Published in final edited form as:

Drug Discov Today Dis Models. 2014 ; 14: 1–2. doi:10.1016/j.ddmod.2014.12.002.

Computational models of heart disease

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Over the last two decades, major breakthroughs in the research methodologies employed by experimental physiologists have paved the way for an explosion in the quality and quantity of available data. These developments have underpinned many of the post-genomic era's advances in understanding, enabling the analysis of specific physiological systems through the collection of unique individual data sets. In parallel with these experimental developments, advances in computational and numerical techniques have accelerated our capacity to derive new knowledge making possible the integration of multiple data sets through the application of biophysically based computational models. These modelling developments now provide the potential for analysing complex cause and effect relationships and facilitating the development of improved mechanistic understanding in a range of physiological systems.

Arguably more than any other organ system, the confluence of computational and measurement technology has been most effectively exploited to increase our understanding of the heart. The current diversity and quantity of experimental and clinical imaging data, including measurements of single cells, wall motion, electrical mapping and blood flow, has produced opportunities to improve both physiological understanding and ultimately clinical care for cardiovascular disease. Focusing on using these frameworks to integrate both cellular and whole organ level measurement, continues to provide significant opportunities for reconciling observation across cellular and organ level functions within a consistent framework.

Of specific relevance for this publication, the potential to use this type of reconciliation within the drug discovery (or drug rescue) pipeline is significant. However, the multiple requirements of representing mechanisms in sufficient detail, obtaining the data required to determine and validate model parameters while simultaneously maintaining computational tractability remains a challenge to navigate. The papers within this volume represent a number of cardiac modelling state of the art exemplars that show both the foundation work towards this goal and, by inference, the current gap to *in-silico* drug discovery being achieved.

The review by Clancy *et al.* makes the point that current computational pharmacology models, while expandable, scalable and presenting potential for automation, focus only on constituent elements of the system. However, the effects of multifaceted drug interactions

are emergent and unpredictable, particularly those aimed at treating heart rhythm disturbances. The way forward is to use these technologies in conjunction with computational models of the heart, forming an interactive technology-driven process that can be used in industry for drug and disease screening, in academia for research and development, and in the clinic for individualized patient treatments.

Central to our theme of integration, at the cellular level, Louch *et al.* summarize the evolution of calcium handling in cardiomyocyte mathematical models, and emphasize the importance of data-driven model parameterization. Consistent with the message brought forward by the full collection of papers, these authors also stress the need for and provide examples of efficient data exchange between experimentalists and modellers to formulate novel hypotheses.

Clayton and Bishop focus their review on the use of computational models to understand the mechanisms that initiate and sustain dangerous ventricular arrhythmias, from the cellular level to that of the whole organ. The authors conclude that new model developments trend towards including increased amounts of anatomical and biophysical detail, and that major emphasis has been recently placed on pipelines for generating patient-specific models that would guide interventions in the clinic. Colman *et al.* examine the same subject – arrhythmogenesis from the cell to the entire organ – but in a different system: the atria. The review presents multi-scale atrial models that have been used to dissect the mechanisms underlying atrial fibrillation, provide insight into pacemaking function, and to achieve personalization of heart(atria)-torso models for patient specific modelling.

At the whole organ, and indeed, whole population, scale Young *et al.* describe embedding of data within models. While imaging technology traditionally sees the reconstructed image as the end goal, this study provides a compelling demonstration that in reality it is a stepping stone to evaluate some aspect of the state of the patient, for example shape, location and extent of a particular disease, response to treatment. In this context the image is merely an intermediate visualization of this state, for subsequent interpretation and processing either by the human expert or computer based analysis. Kassab *et al.* focus on this same whole organ scale but specifically on the coronary vasculature, motivated by the significance of coronary artery disease in the majority of western societies. In particular these authors show how understanding physiological mechanisms using models can be translated into clinical understanding.

Across all of the studies in this issue, strong generic components emerge, indicating that the over-arching philosophies can, in many cases, be translated to the integration of state-of-the-art simulation into a number of other contexts and in particular, other organ systems and pathologies. However, the merging the cultures of leading edge simulation research with real world clinical implementation remains a significant challenge. As the included papers demonstrate, major steps in this direction have already been undertaken. The successful integration of experimental and clinical data into detailed biophysically models that can inform understanding and clinical intervention will, we believe, result in a significant impact on both patient outcomes and the medical practice in general.

With best wishes,

Nic Smith and Natalia Trayanova

Biographies

Nic Smith, PhD is Professor and Dean of Engineering at the University of Auckland and visiting Professor of Biomedical Engineering at Kings College London and visiting Professor of Computational Physiology at the Computing Department, University of Oxford. His research is characterised by the development of integrated multi-scale and multi-physics models, which provide the ability to link biophysically detailed experimental data to integrated function from sub-cellular to the whole organ level. Within the scope of this work, he has developed computational techniques to enable specific model developments that have in turn been applied to provide insight into both basic physiology and clinical contexts. This research is focused on electrophysiology and contraction at the cellular level and the multi-scale translation of these models to simulate coronary blood flow and cardiac electro-mechanics at the tissue level.

Natalia Trayanova, PhD is the Murray B Sacks Professor of Biomedical Engineering and Medicine at Johns Hopkins University. She directs the Computational Cardiology Laboratory at the Institute for Computational Medicine. She is a Fellow of the Heart Rhythm Society, American Heart Association, Biomedical Engineering Society, and the American Institute for Medical and Biological Engineering. The research in Dr. Trayanova's Computational Cardiology Laboratory centers around understanding the pathological electrophysiological and electromechanical behavior of the heart, with emphasis on the mechanisms for cardiac arrhythmogenesis and pump dysfunction, and the improvement of the clinical therapies of defibrillation, atrial and ventricular ablation, and cardiac resynchronization therapy using a personalized approach.