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Editorial

Model interactions: '*It is the simple, which is so difficult*'☆

By definition, models are simplified representations of reality. This is the case, regardless of the nature of a model, and hence applies equally to conceptual, experimental, computational, and other representations of reality.

The process of simplification, driven by the question being asked, inevitably leads to multiple models of "the same reality". These may either incorporate various levels of detail at one and the same structural scale (*e.g.* an oscillatory response, such as cardiac excitation and relaxation, can be described by as little as two equations, or highly complex models, and each of them will have its own utility and limitations (Garny et al., 2003; van der Pol and van der Mark, 1928)), or focus at the different levels of structural complexity of one and the same biological entity (*e.g.* exploring a biological function at various scales, from molecule to man (Bassingthwaighte and Chizeck, 2008; Hunter et al., 2008)).

From this follow (at least) two conclusions: [i] the presence of multiple models of "the same reality" should not be regarded as a shortcoming (it necessarily follows from the definition), but as an asset, for example where we explore the validity of assumptions by linking experimental model and simulation (Kohl et al., 2000; Smith et al., 2009); [ii] we need to learn how to better interrelate the different models, if we wish to develop a systemic understanding of reality (Kohl et al., 2010; Noble, 2002; Rudy, 2000). While point [i] finds ample reflection in experimental, mathematical and computational modelling of biological function, the approach to [ii] needs an improved conceptual foundation and more robust tools and techniques for implementation, in particular where related to multi-scale and multi-physics approaches.

To explore the present state of affairs, therefore, this focused issue of *Progress in Biophysics and Molecular Biology* targets experimental and computational model interactions in bio-research. This continues a tradition, launched about a decade ago, to publish focused journal editions (*e.g.* (Hunter et al., 2001, 2010; Kohl and Richard, 2006)) that are dedicated to offering a snap-shot of the development of the International Physiome Initiative (Bassingthwaighte et al., 1999; Hunter, 2004; Popel et al., 1998) and its European contributions under the Virtual Physiological Human umbrella (Fenner et al., 2008; Kohl and Noble, 2009).

For the present volume, papers were invited from all spheres of model development and application, as long as they addressed questions of interoperability at the interface between models. They start with a proposal for a draft reporting standard, called *Minimum Information about a Cardiac Electrophysiology Experiment* (MICEE), which – if adopted by the community – will support more complete documentation of experimental results (Quinn et al., 2011), thereby facilitating our ability to develop and validate computational models based on experimental data. This communication is currently supported by leading investigators from 44 academic institutions across Europe, North America, Oceania, and Asia, and it is hoped that others will join the authors in the commitment to adhere to the proposed reporting standard for at least 12 months from the inception, in January 2012, of the MICEE repository on the *CardioVascular Research Grid* (www.cvrgrid.org). The standard itself is devised with flexibility and development in mind, and it is integrated into a larger set of activities to provide *Minimum Information about Biomedical or Biological Investigation* (see http://mibbi.org/index.php/Projects/MICEE).

Initiatives such as the MICEE repository will provide a valuable resource for the development and validation of computational models, as carefully reported experimental data will help in the curation of computational models, if simulation results are linked back to data sets in the MICEE repository. The difficulties of model curation are addressed in detail in the next paper (Cooper et al., 2011b). This is a major challenge for the development of validated model repositories, not only at the level of single cells, but equally for multi-scale investigations (Qu et al., 2011). Tools to address related issues include OpenCMISS (Bradley et al., 2011), used at present predominantly for scaling models from micro to macro, and OpenCOR, which focuses at the cellular level (Garny et al., 2009). Both programme environments are integrally linked to Cell*ML* (http://cellml.org/) which, together with other mark-up languages such as SB*ML* (http://sbml.org/) and Field*ML* (http://fieldml.org/), is aimed at improving model interoperability.

Going to 'the other side' of the single cell level, multi-scale exploration of structure-function interrelations in the micro to nano domain poses an equally formidable set of challenges (Winslow and Greenstein, 2011). This is a major frontier for further development, as the lack of understanding of cell signalling in nano-domains forms *the* bottle-neck between insight into protein- and signalling-network interactions (both experimental and computational modelling-based) and its application to the exploration of patho-physiological behaviour (as it is captured at the level of cells, tissues, organs, and so on), and *vice versa*.

Among organ-specific simulations, cardiac modelling has played a pioneering role, having been established more than half a century ago (Noble, 1960) and having enjoyed a prolific development ever since (Greenstein and Winslow, 2011; Noble, 2007; Smith et al., 2009). For the present journal issue, focusing on model *inter* actions, such a track record is undoubtedly an advantage. This is

☆ Bertholt Brecht: from 'The Mother', 1931.

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witnessed by the fact that the next 10 papers all target cardiac model interactions. This ranges from ventricular cell model comparisons (Romero et al., 2011), to consideration of the incorporation of cells into functional tissues (Cooper et al., 2011a), and comparison of their electro-mechanical interactions in experiment and simulation (Katsnelson et al., 2011). Electrical activation and electro-mechanical cross-talk in the heart are, of course, a function of cardiac histo-anatomical structure. This needs to be considered when exploring electrical conduction in health (Bordas et al., 2011) and disease (Clayton et al., 2011), as well as mechanical behaviour such as captured by ventricular torsion (Evangelista et al., 2011). With the existence of multiple models, inter-model consistency of computational predictions (Camara et al., 2011) and the 'individualisation' of simulations (Aguado-Sierra et al., 2011; Konukoglu et al., 2011) pose further important challenges for patient-specific applications of whole-organ modelling. That said – most current models of the heart are whole-ventricle, rather than whole-organ, although atrial structure-based models have started to 'catch up' (Aslanidi et al., 2011), bringing the development and application of a truly whole-organ model of the working heart into the realms of possibility.

Of course – what is a pump without the plumbing? Linking heart models to blood flow and pressure remains a challenge (Hernández et al., 2011) on the path towards a virtual physiological human. The final three papers in this issue highlight the current state in three other highly relevant areas of physiological systems modelling and simulation, focusing on quantitative structure-function assessment of uterine patho-physiology (Atia et al., 2011), cancer (May et al., 2011), and microbes (a suitable reminder that the human body contains at least one order of magnitude more microbial than 'own' cells (Joshi et al., 2011)).

To conclude: the ability to interrelate insight into reality, obtained from various 'simplified representations', is key to the development of an integrated, or systemic, understanding. '*It is the simple, which is so difficult*' and requires, in the given context, improved approaches and tools for interrelation of experimental and computational data, and their contextualisation. The editors hope that the present issue of *PBMB* will serve the purpose of providing an interesting update on efforts in this field, stimulating further research that may – perhaps from the outset – consider interoperability with other conceptual and formalised models, such as developed by the Physiome/Virtual Physiological Human (VPH) efforts. The challenges identified in this issue will, no doubt, also feature prominently at the forthcoming VPH2012 meeting, 18–20 September 2012, in London.

See you there.

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