SA2

FROM BACTERIA TO HUMANS: MOLECULAR MODELLING AND SIMULATION OF ION CHANNELS

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Membrane proteins are central to many cellular processes. From a post-genomic perspective, their importance is demonstrated by the observation that ~25% of genes code for membrane proteins. Thus there are ~8000 membrane proteins encoded within the human genome. Despite the importance of membrane proteins, they remain under-explored territory. High resolution structures are known for ~50 membrane proteins, in contrast to ~22,000 structures for water soluble proteins. Computational methods play an essential role in understanding the relationship between structure and function of membrane proteins. Ion channels, in addition to their intrinsic physiological importance, provide a well studied paradigm for developing such computational approaches for membrane proteins in general. The overall aims of our studies of ion channels are to understand fundamental physical mechanisms of ion channel processes, including permeation, selectivity and gating; and to relate atomic resolution structures of ion channels to their physiological function, with a longer term aim of prediction of the functional consequences of channel mutations. Current research embraces a number of channels, with a particular focus on: (a) potassium channels (voltage gated, Kv, and inward rectifier, Kir, channels); (b) nicotinic acetylcholine receptors and related 'cys-loop' receptor-channels; and (c) ionotropic glutamate receptors. Three areas of application of computational methods will be discussed: (a) understanding physical processes of ion and water permeation; (b) development of computational approaches to bridging multiple timescales, enabling us to relate atomic resolution structure to physiological function; and (c) development of accurate models of the mammalian channel proteins based on X-ray structures of bacterial homologues.

Domene, C., Grottesi, A., and Sansom, M.S.P. (2004) Filter flexibility and distortion in a bacterial inward rectifier K+ channel: simulation studies of KirBac1.1. Biophys. J. 87:256-267.

Beckstein, O., Biggin, P.C., Bond, P.J., Bright, J.N., Domene, C., Grottesi, A., Holyoake, J. and Sansom, M.S.P. (2003) Ion channel gating: insights via molecular simulations FEBS Lett. 555:85-90.

Beckstein, O. and Sansom, M.S.P. (2003) Liquid-vapor oscillations of water in hydrophobic nanopores. Proc. Natl. Acad. Sci. USA 100:7063-7068

SA3

THE ROLE OF GRO/TLE1 IN HESL OSCILLATIONS

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The transcriptional repressor Hes1, which is a basic helix-loop-helix family protein, periodically changes its expression in the presomitic mesoderm. Drosophila Groucho
(Gro) and its vertebrate counterpart, the transducine-like enhancer of split/Groucho-related gene product 1 (TLE1) protein, is a corepressor required by a number of NA-binding transcriptional repressors, including Hes1.We propose three models for the regulation of observed Hes1 oscillatory expression, and search for common parameter value requirements. We introduce a model for Hes1 oscillatory expression that includes regulation of Hes1 transcription by Gro/TLE1. From detailed linear stability analysis, numerical bifurcation analysis and simulations, we conclude that the cooperativity coefficient (h) for Hes1 self-repression should be greater than 4.
The characteristic turnaround duration of the repression loop is between 40 and 60 min. Depending on the model, explicit delays range from 10 to 40 min.
Models of direct repression via Hes1 typically show an expression overshoot after transcription initiation in contrast to experimental data. Numerical simulation and theoretical predictions show that the cofactor Gro/TLE1 reduces the overshoot and is thus necessary for a rapid and finely tuned response of Hes1 to activation signals.

SA4

THE P53-MDM2 SYSTEM MODELLED AS A DIGITAL OSCILLATOR WITH A TIME DELAY

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The P53 system suppresses tumors by arresting cell cycle when chromosomal DNA is damaged to allow for specialized enzymes to repair the DNA breaks. When the damage is too severe to be repaired, then the P53 system induces apoptosis. The critical role of P53 in suppressing tumors is underscored by the observation that over 50% of all cancers involve a disruption of this system. In response to DNA damage, protein level of P53 and its antagonist MDM2 oscillate roughly out of phase with respect to each other. The response has been termed a "digital oscillator" because the average number of cycles increases with the amount of DNA damage, whereas neither the heights of the oscillation nor the period is strongly affected (Lahav et al., Nat Genet. 36(2):113-4, 2004). Such a response is in sharp contrast to damped oscillations or strictly analog behavior that was previously assumed for this system. However, generating dynamical systems with digital oscillations is not straightforward using typical small systems of nonlinear state equations. As previously suggested (Monk, Curr Biol. 13(16):1409-13, 2003), the robustness of oscillations can be increased with inclusion of a pure time delay to represent the processes involved in transcription, splicing, and translation. Intuitively, there is a delay of 20-30 minutes between the induction of a gene and the appearance of the active protein that is the gene product. Using standard dynamical systems analysis, the inclusion of the time delay has no effect on the location of the fixed points of the system, but there can be pronounced effects on the stability of fixed points and the shape and location of the nullclines in the phase space. Using P53 as an example system, we show that inclusion of the time delay produces a robust dynamical system with roughly digital behavior like the biological system.

SA5

MODELLING THE INFLAMMATORY PROCESS IN TYPE 1 DIABETES AND ALZHEIMER'S DISEASE

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Macrophages are professional phagocytes, responsible for clearing apoptotic cells and debris, and preventing the buildup of necrotic tissue. Factors secreted by these cells, including cytokines and reactive oxygen species can, however, cause significant tissue damage leading to an escalating inflammatory condition. We report on progress in mathematical modeling of two diseases in which these innate immune system cells may be adversely implicated, Alzheimer's Disease (AD) and Type 1 diabetes (T1D). We discuss the dual roles of microglia in the brain and macrophages in the pancreas. In T1D, macrophage activity following some initial stimulus could set the stage for insulitis and eventual destruction of insulin-secreting beta-cells by cytotoxic T cells. In AD, the reaction of microglia to amyloid beta can escalate to neuroinflammation and lead to stress and death of neurons. A fine balance exists between factors that ensure resolution of inflammation versus those that accelerate it. Mathematical modeling can help to rigorously and quantitatively explore how these competing influences play out. A comparison of the feedbacks and conditions for healthy or pathological outcomes in the two diseases is discussed.

In the case of T1D, theoretical work has been accompanied by in vitro experiments to quantify macrophage phagocytosis, including rates of engulfment and digestion of apoptotic cells. These experiments reveal significant differences between animals prone to T1D, the non-obese diabetic (NOD) mice versus normal (Balb/c) mice. We found that NOD mouse macrophages engulf apoptotic cells more slowly than their normal counterparts. We have conjectured that this defect may be significant in initial stages of T1D pathogenesis, and we continue to explore this hypothesis. Mathematical models have led to improved experimental design, and have been informed by experimental results.

This work has been supported by the Mathematics of Information Technology and Complex Systems (MITACS) Networks of Centers of Excellence of Canada, the Juvenile Diabetes Research Foundation, and the Canadian Institutes for Health Research.

SA6

ROLE OF INDIVIDUAL ION CHANNELS IN THE CARDIAC CELL FUNCTION, A MODEL STUDY

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We aim at clarifying the role of individual ion channels in the cardiac cell function by constructing a comprehensive cell model (Kyoto Model) based on the cardiac cell model developed by DiFrancesco and Noble (1985), the sarcomere contraction model by Negroni and Lascano (1996) and the mitochondria oxidative phosphorylation model by Korzeniewski and Zoladz (2001). To access the central role of L-type Ca^{2+} channel (I_{CaL}), the model of Ca^{2+}-dependent inactivation developed by Shirokov et al (1993) was used. The amplitude factor of I_{CaL} was adjusted to simulate the I_{CaL} recorded by the action potential clamp experiment by Linz and Meyer (1998). The gating kinetics of the Ca^{2+}-releasing (RyR) channel of the sarcoplasmic reticulum (SR) (Hilgemann & Noble, 1987) was adjusted to give the staircase phenomena of single cell contraction, and the time course of Ca^{2+} transient was adjusted based on the experimental measurements of SR Ca^{2+} release, Ca^{2+} leak and Ca^{2+} pump uptake (Wier et al., 1994). The Ca^{2+}-gain, which is given as the ratio of peak Ca^{2+} fluxes via IRyR to that of I_{CaL} is in the range of experimental measurements reported by Wier et al (1994). The Kyoto model well reconstructed the positive inotropy as well as the shortening of the action potential at higher $[Ca^{2+}]o$, and revealed the time-dependent changes in the open probability of Ca^{2+} gate of I_{CaL} in the ventricular cell model. The same Ca^{2+}-dependent gate of I_{CaL} also took the pivotal role in the sinoatrial node cell model when reconstructing the increase of the pacemaker rhythm accompanied with the action potential shortening with increasing $[Ca^{2+}]o$. The role of Cl^- channels was assessed by including a hypothetical and background Cl^- channel in the Kyoto model. The intracellular $[Cl^-]i$ homeostasis was established by implementing the $Na^+,K^+,2Cl^-$ cotransporter model developed by Benjamin & Johnson (1997). Increasing the membrane Cl^- conductance, simulating the activation of the cAMP-dependent Cl^- channel, the cell volume was decreased with a membrane depolarization of a few mV as observed in the experiment (Wang et al., 1997, Sasaki et al. 1999). If the Na^+/K^+ pump was blocked, the cell volume gradually increased. The model revealed that this volume increase was in parallel to the net Cl^- influx caused by membrane depolarization via redistribution of K^+ across the cell membrane. The model indicated that the Cl^- flux takes the central role in the acute phase of cell volume regulation.

Matsuoka et al. Role of individual ionic current systems in ventricular cells hypothesized by a model study. Jpn J Physiol 53;105-123 (2003)

Sarai et al. Role of individual ionic current systems in the SA node hypothesized by a model study. Jpn J Physiol 53:125-134 (2003)

Matsuoka et al. Simulation of ATP metabolism in cardiac excitation-contraction coupling. Prog Biophy Mol Biol 85;279-299 (2004)

DiFrancesco D & Noble D. A model of cardiac electrical activity incorporating ionic pumps and concentration changes. Philos Trans R Soc Lond B biol Sci 307;353-398 (1985)

Negroni JA & Lascano EC A cardiac muscle model relating sarcomere dynamics to calcium kinetics. J Mol Cell Cardiol 28;915-929 (1996)

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SA7

MODELLING ELECTROMECHANICAL FUNCTION OF HETEROGENEOUS MYOCARDIUM

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Structural, functional, and biochemical heterogeneity of myocardial tissue has been documented at different levels of functional

integration, from molecular to whole organ. In isolated cells, transmural heterogeneity of biochemical properties, electrical and mechanical characteristics, and excitation-contraction coupling have been experimentally confirmed. There are, however, a many unresolved question, such as: How does cellular heterogeneity correlate with mechanical conditions and the electrical activation sequence in the intact heart? What is the physiological significance of myocardial heterogeneity? How does it affect pathologies?

To study basic effects of the dynamic interaction between myocardial elements on the electro-mechanical function of a heterogeneous system, we developed a condensed model of cardiac heterogeneity, termed 'duplex'. A duplex consists of a pair of interacting cardiac muscle preparations that are mechanically interconnected. We have implemented six duplex configurations [1], based on mechanical connection of elements *in-parallel* or *in-series*, using all possible combinations of *biological* and/or *virtual* muscle segments. The combinations are: i) *biological duplex* (two biological samples, such as thin papillary muscles or trabeculae); ii) *virtual duplex* (two mechanically interacting mathematical models of cardiac muscle); and iii) *hybrid duplex* (combination of a biological sample and a model-driven I/O system that interact mechanically in real-time).

For all duplex configurations, we studied the mechanical activity of each individual element in isolation, and after coupling within a duplex, during isometric, isotonic, and auxotonic modes of contraction. Introducing different time lags between element stimulation, we furthermore studied effects of the electrical excitation sequence on duplex function.

We found that, the contractile function of each individual element (quantitatively assessed as length-force and force-velocity relations) is significantly affected by the dynamic interaction of elements (representing a model of the *in situ* mechanical environment), depending on individual mechanical properties, electrical activation sequence, and connection pattern of elements. Using virtual duplexes, we showed that mechanical interaction between functionally heterogeneous virtual muscle elements affects their electrical activity in the sense of mechano-electrical feedback (MEF). The models yielded opposite changes in the action potential duration (APD) of elements after duplex formation (both in-parallel and in-series), where an increase in APD of one virtual muscle correlates to a decrease in the other. The sense of that APD change depends critically on the excitation sequence. As a result, dispersion of repolarisation within the duplex is significantly different from that observed in uncoupled muscles, and varied from zero to values that significantly exceeded intrinsic activation delay times. This prediction may explain contradictory data on dispersion of repolarisation, experimentally registered in either isolated cells or in intact tissue.

From modelling results we derived mechanisms that are possibly responsible for the effects of heterogeneity on duplex electromechanical function. We conclude that functional alteration of the electromechanical activity of duplex elements involves complex interplay of cellular processes, where mechano-dependent Ca^{2+} kinetics (via co-operative modulation of Ca2+ binding to troponin C, and influence on Ca^{2+} dependent ionic currents) plays a key role in the tuning of mechanical and electrical activity. Additional effects of stretch-activated channels are subject of further investigation.

Along with rapid responses of coupled muscles to change in external conditions (e.g. excitation sequence, duplex length, afterload) we studied more slowly occurring changes in steady state behaviour. Particularly, we assessed SR Ca^{2+} levels in duplex elements (either directly by calculating this in virtual muscle or indirectly by registering force change in real muscle) before and after mechanical coupling. We found in hybrid and virtual duplexes that there is a relative re-distribution of SR Ca^{2+} load between mechanically interacting elements, even in the absence of common Ca^{2+} source. This could shed light on one of the potential physiological relevance of MEF in heterogeneous myocardium, which could be related to the maintenance of an adequate Ca^{2+} load in the individual cells of the heart, to optimize their function.

Markhasin V.S. et al. Prog Biophys Mol Biol 2003/82:207-220.

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SA8

MODEL DEVELOPMENT FOR CARDIAC EXPERIMENTATION: ASSOCIATION OF ENGINEERING AND COMPUTATION

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The concise Oxford dictionary of current English defines a model as *'a simplified [...] description of a system [...] to assist calculations and predictions'*. One can apply this definition, in its wider sense, to any intellectual activity (or its product) that tries to make out the components of a system and to predict the outcome of their interaction.

Since models are simplified descriptions of reality, no single model will capture all aspects of a system, down to its finest components and interactions, as a 'complete' model would cease to be a model and turn into a copy of the original (or, in biology, a clone). Models, like tools, are developed for a particular purpose and applicable to a restricted set of tasks. This applies equally to 'wet' experimental and 'dry' computational models.

A major challenge for bio-medical research is to bridge the enormous span from whole body structure and dynamics to the molecular level. This involves about 10^{10} orders of spatial magnitude (from metres at the organisms' level to Angstrom for ion channel pores) and 10^{18} orders of temporal magnitude (from decades to describe organisms' life spans to nano-seconds for atomic level molecular dynamics). The range of reasonable spatio-temporal combinations by far exceeds experimental and theoretical 'modelling power'. Thus, a multitude of modular and complementary models are required.

Advanced bio-engineering leads the way towards building wet experimental models that are increasingly relevant (for the questions of modern research), representative (of the system modelled) and reproducible (to allow solid characterisation of components and their interaction). Computational modelling, on the other hand, provides the way to re-integration of the pieces of the jig-saw identified using advanced experimental tools.

This process involves the continuous iteration between theoretical and practical work, for model construction, validation, interpretation, and hypothesis formation. This is a bi-directional

process which, if applied successfully, reduces time and resources required for biomedical research, while improving quality and applicability of findings.

Kohl P, Noble D, Winslow RL & Hunter P. Computational modelling of biological systems: tools and visions. Philosophical Transactions of the Royal Society A 2000; 358: 579-610.

Garny A & Kohl P. Cardiac research at the interface of engineering and computing. The Chemical Engineer, 2004 (in press).

SA9

CANCER MODELLING: GETTING TO THE HEART OF THE PROBLEM

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Paradoxically, improvements in healthcare that have enhanced the life expectancy of humans in the Western world have, indirectly, increased the prevalence of certain types of cancer such as prostate and breast. It remains unclear whether this phenomenon should be attributed to the ageing process itself or the cumulative effect of prolonged exposure to harmful environmental stimuli such as ultraviolet light, radiation and carcinogens (Franks and Teich, 1988). Equally, there is also compelling evidence that certain genetic abnormalities can predispose individuals to specific cancers (Ilyas et al., 1999).

The variety of factors that have been implicated in the development of solid tumours stems, to a large extent, from the fact that 'cancer' is a generic term, often used to characterize a series of disorders that share common features. At this generic level of description, cancer may be viewed as a cellular disease in which controls that usually regulate growth and maintain homeostasis are disrupted. Cancer is typically initiated by genetic mutations that lead to enhanced mitosis of a cell lineage and the formation of an avascular tumour. Since it receives nutrients by diffusion from the surrounding tissue, the size of an avascular tumour is limited to several millimeters in diameter. Further growth relies on the tumour acquiring the ability to stimulate the ingrowth of a new, circulating blood supply from the host vasculature via a process termed angiogenesis (Folkman, 1974). Once vascularised, the tumour has access to a vast nutrient source and rapid growth ensues. Further, tumour fragments that break away from the primary tumour, on entering the vasculature, may be transported to other organs in which they may establish secondary tumours or metastases that further compromise the host. Invasion is another key feature of solid tumours whereby contact with the tissue stimulates the production of enzymes that digest the tissue, liberating space into which the tumour cells migrate. Thus, cancer is a complex, multiscale process. The spatial scales of interest range from the subcellular level, to the cellular and macroscopic (or tissue) levels while the timescales may vary from seconds (or less) for signal transduction pathways to months for tumour doubling times

The variety of phenomena involved, the range of spatial and temporal scales over which they act and the complex way in which they are inter-related mean that the development of realistic theoretical models of solid tumour growth is extremely challenging. While there is now a large literature focused on modelling solid tumour growth (for a review, see, for example, Preziosi, 2003), existing models typically focus on a single spatial scale and, as a result, are unable to address the fundamental problem of how phenomena at different scales are coupled or to combine, in a systematic manner, data from the various scales. In this article, a theoretical framework will be presented that is capable of integrating a hierarchy of processes occurring at different scales into a detailed model of solid tumour growth (Alarcon et al., 2004). The model is formulated as a hybrid cellular automaton and contains interlinked elements that describe processes at each spatial scale: progress through the cell cycle and the production of proteins that stimulate angiogenesis are accounted for at the subcellular level; cell-cell interactions are treated at the cellular level; and, at the tissue scale, attention focuses on the vascular network whose structure adapts in response to blood flow and angiogenic factors produced at the subcellular level. Further coupling between the different spatial scales arises from the transport of blood-borne oxygen into the tissue and its uptake at the cellular level. Model simulations will be presented to illustrate the effect that spatial heterogeneity induced by blood flow through the vascular network has on the tumour's growth dynamics and explain how the model may be used to compare the efficacy of different anti-cancer treatment protocols.

Alarcon, T., Byrne, H.M. and Maini, P.K. (2004). Prog. Biophys. Mol. Biol. 85: 451-472.

Folkman, J. (1974). Tumour angiogenesis. Adv. Cancer Res. 19: 331-358.

Franks, L.M. and Teich, N. (1988). Introduction to the cellular and molecular biology of cancer. Oxford Science Publications.

Ilyas, M. et al. (1999). Eur. J. Cancer 35: 1986-2002.

Preziosi, L. (2003). Cancer modelling and simulation. CRC Press, UK.

SA10

UNIVERSAL PATTERNS OF CARDIAC ACTIVITY

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Cardiac arrhythmias in people display a bewildering variety. This variety arises as a consequence of a small number of basic processes in which oscillations can spontaneously start or stop, or in which conduction can occur abnormally as a consequence of abnormal anatomy, or block in the normal pathways. We describe experimental studies of cardiac activity in heterogeneous tissue culture. The physiological properties of the tissue culture can be modified by using a number of different techniques including the addition of drugs, changing the density, and changing the age in culture. The cells can also be grown in different geometries. Independent of the manipulations, we observe certain types of rhythms including stable pacemakers, stable spirals, bursting rhythms in which there is a spontaneous starting and stopping of the rhythm, and fractionated disorganized rhythms. Investigation of mathematical models of cardiac tissue demonstrates the same types of dynamics as the parameters describing cardiac excitability, cardiac coupling and use-dependent fatigue are modified. This work thus provides a basis for analyzing the rich spontaneous nature of cardiac arrhythmias in people.

SA11

A MULTISCALE MODEL FOR COLLAGEN ALIGNMENT IN WOUND HEALING

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It is thought that collagen alignment plays a significant part in scar tissue formation during dermal wound healing. We present a multiscale model for collagen deposition and alignment during this process. We consider fibroblasts as discrete units moving within an extracellular matrix of collagen and fibrin modelled as continua. Our model includes flux induced alignment of collagen by fibroblasts, and contact guidance of fibroblasts by collagen fibres. We can use the model to predict the effects of certain manipulations, such as varying fibroblast speed, or placing an aligned piece of tissue in the wound. We also simulate experiments which alter the TGF-β concentrations in a healing dermal wound and use the model to offer an explanation of the observed influence of this growth factor on scarring.

SA12

30 YEARS OF COLLABORATION ON HEART RESEARCH: THE OXFORD-AUCKLAND HEART PHYSIOME PROJECT

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The development of cardiac models began in 1960 when Denis Noble published his first paper on a model of cardiac cellular electrophysiology [1]. Peter Hunter published his first paper on cardiac electrical modelling in 1975 [2], following his DPhil at Oxford with Derek Bergel on cardiac mechanics. In the following decades the Noble group developed increasingly sophisticated cellular electrophysiology models and the Auckland group (led by Hunter and Smaill) measured and modelled the fibrous-sheet structure of the heart and developed the computational framework for linking cellular physiology to tissue and whole heart function. Over the last 10 years this increasingly collaborative Oxford-Auckland effort has led to the idea of a cardiac 'physiome' project, developed under the auspices of the International Union of Physiological Sciences (IUPS) .

The Heart Physiome Project is intended to be an internationally collaborative open-source project to provide a public domain framework for computational heart physiology, including the development of modeling standards, computational tools and web-accessible databases of models of structure and function at all spatial scales [3,4,5]. It aims to develop an infrastructure for linking models of biological structure and function across multiple levels of spatial organization and multiple time scales. The levels of biological organization, from genes to the whole organism, includes gene regulatory networks, protein-protein and protein-ligand interactions, protein pathways, integrative cell function, tissue and whole heart structure-function relations. The whole heart models include the spatial distribution of protein expression.

The project requires the creation of web-accessible databases of mathematical models of structure and function at spatial scales which encompass nano-scale molecular events to the meter scale of the intact heart and torso, a range of 10^9, and temporal scales from Brownian motion (microseconds) to a human lifetime (10^9s), a range of 10^{15}. Clearly this cannot be represented by one model but rather a hierarchy of models and modeling approaches such as stochastic models of ion channels and receptors for ligand binding calculations, ordinary differential equation lumped cell models, and partial differential equation continuum models at the tissue and organ levels. It also requires the model parameters at one scale to be linked to detailed models of structure and function at a smaller spatial scale – hence the need for "multi-scale modeling".

The long term challenge for the Physiome Project is to build a modeling framework in which the effect of a gene mutation can be modeled all the way from its effect on protein structure and function to how the altered properties of the protein affect a cellular process such as signal transduction, and how the changed properties of that process alter the function of tissues and organs. There will be many other benefits from this integrative framework. Understanding how model parameters are affected by individual variation, by embryological growth, by ageing and by disease, for example, will bring benefits to the design of medical devices, the diagnosis and treatment of disease and the development of new drugs.

1. with Denis Noble and Peter McNaughton (another Oxford kiwi)

2. many others of course have now made major contributions to this collaborative effort, most notably Andrew McCulloch (an Auckland graduate) at UCSD and Peter Kohl and David Paterson at Oxford. A five year grant from the Wellcome Trust, to start in Jan 1st, 2005, will greatly enhance this Oxford-Auckland collaboration and bring in other Oxford cardiac researchers (Richard Vaughan-Jones and Mark Sansom).

Noble, D. Cardiac action potentials and pacemaker potentials based on the Hodgkin-Huxley equations. Nature Lond., 188, 495-497, 1960.

Hunter, P.J. McNaughton, P.A. and Noble, D. Analytical models of propagation in excitable cells. Prog. Biophys. Molec. Biol. 30, 99-114, 1975.

Hunter, P.J., Robbins. P. and Noble, D. The IUPS Human Physiome Project. European Journal of Physiology. 445 (1), 1-9, 2002.

Hunter, P.J. and Borg, T.K. Integration from proteins to organs: The Physiome Project. Nature Reviews Molecular and Cell Biology. 4, 237-243, 2003.

Crampin, E.J., Halstead, M., Hunter, P.J., Nielsen, P.M.F., Noble, D., Smith, N.P.and Tawhai, M. Computational physiology and the Physiome Project. Exp. Physiol. 89, 1-26, 2004.

SA13

COMPUTER MODELING OF THE URINE CONCENTRATING MECHANISM. A HISTORICAL PERSPECTIVE

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The years of the 1950s and '60s were very exciting times to be a renal physiologist because of the upsurge of interest in a previ-

ously most resilient problem of urine concentration and dilution by the mammalian kidney which occurs according to the state of hydration of the organism. Active transport of water across membranes was a most unattractive hypothesis as the micro structure was unsuitable and the high energy requirements for it were not satisfied in the kidney.

The first impulse towards solution originated from Werner Kuhn, a physical chemist in Basel. In 1942, he described an apparatus that could make concentrated solutions from dilute ones by a countercurrent model system. The basic principle is that two streams, moving in opposite directions, are so juxtaposed as to facilitate the mutual exchange of energy or substance through a membrane that separates them (Smith & Bull, 1959). Kuhn and Heinrich Wirz, a physiologist also in Basel, noted that in the mammalian renal medulla there are both tubular and vascular loops in countercurrent arrangements. Other renal physiologist, first cautiously then enthusiastically joined Kuhn's inspired lead.

Among Kuhn's models the one that provided the best fit (Kuhn & Ramel, 1959) to the morphological and physiological reality of the kidney was published in 1959. In this model the membrane transported sodium. The differential equations described the model with variables including length of the loop, velocity of flow through the system and membrane transport activity. Paper and pencil calculations based on the model allowed an increasing number of researchers to seek a one-to-one correspondence between the model and physical reality. Soon a major discrepancy was discovered: While the model required that active sodium transport be continuous in the tubular loop throughout the entire region where concentration kept increasing, in reality, this was the case only in the outer medulla. In the inner medulla, in the thin-walled structures, cellular machinery appeared to be lacking for active sodium transport. Yet, in reality, solute concentration showed a steep continuous increase throughout the medulla to the papillary tip.

The magic word on modeling is attributed to Einstein: "Make everything as simple as possible, but no simpler". We thought that Kuhn's model has been far too simplified. The model we developed (Pinter & Shohet, 1963; Shohet & Pinter, 1964) included both the tubular and the vascular loops, and also the feature that active transport of sodium was restricted to the loop segment in the outer medulla. A set of ordinary *linear* equations was developed which assumed that, except for the thick segment of the loop of Henle, membrane transport of sodium was proportional to the concentration difference across them. The mathematical description was rather messy. Fortunately, one of us (JLS) had access to an analog computer. The results were graphs showing that in this model there can be a continuous increase of sodium concentration in the inner medulla, in absence of active transport from the loop.

Our model quickly generated criticism the essence of which was that we made two assumptions implicit in the model, each of which alone being fully justified, but used together contradicted each other. One of these was that diffusion of solute along the length of the loops could be neglected, as this longitudinal dimension is several hundred times greater than transverse distances. The second assumption was that discontinuities could not exist in solute concentration along the longitudinal axis without specifying whether the concentration should go up or down. As detailed analysis by the Mathematical Division of the NIH, led by John Stephenson, showed our model was over-determined.

Now, 41 years after our initial effort, it seems that Einstein might have been right all along. In recent journals on mathematical biology we find new models that use more solutes, much more complex structural layout, and highly increased number of variables. And they use, of course, very powerful computers which make all this possible. It is, perhaps, not too presumptuous of us to try to complement Einstein's rule by saying: Make models as complicated as necessary, but not more complicated.

W. Kuhn & A. Ramel (1959). Helv. Chimica Acta 42, 628.

G.G. Pinter & J.L. Shohet (1963). Nature 200, 955.

J.L. Shohet & G.G. Pinter (1964). Nature 204, 689.

H.W. Smith & Bull (1959). NY. Acad. Med. 35, 293.

SA14

MODELLING VENTILATION DISTRIBUTION: COUPLING SOFT TISSUE MECHANICS TO AIRFLOW IN ANATOMICALLY-BASED MODELS OF THE PULMONARY SYSTEM

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To understand the relationship between branching structure, ventilation distribution, and lung mechanics in health and disease, we have developed a model of coupled parenchymal soft-tissue mechanics and airflow in anatomically-accurate meshes of the lungs and airways.

The geometric models are constructed by (1) geometry-fitting a volume mesh[1] to surface data from CT imaging of the lung lobes[2], (2) fitting centerlines and diameters from the trachea to generations 6-9, and (3) generating airways to fill the lung using a bifurcating-distributive algorithm[3,4]. The lung model is surrounded by a surface mesh that represents the pleural cavity, and is filled with a fine mesh of 'blocks'; each block is associated with a single terminal branch.

Mechanics is solved using finite elasticity, with a strain energy function for the compressible lung 'tissue'. Displacement boundary conditions are applied to the pleural mesh to mimic ventilation. Contact mechanics couples the pleural and lung meshes. For a small displacement, the deformed block volumes are calculated and their changes in volume over time are used as flow boundary conditions for an airflow model in the embedded airway mesh. This predicts terminal node pressures, which are fitted to nodal pressures in the lung mesh. The solutions are iterated, using updated flow boundary conditions and fitted pressures for each solution. Upon convergence, the next incremental deformation is solved.

This modeling approach allows analysis of ventilation distribution in response to changes in volume of the pleural cavity, with eventual application in understanding the influence of regional changes in material properties – such as occurs during disease – on the re-distribution of flow. Further extensions to the work will couple the ventilation model to an anatomically-based model of perfusion[5].

Challenges in developing this model include establishing an appropriate material law, accounting for the influence of the airways, and determining methods for validating the model predictions.

Fernandez J JW, Mithraratne P, Tawhai MH, and Hunter PJ. Geometric fitting and customization of anatomically based cubic Hermite finite element volume meshes. Biomech Model Mechanobiol. 2(3): 139-155,2004.

Zhang L, Hoffman EA, and Reinhardt JM. Atlas-driven lung lobe segmentation in volumetric X-ray CT images. In: SPIE Medical Imaging, San Diego, CA, USA. Proceedings of SPIE 5032: 309-319, 2003.

Tawhai MH, Pullan AJ, and Hunter PJ. Generation of an anatomically based three-dimensional model of the conducting airways. Ann Biomed Eng 28(7): 793-802, 2000.

Tawhai MH, Hunter PJ, Tschirren J, Reinhardt JM, McLennan G, Hoffman EA. CT-based geometry analysis and finite element models of the human and ovine bronchial tree. J Appl Physiol, in press.

Burrowes KS, Tawhai MH, and Hunter PJ. Modeling blood flow distribution through the pulmonary arterial and venous trees. 100th International Conference of the American Thoracic Society, Orlando FL. F34, 2004.

SA15

STUDY OF RE-ENTRANT ARRHYTHMIAS IN ANATOMICALLY BASED MODELS OF THE HUMAN HEART

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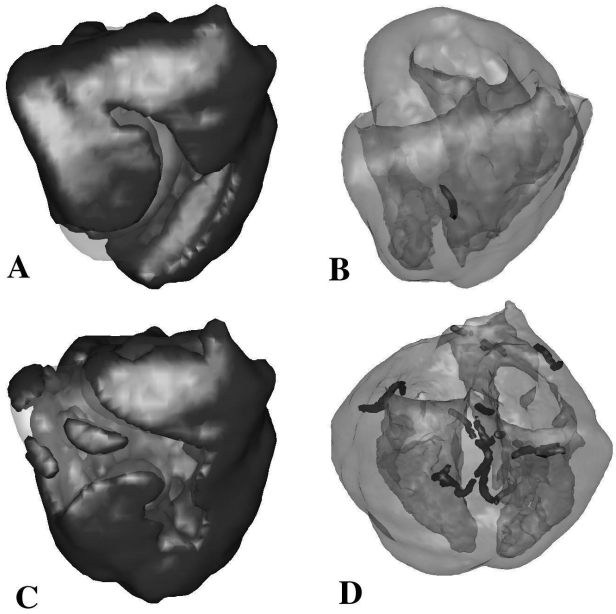
We report on the development of models for the human ventricles. The model is based on anatomical data on the geometry and fibre orientation in the human heart which was gathered and computerized by Hren (1996). It uses the monodomain description of cardiac tissue and employs the 'weighting functions' numerical approach, which allows integration of the equations in domains of complex shape with explicit numerical integration schemes. The main framework of the model can be coupled with any type of description of cardiac cells. We discuss different types of such description: low dimensional models, reduced, gamma ionic models and the full ionic models for human ventricular cells.
We discuss in details the ten Tusscher at al., (2003) model which is based on recent experimental data on the major ionic currents for human ventricular cells: the fast sodium, L-type calcium, transient outward, rapid and slow delayed rectifier, and inward rectifier current. The model includes intracellular sodium, potassium and calcium dynamics, allowing for the realistic modelling of calcium transients, frequency dependence of the intracellular sodium concentration, and the positive contraction staircase typical for human ventricular myocardium.
Using this model we study normal and abnormal wave propagation. We show that for normal parameter values the re-entrant arrhythmia (scroll wave) persists in the course of time and does not break-up into fibrillation. The dynamics of the scroll wave is meandering, however the meandering of the scroll wave rotating in the right ventricle is less pronounced than that in the left ventricle of the heart. The computed electrocardiogram (ECG) in the right ventricle is similar to that of monomorphic tachycardia, while the ECG of a scroll wave rotating in the left ventricle is similar to that of polymorphic tachycardia. The upper row of the figure shows the scroll wave pattern of excitation in the right ventricle of the heart (A) and the corresponding filament (B).
By modifying the properties of the cardiac tissue, we were able to find parameters for which the scroll wave becomes unstable and breaks down into a multiple wavelet pattern that is considered to be a model of ventricular fibrillation. We compare the results of these simulations with the recent clinical data by Nanthakumar et al.(2004), who performed epicardial recordings of excitation patterns during fibrillation in the human heart using a 4x5cm electrode plaque. First, we show that the ECG pattern occurring in our model is similar to that during ventricular fibrillation and that its dominant frequency is close to that recorded by Nanthakumar et al. (2004) and others. We also compare the wavelet dynamics occurring in the 4x5cm left ventricular epicardial patch in our model to those observed by Nantakumar et al. We find that surface re-entry can be observed during approximately 10% of the time, and find large activation fronts following repeatable pathways, smaller fractionated wave fronts and
epicardial breakthrough waves, similar to the observations by Nanthakumar et al. Finally, we study the role of re-entry in the three-dimensional organization of fibrillation in the ventricles by counting the number of filaments, the organizing centers of scroll waves and hence a measure for the number of re-entrant sources present. We determine the number of filaments as a function of time, compute their individual and total lengths and compare them with previous simulations using a canine ventricular geometry. The bottom row of the figure shows a typical activation pattern during fibrillation (C) and the scroll wave filaments present at that same moment (D). Our study supports the results by Nanthakumar et al. (2004) that ventricular fibrillation in the human heart may be organized by only a small number of sources.



Hren, R. 1996 A realistic model of the human ventricular myocardium: application to the study of ectopic activation, PhD. thesis, Dalhousie

University, Halifax, Canada, (1996).

Ten Tusscher K.H, Noble D, Noble PJ,Panfilov AV.,' A model for human ventricular tissue.'. Am.J.Physiol., v.286,p.H1573-1589,(2004).

Nanthakumar, K., Walcott, G. P.,Melnick, S.,Rogers, J. M.,Kay,

M. W.,Smith, W. M.,Ideker, R. E.,Holman, W.,Epicardial organization of human ventricular fibrillation, Heart Rhythm,v.1,14-23,(2004)

SA16

ARRHYTHMOGENESIS IN REGIONAL ISCHEMIA: INSIGHTS FROM COMPUTER SIMULATIONS

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Introduction. Regional ischemia resulting from coronary occlusion is widely known to be arrhythmogenic; however, the mechanisms are not well understood. The goal of this study is to examine the role of the ischemic border zone (BZ) in the mechanisms that lead to establishment of reentry in regional ischemia.
Methods. A novel geometrically accurate finite element model of a cross section of the rabbit ventricles that incorporates a zone of ischemia (see figure) is used. Ischemic zone geometry mimics LAD occlusion and incorporates a central ischemic zone (CIZ) and BZs (epi/endocardial and lateral) with a linear transition to the surrounding normoxic tissue. Ischemia results from hypoxia, acidosis, and hyperkalemia (in figure, black to white color represents change in $[K^+]_o$ from 5.4 to 15mM) of varying degrees (0-10min of occlusion). The width of the lateral BZ is 5.5mm, while the epi/endocardial BZ is varied (0.25-0.5mm). The model is paced (see figure) at 175-300ms cycle lengths (CLs). A premature stimulus is applied in the LV 155ms following the last paced beat in an attempt to initiate reentry.
Results. Reentry occurred only when CIZ was severely ischemic; propagation failed in the CIZ (site A) as well as in the lateral BZ. Conduction continued in the epi/endocardial BZs, however, it exhibited alternans (site B). The alternans increased with decreasing CL and decreasing epi/endocardial BZ width. At CLs below 200ms and BZ widths below 0.5mm, propagation failed in LV and septum, and reentered through the RV epicardial BZ (see arrows). Further decrease in epi/endocardial BZ width led to conduction failure eliminating the reentrant pathway.
Conclusions. This study provides insight into the arrhythmogenic effects of the ischemic BZ width for various degrees of ischemia severity in CIZ. It demonstrates that formation of a reentry around the ischemic zone is preceded by alternans in the epi/endocardial BZ.

SA17

CHEMOTACTIC CELL MOVEMENT AND ITS ROLE IN DEVELOPMENT

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Embryonic development is critically dependent on a number of distinct cellular behaviours such as cell division and cell death, cell differentiation and cell movement, which all have to be precisely controlled in space and time. In many cases cell movement is controlled by diffusible chemical signals that act as chemoattractants or repellents. We investigate the molecular mechanisms by which cells signal each other during development, how cells detect these signals and how they translate this information in directed movement. We study these questions in two different experimental systems, in the social amoebae *Dictyostelium discoideum*, a simple genetically tractable micro-organism showing a relatively simple starvation induced multicellular development, where thousands of individual amoebae aggregate to form a fruiting body and during gastrulation in the chick embryo During Dictyostelium development the movement of tens of thousands of individual amoebae is coordinated by propagating waves of the diffusible secreted chemo-attractant, cyclic AMP. These cAMP waves direct the chemotactic aggregation of thousands of cells dispersed in the leaf litter of the soil towards an aggregation centre where they form a hemispherical aggregate. In the aggregate the cells differentiate into two cell types, prestalk and prespore cells, which continue to form a migratory slug. The slug migrates to the surface to form a fruiting body consisting out of a stalk supporting a mass of spores. The movement of the cells during all these stages of development is controlled by propagating cAMP waves. I will discuss the molecular mechanisms that underlie cAMP wave generation and propagation and the mechanisms by which cells detect these dynamics gradients of cAMP, and translate this information in cell polarization and directed motion. These investigations rely heavily on the use of mutants to characterize signaling pathways and advanced imaging methods to follow the dynamics of signaling pathways and resulting changes in the cytoskeleton in wildtype and mutant strains as well as mathematical modeling of the interactions between signal propagation and the resulting cell movement (Dormann and Weijer, 2003; Vasiev and Weijer, 2003). We have also started to explore control of cell movement during early vertebrate development, especially the control of migration of mesoderm cells during the early stages of gastrulation in the chick embryo. Mapping of the movement trajectories of cells expressing the green fluorescent protein during the early phases of gastrulation shows that the cells move very directed over long distances. The movement of mesoderm cells appears to be guided by both attractive and repulsive cues involving distinct members of the FGF and VEGF families of growth factors (Yang et al., 2002). Signal detection and gradient reading appears to involve the extension of long cellular processes to sense signals in the environment. We are now investigating the molecular mechanisms involved in detection and translation of these signals in directed movement using in-vivo imaging techniques.

Dormann, D., and Weijer, C. J. (2003). Chemotactic cell movement during development. Curr Opin Genet Dev 13, 358-364.

Vasiev, B., and Weijer, C. J. (2003). Modelling of Dictyostelium discoideum slug migration. J Theor Biol 223, 347-359.

Yang, X., Dormann, D., Munsterberg, A., and Weijer, C. (2002). Cell Movement Patterns during Gastrulation in the Chick Are Controlled by Positive and Negative Chemotaxis Mediated by FGF4 and FGF8. Dev Cell 3, 425-437.

SA18

MODELLING TRANSPORT, EXCHANGE, AND REACTION IN CARDIAC ENDOTHELIUM AND MYOCYTES

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Endothelial cells lining myocardial capillaries not only impede transport of blood solutes to the contractile cells but uptake

and release substrates in competition to myocytes. To distinguish myocyte exchanges, one can use models to characterize such events using the multiple indicator dilution method. For analyzing tracer kinetic experiments one tries to account for all of the available observations simultaneously in order to impose maximal constraint on the model parameters. Where one can't make observations in every tissue region in every experiment, one uses data from previous studies to constrain the parameters being evaluated.

We avoid compartmental models for parameterization of data: they give biased estimates because the stirred tank analogy creates a sharp discontinuity between arterial concentration and that in the capillary. Axially distributed blood-tissue exchange models, using partial instead of ordinary differential equations account for the exchange and reaction events and for smoothly graded intracapillary concentrations. There are standing arteriovenous gradients for any substance that is consumed or formed in the tissue,

Experiments using bolus injections of ^{15}O-oxygen into the coronary inflow in blood-perfused rabbit hearts indicates that oxygen is flow-limited in its blood-tissue exchange. This means there are no effective barriers to exchange in the radial direction, that is, membrane permeation and radial diffusion are so fast that there are no significant gradients perpendicular to the axis of convection. Flow alone controls the rate of solute movement through the organ. These observations contradict the idea that the endothelium and the sarcolemma are barriers for oxygen transport.

In dogs and humans, using positron emission tomography with a single breath of ^{15}O-oxygen gas as input, the time-activity curves in regions of interest (ROI) in the myocardium are analyzed via a multipath model accounting for the reaction, oxygen to water. Fitting the composite signal gives separation of the ^{15}O-oxygen and ^{15}O-water signals; the fractional conversion times the flow times the inflow oxygen content gives the local oxygen utilization rate, $rMRO_2$. Estimates of $rMRO_2$ are roughly proportional to rMBF, regional myocardial blood flow. Flow and metabolism are both spatial fractals, with positive near-neighbour correlation. Diffusional exchanges among nearby regions smoothes the variation somewhat.

Bassingthwaighte & Beard (1995) constructed a three-dimensional mathematical model of the coronary arterial network of the pig heart from the morphometric data of Kassab et al. (1993) so that it had the same segment lengths, diameters and connectivity properties as the real network. Assuming steady flow through the network, residue washout and outflow concentration-time curves were simulated for an impulse injection of tracer into the arterial inflow. Washout curves for tracer were power law type, with exponents the same as were found experimentally, 2.2 ± 0.3 for the water washout experiments versus 2.0 for the reconstructed networks. Also, the regional flow distribution showed fractal correlation structure with the same fractal dimension as found in animal studies. While the spatial fractal nature of the flow distribution is explicable in terms of the morphometry of the network, this does not explain why the normal heart shows an 8- to 10-fold range of flows in all species studied and, further, why this heterogeneity is basically stable.

Tracer studies on purine nucleoside exchanges show rates of endothelial uptake and transformation similar to those in myocytes: endothelial cells assuredly influence delivery of adenosine to both smooth and cardiac muscle cells. During hypoxia endothelial cells can have a role in purine salvage, taking up adenosine and inosine released by nyocytes in the transient and returning purine as hypoxanthine (Schwartz et al. 1999). This may be particularly important when purine nucleotides are released, losing their high-energy phosphates to interstitial phosphatases.

NMR data from isolated rabbit hearts at low perfusion levels (Gustafson & Kroll, 1998) help to reveal the kinetics of these interactions. With a second underperfusion after a brief recovery, much less adenosine and inosine reaches the coronary effluent, the result being attributable to a combination of events including down-regulation of 5'-nucleotidase in myocytes as well as the interplay between the two cell types. Our modelling therefore must include these cell-to-cell interactions to explain the multiple data sets of different types.

Bassingthwaighte & Beard (1995). Circ Res 77, 1212-1221.

Kassab et al. (1993). Am. J. Physiol. 265, H319-325.

Schwartz et al. (1999). Am J Physiol Heart Circ Physiol 277, H1241-1251.

Gustafson & Kroll (1998). Am J Physiol Heart Circ Physiol 274, H529-538.

SA19

COMPUTATIONAL INFRASTRUCTURE FOR BIOMEDICAL MODELLING, SIMULATION AND VISUALISATION

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Computational infrastructures provide the framework in which computing can support a particular application. A good infrastructure can be critical to a project as it determines how a program (or set of programs) looks, feels, and is amenable to extension and change. Problem solving environments (PSEs) are a form of computational infrastructure that seeks to provide an integrated set of tools for a particular application area. In this talk, I discuss our recent research and development of component-based PSEs for biomedical computing. Specifically, I will discuss the BioPSE and SCIRun2 problem solving environments. BioPSE is a component-based visual problem solving environment (PSE) that is designed specifically to address large-scale computational problems in biomedicine. SCIRun2 is an evolving PSE based upon the idea of meta-components that "bridge" easily to other component models, allowing one to integrate other existing programs into the shared SCIRun2 framework. BioPSE and SCIRun2 support the entire life cycle of scientific applications by allowing scientific programmers to quickly and easily develop new techniques, debug new implementations, and apply known algorithms to solve novel problems. BioPSE and SCIRun2 also contain many powerful visualization algorithms for scalar, vector, and tensor field visualization, as well as image processing tools (such as ITK). To illustrate the feasibility and utility of computational infrastructures, I will provide examples of several driving biomedical research applications in cardiology, neuroscience, and medical imaging.

SA20

A COMPUTATIONAL INFRASTRUCTURE FOR INTEGRATIVE MODELLING IN BIOLOGY

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In this talk I will give a brief introduction to one of the new projects in which Denis is playing a leading role - the EPSRC-funded Integrative Biology e-Science Pilot Project. This project aims to begin to build a computational infrastructure for Physiome-style modelling, focusing initially on modelling of the heart and of cancer. The aim is to build a user-friendly, transparent system that allows seamless use of: high-performance computing facilities; state-of-the-art visualisation and collaborative visualisation techniques; computational steering; and advanced data management technologies. The project has close links with many of the first round of UK e-Science pilot projects, and therefore builds extensively on existing Grid Middleware.

I will end by giving a brief overview of the presentations made during this two-day workshop, and will attempt to draw out areas of potential synergy arising across the broad range of applications and across the spatio-temporal scales that will be considered.