Preface

Towards the virtual physiological human: mathematical and computational case studies

Until recently, much of the investigative effort in the life sciences has been data-gathering orientated, the ‘genetic revolution’ being an exemplary case. It has become clear in recent years that (i) this data-driven science is not sufficient to understand the function of the incredibly complex biology of interactions from molecular-level to organ-level processes within the human body and (ii) a purely statistical (or evidence based) understanding of health- and disease-related data is not going to allow one fully to apply insight to an individual patient. The virtual physiological human (VPH) initiative is a direction in computational biomedicine that aims to develop a thoroughly data-based framework of methods and technologies that will facilitate the understanding of integrative function from sub-cellular structures, through cells and organs, to the human body as a whole [1]. Many of the methods and technologies needed for this endeavour are model-driven approaches to prediction that have long been used in the physical sciences. Building upon international physiome activities [2], the Strategy for the EuroPhysiome (STEP) project [3] developed a research roadmap that conceived the VPH concept. This roadmap identified the need to break down barriers between life scientists, physical scientists and medical practitioners to enable the fully integrative approach necessary for tackling the challenges that lie ahead.

Since long before the STEP project, attempts to overcome such barriers have included the Mathematics in Medicine Study Groups. These annual workshops continue to bring together biologists and mathematicians with the aim of developing mathematical models that address very specific biology- or health-related questions. Researchers from experimental and industrial laboratories are invited to present technical problems for study in working sessions with leading mathematicians from the academic community. In a week of brainstorming and mathematical modelling, which involves significant communication between the disciplines, there is usually enough time to generate and assess many ideas for solving the problem. A significant number of interdisciplinary collaborations have stemmed from and been fostered by such activities; examples include models for cyst growth [4], cell signalling and differentiation [5], glaucoma [6] and placental transport [7]. Study groups were identified by the VPH community as a useful


One contribution of 11 to a Theme Issue ‘Towards the virtual physiological human: mathematical and computational case studies’.

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format for integration; the VPH Network of Excellence (NoE) has since held two study groups devoted to physiome-style interdisciplinary research. The first, held at the University of Nottingham in 2009, studied problems of epithelial cell and tissue regeneration; while the second, held in Barcelona in 2010, focused upon integration of data across disciplines, new knowledge extraction and demonstration of the tangible benefits of patient-specific computational modelling.

With this Theme Issue, we bring together case studies that outline mathematical and computational modelling programmes strongly inspired and motivated by biological problems. In particular, we invited papers that originated from successful activities such as the Mathematics in Medicine and VPH Study Groups that have enabled the bridging of gaps between physical and life scientists. The focus of this Theme Issue is on mathematical and computational modelling aspects of physiome-related interdisciplinary research. Through case study, each paper illustrates different key features that arise in the modelling process.

The Theme Issue begins with a philosophical discussion from Viceconti [8] on the problems we face when developing predictive models in the interdisciplinary region between the life and physical sciences. When the observations we start from, in order to develop a predictive physics-based model, are subject to severe uncertainty, how do we assess the accuracy of the models and, thus, the reliability of predictions? This sets the scene for the remaining nine papers, in which readers will encounter specific examples of model development, simulation and benchmarking with an emphasis on validation. In doing so, the papers represent modelling efforts across a wide range of organs and systems.

Chernyavsky et al. [7] investigate homogenization approaches in a model of maternal haemodynamic transport of nutrient and its uptake by the foetal circulation in the villous trees of the placenta. The study highlights the importance of looking beyond the leading-order approximation and, in particular, of quantifying errors owing to spatial disorder in multi-scale approximations of physiological systems. Szalai et al. [9] develop a simplified model of mechanosensory hair cells in the mammalian cochlea that combines the effects of ion channel interactions within the inner hair cells and of electro-motility within the outer hair cells in order to explain observed amplification and compression in experiments. Carro et al. [10] introduce modifications to a human ventricular action potential model to investigate cardiac arrhythmias, demonstrating the value of basing action potential model development on the computation of arrhythmic risk biomarkers. The new framework not only was shown to be able to replicate experimental data, but also exhibited good predictive capability.

Clinically motivated models in the next three papers illustrate the potential role of predictive models in clinical diagnosis and treatment. Payne et al. [11] present work towards developing a simulation tool to optimize radio frequency ablation treatment of liver tumours. Based on a mathematical model of bio-heat transfer and cell death, and validated against imaging data of lesions, the tool is shown to enable quantification of errors and thus possible routes towards clinical implementation. Burrowes et al. [12] demonstrate, via computational simulation of patient-derived vascular occlusions in a model of the pulmonary circulation,

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2First VPH NoE study group video: http://www.youtube.com/watch?v=PtLnwvH4kuE.
3Second VPH NoE study group video: http://www.youtube.com/watch?v=B46_CYbOz-g.
that mechanical obstruction alone is not sufficient to cause pulmonary arterial hypertension, additional downstream occlusion being needed to increase pressures significantly. The study by Gómez-Benito et al. [13] is aimed at determining the influence of high-frequency, low-amplitude cyclical stimulation on the bone-healing process. Combining experiments and predictions of a previously published mechano-biological model, the authors propose the design of a new bone-healing treatment.

The ‘virtual athlete’ and the ‘virtual patient’ are the subjects of the next two papers. In the former, van Beek et al. [14] present a multi-scale simulation of endurance cyclists in which models enable coupling of energy conversion on the whole body scale to high adenosine triphosphate hydrolysis during cyclical muscle activity at the sub-cellular scale. In the latter, Baretta et al. [15] consider testing of the predictive capability of a closed-loop model (consisting of a lumped parameter network representing the whole circulation and a patient-specific three-dimensional finite volume model) for the virtual planning of surgical repairs in patients with congenital heart diseases. Finally, the study of Niederer et al. [16] focuses on the development of a benchmark for code simulating cardiac tissue electrophysiology. This is an important step towards improving the verification of code and the reproducibility of simulation results and will be essential in providing confidence in complex cardiac models applied to physiological and clinical questions.

This Theme Issue provides a snap-shot of VPH-related research and development, and the editors hope that this may be as informative and helpful to the reader as previous issues have been. In this context, we would like to thank the Royal Society in general and the editorial board of the *Philosophical Transactions of the Royal Society A* in particular for continued support of the VPH initiative, in the form of a series of focused journal issues: this commenced over a decade ago, when the physiome concept was still only emerging on the international research horizon, and before the VPH process was initiated in Europe [17]. Subsequently, and following the launch of the VPH initiative, a series of Theme Issues has been published, focusing on ontologies, tools, applications and simulations, and thus highlighting different aspects of the VPH process [18–21], making the *Philosophical Transactions of the Royal Society A* a leading source of information in this field.

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