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A vision and strategy for the virtual physiological human: 2012 update

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European funding under Framework 7 (FP7) for the virtual physiological human (VPH) project has been in place now for 5 years. The VPH Network of Excellence (NoE) has been set up to help develop common standards, open source software, freely accessible data and model repositories, and various training and dissemination activities for the project. It is also working to coordinate the many clinically targeted projects that have been funded under the FP7 calls. An initial vision for the VPH was defined by the FP6 STEP project in 2006. In 2010, we wrote an assessment of the accomplishments of the first two years of the VPH in which we considered the biomedical science, healthcare and information and communications technology challenges facing the project (Hunter *et al*. 2010 *Phil. Trans. R. Soc. A* **368**, 2595–2614 (doi:10.1098/rsta.2010.0048)). We proposed that a not-for-profit professional umbrella organization, the VPH Institute, should be established as a means of sustaining the VPH vision beyond the time-frame of the NoE. Here, we update and extend this assessment and in particular address the following

issues raised in response to Hunter *et al.*: (i) a vision for the VPH updated in the light of progress made so far, (ii) biomedical science and healthcare challenges that the VPH initiative can address while also providing innovation opportunities for the European industry, and (iii) external changes needed in regulatory policy and business models to realize the full potential that the VPH has to offer to industry, clinics and society generally.

1. The virtual physiological human vision

Specialization, in both clinical and scientific practice, has supported the most rapid growth in medical knowledge ever known. Yet drug discoveries are faltering, healthcare budgets are unsustainable and patients are sometimes falling between the cracks of medical specialists who cannot treat the patient holistically. Meanwhile, biophysically based computational modelling of the human body and physiology is poised to revolutionize twenty-first century bioscience by fundamentally shifting the basis for the diagnosis and treatment of disease. Medical innovation should therefore now be directed towards optimizing treatments using integrated functional simulation *in silico*, assembling a customized computer model of the patient's condition across multiple organ systems and length scales, and across time and environment. This is the vision for future patient care that drives the personalized virtual physiological human (VPH) project.

The physiome, systems biology, the virtual physiological human, personal health systems, biomedical informatics, life science e-Infrastructures, systems pharmacology— these domains share one issue: the need for integration. To implement the outputs of biomedical research in clinical practice and within the healthcare industry, we need to integrate data, information, knowledge and wisdom. As in [1], we need to integrate

— data for the same patient stored across different systems, across different hospitals, across different member states and in clinical research databases [2];
— patient-specific knowledge with domain-specific knowledge;
— information related to various parts and processes of the human body into a systemic understanding of pathophysiology;
— knowledge digitally captured via metadata, ontologies and models in order to respond to the combinatorial explosion of complexity that integrative research is producing; and
— wisdom produced in the research laboratories and in clinical practice, which will be formalized in guidelines, standards and protocols and used to promote translation of basic science and integrative models into healthcare benefits.

Our vision for the VPH-Physiome initiative is therefore:

— To establish an ICT (information and communications technology) and computational science framework for digital, personalized and predictive medicine.
— To link discoveries in molecular biology with clinical imaging and other technologies using computational physiology, based on the mathematical and engineering sciences.
— To link genotype to phenotype for humans and other animals through anatomical and biophysical multiscale models of physiological structure and function, at the levels of proteins, cells, tissues, organs and systems.

The concept of a fully informed 'Digital Patient', maintained with each person's current healthcare data, is powerful and compelling, and in meeting the challenge of its design we will make a significant impact on the lives of our citizens and on the economy. Yet the range of application means the complexities are significant, not least in areas of privacy and security; a few examples of the consequences of building the Digital Patient expose the complexities:

— biomedical professionals require approved secure access to my personal data, routinely and in emergencies;
— my wearable and implanted technology must update my Digital Patient routinely with status data;
— an alarming event, detected by device or Digital Patient computation, must inform me, my family and friends, and my trusted healthcare providers of the need for an intervention;
— the infrastructure must support the collaboration of trusted specialists around my complex systemic diseases;
— models must be able to employ the totality of my data to predict the future development of my health;
— models must be able to access a wealth of anonymized reference data, routinely amassed from patients; and
— my goals are fully self-aware lifestyle and health management, disease prevention, and optimized intervention at any time.

The Framework 7 (FP7) VPH Network of Excellence (NoE) is addressing these challenges by promoting and facilitating the use of computational models, software tools and Web services [3–5], and this work is being extended and exemplified by the FP7 call 6 infrastructure projects P-MEDICINE (http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/502-p-medicine) and VPH-Share (http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/506-vph-share), which are developing frameworks under which the VPH community can streamline developments. Stability and overarching authority have been added to the initiative with the establishment of the VPH Institute, an international non-profit body whose mission is to ensure that the VPH is fully realized, universally adopted and effectively used both in research and in clinical practice. In another significant move, the biomedical community has now adopted a new model for data standards and a common set of reference ontologies with which to understand genotype–phenotype relationships by linking databases of genetic and proteomic data to anatomy and function at the cell, tissue and organ levels.

The success of this opportunity is highly dependent on the development, adoption and integration of ICT and e-Health infrastructures throughout Europe [1], and on the coordination of this effort with other related international initiatives such as the IUPS (International Union of Physiological Sciences) Physiome Project. A Roadmap (http://www.europhysiome.org/roadmap) for the VPH project was laid out in 2006 by the STEP coordinated action [6]. The outcome of the first FP7 VPH funding round in 2007 (call 2) was the VPH NoE, three Integrated Projects (IPs), nine Specific Targeted Research Projects (STREPs) and two Cooperative Actions (CAs), all of

which formed the initial core of the European VPH Initiative (VPH-I). The second and third funding rounds (calls 4 and 6) added four more IPs and six more STREPs, and call 9 is about to introduce a further series of projects. The NoE is concerned primarily with ICT infrastructure, coordination and training, and the VPH-I projects themselves are primarily focused on developing and implementing biophysically based computational models into clinical environments via industrial partners. The success of these endeavours is significantly dependent on the continued progress of biomedical science in revealing the biophysical mechanisms underlying structure and function at all spatial scales, and the continued development of the integrated structures established by the VPH/Physiome initiative.

With nearly six years of experience behind us, and with Horizon 2020 taking shape, it is time to assess our achievements and plan for the short-, medium- and long-term future of the VPH. A more extensive version of this paper is available in [7].

2. What have we achieved so far?

The importance of establishing a solid foundation for the VPH by creating model and data standards [4,5], together with mechanisms for achieving model reproducibility and reuse, was recognized in the STEP Roadmap. This, together with the development of plans for dissemination, training and outreach to the communities of researchers, physicians, patients, students, industry and the public in general, was the primary focus for the first year of the NoE. Direct engagement with the other VPH projects and clear examples of how standard-based models, software tools and Web-based services can be used to facilitate clinical outcomes have now become the top priority targets [3]. These goals are discussed below, along with proposals for the identification and use of additional resources and engagement needed to establish digital, personalized, and predictive medicine in Europe.

2.1. Standards, tools and services

The first stage of the NoE project was largely concerned with recognizing the need and establishing standards for models and data, as well as building model and data repositories for published models, and assembling a toolbox of existing software programs that are relevant to the VPH (known as the VPH-NoE ToolKit [8,9]). Most content of the NoE ToolKit is open source. More recently, the NoE's preoccupation with standards has precipitated support for high quality ToolKit submissions. This has involved the development of formalized, 'best practice' guidelines. These outline the nature of 'desirable' ToolKit content, encouraging submissions that offer maximum utility to the end user. Currently, eight guidelines have been released, covering tool, model and data characterization, ontological annotation, interoperability, ethico-legal and provenance issues, licensing, and usability and training.

A high priority for the NoE is that all efforts must be considered in the light of sustainability. The latter refers to mechanisms and strategies that enable the VPH to continue to profit from the legacy of the NoE, even beyond the official lifetime of the project. This influences every corner of its activities. The production of the guideline documents is one example and the sustainability of the NoE model/data repositories is another. This denotes transitional mechanisms that have been negotiated and are currently being put in place, to secure the longevity of the model/data repositories that have been nurtured within the NoE. Links with FP7 call 6 infrastructure projects have proved particularly productive in this regard. Population of these repositories continues to be an explicit outreach function of the NoE, overseen by working groups from partners responsible for the ToolKit. This is an inclusive exercise that forages beyond the badged VPH projects to include globally sourced biomedical tools and data (e.g. BIRN, JSim etc.). This expands the ToolKit, and also helps one to forge wider VPH-Physiome collaborations. Complementary to this effort is development and support for workflows. Links between the NoE and the FP7 call 6 infrastructure projects are key to the success of these activities.

Finally, a specific strand of effort addresses training and dissemination, which is particularly important if the reach of the ToolKit and its contents is to be maximized. Here, a fresh cooperation with the education community is proving valuable, and details of this area are presented more fully in the VPH NoE September 2012 newsletter [7].

2.2. International connections

Internationally, the WIRI agreement (http://www.biomedtown.org/biomed_town/LHDL/Reception/lhpnews/wiri) and the Osaka Accord (http://www.biomedtown.org/biomed_town/VPH/wiri/OsakaAccord) have established a worldwide agenda for physiome research under the patronage of the European VPH initiative and the IUPS Physiome Project [10–13]. Other important recent events have been the participation of a European delegation at the IMAG[1] symposium in Washington in 2010; the annual CellML meetings (http://www.cellml.org/community/events/workshop) (2007–2012), and the Virtual Tissue conference organized by the US Environmental Protection Agency and the European Commission in Spring 2009. These and similar earlier events have been of considerable political relevance, and have strengthened the role of the European VPH community in the international research scene. Note that many of the VPH-I projects have international partners and the NoE itself has 'International General Members'. This formal recognition of international membership is also important for VPH-linked co-funding arrangements in countries outside Europe. The five 'International Cooperation projects' funded under VPH are RICORDO, TUMOR, NMS, Sim-e-Child and MSV. The ARGOS project, to promote common methods for responding to global e-Health challenges in the EU and the USA (http://argos.eurorec.org/), is another opportunity to encourage US input to the VPH as well as VPH input to IMAG [14].

2.3. VPH-I projects

The goals of the current 30 VPH projects (not including the VPH NoE) are summarized in [7]. There are major technological achievements in various areas, including: data collection, management and integration; processing and curation of data; reductionist and integrative modelling of pathophysiological processes; presentation, deployment, usability and end-user applications. It is also notable that there is already an active involvement of companies participating in VPH consortia, both at the level of small and medium-sized enterprises and large corporations, and that the involvement is moving from their R&D departments to their strategic management as the

first business scenarios emerge. Clinical partners are providing a vital contribution to many of the VPH projects, participating enthusiastically and with considerable commitment. Note that the NoE advisory board is now playing a more active role and provides a mechanism for generalizing and disseminating the lessons learned from clinical partners of the individual VPH-I projects.

Nearly all of the VPH-I projects deal with challenges relating to patient-specific, multiscale modelling and the implementation of models and software in clinical environments. A broader analysis of the VPH-I indicates that strengths include simulation, data handling, scientific visualization (although not yet sufficiently user-friendly in general) and an appreciation of community. Previously identified limitations in ontology annotation and inadequate infrastructure for the secure and wider sharing of models and data (authentication, authorization, etc.) are being addressed, for example through the RICORDO project. Similarly, the new VPH-Share project has particular relevance to the commercial, health and societal sectors of the VPH, all of which are vulnerable to legal uncertainty (e.g. lack of harmonization of EU law across member states), evolving quality standards and inadequate provenance.

3. What are the biomedical science challenges?

The VPH project is achieving important outcomes within the lifetime of the current NoE by introducing computational modelling into the diagnosis and treatment of some diseases (with an initial emphasis on cardiovascular, orthopaedic and respiratory diseases), but the real impact in the long term will be to transform healthcare into a more personalized, predictive and preventative process (see §4). The resources needed to achieve this long term goal must be realistically assessed and, in particular, we must now instigate projects to fill identified gaps in the necessary know-how and infrastructure.

Many challenges in personalized medicine reflect a lack of understanding of what is called the genotype–phenotype map (GP map), i.e. the aggregated phenotypic effects across different length and time scales of different constellations of genetic networks, related epigenetic information on the DNA, RNA and protein level, and the environment. The challenge of relating genomic networks with multiscale physiological models, such that one can address and understand the genomic networks of complex diseases in a population context, defines a large and ambitious research topic that needs to be given specific attention in the coming years if personalized clinical treatments based on simulation studies that take into account the genetic profile of the individual patient are to become a reality [15]. The biomedical genetics community is now facing serious challenges concerning the overall applicability of the genome wide association study (GWAS) approach when it comes to drug development and personalized medicine. The VPH initiative may be of substantial help by providing mechanistic model descriptions of the phenotypic effects originating from genomic network variation [3]. Such causally cohesive genotype–phenotype models are very advanced multiscale physiological models with an explicit link to molecular information and with the capacity to describe, for example, how genetic variation manifests in phenotypic variation at various systemic levels up to the tissue, organ and whole-organism level.

To facilitate the construction of such models an important task is to identify and connect with other communities who are already working on standards and data repositories within their fields. This is most pressing for molecular data such as protein–protein interactions, protein structure databases, gene expression and metabolic databases. New technologies based on second and third generation sequencing instruments (DNAseq, RNAseq, CHiPseq, etc.) are now producing terabytes of data. VPH models increasingly incorporate the signalling, metabolic and gene regulatory networks that underpin a mechanistic explanation of physiological function at the molecular level. Given the large role of signalling, metabolism and gene regulation in human disease processes such as cancer, diabetes, neurodegeneration, heart failure, etc., a description of these networks within multiscale VPH models is vital. To this end, there are a number of active communities outside the VPH community that possess experimental and theoretical competences of vital importance, and it is important for scientific advancement of the VPH vision to facilitate better communication with communities dealing with different types of data, from the molecular level and up to the clinical level [10].

It should be acknowledged that gaining a quantitative understanding of the phenotypic variation in humans as a function of genes and environment in a mechanistic sense, i.e. understanding the GP map, in both the explanatory and predictive sense, is a tremendous challenge that awaits technological, conceptual and methodological breakthroughs [16]. Only large-scale systematic and concerted efforts by a wide range of scientific communities are capable of realizing this vision.

One major challenge is to account for the fact that age is the dominant risk factor for most complex diseases. The making of multiscale physiological models capturing the ageing process defines a very ambitious long-term theoretical–experimental research programme of vital importance to the VPH vision.

Further development and use of multiscale and multiphysics modelling as envisioned above will be very much dependent on the development of new high-throughput phenotyping technologies (phenomics). This provides a tremendous opportunity window for new innovations and subsequent European industrial developments with a worldwide market potential. On the other hand, without guidance from multiscale models, such technology development and subsequent large-scale phenotyping programmes will risk becoming highly unfocused and unnecessarily costly. This synergistic relation between the VPH initiative and a new innovation arena for European high-tech industry should be given attention within Horizon 2020. Below we discuss in more detail the challenges outlined above requiring specific attention in the years to come.

3.1. Further inclusion of molecular systems biology

The last 50 years have seen a revolution in our understanding of the molecular basis of life, much of it driven by the development of new imaging and measurement technologies. As molecular data were accumulated in Web-accessible databases, the new discipline of *molecular systems biology* emerged to make sense of the enormously complex interactions underpinning life [17,18]. These developments have been accompanied by an equally important revolution in our ability to image and measure physiological-scale structure and function with confocal microscopy, magnetic resonance imaging, computed tomography, positron emission tomography and other such

clinical imaging technologies, and also by the rapid improvement in computing hardware performance that has enabled the new discipline of *computational physiology* to emerge. This discipline invokes the mathematical equations representing the conservation laws of physics, themselves the great achievement of nineteenth century science and on which, along with the law of evolution, all life is based. Mathematics is the language of quantitative science and predictive models based on biophysical principles are essential for understanding complex phenomena. The equations, incorporating multiple coupled physical processes, are solved numerically on anatomically realistic geometries with models that include both tissue structure and the link to cellular function. As elsewhere, the key to progress in the biomedical field is the right combination of data-driven, physics-driven and computationally-driven science. The 'bottom up' molecular systems biology approach has been largely data-driven, while the 'top down' computational physiology has been largely physics-driven. These are complementary approaches and it is time they were more integrated.

Most of the models being developed by the VPH-I projects deal with structure–function relations at the tissue, organ or organ system level, with applications primarily to clinical diagnosis, surgical planning and the development of medical devices. Some link to proteins—for example, preDICT (http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/47-predict-strep) examines the influence of cardiac drugs on ion channel models, and euHeart (http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/44-euheart-ip) includes a number of cellular protein mechanisms in whole heart models—but there is very little linkage to molecular systems biology in many of the VPH projects. The systems biology projects in Europe, on the other hand, are providing a comprehensive data-driven framework for understanding cellular physiology in terms of signalling pathways, metabolic networks and gene regulatory networks that are linked to molecular mechanisms. They seldom, however, interpret these molecular pathways in the context of structure–function relations at the cell, tissue or organ level. The first project that is attempting to bridge this gap comprehensively is the Virtual Liver Network (http://www.virtual-liver.de), funded by the German Federal Ministry for Education and Research (BFBM), which is midway through a 5-year programme.

Integrating molecular systems biology into the higher scale modelling has always been the goal of the VPH-Physiome project, but it is an enormously challenging task and establishing the link to clinical outcomes was the higher priority. However, achieving this integration is clearly essential if we are to understand and diagnose human disease, exploit personalized pharmaceutical interventions, and improve many other aspects of twenty-first century healthcare. A white paper published in January 2012 [15] addresses the opportunities and obstacles that confront us as Europe explores the translational role of bioinformatics and systems biology in drug discovery and clinical medicine.

3.2. Genomic networks—models and databases

The term 'genomic networks' often includes three levels of data. First, at the DNA level, there is the raw DNA sequence, promoter regions, enhancer regions and genetic variants (SNPs (single nucelotide polymorphisms) and copy number variation). A major effort within the biomedical community during the last 5 years has been the use of GWAS designs to identify a select set of putative SNPs. The requirements for standards and databases are active research areas in bioinformatics that, within Europe, are exemplified by efforts such as ELIXIR (http://www.elixir-europe.org; a European effort to develop an infrastructure for the life sciences), and recommendations that make full use of the integration of genome-based data resources with resources detailing disease-based and other human phenotypes [19].

The second level of information refers to transcription or the RNA level. Here, there are large databases on gene expression based on 'classical' technologies developed during the last decade that represent only a subsampling of the annotated genome. Recent developments of second and third generation sequencing technologies are currently producing whole genome digital transcriptomic data which also include splicing variants and non-coding RNA. At this level, there is an abundance of data about how different protein products, as well as non-coding RNA, can provide feedback and affect transcription. This includes transcription factor binding sites, histone modification, methylation sites and chromosomal interactions, all relevant for epigenetic modifications. This is one of the fastest developing areas in biomedicine and raises significant challenges on standardization regarding storage, annotation and analysis.

Protein–protein interactions and protein structure provide the third level of data of relevance for genomic networks. Different proteins can interact with DNA and thereby affect the transcription as indicated above. In addition, experimental and computational analysis of protein–protein networks in different species has been a most active research field in molecular systems biology during the last decade. Interactions between DNA and proteins have been studied using hybridization methods such as Chip–Chip but are now being replaced with sequencing-based methods such as Chip-seq.

There are significant challenges in how to integrate this variety of molecular information as well with standards and storage. It is important that the VPH community establishes links to these ongoing efforts in one of the most active areas in biomedical research of clear relevance for understanding diseases and therefore important for health.

3.3. Human metabolic networks—models and databases

Metabolism provides the energy for all physiological processes, and biochemical processes are therefore closely coupled to the physiological functioning of cells and organs. Molecular networks for intracellular signalling link extracellular stimuli such as hormones to adaptive responses of the cell. Intracellular signalling networks and metabolism are not separated but interact strongly, regulating each other. Modelling human physiology requires not only consideration of the large metabolic networks inside the cell, but also the exchange of metabolites among various cell types in a tissue (for instance between astrocytes and neurons in the brain). Transport processes of metabolites between organs in the body including transport in the blood, across blood vessel walls and cell membranes must be included in physiological models.

A large body of biochemical literature on human metabolism is available, and metabolic genes in the human genome have been partially characterized. There are several sources available for reconstruction of metabolic networks including KEGG (http://www.genome.jp/kegg) and BioCyc (http://

biocyc.org). A consortium of almost 50 scientists from about 20 academic departments worldwide, including members of the VPH, has produced a reconstruction of the human metabolic system which integrates data from several prominent, already existing databases. This reconstruction is captured in a database containing 7440 biochemical reactions forming a descriptive model of metabolism in the human body.

3.4. Physiology—models and databases

A further significant gap is the lack of comprehensive Web-accessible databases of physiological data, encoded with well-established data and metadata standards [20,21]. Such data provide numerical parameters for use in computational models. This need was expressed in §3.2.3 of the VPH STEP Roadmap. One standard, DICOM, does exist for medical image data. Others such as C3D (http://www.c3d.org) are well established binary data formats for specialist communities (biomechanics, animation and gait analysis in the case of C3D). A more general purpose metadata standard (BioSignalML) is being developed for annotating physiological time-dependent signals encoded in a wide variety of existing specialist standards. But even this represents a small fraction of what is needed. A major effort is now needed by the physiology community to identify the types of physiological data that are available and to begin the development of a broad range of data standards and data repositories; as a first step, example datasets are being collected from the VPH-I and VPH NoE-Exemplar projects. The tools for interpreting these data are being developed by the VPH and Physiome projects. These data resources have to be aligned to corresponding efforts on physiological models (§5.1).

The incorporation of ageing in multiscale and multiphysics models, the use of the VPH as a potential platform for a new drug targeting paradigm, and 'phenomics technology' as a new innovation arena for European industry are all discussed further in the VPH NoE September 2012 newsletter.

4. What are the healthcare challenges?

Major diseases such as cancer, neurological and cardiovascular diseases are complex in nature involving environmental, lifestyle, ageing and genetic components. A major challenge for the future is to integrate the knowledge of all these different components into robust and reliable computer models and *in silico* environments that will help the development and testing of new therapies and better disease prediction and prevention tools in healthcare. The progressive advance in computing power and associated information technology offers the potential to deliver tailored clinical treatments based on simulation studies that take account of the genetic profile and clinical indicators (interpreted via physiological models) of the individual requiring treatment.

4.1. The needs

The European healthcare system, including its biomedical research and technological development component, is a huge, complex and highly articulated system. Owing to the peculiar political history of the EU, it is not a surprise that such a system is highly fragmented, not only between members states, but also between regions, districts and even single hospitals. However, in spite of this extreme heterogeneity, common requirements are emerging in a number of analysis documents produced by very different sources [22] (http://www.inbiomed-vision.eu/PDF/D4.1_INBIOMEDvision_First%20think-tank%20report_v5_Final.pdf [14]).[2,3,4,5] Such requirements can be summarized in three keywords: *personalized*, *predictive*, and *integrative* healthcare. A fourth keyword, *affordable*, is implicit, as the sustainability of healthcare systems is becoming the number one issue in member states dealing with a constantly ageing population.

More specific common needs are: to maximize the yield of biomedical research expenditure; to achieve personalized healthcare for individuals and groups (women, children, etc.); to improve the reliability, repeatability and timeliness of medical decisions; to integrate digital health information on a global scale; and to resolve the individual–society conflict around the privacy of health data. It should be noted that at this stage these needs are very hard to quantify because the information is fragmented over dozens of reports produced by different medical specialities, and much effort is required to elaborate into a single coherent framework a detailed and quantifiable description of needs. To address these issues it might be appropriate for the European Commission to consider funding a specific support action to collect, organize and compose all this evidence into a fully justified and quantified needs analysis.

4.2. Personalized, predictive and integrative healthcare and the 'Digital Patient'

A new generation of medical technologies is needed to integrate the data available about a patient to support a more personalized diagnosis, prognosis, treatment planning and monitoring, as well as to develop new drugs, therapies, medical devices, assistive and diagnostic technologies that are optimized for specific groups of patients (age, gender, co-morbidity, etc.). Diagnostic workflows are required, not on pre-defined general protocols, but on the prediction of risk obtained by models that combine both population and patient-specific information.

The *Digital Patient* is a vision of a coherent digital representation of each patient that is used to provide an integrative framework for personalized, predictive, and integrative medicine. This vision and the currently open call for a support action targeting the so-called 'Digital Patient' include three major challenges.

(i) To provide medical professionals and biomedical researchers with advanced user interfaces based on the digital patient metaphor, that make it easier to cope with large amounts of information related to different organ systems, different space–time scales, and different diagnostics, e.g. imaging modalities.
(ii) To provide healthcare providers with an ICT layer capable of recovering and integrating all health information available for each patient into a coherent whole.
(iii) To provide biomedical researchers and clinical research settings the technology to capture existing knowledge into digital artefacts in the form of predictive models, and to compose such digital quanta of knowledge into integrative models of complex systemic mechanisms, thus generating new insights.

In our opinion, the Digital Patient roadmap should focus on problems close to the deployment of the VPH vision, i.e.

on problems such as user interface, information systems interoperability and integrability, generalization and wide use deployment of the concept of integrative model. The issues of access to clinical data, European Commission regulatory policy and impact analysis are discussed further in [7].

5. What are the information and communications technology challenges?

The VPH-Physiome Project aims to provide a systematic framework for understanding physiological processes in the human body in terms of anatomical structure and biophysical mechanisms at multiple length and time scales. The importance of establishing a solid foundation for the VPH by creating model and data standards, together with mechanisms for achieving model reproducibility and reuse, was recognized in the STEP Roadmap. The framework includes modelling languages for encoding systems of differential-algebraic equations—CellML (http://www.cellml.org) and SBML (http://www.sbml.org)—and the spatially varying fields used with systems of partial differential equations—FieldML (http://www.fieldml.org). In both cases the parameters and variables in the mathematical models are annotated with metadata that provides the biological meaning. The languages encourage modularization and have import mechanisms for creating complex models from modular components. Model repositories have been established, together with freely available open source software tools to create, visualize and execute the models. The CellML repository (http://models.cellml.org) includes models for a wide variety of subcellular processes.

5.1. Model and data encoding standards: model reproducibility

Mathematical models for the VPH-I are developed by bioengineers, biomathematicians and experimental physiologists to quantitatively describe complex biological processes. When these models are based on biophysical mechanisms and, where appropriate, incorporate anatomical detail, their predictive capability can provide physical insights into the interpretation of experimental data and can help formulate experimental hypotheses. In fact, the most powerful application of modelling occurs when there is a close interplay between modelling and experiment. With the increasing interest in clinical application of these VPH models, a range of new challenges have arisen [1]: in order to be used in clinical decisions, models must be *verified* (e.g. Are the units consistent and are physical laws obeyed?), *reproducible* (Can someone other than the author generate the model outputs from specified inputs?), *validated* (How accurately and under what conditions does the model match reality?) and *available* (Is the model encoded in a standard form? Is it available as open source?). The functional benchmarks mentioned in the previous section are an important component of verification and validation strategies for sophisticated numerical codes developed by the VPH community. There are other less essential but highly desirable aspects such as *parameter sensitivity* (How sensitive are the model outputs to particular parameter values?), *modularity* (Can the model be incorporated as one component of a more comprehensive model?) and *usability* (Is there freely available software to run the model, display results and if necessary modify parameters? Does it have a good user interface?). The understanding of parameter sensitivities is also important in the context of the interpretation of the physiological envelope of the individual.

Biological systems are characterized by multiple space and time scales. New multiscale modelling techniques are needed to help connect the large range of spatial and temporal scales involved in the VPH. To attempt a description and planning of such complex activity, it is useful to start from a preliminary classification of problems that typically need the application of model reduction strategies and multiscale integration techniques in order to be efficiently addressed by computational methods.

Other issues discussed in [7] are: (i) the challenges of model reduction, (ii) multiscale model integration, (iii) incorporating stochastic behaviour into the multiscale VPH models, (iv) convergence of image-based integrative prototyping frameworks, (v) multiscale simulation and visualization software, (vi) supercomputing challenges for the VPH, and (vii) informatics and 'big-data' and data security.

6. A strategy for the virtual physiological human

Currently, coordination of the VPH-I projects is via the VPH NoE, which is also pursuing additional specific goals such as the VPH Toolkit. In order to transform the VPH vision into a reality for European stakeholders, a long-term coordination action is needed in order to:

— develop coherent strategies and periodically revise the concrete research and technological development goals that should make the vision come true;
— sustain the standardization and interoperability efforts;
— further the development, maintenance and provision of tools, services, databases and other infrastructure for common use;
— monitor the development, adoption and impact of VPH technologies;
— sustain the global adoption of VPH-based protocols that have proved effective; and
— provide training in the use of VPH technologies.

These activities cannot be maintained in the long term by the NoE or by any other initiative that has funding for a limited period. They require the attention of a permanent organization, capable of ensuring continuity over actions that may last for decades. We have therefore established a non-profit European 'VPH Institute' (http://www.vph-institute.org) with a mandate to support the maintenance of VPH databases and the continued development of standards and business-friendly open source software.

6.1. The next steps

The VPH is a grand challenge. Here, we identify some current and future specific actions.

6.1.1. 2009–2011: establish a collective identity

It is important that the multitude of players involved be able to speak with a single voice in a few strategic situations. This requires the creation of a collective identity around the VPH brand name. This process was completed in late 2011 with the full activation of the VPH Institute. From now on the

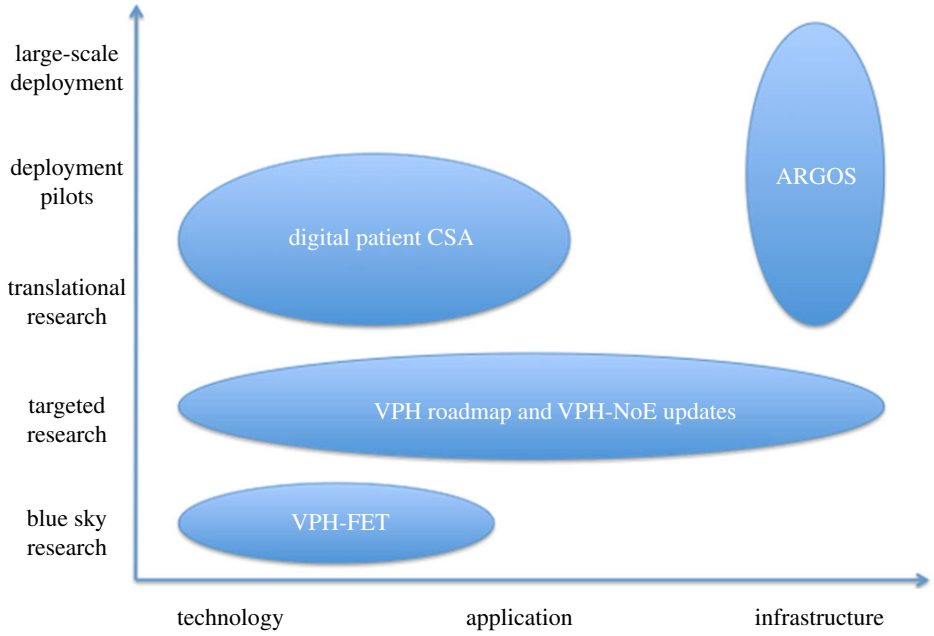

Figure 1. The VPH in relation to other related initiatives. (Online version in colour.)

VPH community will have a collective identity represented by this democratic and participative non-profit organization.

6.1.2. 2010–2012: definition and quantification of needs

The STEP experience showed that when properly managed by a motivated consortium, and when embraced by a lively and receptive community, a road-mapping exercise could be of great value to capture and quantify needs and to develop a vision around them. In the 2009 version of this document we recommended three additional road-mapping exercises.

— Road-mapping CSA (coordinated support action) on VPH FET ('Future and Emerging Technologies').
— Road-mapping CSA in integrative health research.
— Road-mapping CSA in health e-infrastructures.

We proposed that these actions should have been sustained by other units of the European Commission (namely DGINFSO FET Proactive, DGRTD Systems Biology and DGINFSO e-infrastructures as part of the Capacities programme) and should involve significant portions of the traditional constituencies of these units, as it is necessary to include in the action complementary expertise that is well represented in these constituencies. We also recommended that similar actions should have been undertaken to push the VPH agenda as high as possible in those European institutions that fund fundamental research such as the ESF or the ERC.

Figure 1 shows how the VPH initiative is positioned in this regard to date.

6.1.3. 2013–2020: the virtual physiological human in Horizon 2020

The VPH Institute recommends that priority should be given to the following three streams of research funding.

Digital Patient: the use of VPH modelling to provide personalized, predictive, and integrative technologies to the medical professionals. The Digital Patient is intended to be a framework of information technologies that enable a more integrative, predictive, personalized, and patient-centric medicine, following the indications that will emerge from the specific research roadmap the *Discipulus* support action is expected to produce. By its nature the Digital Patient programme should begin from targeted research, followed by innovation and deployment pilots as the framework develops.

In silico clinical trials: the use of VPH modelling to provide the biomedical industry with a personalized, predictive and integrative approach to the assessment of medical devices and pharmacological products. *In silico* clinical trials research targets the use of ICT to simulate how large cohorts would react to new drugs, medical devices, biotechnology and tissue engineered products. If proved effective these new technologies could be positioned before real animal and clinical trials, in order to increase the efficacy of their design, reduce the size of the cohorts, the risks for the patients (or the invasiveness for the animals), and the costs for the biomedical industry (which could turn into a reduction of costs for these products). It could also open an entirely new market, for *in silico clinical research organizations*, a new type of clinical research organization that would conduct these simulated clinical trials on the next-generation computing cloud.

Personal health forecasting: the use of VPH modelling to provide personalized, predictive and integrative services to patients/citizens. What we propose is to develop personalized VPH models (integrative predictive models) that constantly elaborate all the data transmitted by personal health systems, wearable sensors/body sensor networks, ambient assisted living technologies, mobility monitors, etc., and predict how specific aspects of our health will evolve in a near or not-so-near future. Such models should account for chronic diseases, recurrent prescriptions, or specific disabilities and could be further personalized with clinical data such as medical imaging, biomedical instrumentation, biomarkers, etc.

6.2. Towards a European virtual physiological human meta-infrastructure

We conclude this review with a brief list of other European research infrastructures (or e-infrastructures) that are currently being established or considered.

— Biobanking and Biomolecular Resources Research Infrastructure (BBMRI).
— European Life Sciences Infrastructure for Biological Information (ELIXIR).
— European Clinical Research Infrastructures Network (ECRIN).
— European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences (Euro-BioImaging).
— European Advanced Translational Research InfraStructure in Medicine (EATRIS).
— Biological NMR infrastructure (Bio-NMR).
— European Mouse Mutant Archive (EMMA).
— European Infrastructure for phenotyping and archiving of model mammalian genomes (INFRAFRONTIER).
— Integrated Structural Biology Infrastructure (INSTRUCT).

There are also complementary e-infrastructures that are aimed at managing very large databases, networking services and high-performance computing systems. In all recent roadmaps for European biomedical infrastructures computer modelling, multiscale models and simulation are repeatedly cited, but it is not clear by whom or where these activities are going to happen.

We are in the midst of an explosion of online biological and medical data. Moreover, the *European Strategy Forum on Research Infrastructure* (http://www.ugent.be/nl/onderzoek/financiering/int/ESFRI.htm#biological-and-medical-sciences) (ESFRI) will be providing new data production services (sequencing, imaging, etc.) across many fields of biological science. The rationale for many of these initiatives is to understand high-level phenotypes from genomic, metabolomic, proteomic, imaging and other types of data. But establishing high-level phenotypes from lower level data requires multiscale models. The multiscale modelling framework being developed by the VPH project is an ideal environment for guiding this endeavour because, as in all other fields of science, mathematical models based on physical principles provide the only method for guiding experimental measurement and integrating and interpreting large amounts of heterogeneous data.

Many people have contributed to this document and the more extensive Roadmap [7] that formed the core of a report to the European Commission in 2009 that was updated in 2010 and again in 2011. The main task of drafting the document and seeking feedback for the 2009 and 2010 versions was undertaken by Peter Hunter and Marco Viceconti, and for the 2011 version by Peter Hunter, Peter Kohl, Pat Lawford and Stig Omholt. All the other authors have made substantive contributions in the form of corrections, suggested improvements or additional text. We are also grateful to members of the NoE Steering Committee and Scientific Advisory Board for their suggestions. We sought feedback on earlier drafts of both this document and its predecessor from the VPH-I community generally, including the project leaders for all the currently funded VPH projects.

Endnotes

[1]The Interagency Modelling and Analysis Group (IMAG) coordinates multiscale modelling initiatives from various United States agencies including the National Institutes of Health, National Science Foundation, National Aeronautics and Space Administration, Department of Energy, Department of Defense, United States Department of Agriculture, and United States Department of Veteran Affairs.
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[3]'The benefits from translating biomedical research into the health care system'. Report to Bio21 Australia, 2007.
[4]'Personalized health care: opportunities, pathways, resources'. US DHHS, 2007.
[5]'Pharma 2020: Virtual R&D', PWC, 2008.

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