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Editorial

Modelling cellular and tissue function

This volume contains reports arising from a conference held in Auckland, New Zealand, in July 2003 as part of a programme funded by the New Zealand Institute for Mathematics and its Applications entitled 'Modelling Cellular and Tissue Function'. With the theme of integration across the range of scales of biological organisation, the meeting brought together researchers concerned with the application of mathematical and computational techniques to a wide variety of problems in cell and tissue physiology.

It is now widely recognised that mathematical and computational approaches are needed to make progress on understanding complex biological problems. Quantitative approaches to unravelling biological function are well established in physiology, which is an inherently integrative science bringing together elements of molecular and cellular biology, biophysics and biochemistry to study cell and tissue function in the context of the organism. Mathematical modelling in physiology has, of course, a long and illustrious history, both in deciphering the biophysical mechanisms underlying processes such as the generation and transmission of the nerve impulse and the molecular mechanisms of active contraction of muscle cells, for example, and in large scale systems analyses, as pioneered in the cardiovascular arena by the late A. C. Guyton (Annu. Rev. Physiol. 1972, 34, 13–46).

A current approach to physiological modelling, illustrated by a number of studies in this volume, combines both these elements using explicit representations of biophysical processes and integrating of these components into a large-scale modelling framework. While there is still a great deal to be learned from mathematically refined and abstracted models of biological processes, there can be little question that a high degree of the true complexity of living tissue must be represented if clinically applicable insights are to be gained from model simulations. One possible mechanism for handling this complexity is to adopt a modular and hierarchical approach to modelling, whereby mathematical representations of biological components are brought together and tuned appropriately to produce a model of a specific cell or tissue type. For example, models of the kinetics of individual ion channels can be formulated using membrane patch-clamp data, and these sub-models combined in an electrophysiological model for the action potential of a particular cell with parameters tuned to fit voltage-clamp data. Perhaps the most transparent way of achieving this is to retain biophysical detail at each level in a modelling hierarchy, which also provides an obvious mechanism for revision or improvement of selected parts of a large-scale simulation as new data are collected.

The physiological processes in which we are interested are typically characterised by a wide range of spatial scales (from the molecular to the tissue level) and time scales (from sub-millisecond biochemical reactions to progression of disease over days or even years). It is a

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significant challenge, both mathematical and computational, to construct *multiscale* models which deal with this complexity while remaining computationally tractable, and which are still capable of providing insights when the model does not behave as expected (as it sometimes must if we are to learn anything new!). Retaining biophysical detail provides confidence in the ability of a model to extrapolate from the data used for parameterisation, and to provide detailed, even patient-specific predictions. This requires the development of approaches to deal with model complexity, parameterisation, and indeed the communication and sharing of models. These themes are amply illustrated by the reports contained in this volume.

Focusing on complexity exhibited at the cellular scale, several authors report on aspects of calcium signalling in a number of different physiological situations. Sneyd et al. review models of the IP_3 receptor, responsible for triggering calcium release from internal calcium stores in a variety of cell types. Soeller and Cannell demonstrate the importance of local control of calcium release in understanding excitation–contraction (EC) coupling in the cardiac cell. The feedback between calcium activation and contraction is also the subject of two further papers. Puglisi et al. review the historical development and future directions for mathematical models of ionic activity in the cardiac cell with particular reference to underlying calcium cycling and EC coupling. Rice and de Tombe postulate cooperative interactions in a myofilament model to explain the generated tension observed for different amounts of intracellular calcium.

Stochastic aspects of calcium release from individual release sites in generating intracellular calcium waves are discussed in the paper by Coombes et al. Multiscale modelling that includes stochastic molecular events is also the subject of the report by Burrage et al., on simulation of chemical reaction dynamics, and Schnell and Turner report on simulation of biochemical reactions in crowded, heterogeneous intracellular spaces, revealing fractal-like kinetic rate laws. Cellular signalling and metabolic pathways also demonstrate complex interactions and feedback over a variety of timescales, as demonstrated in the reports by Saucerman and McCulloch, who describe how systems models can advance the quantitative understanding of cellular signal transduction networks, and Matsuoka et al., who couple metabolic processes to a model of excitation and contraction in the myocyte, providing scope to simulate pathologies such as anoxia in heart disease. Parameter variation in cellular models representing spatial gradients in cell properties across a tissue is addressed by Lovell et al. in the context of the sino-atrial node, the pacemaking region of the heart. In their study, model parameters are extracted by fitting a generic cell model to action potentials recorded at different locations in the cardiac pacemaking tissue.

Iteration between simulation and experimentation is essential in a model-based approach to understanding the behaviour of complex systems. Kuchel discusses this challenge in the context of using a biophysically based model of erythrocyte metabolism to interpret the time course of NMR metabolite spectra. Bhanot has used a modelling approach to reinterpret immunological data on B-cell activation in the immune system. In the cancer field, Basse et al. use a model to interpret flow cytometric data on human tumour cell lines to study the effects of cancer therapy. Steyn-Ross et al. present a theoretical framework for understanding anaesthesia which is consistent with electrical fluctuations observed in EEG recordings of subjects during the transition to unconsciousness.

As we have argued, the development of detailed multiscale computational models raises important issues for model construction and parameterisation, of communication and reuse of models and the need for database repositories for models. Processes operating on widely differing timescales to the regime of interest can usually be approximated to simplify models for

computational simulation. Smith and Crampin demonstrate how to rationalise models using a formal timescales analysis, taking as an example a model of the cardiac sodium pump. While biophysically detailed models may provide a more transparent mapping to observable biophysical states, there are associated difficulties with model parameterisation should sufficient data not be available to constrain the many parameter values. Dokos and Lovell address this issue for a cardiac cell model to determine whether the parameters for ionic currents can be obtained from membrane potential data alone. Complicated mathematical models containing large numbers of equations and parameters are prone to 'communication' errors which hinder their application by others. Lloyd et al. report on the development of the CellML standard to unambiguously represent mathematical cell models and eliminate model representation errors. By achieving this aim the development, application and reuse of models can be facilitated for the wider modelling and life sciences community. Many of the models described in this volume are available from the CellML website (www.cellml.org).

The report by Alarcón et al. describes a cellular automaton representation of a cell-cycle-based model for tumour growth in heterogeneous tissue, which is coupled to blood flow through the tissue in order to predict the effects of drug delivery. Heart disease is another pathology which involves interactions of processes across many different scales. Clayton and Holden show how a spatial variation in cellular properties can affect the spread of electrical activation in cardiac tissue. Nash and Panfilov investigate the effects of active tension generation within an excitable tissue which has electrical properties which are themselves sensitive to the contraction of the muscle cells. This mechano-electric feedback is an important example of coupling between events occurring at different spatial scales, and is the subject of another recent issue of this journal (Prog. Biophys. Mol. Biol., Vol. 82, 2003). Pullan et al. have applied similar computational techniques to the gastro-intestinal system. Their paper describes the construction of a detailed anatomically-based model which links cellular electrical pacemaking in the tissue lining the stomach and duodenum through to body surface recordings of the magnetic and electrical fields generated by the electrical activation of the gastrointestinal tract. The final paper in this volume outlines an international collaborative effort to link models across multiple scales of physiological organisation. Hunter presents examples of educational and surgical training software and discusses long term opportunities and challenges for the life sciences modelling community.

Many of the techniques developed to model one cell type, tissue or organ, illustrated in this volume, are equally applicable to other cells, tissues and organs. We can therefore expect the pace of biological modelling to accelerate and look forward to an increasing degree of integration in models of physiological systems.

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