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Editorial for Special Issue on Validation and Models in Computational Biomedical Sciences: Philosophy, Science, Engineering.

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Guest editors: Annamaria Carusi, Blanca Rodriguez, Kevin Burrage.

Computational modelling and simulation in all areas of biological and biomedical research have developed to a point where there is a highly sophisticated array of tools and techniques. Data intensive methods, network and multiscale models have the potential to provide new insights into biological mechanisms integrating sub-cellular, cellular, tissue, organ and potentially whole organism levels. Intensive research is currently focused on how to harness these methods and approaches for translational medical research, such as for drug discovery, drug and medical device safety testing, diagnosis and treatment régimes. In addition these approaches are poised to enhance the capacity to use human derived data, and to contribute to the refinement, replacement and reduction of animal based research.

Validation of models in biomedicine is central to their utility; yet it is not always clear how to achieve validation. While methodologies to tackle validation are often discussed, the deeper conceptual frameworks in which methodologies are embedded get less attention. As issues such as the pervasive variability of biological systems and model uncertainty increasingly come to the fore; and as the drive to apply computational modelling and simulation to medical applications gains momentum, there is a need for creative reconceptions of the whole modelling process. This encompasses not only the scientific and engineering approaches, but also, crucially, the disciplinary, social and institutional dynamics associated with translation. Computational biology and biomedical sciences are highly interdisciplinary, but different disciplines and sectors often have conflicting conceptual frameworks for understanding validation. This makes the social, cultural and institutional aspects of modelling and simulating vital, and this becomes even more marked as computational approaches cross over into the clinical and pharmaceutical sectors, and then take on radically different uses and purposes. Furthermore, the broad public of health care users, who also need to become active stakeholders in the enterprise of computational modelling and simulating, have their own different understandings of when models are valid and ought to be accepted. These potentially conflicting conceptual frameworks and understandings can have a significant impact on the success of collaborations across disciplines and across academic, clinical and industrial sectors, as well as public acceptance. This in turn impacts on the successful implementation of computational modelling and simulation in biomedical applications.

At the same time, a number of social scientists and philosophers have focused their attention on the social factors and epistemology of modelling spurred by the advent of new computational tools and techniques (now classic examples are Morgan and Morrison 1999, Sismondo and Gissis 1999, Boogerd et al 2007) There is however relatively little dialogue across the social science, philosophy, science, engineering and technology development communities. There are missed opportunities here, for learning and broaching the issues that challenge the implementation of computational modelling in biomedical contexts.

The lead up to the workshop interdisciplinary research conducted by the three editors of this special issue. Through a series of discussions and close interactions beginning in 2011, we made a start in thinking of how to bring together different

perspectives on the nature of the emerging forms of modelling in computational biological and biomedical sciences, and the issues raised for validation. This resulted in two publications, one in a scientific publication, and the other in a philosophical publication, each one expanding on different aspects of modelling and validation (Carusi et al 2012; Carusi et al 2013). In these papers we proposed a conceptual framework that shifts focus from individual models, to the Model-Simulation-Experiment System, or MSE-system, stressing the close interconnections between each of these elements, and the way in which they co-evolve and inter-define each other. The MSE-system brings attention to two highly important aspects of computational modelling: its necessary holism, and the fact that the complexity of biological systems modelled is matched by the complexity of the social and technological epistemology of the modelling process. Validation of computational models of biological processes does not occur through direct comparison with that which they attempt to model; rather the whole process of modelling is an iterative process of establishing what would count as criteria for comparison, or the grounds of comparability, that make validating experiments interpretable (Carusi et al 2013). The variability of biological systems presents a profound challenge to computational modelling in biomedical contexts, and our research team has proposed the methodology of an experimentally calibrated population of models approach to addressing it, with Carusi (2014) presenting a social and philosophical view of the epistemological aspects of this methodology, and Muskiewicz et al (2016) setting out the methodology in the context of cardiac electrophysiology.

The *'Validation and Models in Computational Biomedical Science'* workshop and special issue held in Sheffield in December 2015 provided one such opportunity. Our aim with organising the workshop was to provide a platform for discussion and practice across scientific, engineering, clinical, philosophical and social perspectives on the central question of model validation that transcends any single discipline or sector, but which will potentially make a difference to practice. In particular, the workshop focused on understanding the conceptual frameworks that scientists and engineers use in their practices of modelling and simulation, and how philosophers and social scientists can make an input in shaping computational biomedicine, as active participants. We asked workshop participants to consider the following questions for their contributions in presentations and discussions:

- What are the conceptual frameworks for validation, and what are their limits? How can these limits be overcome?
- What can 'validation' mean in the face of biological variability, model uncertainty and other challenges?
- Is 'validation' the right term to use? What does it imply, what does it mean, and are there alternatives? What is the relationship between validation and other terms, such as 'explanation' and 'prediction'?
- How does the understanding of validation shift according to the purpose or use of modelling? What are the criteria of validation of different sectors (academic, clinical, pharmaceutical or regulatory)?
- What are the social / epistemic conditions for model validation? What are the interconnections between these social and epistemic conditions?
- How can socially and philosophically informed epistemologies of validation contribute to debates about validation?
- How do conceptions and cultures of model validation play out in the social and public sphere of health care users and patients?

Participants took up the opportunity with alacrity and enthusiasm judging by the lively discussions of the day. People who are working actively in the field of computational biomedical sciences clearly feel the need to talk about what they are doing as well as just getting on and doing it. They are alive to the conceptual puzzles and indeterminacies of the emerging paradigm in which they are immersed, and acutely aware of its social dimensions.

The discussion of the workshop showed the extent to which taking into account the social nature of scientific knowledge, and the philosophical frameworks that are jostling together as new technologies and techniques come to be used, is experienced by scientists as adding an indispensable dimension to their practice. At the same time, philosophical and social studies of science benefit hugely in their own understandings of science from being able to interact with scientists in open fora such as this. The benefit is in producing research that is more scientifically robust because it is more socially and conceptually robust.

The papers gathered in this special issue attest to the wide diversity of perspectives that the workshop brought together. Fridolin Gross and Miles MacLeod explore what is needed to pursue the goal of standardization of validation in systems biology, and why current modeling and data practices resist attempts at standardization; this is, however, not a deficit, but can be the source of a great deal of productivity, giving the field the flexibility and adaptability it needs at this stage. In their contribution, Eann Patterson and Maurice Whelan set out credibility as an alternative to validation, particularly when the purpose of modeling is to inform decisions, rather than being pursued for scientific purposes alone. They set out a framework based on a matrix categorizing models according to their testability, and their epistemic foundations in known biology. Philip Gemmell picks up on the idea of the Model-Simulation-Experiment System proposed by Carusi et al (2012), and extends it to the population of models approach, showing how Kuhn's notion of a paradigm can be applied to the epistemic robustness of the population of models. Mieke Boon also invokes Kuhn's notion of paradigm, claiming that the type of modeling practices we are seeing in current biological settings has shifted from the scientific to the engineering paradigm, which aims at producing knowledge for solving problems. This paradigm shift sees a shift from the notion of models as representations, to the notion of models as epistemic tools. These four conceptual papers are followed by two papers where we see investigations of validation being carried out in practice.

Dutta et al. evaluate the ability of four models of the electrophysiology of human ventricular cardiomyocytes to reproduce the effect of disease (acute ischaemia) observed in experimental recordings. The authors show how two models require modifications in concentrations and/or currents to reproduce the expected ischemic changes. With these modifications the models are able to reproduce alterations in conduction velocity and repolarization known to occur in acute myocardial ischaemia, a common cause of sudden cardiac death. These models, however, exhibit quantitative differences with two of the models showing closest agreement to experimental data. The study illustrates the importance of evaluating inter-model differences and comparison to experimental data as key steps for validation.

Carro et al. also use the four human ventricular models to conduct a multiscale simulation study investigating the estimation of ionic current conductances from single cell versus tissue measurements. The authors focus on two important problems: the voltage dependent inactivation of the L-type calcium current, and the identification of the major ionic conductances contributing to action potential duration at different phases of repolarization along with other action potential biomarkers. The authors report differences between I_{CaL} inactivation as calculated from the model equation and I_{CaL} inactivation from the in silico simulations, and also between cellular and tissue simulations in the role of specific currents, especially during the depolarization phase of the action potential. The study highlights the importance of reproducing experimental conditions as closely as possible in the simulations to allow an effective comparison between experiments and simulations for validation.

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Annamaria Carusi, Blanca Rodriguez, Kevin Burrage. Guest Editors.