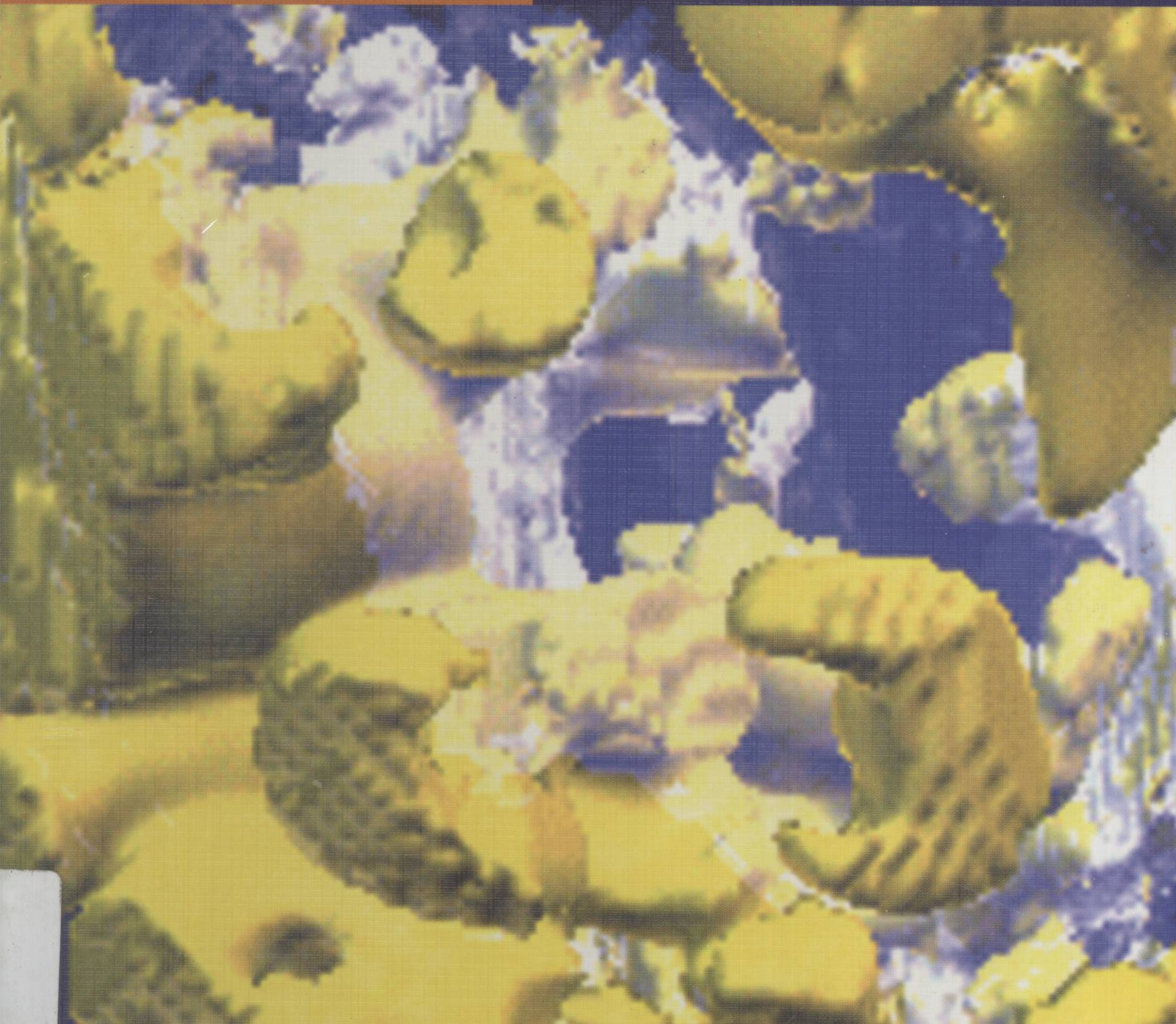
STUDIES IN MULTIDISCIPLINARITY

VOLUME 3

ELSEVIER

Multidisciplinary Approaches to Theory in Medicine

EDITED BY
Ray Paton † and
Laura A. McNamara



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On the cover:
Cover image caption: A visualisation of ventricular fibrillation. Depolarisation wavefronts are computed in an anisotropic geometrical model of the canine heart, obtained from diffusion tensor imaging, using the Fenton-Karma (1998) equations: see Chapter 21 of this volume.
(Fenton, F. & Karma, A. (1998) Vortex dynamics in three-dimensional continuous myocardium with fibre rotation: Filament instability and fibrillation. Chaos 8 20–47).

Series Dedication

Studies in Multidisciplinarity is dedicated to the memory of Ray Paton.

Sure, he that made us with such large discourse,
Looking before and after, gave us not
That capability and god-like reason
To fust in us unused.

– William Shakespeare, Hamlet

Foreword

Gordon Shepherd
Department of Neurobiology
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It is a pleasure to open this volume with a few words of praise for its editor, Ray Paton.

We became acquainted a number of years ago when Ray contacted me about joining him in the effort to bring together investigators who were developing methods for applying theoretical approaches to biology and medicine. The present volume is a testimony to his vision and persistence. Although younger investigators may take theory in these fields for granted, it was not always so. The magnitude of Ray's achievement can be appreciated with a brief perspective on where he started.

Traditionally, biology and medicine have been driven by inventions of new experimental instruments and methods, as expressed by the byword of the nineteenth century, "Teknik ist alles". While fundamental insights in physics could be obtained by a combination of mathematics and relatively simple mechanical instrumentation until well into the nineteenth century, biology had to wait for the development of a combination of highly sophisticated technical advances in chemistry, optics, and electromagnetism, among others. No real biology could be done until the cell could be seen, no real understanding of the nervous system was possible until electrical activity could be recorded, as occurred in the middle of the nineteenth century.

This focus on technique yielded the birth of biologically based medicine, which continued to build into the twentieth century. It was however significant that, from the start, this new field differed from physics in a crucial aspect. Whereas the rise of physics had been driven by a combination of experiment and theory, biology lacked the kind of theoretical basis that had been essential for physics, as expressed in the well-known observation, "You can't understand a fact without a theory". This was largely due to the extraordinary complexity of biological phenomena, a complexity that was only magnified by the need in medicine to account for both normal and pathological phenomena.

In the twentieth century, theory in biology at first rested on analytical mathematics, such as the models developed by N. Rashevsky in Chicago and A. V. Hill in London. For all their sophistication, these theories had little impact on experimentalists, who by mid-century were engaged in founding what we call modern biology. The cornerstone of course was the identification of DNA in 1953 by Watson and Crick. The fact that this great achievement involved not only the essential experimental evidence but also a theoretical model – an actual palpable three-dimensional model – was not the least reason for the persuasiveness of this new insight into the fundamental nature of biological matter.

Even more persuasive as a harbinger of a new marriage between experiment and theory in biology and medicine was the model of Hodgkin and Huxley for the action potential. This has been the foundation for understanding the structure and function of all membrane channels, which are the ubiquitous carriers of ion fluxes that are essential to the functioning of virtually every cell and organ system in the body. Their medical importance multiplies daily with the evidence for genetic disorders that result in channelopathies that affect these functions throughout the body.

The lore of the Hodgkin–Huxley model includes the account of how Huxley cranked out the differential equations underlying the action potential on a hand calculator, illustrating the fact that the development of theory is also methods-limited. These limitations were of course overcome with the introduction of the digital computer. This did not happen overnight. For example, many years were required just to get the H–H model into a digital form that could be widely accessed and used.

During this time, the revolution in modelling methods took place with the development of the digital computer. The constraints of oversimplified analytical models were replaced by the arbitrary complexity that could be built into numerical representations of biological phenomena and medical applications. Thus, as in the case of experimental biology and clinical medicine, theory also depended on technical breakthroughs.

Some of the first numerical models were developed in the 1950s to analyse the passage of radioactively labelled substances injected into humans through the different body compartments – blood, extracellular space, intracellular space, cerebrospinal fluid, etc. This involved generic representations of compartments in terms of capacities and flux rates between them. These in turn could be used as the basis for developing other types of compartmental representations, such as the compartmental modelling of the functional properties of neuronal dendritic trees by Wilfrid Rall. Our work on the functional interactions between dendrites had its origins in the Hodgkin–Huxley model for the action potential, and looked forward to the increasing use of models today for analysing dendritic, neuronal and circuit functions in the brain. This software is now easily accessible at websites for NEURON and GENESIS.

Establishing modelling as an essential theoretical component to the interpretation and guidance of experimental studies during this time had to overcome often strong opposition from experimentalists, for several reasons. Most experimentalists are convinced they don't need theory, although all studies are motivated and interpreted within a theoretical framework, whether explicit or not. Many experimentalists who might be interested in applying theory are critical of available models as too simplistic, or too recondite. Many theories that explain the data do not offer hypotheses that can be tested in the real world. And there are often gulfs of communication and terminology between experimentalists and theorists, as well as between those working in different systems.

All of this is relevant to understanding the huge challenges that Ray Paton faced as he began the task of encouraging the application of theory to problems in medicine. One of the cardinal aspects of his approach was to base it broadly on bringing people together from many different fields. Thus, he recognised that biology involves many levels of organisation, from molecules and cells to systems and behaviour. He recognised that it involves many disciplines, from molecular biology through the basic sciences to the clinical disciplines. And he recognised that it required bringing people together with these disparate backgrounds and interests, at meetings and in volumes such as this, in order to begin to put together coherent concepts of how the body functions and how medicine can bring modern technical advances to bear on correcting pathologies of body functions.

All these qualities were found in the international meetings that he organised over the past more than a decade, and all are on display in this volume. Readers can find here a rich harvest of articles. Topics covered include practical applications of theory to genotypes and phenotypes of disorders of haemoglobin, T cell activation and beyond, vasopressin and homeostasis, cardiac arrhythmias, angiogenesis, and liver fibrosis in biopsy specimens. They include fundamental biological concepts of molecular evolution and its implications for medicine, modelling stochastic neural systems, physiological modelling, systems biology, and tissue as a network. They include theory behind medical imaging. They include new informatics approaches such as advanced data mining and personalised medicine, and data mining applied to studies of hepatitis. They include topics in the theoretical basis of medicine itself, such as the basis of medical decision making, what is a medical theory, expert systems, and reliability of measurements. They include moral issues such as medicine and moral epistemology, and hope and despair in tissue engineering. And they include topics in medical education and educational theory.

This volume therefore is an excellent representative of Ray Paton's concept of theory in medicine. It includes the kinds of theories that he wanted to see developed for all aspects of medicine, across the different biological levels, the different technical disciplines, and the different medical fields. It expresses his steady commitment to an integrated approach, bringing together theory and experiment for the benefit of biology and medicine, just as they had and continue to do for physics and chemistry in the preceding century. It is a testament to a loyal friend, warm colleague, skilled theorist, and a true visionary.

Gordon M. Shepherd
December 15, 2004

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Biographies

Tomas Alarcon received his degree in Theoretical Physics in 1996 and his PhD in Physics in 2000, both from the University of Barcelona. Later he spent three years as postdoctoral fellow at the Center for Mathematical Biology, Oxford, working under the supervision of Philip K Maini (Oxford) and Helen M Byrne (Nottingham). Currently he is a Research Fellow at the Bioinformatics Unit, Department of Computer Science, University College London.

Werner Arber received his Diploma in Natural Sciences from the Swiss Polytechnical School in Zürich and completed his doctorate in Biological Sciences at the University of Geneva. Dr. Arber has spent most of his career teaching and conducting research in molecular biology at the Universities of Geneva and Basel in Switzerland, but he has also held postdoctoral research and Visiting Professor positions at the University of Southern California in Los Angeles, at the University of California in Berkeley, at Stanford University and at the MIT in Cambridge, Massachusetts. Dr. Arber is a past President of the International Council for Science (ICSU) and a past member of the Swiss Science Council. His research interests include microbial genetics, horizontal gene transfer, bacterial restriction and modification systems, mobile genetic elements, site-specific recombination, and the molecular mechanisms of biological evolution. In 1978, he was awarded the Nobel Prize in Medicine and Physiology for the discovery of restriction enzymes and their application to problems of molecular genetics.

Oleg V. Aslanidi studied at the Department of Applied Mathematics, Tbilisi State University, Georgia (1990–1993), before moving to the Pushchino State University, Pushchino, Russia, where he received his BS degree in

Biophysics (1996) and the PhD degree (1999). He is a postdoctoral research fellow at the Computational Biology Laboratory in the School of Biomedical Sciences, University of Leeds, since 2001. His research interests are in computational biology, nonlinear phenomena, and parallel computing.

Stephen Baigent is a Lecturer in the Mathematics Department at University College London (UCL). He holds BA, MSc, and DPhil degrees in Mathematics from the University of Oxford. For his doctorate he studied geometrical aspects of geophysical fluid mechanics, but upon joining to UCL as a Research Assistant his interests shifted towards biomathematics, and in particular the modelling of cell–cell communication. Before taking up his current post he held a Wellcome Trust Biomathematics Fellowship for five years. He is now involved in a variety of biomathematics projects, including the building of models of brain circulation, arteriovenous malformations, and liver function.

Murad Banaji grew up in India and the United Kingdom. He studied physics at King's College London, then underwent training as a secondary school teacher. After teaching science for a few years in an inner-city London school, he returned to the university to do a PhD in mathematics. Since completing his PhD in 2001, he has been working at University College London on constructing a computational model of the cerebral circulation. Dr. Banaji lives in London with his eight-year-old son, Amlan.

Sergio E. Baranzini, PhD is an Assistant Professor in the Department of Neurology at the University of California at San Francisco. Dr. Baranzini has a BS/MS in Biochemistry and a PhD in Human Molecular Genetics from the University of Buenos Aires, Argentina. Dr. Baranzini joined the Department of Neurology at UCSF in 1997 as a postdoctoral fellow. His current research focuses on molecular mechanisms of complex diseases with an emphasis on functional genomics and bioinformatics in the neurological disorder, multiple sclerosis.

Vadim N. Biktashev received his BSc+MSc degree in Biophysics from the Moscow Institute of Physics and Technology, Moscow, Russia, in 1984, and the PhD degree from the same institute in 1989. He is a Reader of Applied Mathematics in the Department of Mathematical Sciences, The University of Liverpool. He has been in Liverpool since 1999. His research interests are in the mathematical theory of autowaves, with applications in mathematical biology, particularly mathematical cardiology.

Irina V. Biktasheva received her BSc+MSc degree in Physics and Technology from Tomsk State University, Russia, in 1985, and then two PhD degrees, from Institute of Theoretical and Experimental Biophysics, Russian Academy of Science in 2000 and from Leeds University in 2001. She is a Lecturer in Biocomputing at the Department of Computer Sciences, The University of Liverpool. She has been in Liverpool since 2002. Her research interests are in computational biology and dynamics of spiral waves, in particular computational cardiology.

Helen Byrne has been a member of the School of Mathematical Sciences at the University of Nottingham since 1998, and was promoted to a Chair in applied mathematics in 2003. After training as an applied mathematician at the Universities of Cambridge and Oxford, she now works in the field of mathematical biology, focusing in particular on aspects of solid tumour growth. She currently holds an EPSRC advanced research fellowship which enables her to concentrate full time on her research interests. Through active collaboration with experimentalists and clinicians, she aims to ensure that the mathematical models that researchers develop and analyse can provide genuine insight into problems of medical interest.

Robin E. Callard, Professor of Immunology at the Institute of Child Health, University College London, has been an experimental immunologist for 35 years and headed Infection and Immunity at ICH from 1998 to 2004. His research interests in experimental immunology include dendritic cell responses to *Neisseria meningitides* and interactions with T cells; genetic epidemiology and skin biology in allergic dermatitis; and function of cytokines in human antibody responses. Over the past five years, he has developed a research programme on mathematical modelling of T cell proliferation and differentiation directed at understanding homeostatic control of T cell populations; transcription factor and cytokine control of Th1 and Th2 cell differentiation; and p53 regulation of apoptosis following DNA damage. Along with Professor J Stark, he initiated and set up CoMPLEX (Centre for Mathematics and Physics in the Life Sciences and Experimental Biology) at UCL. He is presently on the CoMPLEX Executive Committee and Co-Director of the CoMPLEX Four Year PhD Programme in Modelling Biological Complexity. His research over the past ten years has been supported by grants from the BBSRC, MRC, EPSRC, Wellcome Trust, Spencer Dayman Meningitis, and National Eczema Society.

Cliburn C. T. Chan has a medical degree from the National University of Singapore and a PhD in nonlinear dynamics from the University College