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DOI
10.1098/rsfs.2020.0082

Publication date
2021

Document Version
Final published version

Published in
Interface Focus

INTERFACE FOCUS

royalsocietypublishing.org/journal/rsfs

Computational biomedicine. Part II: organs and systems

Peter V. Coveney[1,2], Alfons Hoekstra[2], Blanca Rodriguez[3] and Marco Viceconti[4]

[1]Centre for Computational Science, University College London, London, UK
[2]Informatics Institute, University of Amsterdam, Amsterdam, The Netherlands
[3]Department of Computer Science, University of Oxford, Oxford, UK
[4]Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna, and Laboratorio di Tecnologia Medica, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

PVC, 0000-0002-8787-7256; AH, 0000-0002-3955-2449; BR, 0000-0001-6361-3339; MV, 0000-0002-2293-1530

Introduction

Cite this article: Coveney PV, Hoekstra A, Rodriguez B, Viceconti M. 2021 Computational biomedicine. Part II: organs and systems. *Interface Focus* **11**: 20200082. https://doi.org/10.1098/rsfs.2020.0082

One contribution of 11 to a theme issue 'Computational biomedicine. Part II: organs and systems'.

Subject Areas:
computational biology

Keywords:
computational biomedicine, high-performance computing, organs and systems

Author for correspondence:
Peter V. Coveney
E-mail: p.v.coveney@ucl.ac.uk

The domain of computational biomedicine is a new and burgeoning one [1,2]. Its areas of concern cover all scales of human biology, physiology and pathology, commonly referred to as medicine, from the genomic to the whole human and beyond, including epidemiology and population health [3].

This two-part theme issue on *Computational Biomedicine* is about modelling and simulation approaches, allied with theory, machine learning and other methods from artificial intelligence in which mechanistic descriptions, based on the laws of nature and high-quality biomedical and clinical data, are central. The aim is to provide high fidelity descriptions and predictions of the behaviour of biomedical systems of both fundamental scientific and clinical importance. The papers which are contained in this two-part theme issue were selected from a two-stage peer review process. The first stage involved the selection of extended abstracts of papers which were submitted to an open call for papers associated with the Computational Biomedicine 2019 Conference, held in London 25–27 September 2019 (https://www.compbiomed-conference.org/compbiomed-conference-2019/), organized by the Computational Biomedicine Centre of Excellence (https://www.compbiomed.eu/), funded by the European Commission. The authors of successful abstracts were invited to submit full papers for possible publication in *Interface Focus* following further peer review. Part 1, published online on 16 October 2020, was dedicated to molecular medicine.

In Part 2, we focus on organs and systems, those aspects of the subject which deal with higher levels of structure and function, and those closest to the whole human scale. At these higher levels of biological organization, the time scales of concern typically stretch from milliseconds to hours with length scales ranging from microns to metres. Compared to molecular medicine, the modelling methods less commonly involve particle-based approaches and are more typically of a continuum nature, involving the solution of partial differential equations in three-dimensional space and time. Solving such equations subject to the appropriate boundary conditions is demanding, doing so rapidly and accurately even more so. It calls for the use of powerful supercomputers and scalable codes that are able to exploit modern computing hardware to the full. The increasing complexity and heterogeneity of emerging exascale architectures makes this a challenging task for most existing algorithms and software implementations.

The most studied organ system is the cardiovascular system [4–9], with the heart receiving much of the attention [3]. Models of the human heart run on numerous supercomputers across the world where they are used to study many aspects of cardiac physiology and pathology [10]. Today, the most sophisticated versions are capable of describing its electromechanical beating while simultaneously pumping simulated blood into and out of the aorta. The geometry is provided by digital images that vary from subject to subject [11,12].

The heart drives blood around the body, delivering oxygen, nutrients and other components to their intended destinations. Modelling and simulation of the vasculature—the set of arteries and veins which carries the blood—is therefore another major target of computational biomedicine. Blood may be described at various levels of detail, depending on the context and the nature

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of the problems being studied. At the lowest levels of resolution, it can be described as a continuum fluid with designated rheological properties; at higher levels of resolution, the presence of blood cells needs to be explicitly included and the flow properties are emergent from the way on which the red blood cells crowd together and move past one another [13–16]. The combination of the beating heart and the circulatory blood flow it drives are key elements of the first whole human scale simulations which are now becoming feasible, adumbrating the advent of the virtual human. The full-blown neuromusculoskeletal system is of course another integral part of this.

Movement is probably the most important function for animals; the ability to move is essential to the survivorship of most species. In large vertebrates such as humans, the ability to move is provided by a complex collaboration between the central and the peripheral nervous system, the skeletal muscles, and the skeleton itself, including its joints, ligament, fasciae, etc. This complex organ system is sometime referred to as the neuromusculoskeletal system. The pathologies affecting the neuromusculoskeletal system are many and include conditions that produce a very large burden of disease such as Parkinson's, arthritis or osteoporosis. Computational biomedicine approaches have been used to predict the force required to fracture bones [17], to model the force generation process of whole muscles [18], or to investigate pathological neuromuscular control [19], to name but a few examples.

Imaging technology is an essential component of virtually all studies of organ systems. Ways of accumulating and processing imaging data are essential in order to provide high fidelity, patient-specific geometries on the basis of which simulation studies can be conducted. Machine learning is particularly powerful for image-based pattern recognition and has become integral to feature detection in biomedical imaging. This is frequently of great benefit in the initial stages of segmentation and reconstruction of complex three-dimensional geometries. Machine learning also has considerable promise in classifying categories of observed behaviour and as a less computationally demanding surrogate for inclusion within clinically based decision support systems.

In the current theme issue, ten articles capture aspects of the state-of-the-art in modelling and simulation of organs and systems.

Comparison and validation of simulation results with experimental or observational data are critical for *in silico* testing to be accepted by the medical community. A demonstration of good practice of this is provided by Van Rooij *et al.* [20] in their examination of whole blood flow through a flow chamber representative of a stenosed vessel. The formation of thrombosis is a significant factor in global mortality and the authors make use of physical experiment to study platelet aggregation as an indicator of the initiation of potential thrombi. These are complemented with a numerical analysis of shear stress and shear rate—parameters that are much more difficult to assess in a physical specimen. Their results indicate how cell-based modelling may help explain the differences in thrombus formation seen to occur in whole blood and platelet-rich plasma.

High-performance computing has become a fundamental component of many areas of computational biomedicine and is indeed a driving factor in the generation of these theme issues. As these resources become more widespread, and their performance capabilities advance, it is continually necessary for simulation codes to be updated to take advantage of this. Kostalos *et al.* [21] describe advances in the implementation of the Palabos library to enable it to conduct massive simulations on coupled CPU-GPU architectures. This capability is essential as we approach exascale performance and permits larger and more detailed studies of complex biophysical phenomena. In their study, the authors examine fully resolved flow of red blood cells and platelets within the plasma. They illustrate how their model can capture experimentally observed behaviour such as the migration of these suspended particles in a simulation domain significantly larger than many existing studies in the literature.

The development of organ and system models frequently requires the consideration of phenomena occurring at multiple lengths or time scales. One example of this is by Padmos *et al.* [22] where the authors develop a model for the study of stroke in patient-specific cerebral vasculatures. They construct a one-dimensional model of blood flow from the heart, through the circle of Willis and into the vessels within the brain. The extremities of this network are finally mapped to a three-dimensional pial surface to allow estimates of how blood perfuses throughout this vital organ. The geometry of the key vascular structure of the circle of Wills is determined from a scan and is incorporated into a flow simulation. The authors demonstrate that their model can realistically identify the infarcted areas of the pial surface when a clot is introduced.

In a complementary work to [22], Jozsa *et al.* [23] focus on the development and evaluation of an organ-scale microcirculation model of the human brain for perfusion prediction. Their approach makes use of a three-compartment porous continuum model to represent the microcirculation within the brain's arterioles, capillaries and venules. When compared to blood perfusion through a healthy brain, the authors illustrate that their model can qualitatively replicate the position and volume of an observed occlusion due to stroke. In the treatment of stroke, time is of the essence and these studies highlight how *in silico* models can study this condition digitally to help inform and accelerate physical treatment.

In silico methods can be used to not only predict the impact of a condition such as acute ischaemic stroke on an individual but also to assess the viability of treatment options. The study presented by Luraghi *et al.* [24] demonstrates the significant advances being made in this latter direction. They develop a three-dimensional finite-element model to replicate the four stages of a stent-retriever thrombectomy and compare their *in silico* results to *in vitro* tests conducted in benchtop experiments. The simulated retrieval of a clot replicates both successful and unsuccessful attempts with the physical apparatus in both simplified and realistic vascular geometries.

Heart disease is a leading cause of death, particularly in western countries. The work presented by Martinez-Navarro *et al.* [25] seeks to shed light on the mechanisms of arrhythmia caused by ischemic disease, under variable sodium current levels through human-based multiscale modelling and simulation. Their simulations highlight the important role played by the asymmetric biventricular anatomy in modulating arrhythmic risk. The results generated by this work may provide an explanation as to why some patients may be more susceptible to side-effects from certain heart medications.

A significant hurdle limiting the full potential of simulations to assist in the diagnosis and treatment of diseases

in a clinical setting is the generally limited computational resources available within a hospital. With necessary legal protections of patient data preventing its export to more powerful machines, one approach to overcome this is to develop reduced-order models based on pre-simulated data that can be run cheaply by clinicians. Bubak *et al.* [26] present an infrastructure for conducting detailed fluid dynamics simulations of valvular heart conditions to generate the data necessary to develop a suitable reduced-order model and discuss the technical considerations surrounding this. They report that 73% of surveyed clinicians felt that the information generated from their framework was useful and would aid clinical management.

On the other hand, further evidence of the efforts being made to increase the efficiency and performance of simulation tools on large supercomputers is provided in the work of McCullough *et al*. [27]. Here the authors highlight several examples as they demonstrate their ongoing developments towards a model for three-dimensional blood flow in coupled, human scale arteries and veins. They demonstrate the excellent strong scaling performance of their blood flow solver, HemeLB, to over 300 000 CPU cores and provide proof-of-concept studies of coupled blood flow in large scale vascular structures. This work identifies several steps being made towards the goal of many researchers in computational biomedicine of developing the virtual human.

Studies of the cardiovascular system are not the only section of the human body that are suitable for detailed computational investigation and analysis. Ascolani *et al*. [28] examine the skeletal system as they present a three-dimensional hybrid-multiscale computational model for simulating mechanotransduction in osteoblast and its interaction with the extracellular matrix. The model and the analysis method predict that within the noise of mechano-transduction, due to modulation of the bio-mechanical stimulus, and consequent gene expression, there are unique events that provide signatures for a shift in the system's dynamics. The study additionally uncovered molecular interactions that can be potential drug targets for the treatment of osteoporosis.

Finally, it must be recognized that the field of computational biomedicine is not just focussed on the simulation of specific phenomena that occur within the human body, it can also provide a powerful tool in assisting clinicians to make diagnostic decisions in the face of ever-increasing quantities of available data. Getty *et al*. [29] present a deep learning model that can assess MRI images to identify and classify brain tumours. They demonstrate that their capsule network-based model is able to accurately classify up to 87% of tumours and accuracy remained above 75% when the amount of training data was reduced. Both of these measures represent improvements over existing models. They conclude by suggesting avenues where learning techniques could accelerate and enhance the current performance of imaging techniques such as MRI.

Data accessibility. This article has no additional data.

Authors' contributions. All authors contributed to the manuscript equally.

Competing interests. We declare we have no competing interests.

Funding. The theme issue is based on an open call for papers associated with the Computational Biomedicine 2019 Conference, held in London 22-27 September 2019, organized by the Computational Biomedicine Centre of Excellence, funding by European Union's Horizon 2020 Research and Innovation Programme under grant agreements 675451 and 823712.

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