009). Models as fictions. In Mauricio Suarez (Ed.), *Fictions in science: Philosophical essays on modeling and idealization*. Routledge.

Sarkar, A. X., Christini, D. J., & Sobie, E. A. (2012). Exploiting mathematical models to illuminate electrophysiological variability between individuals. *The Journal of Physiology*, 590(Pt 11), 2555e2567.

Vermeulen, N. (2009). *Supersizing science. On building large-scale research projects in biology*. Maastricht: University Press Maastricht.

Vermeulen, N., Parker, J. N., & Penders, B. (2013). Understanding life together: A brief history of collaboration in biology. *Endeavour*, 37(3), 162e171.

Weisberg, M. (2013). *Simulation and similarity: Using models to understand the world*. Oxford: Oxford University Press.

Winsberg, E. (2009a). A tale of two methods. *Synthese*, 169(3), 575e592.

Winsberg, E. (2009b). Computer simulation and the philosophy of science. *Philosophy Compass*, 4(5), 835e845.

Wolkenhauer, O., Auffray, C., Jaster, R., Steinhoff, G., & Dammann, O. (2013). The road from systems biology to systems medicine. *Pediatric Research*, 73(4 (Pt 2)), 502e507.