INTERFACE FOCUS

Introduction

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Virtual physiological human 2016: translating the virtual physiological human to the clinic

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1. Introduction

Ten years ago, a group of scientists published the roadmap *Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human* (STEP, http://www.vph-institute.org/upload/step-vph-roadmap-printed-3_5192459539f3c.pdf). This triggered a major investment in research in the virtual physiological human (VPH). The VPH was defined as a 'methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system.' The roadmap also stipulated that 'VPH is not 'the supermodel' that will explain all possible aspects of human physiology or pathology. It is a way to share observations, to derive predictive hypotheses from them, and to integrate them into a constantly improving understanding of human physiology and pathology, by regarding it as a single system.'

Even earlier, 10 years before the publication of the STEP roadmap and following the 33rd IUPS World Congress in St Petersburg in 1997, the Physiome committee was established, which had the ambitious goal to provide computational frameworks for integrative multiscale modelling and simulations of human physiology, including reproducible, reusable and modular components that would enable the creation of complex multiscale models of human health and disease.

We may conclude that the STEP consortium adeptly sensed the wave of technological innovations that were about to happen and that VPH researchers and engineers have used to their full advantage to push forward the VPH. Today, we live in a fully connected world, with an abundance of available (medical) data that can be accessed via dedicated interfaces and analysed with workflows that can execute in seemingly unbounded cloud computing resources. Individuals have unprecedented opportunities to instrument themselves with, for instance, smart watches, and instantaneously share data on their own physiology with the rest of the world. And many people actually do that! Within healthcare and in the clinical setting, these technological advancements have a strong impact that in combination with ever-improving medical technology will lead to further improved and more personalized medicine.

The VPH/Physiome has become a mature and flourishing scientific community. Research in the VPH/Physiome contributes to many aspects of computational biomedicine, ranging from developing descriptive complex multiscale models for deeper understanding of human physiology and pathophysiology and their related (simulation) technologies, to patient-specific models and their related (IT) technologies, with clinical relevance for applications in diagnosis and treatment prediction [1]. And, as Viceconti and Hunter write, 'in 2011 the vision of the VPH was fully developed', with three main targets for VPH research: (1) the digital patient (VPH for doctors); (2) *in silico* clinical trials (VPH for the

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biomedical and pharma industry; and (3) personal health forecasting (VPH for the patient/citizen) [1].

Currently, the VPH is a worldwide effort to integrate all information available, from genetics to medical images to clinical data, for each patient, and generate computer models capable of predicting how the health of that patient will evolve under certain conditions or after personalized treatment. VPH strongly contributes to improving healthcare, well-being and healthy ageing. VPH has seen tremendous scientific development and impact, as for example, witnessed in previous special issues, also in this journal [2–11].

In September 2016, the biannual *Virtual Physiological Human Conference* was held at the Royal Tropical Institute in Amsterdam, The Netherlands (http://2016.vph-conference. org). The conference was organized by the Virtual Physiological Human Institute (http://www.vph-institute.org) and was the fourth in a row, starting in 2010 in Brussels, Belgium, then in London, UK, in 2012 and in Trondheim, Norway, in 2014. The next VPH conference is currently being organized and will be held in Zaragoza, Spain, in September 2018.

The theme of the VPH2016 conference was 'translating VPH to the clinic'. We have already seen some examples of VPH applications that have been applied, or are close to being applied, in clinical settings [1]. The first VPH model to receive full FDA approval was virtual Fractional Flow Reserve based on computed tomographic angiography. Moreover, a phase 1 clinical trial for virtual Fractional Flow Reserve using rotational coronary angiography was recently completed. VPH models for accurate differential diagnosis of pulmonary hypertension also recently completed a phase 1 clinical trial. VPH technologies for planning transcatheter aortic valve implantation and paediatric percutaneous pulmonary valve implantation have been demonstrated, as well as for predicting the risk of bone fracture in osteoporotic patients [1].

We have selected eight contributions to the VPH2016 conference that not only cover new ground in computational biomedicine, but also contribute towards clinical applications. These papers demonstrate how many years of VPH research can now (potentially) lead to real clinical applications. Five of these papers show examples of personalized digital patient models, two papers address pathologies studied in virtual populations, and finally one paper is on a multiscale modelling framework for the VPH.[1]

The most advanced VPH applications close to, or currently used in, clinical practice are in the field of cardiovascular disease, e.g. the already mentioned virtual Fractional Flow Reserve. A major issue in personalizing such haemodynamic predictions is choosing correct patient-specific boundary conditions, and for some applications also patient-specific mechanical properties of the arterial wall. Itu *et al.* [12] propose a procedure for personalizing aortic haemodynamic computations from four-dimensional magnetic resonance imaging data, which they successfully evaluate on 15 datasets from patients with aortic valve disease. An example of an application that requires such personalized models is the planning of medical procedures in cardiovascular disease. Capelli *et al.* [13] report on their experience with a modelling framework for patient-specific prediction of clinical outcomes. They apply their models to three procedures in relation to congenital heart disease (percutaneous pulmonary valve implantation, stenting of aortic coarctation and surgical repair of double outlet right ventricle) and they include 12 patients in their study. They demonstrate good agreement between simulations and clinical

decisions (such as device choice), and they argue that their study supports translation of such VPH tools for personalization of cardiovascular treatments. The limited number of patients in both studies underscores the preliminary nature of these findings. However, the results show the way forward and seem to warrant evaluation studies of larger patient cohorts.

Predicting the outcome of treatment for decision support is also addressed by Ouzounoglou *et al.* [14] who apply their onco-simulator to simulate progression and response to the treatment of acute lymphoblastic leukaemia (ALL). The mechanistic simulator is combined with optimization and machine learning methods for parametrization of the model, based on data from a cohort of 191 patients. The resulting Hybrid ALL Oncosimulator is then applied to predict the prednisone response category of a newly arrived ALL patients, with correct classification for around 70% of patients. The authors discuss how this could be elevated to 95% and how the simulator could be applied to longer and more complex treatments.

Prediction of risk factors, such as risk of rupture of cerebral aneurysms [1], is another potential use case for VPH models in clinical practice, again in decision support scenarios. Akyildiz *et al.* [15] study atherosclerotic plaque rupture, which is the primary cause of cardiac and cerebral ischaemic events. Accurate rupture risk stratification of atherosclerotic plaques is important for planning preventive treatment strategies. High structural plaque stresses strongly correlate with plaque rupture. Using dedicated heterogeneous finite-element models, Akyildiz *et al.* compute peak cap stresses on atherosclerotic plaques from 12 atherosclerotic human coronaries, and study the sensitivity of this stress in relation to plaque structure. For the first time, heterogeneity of plaque structure was considered to compute the peak cap stresses.

An example of using VPH models in prospective studies, to support analysis and shed light on emerging hypotheses, is provided by Guo *et al.* [16], who use personalized modelling of fluid transport in the brain to help decipher underlying mechanisms regarding Alzheimer's disease. Using subject-specific data from 103 individuals as input for an extended model of perfused parenchymal tissue coupled to subject-specific meshes, permeability tensor maps and cerebral blood flow, the authors aim to build an understanding of the exact nature of emerging evidence, suggesting that Alzheimer's disease is a vascular disorder, caused by impaired cerebral perfusion, which in turn may be promoted by cardiovascular risk factors that are strongly influenced by lifestyle. This paper describes in some detail the underlying models and ways to personalize them, and discusses two specific patient cases.

Virtual populations are computer models of real populations, to which VPH models can then be applied to study phenomena on the cohort level. Such virtual populations or virtual cohorts will be used in, for instance, *in silico* clinical trials [1], and with the recent start of a new wave of EU-funded projects fully dedicated to *in silico* clinical trials, we may expect to see new results with immediate relevance for healthcare and clinical practice. The paper by Clemmer *et al.* [17] provides an exciting example of what we can expect from modelling with virtual populations. These authors use the Humod model, an extended mathematical model of human physiology, to create a heterogeneous virtual population of 1000 virtual patients by randomly varying physiological parameters in the model, and then investigate mechanisms responsible for the change in blood pressure in response to a high-salt diet, both with full kidney mass and after removal of one kidney in the group of

virtual patients. Using topological data analysis, they are then able to distinguish five clusters of salt-sensitive individuals.

Such population modelling can also contribute to reducing the use of animals in preclinical studies prior to any translational studies in human volunteers. Laranjeira et al. [18] study anti-inflammatory treatment with chemerin to find new and safer drugs in routine treatment of mild-to-moderate chronic pain. A mouse model showed the inhibitory effect of chemerin on recruitment of inflammatory cells. The next step is to evaluate the therapeutic potential of optimized protocols for drug concentration and timing of injection. Instead of sacrificing a large number of laboratory animals to do an exhaustive search, Laranjeira et al. use available mouse data to develop and parametrize a mathematical model, which is subsequently used to optimize the therapeutic potential of chemerin.

Finally, to stipulate that although a major goal of the VPH/Physiome is translation to clinical applications, there is strong ongoing research in the underpinning modelling and simulation paradigms and related standardization initiatives, without which it would be very difficult to deliver integrated multiscale models of complex physiology for digital patient modelling, de Bono et al. [19] show how to represent biophysical processes between and within modular biological compartments. They propose a new framework for developing multiscale biophysical models in physiology by combining ApiNATOMY, a representation of functional anatomy, with Bond Graphs, an engineering methodology that represents mass- and energy-conserving processes consistently, and demonstrate its capabilities by linking models for blood and urine flow in the kidney with biochemical and diffusive processes between blood and urine of the proximal tubule in the nephron, and finally with membrane transporters in the renal tubular epithelium.

VPH2016 was a very successful conference, and this special issue catches some of the excitement during the conference. As a community, the VPH/Physiome has made tremendous progress, but the biggest challenges still lie ahead of us. We are on a road of creating our 'digital twins', to be used in clinical digital patient settings when we are ill, or in personal health forecasting to support us in adopting and maintaining a healthy lifestyle, or as part of a virtual population to be applied for in silico trials. This requires extension of not only fundamental research, but even more so of translational research of the type that is described in this special issue. In addition, successful implementation of these efforts also requires strong engagement of EMA and FDA, and solid connections with the medical device and pharma industry, as is currently happening with the help of the VPH institute and the Avicenna Alliance (http://avicenna-alliance.com).

Endnote

[1] Note that another special issue dedicated to VPH2016 will appear in the Journal of Computational Science, 2017. That special issue focusses more on multiscale modelling in VPH, and related VPH technologies.

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