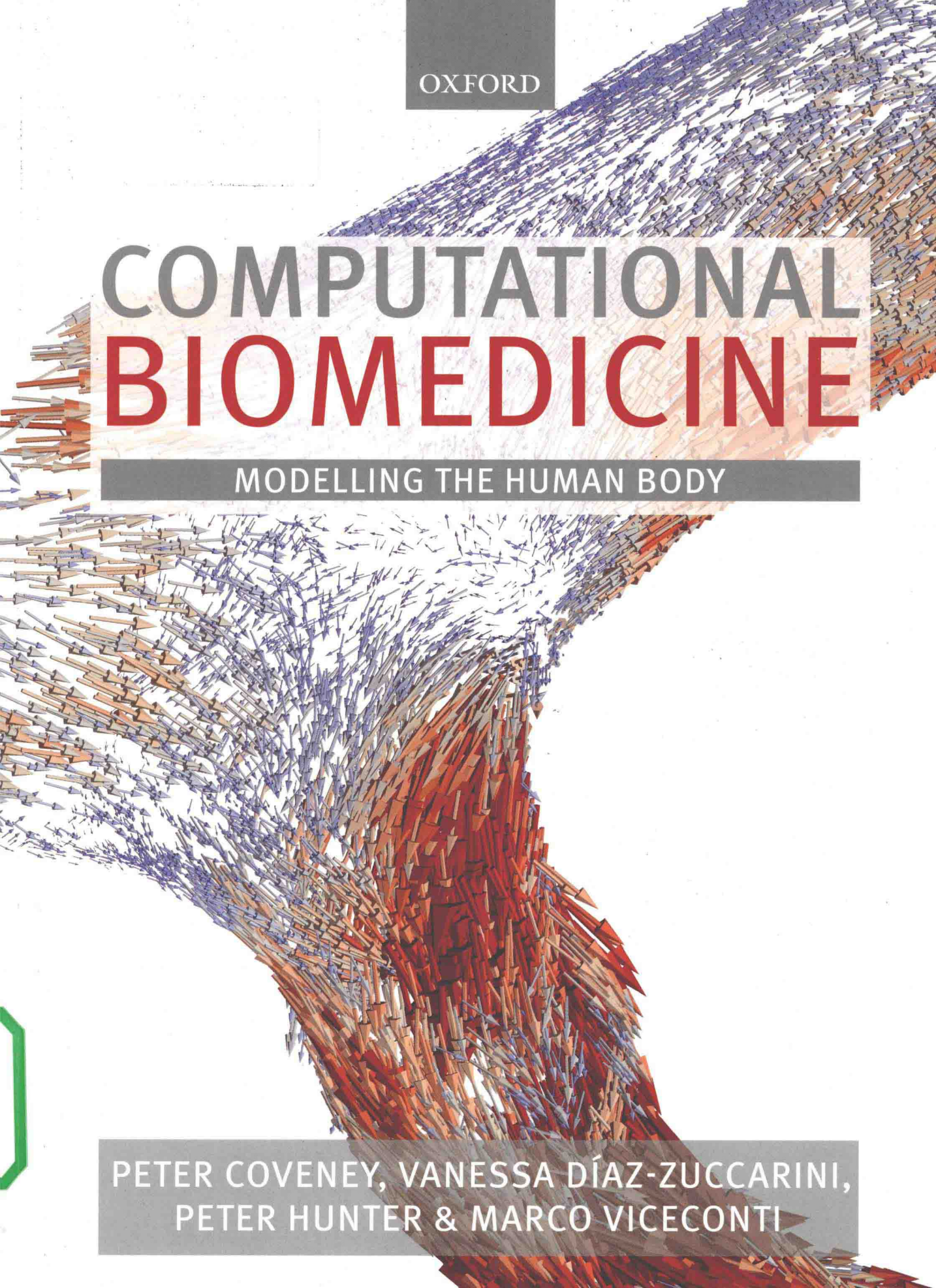
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COMPUTATIONAL
BIOMEDICINE
MODELLING THE HUMAN BODY
PETER COVENEY, VANESSA DÍAZ-ZUCCARINI,
PETER HUNTER & MARCO VICECONTI

COMPUTATIONAL BIOMEDICINE

MODELLING THE HUMAN BODY

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Computational Biomedicine

PREFACE

At the present time, medicine is on the verge of a radical transformation driven by the inexorably increasing power of information technology. We live in what is sometimes called the digital era, wherein information is widely accessible in electronic form, made available over the Internet by the worldwide web. Medical information is no different, and today there is a relentless push to digitize healthcare data, for example in the form of electronic health records, making it more facile for patients, doctors, and other healthcare workers to track the records of individual patients, to improve treatments, and to monitor outcomes of clinical care.

Of course, medicine and human health are intensely personal matters, as well as being subject to scientific understanding, and so accessing such data is surrounded by necessary considerations of privacy and confidentiality. The security of personal healthcare data is subject to rules and regulations in information governance which frequently threaten to undermine the entire programme of digital medicine, when the balance between access to such records is countered by arguments about the need to maintain patient privacy. At all times it is essential to remember that access to such data has the potential to enable medical cures and improve people's lives, while overly zealous attention to protection of personal privacy denies this.

As and when access to human healthcare data is permitted, modern science can progress rapidly. The immediate wins in basic and clinical medicine centre on the analysis of large collections of such data, using a variety of methods collectively referred to today as machine learning. These methods are inherently statistical in nature, providing inferences about medical conditions based on correlations between 'input' and 'output' variables. Their computational cost is relatively low and many medical discoveries of this nature are possible by the mining of vast quantities of data. One of the most promising of such approaches is stratification, the clustering of subsets of the population into groups which are found to be susceptible to a particular disease and, more importantly, a specific form of medical treatment. With increasing quantities of data, particularly whole human genomes being acquired with astonishing speed from so-called next-generation sequencing technology, there is an expectation that we will discover well-defined clustering of human populations, along with the aspiration that we shall be able to target these groups with different treatments (thus, for example, drugs, regimens, and so on can be tailor-made to stratified groups). At this point, medicine for the masses (a kind of average way of treating everyone) becomes more about medicine for well-defined groups of patients.

Thus digital technology points to a new era of stratified medicine, in which specific electronic information on a patient allows a doctor to perform a treatment better tailored to the individual concerned. We are all different, however, and such statistical approaches, being based on data acquired on populations of many different patients, inevitably smear out individual differences. In the case of rare diseases, for example, there may not even be a sufficient number of other similar conditions to make reliable inferences. As we discover more about the intricacies of other diseases—cancer is one case in point—it is becoming clear that the mechanisms behind a disease can vary significantly from one patient to another.

To go beyond the power of inference-based methods, and to develop a truly personalized form of medicine, a different approach is required, one in which a deeper understanding of the *mechanisms* of disease are taken into account. These mechanisms may vary to a greater or lesser extent between individuals, and understanding these differences opens

the door to more scientific ways of treating the disease and curing it in a convincing manner. Full control of disease cases will emerge when we understand these mechanisms in a quantitative manner, and are able to reliably *predict* individual outcomes before applying treatments. This depends on our ability to mathematically represent and thus model the human body and its pathologies. The human body is a complex system, and its mathematical description necessitates the running of models on computers, a medical form of computer simulation. This too is heavily dependent on information technology, including an ability to access powerful computers as well as large-scale data, the aim being to produce 'high-fidelity' descriptions of medical conditions and the effects of proposed treatments, before these are performed. It is this new approach to medical science that forms the basis of this textbook.

We look at the many levels of biological organization in the human body, from the molecular through cellular and tissue to organ systems, and how one can successfully begin to model these using principles taken from the physical and engineering sciences. These approaches always combine some patient-specific data—it might be from a genomic analysis, one or more imaging modalities, or combinations of these—with a mathematically based mechanistic model. In some cases, such models are already gaining a reasonable degree of personal human fidelity and are being used in research contexts to address clinical conditions.

Because the various levels of physiological organization are not independent but in reality influence one another to varying degrees, the modelling challenge we face is compounded by the need to consider how processes occurring on these levels, often on very different space and time scales, interact. This is the heart of systems biology, although it might better be referred to as 'systems medicine' in the present context. The use of 'systems' here implies that we are addressing a multi-scale problem upon which the overall physiological or pathological behaviour depends. And so we look at how multi-scale modelling and simulation are performed today too.

Beyond that, there are the practical issues of how to perform many complex and demanding human body simulations, in a timely and reliable manner, through the use of computer automation, by exploiting computational workflows and distributed high-performance computing environments.

Underpinning all of these emerging capabilities is the management of healthcare data collection and provision with all the attendant privacy issues, which is linked closely to the legal frameworks that pertain within individual countries and for international collaboration. We describe the architecture of the informatics platforms necessary to manage access to patient data in a suitably anonymized format, while permitting the reverse linkage to patient identity in cases where this is needed, in conformance with legal and ethical requirements.

For the future deployment of such models and simulations in clinical decision making it is vital that they are fully verified and validated. This issue, central for building confidence in the medical community, is also in fact a key issue in all forms of computational science today, and receives attention in the final chapter of the book.

To whom is our textbook addressed? Plainly the scope of the domains covered is dauntingly broad and we cannot reasonably expect all readers to be able to comprehend everything in detail. We have primarily focused on providing a comprehensible account for advanced undergraduates and beginning postgraduate students who have a background in any of mathematics, physical sciences, engineering, and computer science. That is, we have tried to present the required biology and medicine to readers who are familiar with mathematics (including discrete and continuous dynamical systems, and ordinary and partial differential equations), numerical analysis, and programming, but who need more explanation about the human phenomena that they will need to model.

We hope that this textbook will provide a firm foundation for future generations to build on the initial progress now being made in predictive mechanistic modelling of the human body using computers. These are the very first steps along the path to virtual humans which we hope will one day assist in enhancing health and wellbeing for all the inhabitants of this planet.

Finally, we wish to thank the many friends and colleagues who have contributed chapters to this book (they are all listed at the start of this book and at the end of the chapters they have composed), along with

numerous others who provided critical and constructive feedback to us at all stages along the way to the published book. We are especially grateful to Dr Clare Sansom who has acted as Assistant Editor to us in the labour of taking all of the original content and transforming it into a homogeneous textbook. In all matters pertaining to the production of the book we are indebted to Jonathan Crowe, our commissioning editor at Oxford University Press, who has taken a very close interest in this work from inception to completion.

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25 October 2013

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Marco Viceconti holds the chair of Biomechanics within the Department of Mechanical Engineering of the University of Sheffield and serves as Scientific Director of the Insigneo Institute for *in silico* medicine there. His main research interests are in the development and validation of medical technology for neuromusculoskeletal diseases. Viceconti is a central figure in the emerging Virtual Physiological Human (VPH) community: co-ordinator of the VPH research roadmap and of the VHPOP osteoporosis project, and 'VPH ambassador' for the VPH Network of Excellence. He is the current chair of the Board of Directors of the VPH Institute, an international non-profit organization.

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CONTENTS

ONLINE RESOURCE CENTRE

The Online Resource Centre to accompany *Computational Biomedicine*, at http://www.oxfordtextbooks.co.uk/orc/coveney/, features the following materials to support teaching and learning:

- Figures from the book in electronic format, for use in lecture slides [for registered adopters of the book only];
- Additional materials to augment topics discussed in certain chapters.

1 Introduction

Learning Objectives

After reading this chapter, you should:

- understand the concept of and the philosophy behind human systems biology and its application in translational medicine;
- be able to describe the philosophy behind major international and multidisciplinary initiatives in this field such as the European Commission's Virtual Physiological Human programme;
- have an overview of topics that will be introduced throughout this book.

1.1 Introduction

When our children and grandchildren visit their doctors in the latter part of this century, what will they find? They may encounter computer-based avatars of themselves, programmed with their individual genetic makeup and physiological conditions. Doctors will be able to use these to refine and test tailor-made, personalized treatment programmes. 'One size fits all' medicine would then truly be part of the past.

If this vision of the future of medicine is to come to pass it will owe much to the new discipline of computational biomedicine. This represents an important paradigm shift in the biomedical sciences and clinical medicine in the early twenty-first century, and it is the topic of this book. Computational biomedicine itself owes much to the last revolution in biomedicine: human genomics [1]. The human genome sequence was first published in 2003 as the culmination of an international project that had taken about 18 years and cost an estimated US$2.7 billion (see **http://www.genome.gov**). Yet the pace of technological development has advanced so rapidly in the 10 years or so since then that the cost of sequencing a single human genome is already well below $10 000 and may well drop to the tantalizing figure of $100 or even less within a few years. By then, the much heralded era of personalized genomics—but not yet that of fully personalized medicine—will have arrived. Already, direct-to-consumer businesses are being set up to profile genomes and feed information back to individuals, providing advice and counselling where needed. The first of these to be set up, such as California-based 23andMe[1], work with profiles based on 0.5–2 million 'interesting' base positions out of the 3.2 billion in the human genome, but similar services based on profiles of the complete genome are not far behind. Furthermore, 23andMe engages its users in research into the genetic causes of disease by encouraging them to take part in surveys and linking user-reported disease incidence to known genotypes.

The growing influence of molecular biology on medicine during the 60-odd years since the discovery

[1] https://www.23andme.com/

of the structure of DNA cannot be doubted. However, it is becoming increasingly clear even to professional geneticists that knowing an individual's genome sequence cannot answer all the questions about their risk of and predisposition to disease and that genomics by itself will never be able to answer all research questions in biomedicine. After all, we humans have (approximately) a mere 23 000 genes in our genomes, fewer than many more primitive organisms. This apparent paradox can be at least partly resolved by considering the complexities that arise from non-linear interactions between genes and their protein products. As yet, we understand only a small part of the function and mechanism of gene–gene, gene–protein, and protein–protein networks and interactions.

Yet even this is not sufficient to explain the full complexity of human physiology. These complex regulatory networks are themselves influenced by events that occur at longer length and timescales than molecular ones, at the level of cells, tissues, organs, individual organisms, and their environment [2,3]. The ways in which interactions and events that occur on the level of an organism's phenotype can act as determinants of genetic behaviour—so-called downward causation as opposed to the upward causation that is the equally important influence of genetic interactions on physiology—are described by Denis Noble in *The Music of Life* [4].

1.2 Systems Biology

The study of living organisms as systems built from different spatial and temporal levels, and the interactions between them, is termed systems biology. Due to its intrinsic complexity, this type of study necessarily involves computer-based modelling and simulation. The techniques that are used can be generically termed computational biomedicine, and this is the title that has been given to our book.

Any given biological phenomenon, whether associated with normal human (or animal) physiology or with disease, is modelled, in Nobel laureate Sydney Brenner's famous phrase, 'from the middle out' [5]. This involves constructing a computational description of the phenomenon based on the most appropriate level of complexity while building in connections from levels both above and below it in the hierarchy [6]. For example, a model of a single cardiac cell might start with equations for currents passing across its membrane through ion channels, whereas a model of the whole heart would start with equations that model its electrical activation and muscle contraction on a much larger scale. This approach is interdisciplinary and relies on scientists trained in disciplines as disparate as mathematics and computation, physics, chemistry, molecular and cell biology, physiology, and medicine collaborating together. It also involves engineers, at least where the modelling of tissues and organs is involved, and, wherever possible, clinicians.

Systems biology is often thought of as being intimately linked to another computational discipline: bioinformatics. This term is used to describe the computational analysis of biological data: generally, but not always, molecular-scale data such as gene sequences and protein structures. Yet these two complementary disciplines are essentially based on completely different philosophical approaches. Systems biology can be thought of as a scientific implementation of the ideas of philosopher Sir Karl Popper (1902–1994), in which models based on aspects of reality are used to make predictions that are tested through observation. The models are judged on their ability to correctly predict natural phenomena. These models will always be approximate and provisional, as adjustments will always be necessary following observations of the external system being modelled: much more rarely, a model will be completely redesigned after the paradigm on which it is constructed is rethought. This cycling from model to observation and back again (or hypothesis testing) is in tune with the way that many biologists think.

Bioinformatics, in contrast, is based on an 'inductivist' view of science derived from the thinking of philosopher Sir Francis Bacon (1561–1626), a pioneer of the scientific method. Put simply, this states that data (and look-up tables) are all that are needed for a complete scientific understanding of phenomena. There is no need for models; should discrepancies between predicted and actual phenomena be observed, it will always be possible to resolve these once sufficient data have been collected. These two approaches remain complementary, however. We still know remarkably little about the fundamental