The virtual physiological human: tools and applications I

This Theme Issue is the first of two devoted to the development of tools and applications within the virtual physiological human (VPH) initiative. It follows on from the 2008 double issue of this journal that introduced the VPH as a European Framework Programme 7 (FP7) initiative that aims to develop the information and communication technologies (ICT) infrastructure to support and progress computational modelling of the human body. In the previous editorial (Clapworthy et al. 2008), we gave an overview of the principal aims of the VPH initiative, focusing on key objectives and the way in which the VPH work programme had arisen from a grass-roots EU FP6-funded initiative, a Strategy Towards the EuroPhysiome (STEP; see http://www.europhysiome.org/ and Fenner et al. 2008). STEP was a focused policies project, which not only provided a seminal roadmap describing how European research in this area might best move forward, but also, crucially, established a strong network of researchers across Europe, reaching out to leading groups worldwide. With the onset of the VPH initiative, which today includes 15 individual VPH projects, the STEP Consortium handed over general coordination of these activities to the VPH Network of Excellence (NoE). This editorial will give an overview of the aims and objectives of the VPH NoE, which are illustrated in these two Theme Issues by examples that give a flavour of the activities that form part of the VPH initiative.

The VPH NoE has been designed with ‘service to the community’ of VPH researchers as its primary purpose. The aims of the network, which comprised 13 Core members, and an open and expanding General and Associated membership (http://www.vph-noe.eu/vph-noe-membership), range from the development of a VPH ToolKit and associated infrastructural resources, to integration of models and data across relevant levels of physiological structure and functional organization, and on to VPH community building, training activities, lobbying, dissemination and support. Here we focus on the VPH ToolKit, a federated ICT resource for the VPH research community.

For the whole of the VPH research community, one of the key challenges in the development of quantitative, integrative and predictive models of human physiology is the provision of, and access to, the necessary research infrastructure. This includes methodologies, databases and computational tools that allow researchers working in different scientific fields (and at multiple physiological levels and scales) to communicate effectively and share data and...
models in a standardized manner. The scale of the activity, in terms of both model development and data handling, requires a computational and data management infrastructure that is not currently available. The majority of the funded activity within the VPH NoE is directed at federating and making openly available just such an ICT infrastructure, through what we have termed the VPH ToolKit. This is an extremely challenging task, the first stage of which—the development of comprehensive documentation describing the results of an initial requirements and technology assessment exercise—has just been completed (see http://www.vph-noe.eu/wp3).

Our goal is that the VPH ToolKit should provide a powerful and user-friendly technical and methodological framework to support and enable VPH-related research work across the VPH initiative, and more widely within the international research community. Meeting this aim requires, among other activities, the development, evolution, application and promotion of standardized markup languages that permit interoperability of models and, where this is appropriate, interoperable codes that may be coupled both horizontally and vertically. Standardized and accessible data, metadata and ontologies, needed to create and describe models, must be made available. Tools and services for data integration and fusion, workflow environments, and means to access high-performance computing resources with increased ease, must all be considered (Kohl et al. 2000; Coveney & Atkinson in press). To meet the objectives both of the VPH initiative and of the global Physiome Project (see http://www.physiome.org.nz/; Bassingthwaighte 2000; Hunter et al. 2001, 2002; Crampin et al. 2004), any VPH standards developed will need to be suitable for, acceptable to and adopted by the relevant community on a global basis. The VPH ToolKit, therefore, will be a shared and mutually accessible research infrastructure, made available not only to the VPH NoE and European VPH initiative projects, but also to all members of the relevant research and development communities.

Any interested institution may contribute to this development and, should it wish to do so, join the NoE community (see http://www.vph-noe.eu/vph-noe-membership/application-procedure). The intention of developing and surveying the VPH research community, prior to embarking on federation/development of the VPH ToolKit, was that the resources made available should be tailored to address existing and emerging needs, while being robust, efficient, usable and extensible, allowing it to be readily and uniformly adopted by the VPH research community.

In particular, the VPH ToolKit will include the following:

— open markup language (extensible markup language, XML) standards for describing data and models at spatial scales that range from proteins to human;
— application programming interfaces (APIs) for implementing agreed VPH standards;
— workflows that use existing middleware for facilitating grid-enabled VPH research;
— web-accessible repositories for data, metadata, models and workflows, based on VPH agreed standards, and including annotation and tutorials for non-expert biologist users;
— a library of open-source computational routines and graphical user interfaces (GUIs) that, via the APIs, can access the data and model repositories; and
— standardized ontologies to underpin the description of VPH models and data, and enable mapping between research levels and domains.

The first five papers in this Theme Issue describe examples of the development of standards, tools and software that will form a basis for the infrastructure that is federated and supported by the VPH NoE. Nickerson & Buist (2009) describe the initial efforts to develop an infrastructure to support interactive examination models, and the data on which they are based, directly from the final published paper describing that research. This is perhaps the holy grail of quantitative biological research—if readers can access directly the standard descriptions of models, and rerun those models to test published results, and immediately adapt models to meet their own needs or incorporate them into more complex (potentially multi-scale) models of their own, then many of the fundamental objectives of the VPH initiative would have been met. A key building block in this process is the provision of standardized modelling languages and associated tools and repositories to facilitate model building and model sharing; the papers by Beard et al. (2009), Christie et al. (2009) and Garny et al. (2009) each addresses a different aspect of this problem. Beard et al. consider recent extensions to the CellML language, which is an open standard, based on XML, used to store and exchange computer-based mathematical models. The paper describes in particular recent extensions to the CellML metadata standard for the biological and biophysical annotations of models. The paper by Christie et al. describes recent developments in a proposed new modelling language, FieldML, which is being developed jointly by the IUPS Physiome Project and the VPH NoE. FieldML will provide a standard markup language for describing the structure and parametrization of spatial fields, and associated functions and operators, used to encode the physical principles governing biological and physiological processes and systems. Before being adopted widely, such markup languages must be supported by the user-friendly tools that support their use not just by technically adroit computational modellers, but also by experimentalists, teachers and students. Garny et al. describe the development of just such a tool—the Cellular Open Resource (COR; http://cor.physiol.ox.ac.uk/)—which has adopted the CellML standard to provide a cellular modelling and collaboration environment that allows the import and export of code from a variety of established modelling languages, and executes programs efficiently by converting them into machine code. The fifth paper by Bernabeu et al. (2009) addresses the development of dependable, fully tested software for physiological modelling, and how complex numerical algorithms using knowledge of the underlying physiology (cardiac, in this case) can be incorporated into such an environment.

The next two papers progress naturally from Bernabeu et al., by examining differing aspects of the modelling of cardiac electrophysiology at the tissue level. First, Linge et al. (2009) give an overview of numerical methods developed over the past 10 years for the solution of the governing bidomain equations, concluding that the full potential of modern computational methods is yet to be exploited. Then, Bordas et al. (2009) follow on from this by considering how recent developments in adaptive finite-element methods may yield much more computationally efficient
solutions to the governing partial differential equations. The paper by van Beek et al. (2009) considers the issue of modelling a very complex system (such as animal metabolic systems) when accurate experimental data, quantifying very large numbers of parameters, are lacking.

The next five papers consider different aspects of bone tissue modelling, each giving a detailed account of the current state of a particular aspect of the field. Lacroix et al. (2009) discuss the modelling of biomaterial scaffolds for bone tissue engineering. Several case studies are described, which allow the authors to highlight areas where further research is required to overcome the current technical limitations in the field. The papers by Gerhard et al. (2009) and Geris et al. (2009) are paired and consider computational approaches to bone modelling and remodelling. In the first of these, the current simulation approaches are reviewed, and one model is extended to explore and discuss the extent to which multi-scale models, which take greater account of the three-dimensional microstructure at a cellular level, might improve future understanding of bone adaptation. The second paper considers the problem of bone regeneration, reviewing the existing work and giving examples of where mathematical modelling has enhanced knowledge within this field. The authors conclude by discussing some of the drawbacks of the current continuum models, highlighting the advantages of a multi-scale approach. The fourth paper, by Sanz-Herrera et al. (2009), builds on these reviews by presenting a novel, multi-scale mathematical approach to modelling bone regeneration within biological scaffolds. Finally, Lenaerts & van Lenthe (2009) cover the application of some of these previously reviewed ideas to computational studies of the treatment of osteoporosis. The authors conclude that the models can still be improved, particularly in the evaluation of multiple loading conditions, and illustrate their arguments with a case study of femoral bone structure calculated from clinical CT scans.

The last paper, by Favre et al. (2009), reviews the state of the art in computational modelling of the shoulder joint, discussing current categorizations of models, and their potential for clinical application. The authors consider the implications of combining the aspects of previous approaches into a comprehensive shoulder model and suggest strategies for validating such models using emerging technologies.

Thus, this Theme Issue is characterized by a focus on the development of VPH-related tools. The subsequent Theme Issue will detail a range of applications to biomedical research and highlight the usage of the VPH approach for biomedical research and development.

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David Gavaghan1,*, Peter V. Coveney2 and Peter Kohl3
1Oxford University Computing Laboratory, and 3Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford OX1 2JD, UK
2Centre for Computational Science, University College London, London WC1H 0AJ, UK
*Author for correspondence (david.gavaghan@comlab.ox.ac.uk).

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