INTRODUCTION

The Virtual Physiological Human

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The Virtual Physiological Human is synonymous with a programme in computational biomedicine that aims to develop a framework of methods and technologies to investigate the human body as a whole. It is predicated on the transformational character of information technology, brought to bear on that most crucial of human concerns, our own health and well-being.

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At the turn of the new millennium, an announcement was made, with great fanfare, of the first drafts of an entire human genome, albeit then only a ‘draft’ with many gaps still to be filled in. The cost of this first sequence is estimated to have reached 2.7 billion dollars (http://www.genome.gov/). Since then, the relentless progress in sequencing technology, data processing and computational analysis has seen the cost drop to a mere $10,000 by the end of last year, while we confidently look forward to an era just a few years hence when this figure will be as little as $100 or less.

Although many are still wondering what the human genome project has achieved, there are now online direct-to-consumer businesses being created to profile personal genomes, and to provide advice and counseling when the data are fed back to the individuals [1]. Moreover, based on genome data, one can now apparently choose the perfect spouse online.

This is the fruit of 60 years of progress in molecular biology initiated by the discovery of the structure of DNA. No one can dispute the success and impact of this understanding and its effect on current and future healthcare.

However, it has become increasingly clear, even to those who pursue genomic research professionally, that the individual genetic sequence (3 billion base pairs per human being) by itself cannot possibly answer all (or even many) research questions in the life and medical sciences, let alone provide the single key which, in the hands of a physician, will unlock the solution to each and every disease [2].

The problem is, of course, that genetics is not the ‘deterministic blueprint’ that it has so often been thought to be; after all, there are a mere 30,000 genes in the entire human genome, and many more rudimentary life forms have more sizeable ones. The resolution of this, perhaps at first sight surprising, paradox is that ‘complexity’ (as opposed to mere complication) arises from the subtleties of nonlinear interactions operating under the far from equilibrium conditions characteristic of living systems. How genes interact with one another in this way is poorly understood today, through gene–gene and gene–protein regulatory networks, but these networks are plainly influenced by events occurring at larger length and timescales than those normally associated with the molecular domain [3]. Larger scale physical interactions, particularly

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with the environment, associated usually with the phenotypical level, are probably more often the determinants of genetic behaviour than the converse. This so-called ‘downward causation’ has been most eloquently explained by Denis Noble in his compelling little book *The Music of Life* [4].

Indeed, the likely futility of purely gene-based studies of processes such as musculoskeletal dynamics and fractures is probably plain to most, if not all. The same is true of the overwhelming majority of medical and clinical conditions. It may be possible to find genetic correlates with a small percentage of these generic conditions, but they have much stronger correlates (determinants) at higher levels of organization and function.

Systems biology is the integrated study of living systems, in which one builds ‘from the middle out’ in Sydney Brenner’s famous phrase [5]. For any given situation and phenomenon under study, one needs to construct models based on that selected level while taking care to build in connections to levels adjacent—to processes ongoing at upper and lower scales of time and space. Enter the VPH (http://www.vph-noe.eu/). VPH is systems biology written on the largest of scales, as a methodological and technological framework within which it is possible to represent the human body as a single, coherent and dynamical system. It reaches down to the level of the human genome, and up to the whole human (and beyond, into population studies). To be precise, the VPH is a European Union (EU) Framework Programme (FP) 7 Initiative within the Information and Communication Technology (ICT) Unit of the European Commission [6]. The EU has long interpreted ICT much more broadly than most national programmes, and has sought to fund research and development that could have an impact in areas relevant to the health and well-being of the citizens of the EU. The VPH Initiative is perhaps one of its most exciting programmes to date.

The VPH Initiative has grown out of EU ICT research programmes in e-Health dating back over many years. One highly influential activity within FP6 was the Strategy Towards the European Physiome (STEP) support action, which produced the Research Road Map for the VPH [7]—a blueprint for the VPH Initiative itself.

Originating in the grass roots movement represented by the International Physio-me Project [8], it is the natural evolution of efforts in computational biology and informatics preceding it: these have led to the very rapid development of bioinformatics as a recognized discipline within the life sciences, designed to meet the challenge of organizing and interpreting many forms of biological data, whose focus so far has been overwhelmingly on the genetic and proteomic levels.

However, ‘physiome’ technology, being based on the computational modelling of organ systems, is qualitatively and conceptually quite distinct from much of what today passes as bioinformatics. The approach to modelling and simulating organ systems is much closer to what is traditionally done in the physical sciences and engineering. In short, it is an implementation of Popperian science, according to which we represent processes by models taken to capture aspects of reality, from which we can then make predictions that may be tested against the ultimate arbiter of experimental observation. The models are judged by their ability to correctly predict the outcome of natural processes, and in no way depend on those *a posteriori* measurements. Such models are always ‘provisional’, in the sense that they may need to be adjusted and, in rarer cases, swept entirely away if a new ‘paradigm shift’ takes hold of our scientific understanding.

Although this Popperian approach is much more in tune with the way in which the average biologist thinks, it is adverse to the philosophy which grips bio-informatics in its sway—that of Baconianism, Sir Francis Bacon’s inductivist model of science, according to which data are all that are ever needed. Data and look-up tables. There is no model here of reality itself: the data alone speak to us. Should there be discrepancies between the predictions of new observations based on regression (or more sophisticated forms of data mining) of pre-existing data, they can be always cleared up by collecting more data.

In modern computational biology, and *a fortiori* within the VPH, we have to confront head-on this clash of doctrines, which seldom arises in the physical sciences [9]. To a far greater extent, biological systems, including the human body, are imperfectly understood. This means we are not often in the comfortable position of knowing the fundamental physico-chemical processes underpinning human health. This is a very common situation at the sharp end of translational research, in which such predictive modelling methods are literally brought up close and personal within a clinical context.

Indeed, all VPH projects by construction involve collaborations with clinicians, which certainly create some unfamiliar challenges to both sides. Scientists working in VPH projects must be able to bring their modelling efforts into relevance to clinical practice, while clinicians for their part have to find time out of their busy schedules to explain what they require, and provide encouragement for the proposed translational developments. From the utilitarian point of view forced upon us by the demands of such a programme, we simply have to draw on whichever scientific approaches can provide insight and understanding and then stitch our computational approaches together based on the most judicious combinations of Popperian and Baconian methodologies.

Examples of such approaches are discernible in most of the papers collected in this Theme Issue of *Interface Focus*. Reflecting the dominant theme in the VPH2010 conference itself, the majority of the papers are on cardiovascular topics. This domain is more mature than many of the others and is producing outcomes that are perhaps closest to making direct clinical impact. Nonetheless, the key requirement for all such modelling efforts is identical throughout—it is the utmost necessity to demonstrate that the models and ensuing simulations are verified and validated. This is essential for eventual
routine inclusion of such methods in medical and clinical practice.

The chapters in this focused issue are testimony to the breadth and depth of this effort. Thus, Mihalef et al. [10] describe patient-specific modelling of whole heart anatomy, dynamics and haemodynamics from four-dimensional computed tomography images, while Pennati et al. [11] consider boundary conditions for patient-specific fluid dynamics modelling with a ‘multi-scale’ flavour within the context of the study of complex congenital cardiac defects: it is fully three-dimensional for the investigated surgical region but treated as a one-dimensional lumped parameter for other parts of the circulatory system. Villa-Uribol et al. [12] present a very extensive study of several hundred patients including hands-on clinical testing to provide a handle in the management of cerebral aneurysms. Shi et al. [13] report a numerical simulation for cardiovascular response during heart failure using an impeller pump ventricular assist device. The model development is rendered facile owing to the use of CellML/OpenCell environments. Bernadini et al. [14] report on the influence of different computational approaches for stent deployment and find common outcomes from a range of methods and simulations, hinting at the likely viability of simpler and faster modelling approaches in the future. Smith et al. [15] detail four clinical applications that integrate multiple types of functional data into a consistent framework using multi-scale modelling and simulation. Tahir et al. [16] describe multi-scale modelling of an in-stent restenosis system in two dimensions, while MacFarlane et al. [17] provide an account of a three-dimensional user-friendly interactive visualization environment for use in left ventricle surgical planning and simulation associated with ischaemic heart failure. Conti et al. [18] show the development and testing of a semi-automated tool to support the diagnosis of left ventricle dysfunction from cardiac magnetic resonance.

Relan et al. [19] aim to create a personalized electrophysiological model to which a virtual ventricular tachycardia simulation procedure can be applied, allowing for testing of strategies in advance of intervention; its ability to produce fast estimation of a number of key parameters may allow the clinical use of such cardiac electrophysiology models in future. Orlowski et al. [20] have developed a model of brain cellular metabolism that simulates the pH response of cells to ischaemia; their findings suggest the value of pH imaging as a basis for clinical decision-support tools for ischaemic stroke.

Nickerson et al. [21] describe their implementation of a multi-scale computational model of the neural nephron system based on specifications and standards already used within the physiome community and promoted by the VPH Initiative, thereby facilitating future development and reuse of their framework. Diaz-Zuccarini & Pichardo-Almarza [22] discuss the formalization of multi-scale modelling in the context of integrative physiology, arguing in favour of the value of an approach based on bond graphs and pseudo-bond graphs to systematize the translation of physico-chemical models into mathematical form, with potential benefits for future development of systems biology software. Gomez-Cabrero et al. [23] present a workflow methodology for generating competing hypotheses from models with parameter uncertainty.

Marias et al. [24] describe the development of an integrated environment for managing the development and deployment of multi-scale modelling and simulation tools in support of clinical decision making for the treatment of lung carcinoma and glioblastoma. The successful integration of heterogeneous clinical data and models has led to novel ideas for clinical decision support in the context of predictive oncology.

Since many VPH-style simulations performed in support of clinical decision making involve large-scale three-dimensional patient-specific models, they frequently require access to substantial computing and, indeed, supercomputing resources, which often reside in remote locations on a distributed infrastructure such as a grid or cloud. Managing this access in a secure but usable way is a significant information technology challenge: Haidar et al. [25] present a security solution that meets these requirements.

As a consequence of all this work, it is now evident that there is a ‘revolution’ taking place in basic and clinical medicine. By the end of this century, from a pedagogical standpoint, the subject will not look much like it does today—information technology is invading medicine, enabling new ways of working, facilitating new discoveries and, with that, improved medical treatment and healthcare. Much of this turns on information assurance: managing and facilitating access to vast quantities of highly heterogeneous distributed data (already at the petascale for most of us), with the added twist that privacy and confidentiality must be maintained, in compliance with regionally differing national and international legislation. For this enterprise to be successful, integrated infrastructures are required, permitting data to be accessed and transferred quickly using fast networks, to powerful supercomputers that are able to perform simulations and analyses—which will frequently be life or death resolving—on timescales relevant to clinical decision making. To exploit all of this, tomorrow’s physicians will need to be trained in very different ways from today.

The papers collected in this Theme Issue of Interface Focus are the consequence of a rigorous selection process, beginning with a call for extended (three-page) abstracts for VPH2010, the first international scientific meeting of the VPH community, held in Brussels, Belgium, on 30 September to 1 October 2010 (http://www.vph-noe.eu/vph2010). One hundred and sixty-nine of these were received, which were reviewed by members of the Conference Programme Committee. From these, around 35 of the most highly rated were invited to submit papers for full-scale peer review, which has resulted in the present issue. The conference itself drew over 230 attendees, coming from 24 countries, many of them far flung indeed (including USA, Japan, Australia, New Zealand, Singapore and South Korea).
REFERENCES


