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EDITORIAL

The Cardiac Physiome Project

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This special edition of *The Journal of Physiology* focuses on the Cardiac Physiome Project, with papers that cover the development of standards, models and databases for computational modelling of the heart and circulation. Also included in this issue are white papers, some of which review the current state of the art in terms of techniques, knowledge and applications, and some of which discuss the opportunities and challenges ahead for the expanding application of these models.

The Cardiac Physiome Project is a subset of the wider Physiome project. This is an internationally collaborative effort, led by the International Union of Physiological Sciences (www.iups.org), with the goal of establishing physiology within a quantitative and integrative framework through the use of biophysically based models that are encoded with established community standards and annotated with biological and biophysical meaning from domain ontologies (Hunter & Borg, 2003). The Physiome Project began in earnest with a decision at the IUPS World Congress in 1997 to establish a 'Physiome Committee' (Bassingthwaighte, 2000). The US NIH biomedical funding agency has also contributed to the project through its multiscale modelling Physiome grants (NBIB, 2003). More recently the Physiome Project has also been closely linked with the Virtual Physiological Human project (www.vph-institute.org) funded by the European Commission, which began with the publication of a roadmap called 'Strategy for The European Physiome' (STEP) under Framework 6 (Step Consortium, 2007). The VPH was funded first under Framework 7 and now under Horizon 2020. The heart and to some extent the whole cardiovascular circulation have been the primary demonstrators for the ability of multiscale models to integrate physiological data collected across multiple scales for both the advancement of fundamental understanding and the enhancement of clinical care (Kohl *et al.* 2001).

A key aspect of the Cardiac Physiome Project is the development of mathematical models to interpret experimental and/or clinical data and to guide new experiments, interventions and treatments. The iteration between mathematical models and the collection of data (and the development of new techniques to make new observations) has long been the underpinning philosophy behind advances in the physical sciences and engineering. The progressive application of this approach in the biological and clinical sciences, as demonstrated in this issue, is an exciting development. However, given that most diseases and certainly drugs operate at the molecular level, while most diseases (and certainly chronic diseases) are manifest and often diagnosed at the whole organ or organ system level, it is imperative that *multiscale* models, often involving multiple types of physics (electrophysiology, biochemical reactions, soft tissue mechanics, fluid mechanics, etc.) are developed to aid in the interpretation of both normal physiological and pathophysiological function. Moreover, with the ever-increasing availability of physiological data and the associated number and complexity of multiscale physiological models, it is becoming more and more important to publish these models in a demonstrably *reproducible* form. This requires open community-agreed standards for the models and data, and the free availability of high quality open source software for authoring, annotating and running the models. It also requires that these models, as much as possible, are based on biophysical mechanisms.

Another essential feature of Physiome models (and supported by the Physiome standards) is the need to define well-characterised modules. Complex models should be broken down into submodels or modules that can be independently validated and imported into a larger more complex model. In the first of the white papers, Cooling *et al.* (2016) discuss this important issue and propose design principles for complex models. They illustrate the principles with an example that includes modules on electrophysiology, thermodynamically compliant metabolism, signal transduction, gene regulation and synthetic biology.

The increase in availability of data, often collected across multiple species, has also been essential for parameterising and validating these types of complex models. This process, however, has also inevitably increasingly embedded the multiple sources of uncertainty and variability contained in the measurements of biological processes into the modelling frameworks. For this reason the techniques for capturing this uncertainty and variability in computational models, and an understanding of the implications for model simulation results, are critical for the Cardiac Physiome Project in general. Following standard practices from the physical sciences (such as in weather forecasting), the white paper of Mirams *et al.* (2016) reviews the current state of the art in this area. Examples of parameter uncertainty and condition uncertainty for cardiac physiome models are discussed in detail, and are followed by consideration of other types of uncertainty.

Despite the unparalleled capacity to acquire and process data that has already been achieved, the translation of emerging solutions to clinical applications remains a challenge. This deficit is arguably most profoundly evidenced in the hospital clinic, where the continued use of population-based metrics to define treatment strategies ignores many of the opportunities for personalisation of care. This current one-size-fits-all approach comes at a time when innovation in healthcare is under significant pressure, due to increasingly stringent regulatory requirements and mounting pressure on healthcare budgets due to ageing populations. It is for these reasons that the clinical application of cardiac physiome models explicitly supported by the VPH has for almost a decade been a significant focus for part of the Cardiac Physiome community, as discussed by Niederer & Smith (2016). They argue that biophysical computational models present three opportunities for translation: (i) the use of a mathematical framework for introducing physical and physiological constraints to interpret diagnostic (particularly image) data; (ii) the development of models that can represent the physiology and pathology

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of the individual patient; and (iii) the development of representative populations of patient models that can be used for general hypothesis testing, informing clinical guidelines and providing potentially valuable information prior to designing clinical trials. In each case the opportunities and challenges are discussed along with the potential for further enriching the Cardiac Physiome through the adoption of techniques developed in related fields.

A tangible demonstration of the multiscale nature of cardiac function is the reflection of repolarization at the cellular level in the T-wave of the ECG at the body surface. The time from the peak inward sodium current (corresponding to the Q-wave on the ECG) to the peak of the T-wave is the clinically observed QT interval. Any mutation that reduces the density of the outward repolarising IK_r or IK_s potassium channels, or detrimentally alters their kinetics, leads to delayed repolarization and a longer-than-normal QT interval – this condition is known as long QT syndrome (LQTS). LQTS is particularly dangerous because reactivation of an inward sodium or calcium current during the plateau can generate a wave of electrical depolarization that spirals around the heart. This arrhythmia, also referred to as *torsade de pointes* ('twisting of spikes') because of the apparently random dancing pattern on the ECG, can quickly break up into multiple spirals. Known as ventricular fibrillation, this phenomenon renders the myocardium an uncoordinated quivering mass unable to pump blood – a heart attack. The use of models to understand the clinical significance of these multi-scale interactions is explored in the next three papers. Vandersickel *et al.* (2016) discuss the factors that prolong torsade de pointes and Karathanos *et al.* (2016) discuss the use of computational models for defibrillation based on optogenetics as an alternative to the use of electrotherapy. An inherited LQTS condition named LQTS2 (resulting from mutations of the *KCNH2* gene, involved in the IK_r channel) manifests as both an LQT interval on the ECG and a splitting of the T-wave, known as a bifid or notched T-wave. The use of cardiac physiome models to improve the precision of clinical diagnosis and therefore risk stratification, in the context of sudden cardiac death from arrhythmias and subsequent ventricular fibrillation, is considered by Hill *et al.* (2016).

The final paper in this special issue on the Cardiac Physiome is on the development of a cardiovascular model that can be used as a community resource. It is an unfortunate fact that there have been few attempts to create such community resources for physiological modelling. To remedy this Safaei *et al.* (2016) propose a model of the cardiovascular circulation that uses one-dimensional Navier–Stokes equations for the larger compliant blood vessels, coupled with linear transmission line models for vascular beds embedded within organs, which are themselves then coupled with lumped parameter models for the capillary networks.

References

Bassingthwaighte JB (2000). Strategies for the Physiome Project. *Ann Biomed Eng* **28**, 1043–1058.

Cooling MT, Nickerson DP, Nielsen PMF & Hunter PJ (2016). Modular modelling with physiome standards. *J Physiol* **594**, 6817–6831.

Hill A, Perry, M, Abi-Gerges N, Couderc J-P, Fermini B, Hancox J, Knollmann B, Mirams G, Skinner J, Zareba W & Vandenberg J (2016). Computational cardiology and risk stratification for sudden cardiac death: one of the grand challenges for cardiology in the 21st century. *J Physiol* **594**, 6893–6908.

Hunter PJ & Borg TK (2003). Integration from proteins to organs: The Physiome Project. *Nat Rev Mol Cell Biol* **4**, 237–243.

Karathanos T, Bayer J, Wang D, Boyle P, Trayanova N (2016). Opsin spectral sensitivity determines the effectiveness of optogenetic termination of ventricular fibrillation in the human heart: a simulation study. *J Physiol* **594**, 6879–6891.

Kohl P, Noble D & Hunter PJ (eds) (2001). *Theme Issue 'The integrated heart: modelling cardiac structure and function' compiled by P. Kohl, D. Noble and P. J. Hunter, Philosophical Transactions of the Royal Society of London, Series A*, vol. **359**, pp. 1047–1337. The Royal Society, London.

Mirams GR, Pathmanathan P, Gray RA, Challenor P & Clayton RH (2016). Uncertainty and variability in computational and mathematical models of cardiac physiology. *J Physiol* **594**, 6833–6847.

Niederer SA & Smith NP (2016). Using physiologically based models for clinical translation: predictive modelling, data interpretation or something in-between? *J Physiol* **594**, 6849–6863.

National Institute of Biomedical Engineering and Bioengineering (NIBIB) (2003). *Interagency Modeling and Analysis Group (IMAG)*. http://www.nibib.nih.gov/research-funding/interagency-modeling-and-analysis-group-imag.

Safaei S, Bradley C, Suresh V, Mithraratne K, Muller A, Ho H, Ladd D, Hellevik L, Omholt S, Chase JG, Mueller L, Watanabe S, Blanco P, de Bono B & Hunter PJ (2016). Roadmap for cardiovascular circulation model. *J Physiol* **594**, 6909–6928.

Step Consortium (2007). *Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human*. http://www.vph-institute.org/upload/step-vph-roadmap-printed-3_5192459539f3c.pdf.

Vandersickel N, de Boer T, Vos M & Panfilov A (2016). Perpetuation of torsade de pointes in heterogeneous hearts: competing foci or re-entry? *J Physiol* **594**, 6865–6878.

Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.