The Human Physiome: a necessary key for the creative destruction of medicine

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The term creative destruction was coined in 1942 by the Austrian American economist Joseph Schumpeter [1]. Within economics, the term, also known as Schumpeter’s gale, refers to the unceasing product and process innovation mechanism by which new production units replace outdated ones, and which capitalism is dependent on. However, it is apt to apply this term to any field or discipline where the invention and application of a new methodology or approach dramatically changes established practices without changing the disciplinary goals as such. And Eric Topol recently used the phrase in his influential book ‘Creative destruction of medicine’ where he envisaged that better sequencing, metabolomics and proteomics technologies together with an array of cellphone-based sensors will be sufficient to revolutionize medical practice. A vista that is apparently shared by a large fraction of biomedical researchers and funding bodies. The title of this theme issue reflects our view that it is mission-critical to acknowledge that the conceived medical revolution will also be heavily dependent on a quantitative understanding of human physiology embedded in a wide array of mathematical representations of normal as well as pathophysiological processes (i.e. a Human Physiome for short [2]).

Establishing an evidence-based personalized medicine standing on the shoulders of a deep understanding of human physiology in the wide sense is a daunting undertaking, and the complexity of the task still does not seem to be appreciated by academics or the industrial biomedical research community. No one is in a position to claim that we will succeed in making the transformation of medical practice envisioned by so many, but we think it is fair to claim that without a Human Physiome this transformation will not materialize. Considering the enormous amounts of money and intellectual effort invested in realizing a personalized medicine, we hope this theme issue will raise a discussion we all will benefit from.

Around 150 years ago, an editorial in an important electrical trade journal stated [3]: ‘We may remark that of late years the (experimental) facilities for obtaining definite ideas on the subject of electrical phenomena have greatly increased. Sciences generally become simplified as they advance, albeit in some branches they may attenuate into the abstruse. In electricity there is seldom any need of mathematical or other abstractions, and although the use of formulae may in some instances be a convenience, they may for all practical purposes be dispensed with’. Considering the role that mathematics since then has played for the technology development based on ‘electrical phenomena’—and which our civilisation is completely dependent on—we all laugh at this. But what if we change the phrase ‘the subject of electrical phenomena’ with ‘the subject of biological phenomena’ and ‘electricity’ with ‘biology’? Then the majority of biomedical researchers would probably agree.

Considering the complexity of biological order compared to the order associated with electrical phenomena, how much more do we not need mathematical thinking to understand this orderliness and transform this knowledge into technology. But a warning is in place. In 1887, the prominent weekly journal The Electrician printed a letter from a practical engineer who wrote [3]: ‘... to enter a protest against the growing tendency to drag mathematics into everything.
I have as high an admiration for mathematics as any one, but I like them as servants, not as masters; and I like to take the shortest, simplest, and surest way to my object, which to my mind, mathematics do not always furnish. . . . Mathematics and theory are dangerous tools; you can never be certain you are using them aright until you have clearly proved them by practice'. He was right, and we should never forget that without tight links between mathematical thinking and experimental biology and the clinic, there would be little progress. The global community of researchers subscribing to the Human Physiome vision is arguably the community where these links are best maintained.

The Physiome Project was established by the International Union of Physiological Sciences (www.iups.org) at the World Congress in St Petersburg in 1997 in order to complement molecular approaches with the principles and methods of physics and engineering. The main task facing the nascent Physiome Project committee was to provide a computational framework for understanding human physiology, including the establishment of standards for encoding models and data such that physiological models could be demonstrably reproducible and reusable. The model encoding standards also needed to support modularity—since complex multi-scale models must be built from independently validated modular components often developed by many different research groups. A related US initiative by the Interagency Modeling and Analysis Group (IMAG) began in 2003.

In 2007, a consortium of European scientists and engineers published a roadmap ‘Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human’ (http://www.vph-institute.org/upload/step-vph-roadmap-printed-3_5192495936c.pdf) that persuaded the European Commission to call for research proposals under Framework 7 on healthcare-related modelling. A Network of Excellence on the Virtual Physiological Human or VPH-I was funded from 2008–2012 to help coordinate European activities [4,5]. In 2013, the Virtual Physiological Human Institute (VPH-I; www.vph-institute.org) was established to provide continued global leadership for the VPH/Physiome Project with the goal of using computational modelling of biological processes to integrate quantitative biological knowledge from molecular to cell, tissue, organ and whole body scales in order to understand physiological systems in terms of both their molecular components and their interaction with the environment and translate this understanding into clinical practice. The VPH-I was formed to advance these goals and to promote the use of standards-based reproducible modelling in healthcare and drug discovery. To this end, the purpose of the VPH-I is to act as a catalyst to bring together policy-makers, science funding bodies, regulatory agencies, educational institutions, clinical organizations and industry in order to maximize the benefit of VPH/Physiome approaches for the healthcare industry and for the public good.

Following up on this mandate, VPH-I was recently funded by the European Commission under the Information Communication Technologies Programme to develop a strategy for in silico clinical trials. The project, dubbed Avicenna, included the creation of a roadmap addressing the steps needed for the introduction of in silico clinical trials [6], and the establishment of a partnership between the biomedical industry and European research organizations, with the aim of developing the technology, methods, protocols and standards required for in silico clinical trials to become a reality. The second objective led to the creation of the Avicenna Alliance, an association of industry and research organizations who have a commercial or research interest in in silico medicine that is now rapidly gaining momentum (http://www.avicenna-alliance.com).

The biannual conference series Virtual Physiological Human grew out of the FP7 Virtual Physiological Human Network of Excellence. VPH-I now manages this conference concept, which has become one of the major instruments for maintaining the coherence and momentum of the highly multidisciplinary VPH community. This theme issue reflects the overarching theme of the third VPH conference, hosted by the Norwegian University of Science and Technology in Trondheim, 9–12 September 2014, namely that the establishment of the Human Physiome is not just nice to have, but is a necessary key to realizing a real predictive, explanatory, preventive and participatory (i.e. personalized) medicine (post-event website at https://www.ntnu.edu/web/vph2014/).

Biophysically based models of physiological processes capture physiological phenotype in a quantitative and predictive form. They should underpin research in physiology in the same way that nucleotide sequence underpins research in genetics, since there is no other way to deal with the complexity of physiological systems in a quantitative fashion. Most importantly, biophysical models bring with them the constraints on physiological behaviour imposed by the conservation laws of physics. Physiological function depends on these laws of nature as much as it depends on molecular biology.

At the heart of physical laws is the concept of continuous fields—and much of physiology is the interaction between these fields and the molecules that support life. Examples are the relationship between a continuous temperature field and the energy of its constituent particles, or a pressure field representing the energy density (J m$^{-3}$) of energetic particles, or the oxygen concentration field in a tissue and its relationship with oxygen sensitive proteins. The ‘particles’ in physiology are molecules (proteins, carbohydrates and lipids) and of course the complexity of their formation, structure and interaction is what biomedical science and drug discovery is all about. Physiological function and the symptoms of disease, however, appear at the tissue/organ scale and the field laws of physics are an essential component of the physiological phenotype.

There are only four equations, or equation systems, needed to capture the laws of physics (conservation of mass, linear and angular momentum and energy, respectively) at the scale of continuous fields. These are the Navier–Stokes equations (dealing with fluid mechanics), the equations of finite elasticity (dealing with the mechanical behaviour of solid materials), Maxwell’s equations (dealing with the behaviour of electro-magnetic fields and underpinning electrical engineering and telecommunications) and reaction–diffusion equations (dealing with conservation of mass for chemical species represented by their concentration fields). These equations are the DNA of the material universe we live in. Just as the 21 000 protein-coding genes in the human genome are encoded by only four nucleic acids, these laws depend on very few parameters—just two (density and viscosity), for example, in the case of the Navier–Stokes equations.

To benefit healthcare, organ and whole organism physiology needs to be understood both at a systems level and in terms of subcellular function and tissue properties. Understanding a re-entrant arrhythmia in the heart, for example, depends on knowledge of not only numerous cellular ionic current mechanisms and signal transduction pathways, but
also larger scale myocardial tissue structure and the spatial variation in protein expression. As reductionist biomedical science succeeds in elucidating ever more detail at the molecular level, it is increasingly difficult for physiologists to relate integrated whole organ function to underlying biophysically detailed mechanisms that exploit this molecular knowledge. And of course genetic background and molecular mechanisms are only one-half of a much more complex story that involves interaction between an individual’s genes and their host environment—involving, not least, lifestyle choices such as diet and exercise, and the consequences of ageing. The enormous progress that has been made over the past 50 years in understanding molecular biology and the human genome has consequently had relatively little impact on diagnostic and therapeutic strategies in medical practice. To bioengineers and the physical sciences community, it is obvious that biological scientists and healthcare practitioners should be making greater use of the multiscale computational modelling strategies used by engineers and physicists to design and analyse complex mechanical, electrical and chemical engineering systems. It is hard to see why similar approaches should not benefit the understanding of physiological systems.

The articles in this theme issue address the rationale for why the establishment of the Human Physiome is critical for realizing a personalized medicine characterized by being predictive, explanatory, preventive and participatory, and what it takes in terms of methodology and technology to establish what may qualify as a clinically relevant Human Physiome v.1.0. The first of these theme components, on the rationale for establishing a Human Physiome, begins with a description of how to make use of realistic psychobiological models of face-to-face interaction together with multiscale models of an individual’s physiology to empower the individual to internalize the need for behavioural changes [7]. The next one by van Beek et al. [8] addresses, with a particular focus on metabolic aspects, why computational physiology is needed to understand the physiological of the ageing individual. Age is still the best predictor of most complex diseases, which strongly implies the need for new approaches that can deal with the systemic complexity induced by the accumulation of somatic damage. Castro et al. [9] describe why we need modelling to understand the complexities of the immune system and to use this understanding in a therapeutic context. Even though use of computational models in immunology is not yet extensive, they show that there are already excellent examples of the synergy between modelling and experiment. The realization of the Human Physiome vision will have to stand on the shoulders of experimental biology producing data that are relevant for construction and validation of models. To this end, Vinnakota et al. [10] discuss how the enhancement of the physiological realism of experimental models is a prerequisite for the production of such data. Although tissue engineering is making rapid progress, Geris et al. [11] show how computational methods advance understanding, reduce R&D costs, increase product quality and productivity, and facilitate much faster market introduction of new tissue engineering therapies. Finally, Nyman et al. [12] use type-2 diabetes to show how multi-level computational approaches can describe long-term disease progression which can linked to decision-support systems and thus become relevant for clinical end-usage.

The second theme component, on the methodology for establishing a clinically relevant Human Physiome, begins with a discussion of modelling and data standards and their associated Web-accessible repositories and open source multiscale modelling tools, since standards for reproducible modelling and modular approaches to handling are essential if we are to use quantitative physiological models in clinical workflows [13]. Strategies for linking the variables and parameters of these models down to molecular biology and bioinformatics databases in order to produce formal representations of pathophysiology mechanisms for clinicians are considered by de Bono et al. [14]. Issues associated with the development and use of Human Physiome models of the heart and the musculo-skeletal system in the clinic and for industry are discussed by Chabinick et al. [15] and Fernandez et al. [16], respectively. Finally, advancements needed for wide practical use of models in the drug development pipeline design and for in silico trials are discussed by Thomas et al. [17].

In conclusion, even though there are many challenges that need to be overcome to establish a Human Physiome that can be applied in a wide array of clinical contexts, we hope the readers will acknowledge its importance for realizing a personalized medicine, and that we do not need to wait 150 years before the majority of people will smile at those who claimed that biology did not need mathematics. But this demands enhanced concerted efforts from several communities and the existence of funding bodies that are willing to come together and design funding mechanisms capable of efficiently supporting this highly interdisciplinary and transnational venture.

References

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