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Integrative approaches to computational biomedicine

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The new discipline of computational biomedicine is concerned with the application of computer-based techniques and particularly modelling and simulation to human health. Since 2007, this discipline has been synonymous, in Europe, with the name given to the European Union's ambitious investment in integrating these techniques with the eventual aim of modelling the human body as a whole: the virtual physiological human. This programme and its successors are expected, over the next decades, to transform the study and practice of healthcare, moving it towards the priorities known as '4P's': predictive, preventative, personalized and participatory medicine.

1. Introduction

Computational biomedicine is the name given to the use of computer-based tools and approaches to simulate and model the human body in health and disease. In the European Union, this new science has become synonymous with the concept of the virtual physiological human (VPH). More specifically, however, the name VPH is given to an ambitious initiative, funded through Framework Seven but building on work funded through earlier frameworks and external initiatives.

Throughout the second half of the last century, most biology was dominated by the molecular scale and by reductionist ideas. The influence of the discovery of the double helical structure of DNA, published almost exactly 60 years ago in April 1953 [1], on the development of modern biology cannot be overestimated. The triumphs of data-driven, reductionist biology that followed included the first complete human genome sequence, published in draft in 2000 [2]; in the subsequent 12 years the cost of sequencing a human-sized genome has fallen meteorically from the original $2.7 billion to a few thousand dollars today. The prospect of the hundred dollar genome, not long ago a science-fiction concept, is now turning into reality.

Yet much of the optimism that accompanied that first genome sequence disappeared as it became clear that it would not, after all, be possible to understand the whole of the biology of a human—or of any organism—from the sum of its molecular and genetic parts. Almost all biochemical and physiological processes arise from complex interactions between molecules and networks that are only just being elucidated and that respond to signals from events that occur at the level of the cell, organ, system or organism, or environmental and lifestyle factors. All diseases apart from the simplest Mendelian disorders arise through complex interactions between genetic and environmental factors. The idea of environmental factors influencing the behaviour of genes, or so-called 'downward causation' is described by Denis Noble in his book *The Music of Life* [3].

Noble [4], who developed his first computer-based models of cardiac physiology in the early 1960s, is recognized as one of the fathers of integrated systems biology. This discipline combines computer modelling and experimental observation of biology on many spatial and temporal scales including those

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of molecules and genes. In a phrase coined by Nobel laureate Sydney Brenner [5], a systems biologist works 'from the middle out', picking the scale that is most appropriate for a particular problem or that makes it most tractable and working 'outwards' to incorporate higher and lower levels in a model. This multi-scale modelling approach to biomedical research fits well with the recognized priorities of what has become known as '4P's medicine': the idea that medicine in this century needs to become increasingly predictive, preventive, personalized and participatory [6].

The European Union generally takes a broader approach to research in information and communication technology (ICT) and its applications than most of its constituent governments, and it has therefore emerged as the most reliable source of funding for projects in the area of integrative systems biology as applied to medicine. Furthermore, the large international collaborations that are favoured by EU funders are ideally suited to the cross-disciplinary nature of systems biology research [7]. A typical project in computational biomedicine will involve experimental and computational biologists, clinicians and often industrial scientists or entrepreneurs.

The VPH initiative (http://www.vph-noe.eu/ [7,8]) encompasses all EU-funded research in the area of integrative systems biology under the Framework 7 programme, which runs for seven years from 2007. Since its inception, over €200 million of European funding has been invested in large- and medium-sized research projects and in supporting activities, with a large majority of the support going to research and development activities. This work builds on a blueprint or roadmap for VPH research that was established under Framework 6; a smaller number of research projects in related areas funded through that framework; and earlier, more informal grassroots initiatives such as the International Physiome Project [9] set up in 2001 by the International Union of Physiological Societies. The objectives of the initiative are to develop and share separate but integrated computational models of the organs and systems that make up the human body and their structure and function in health and disease, with the eventual aim—achievable only when Framework 7 and its projects are a distant memory—of integrating them into a 'virtual human'. All projects funded through this scheme are expected to lead to models and tools that can be of practical use in the clinic, often as aids to decision making, and each project team is expected to include clinicians. In theory, if not yet in practice, the VPH may incorporate studies of all human organs, systems and diseases, and the models developed encompass all relevant spatial and temporal scales.

The VPH Network of Excellence (NoE) was set up as part of this initiative to support VPH-funded researchers and the wider systems biology community, particularly in Europe, through education and training, collecting and disseminating computational tools, research dissemination and networking. The papers collected in this special issue of *Interface Focus* reflect some of the best research presented at the second of two successful conferences organized under its aegis, in September 2012. Organizers of the first such conference, held in Brussels two years previously, noted the preponderance of presented papers dealing with modelling the cardiovascular system, and commented that this reflected the maturity of that sub-discipline [10]. This has proved still to be the case in 2012, although the disparity is now less marked.

Arguably, the core of the VPH initiative is comprised of projects that are concerned with the multi-scale modelling of human physiology and pathology (that is, of structure and function of the human body at all levels in health and disease). A wide variety of papers on multi-scale modelling were presented at VPH 2012, representing a significantly wider range of organs and systems than that presented at the first VPH meeting two years earlier. Complete sessions at the 2012 conference were devoted to modelling the respiratory system, the immune system, the musco-skeletal system and the central nervous system. The conference programme nevertheless reflected the early priorities that had seen five of the first 15 large and medium-sized research projects funded through the VPH initiative devoted to the cardiovascular system, and another four to oncology. However, although the cardiovascular system was undoubtedly the best covered in the conference in terms of both the number and quality of papers, the musco-skeletal, immune and central nervous systems were also well represented with papers describing innovative simulations with potential clinical applications.

Modelling cardiac physiology has come a long way since Noble's first simulations of the movement of ions into and out of heart cells, which involved a mere four differential equations [4]. Researchers from Noble's group in Oxford; that of Peter Hunter in Auckland, a member of the organizing committee for VPH 2012; and many others have collaborated to develop a multi-scale model of a human ventricle that is precise enough to be used in testing candidate drugs for cardiac side effects [11]. Several strands of recent research involve using these and similar models to explore the effects of mutations on cardiac function and drug response, a process that should lead eventually to the development of patient-specific models of a complete cardiovascular physiome. This development is increasingly being embraced by the pharmaceutical industry, and the US Food and Drug Administration is actively assessing the utility of computational approaches to improve prediction of possible cardiac side-effects of new compounds [12].

In recent years, there have been numerous attempts to develop mathematical models of the growth and behaviour of tumours at different levels. The VPH project Contra-Cancrum involved eight groups collaborating to develop a 'composite multilevel simulation model of malignant tumour growth and response to treatment' using several mathematical approaches and with lung cancer and glioma as initial model systems. These models, collectively termed the OncoSimulator, are being coupled to biomechanical models and imaging data to predict morphology and tumour growth, potentially as an aid to clinical decision making [13].

It is self-evident that multi-scale and multi-physics modelling to the scale that is necessary to generate models that are accurate, complex and specific enough to be of use in the clinic requires computer facilities that are not, even now, necessarily available to individual researchers or even single institutions. The VPH is as concerned with developing the infrastructure and technologies that are necessary for integrative biomedical research as it is with the research itself. One of the roles of the NoE is to help coordinate access to supercomputing facilities for VPH researchers, and it has achieved this partly through establishing a VPH Virtual Community on the DEISA supercomputing grid (http://www.deisa.eu/). The large VPH-Share project was set up to develop the Grid- and Cloud-based computational infrastructure required to share data and facilities within and between VPH projects, and to formulate and integrate them into workflows [14].

The term data warehouse is used simply to refer to a collection of data, often from disparate sources, which is stored

and used in analysis, and some important, if perhaps less high-profile, research presented at the conference involved the technical, legal and ethical issues involved in data management. These data are usually held remotely from the researchers involved and accessed via the Cloud or a grid-based system. Data warehouses are often used in VPH simulations, where the data volumes can be very large. Further complications arise from the fact that simulations involve the fusion of many different data types and, crucially, that the data may include electronic medical records, information from clinical trials and other personal medical information. There are clear ethical and legal implications of the use of data relating to individuals, which in most cases must be anonymized or at least pseudonymized before it can be stored or used. This latter concept involves the use of a key through which data may be traced back to an individual if, for instance, analysis suggests that he or she would benefit from a novel therapy. An infrastructure for information technology (e-infrastructure), the Individualized MEdiciNe Simulation Environment (IMENSE) was set up to provide a managed environment for secure access to remotely held clinical data, initially for researchers working in the ContraCancrum project [15]. This work is now being taken forward by those involved in p-medicine (http://p-medicine.eu/), an integrated project that aims to create a complete data sharing and integration platform for personalized medicine, again focusing on cancer.

Understanding genetic variation is one of the keys to the development of personalized medicine. Although systems biology has been defined almost in opposition to a reductionist biology that is dominated by genetics, it is clear that genetic as well as phenotypic differences must be included in any patient-specific models. Many VPH projects and many papers presented at VPH 2012 concerned the relationship between omics (particularly genomics and proteomics), systems biology and systems medicine. One important application of this approach is in predicting disease trajectories and drug responses. This is already being applied to a very wide range of disease states, for example, in understanding the genetic basis of rare and orphan diseases, in dissecting the relationship between genetic profile, obesity and type II diabetes, and in including mutations in growth factor sequences in models of vascular growth. The much more rapid genetic changes in bacterial and viral pathogens are also being incorporated into multi-scale models of infectious disease, in, for example, simulations of the development of resistance pathways in HIV protease inhibitors using molecular dynamics [16].

The objectives of the VPH programme are strongly focused on translating research models into clinical applications. All VPH projects are expected to include clinicians and to aim to produce tools and simulations that are (or, at least, that have potential to be) of practical use in the clinic. Although the tools and techniques used in biomedical informatics are in many cases similar to those in bioinformatics, the two disciplines evolved separately and the research communities have different cultures and make different assumptions. If a computational tool is to be accepted within the clinical community as, for example, an aid to rapid diagnosis or clinical decision making, it must be user-friendly enough for busy, stressed clinicians to accept; it must produce results on a clinically appropriate time-scale; and it must be published in the biomedical literature and validated to accepted standards of accuracy. The models themselves must be based on community standards such as SBML (http://sbml.org), CellML (http://cellml.org/) and FieldML (http://fieldml.org) and model predictions must be reproducible [17]. The INBIOMEDvision initiative (http://www.inbiomedvision.eu/), funded by the EU under the VPH banner, is bringing together experts from the academic, clinical and industrial communities to promote and monitor the development of biomedical informatics within Europe. In 2012, it published a report on the translation of bioinformatics and systems biology into the clinic, suggesting ways of bridging the remaining gap between basic and applied clinical (or industrial) biomedical research [18]. Ethical and legal issues of privacy and security are just as important here as technological ones.

The aims of the p-medicine project, described above, include the integration of disparate data types (including genetic and imaging data) and models into a tool for predicting the prognosis and selecting the optimum treatment for an individual patient with cancer. PredictAD takes a similar approach to Alzheimer's disease (AD), which is becoming increasingly prevalent in Europe as the population ages. Currently, a definitive diagnosis of this disease is only possible after death. Researchers in this project are collecting omics, electromagnetic and imaging data from AD patients and controls and developing mathematical models of disease progression as tools for early and differential diagnosis and prognosis prediction [19].

Framework Seven will be concluded at the end of 2013, and the ring-fenced funding stream for the VPH will terminate with it. Details of its successor framework programme, due to run for seven years from 2014 and named Horizon 2020, are still sketchy, not least because of delays in setting the overall EU budget. Early signs, however, indicate that computational biomedicine will remain a priority for the Commission. The VPH Institute (http://www.vph-institute.org/) has been set up by prominent European researchers in the field with the aim of ensuring that VPH research remains at the cutting edge and that the resulting computational models are adopted in the clinic. A road map for the future development of the VPH concept beyond Framework 7 forms the final paper in this issue.

The ultimate aim of the VPH project, to be realized on a time-scale of many decades rather than a single framework programme, is the development of virtual human beings, or avatars, based on the genetic and physiological make-up of individual patients. Ultimately, these may allow one to conduct all clinical trials, perhaps up to Phase III, *in silico*. Despite the long-term nature of this Grand Challenge, the VPH community has set up the Discipulus initiative to develop a road-map towards this 'digital patient' (http://www.digital-patient.net/). This concept is already widely accepted in many engineering applications. The automotive industry, for example, is already about 20 per cent of the way towards a completely computerised system for car design and testing. We are perhaps only 0.01 per cent towards a computer-based human avatar, but moving with increasing pace for all clinical research and testing.

One essential prerequisite for the continued development of VPH-related research, and for progress towards the digital patient, is investment in e-infrastructure (supercomputers and networks); in innovative technologies (software and hardware); and last but not least, in people (support and training).

There is still no formal postgraduate training for researchers wishing to specialize in this field [20]. The VPH Multi-Institutional Graduate Programme (VPH-MIP) has been funded through the EU Lifelong Learning programme to develop a flexible, multidisciplinary course in computational biomedicine for students at Master's level. This, however, will not be sufficient if VPH-like research is to make its promised contribution to the development of healthcare in this century. This research needs to be disseminated into many other constituencies: patients and the public, scientists and managers in industry, and perhaps above all clinicians. The VPH community is collaborating to produce the first comprehensive textbook of this new discipline of computational biomedicine, which is due to be published by Oxford University Press later in 2013. Wider dissemination of the innovative research presented at each of the VPH congresses should be a further step towards fulfilling this objective.

The articles in this special issue of *Interface Focus* are collected from the full papers presented at VPH 2012, the second of two successful conferences held under the aegis of the VPH NoE. This congress was held in London from 18–20 September 2012 and had over 250 participants from many countries. A total of 156 abstracts were submitted to the conference programme committee; 59 of these were selected for detailed lectures and 60 for shorter talks. Authors of papers selected for oral presentation came from 22 different countries. Over 40 papers were submitted to this special issue, and 23 were selected for publication after rigorous peer review.

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