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The EuroPhysiome, STEP and a roadmap for the virtual physiological human

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Q1 Biomedical science and its allied disciplines are entering a new era in which computational methods and technologies are poised to play a prevalent role in supporting collaborative investigation of the human body. Within Europe, this has its focus in the virtual physiological human (VPH), which is an evolving entity that has emerged from the EuroPhysiome initiative and the strategy for the EuroPhysiome (STEP) consortium. The VPH is intended to be a solution to common infrastructure needs for physiome projects across the globe, providing a unifying architecture that facilitates integration and prediction, ultimately creating a framework capable of describing *Homo sapiens in silico*. The routine reliance of the biomedical industry, biomedical research and clinical practice on information technology (IT) highlights the

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importance of a tailor-made and robust IT infrastructure, but numerous challenges need to be addressed if the VPH is to become a mature technological reality. Appropriate investment will reap considerable rewards, since it is anticipated that the VPH will influence all sectors of society, with implications predominantly for improved healthcare, improved competitiveness in industry and greater understanding of (patho)physiological processes. This paper considers issues pertinent to the development of the VPH, highlighted by the work of the STEP consortium.

Keywords: physiome; EuroPhysiome; integrative biology; virtual physiological human; strategy for the EuroPhysiome

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1. Introduction

Physiome:

> … a comprehensive framework for modelling the human body using computational methods which can incorporate the biochemistry, biophysics and anatomy of cells, tissues and organs.
> (Hunter *et al.* 2002)

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Q3 The physiome concept (Hunter & Borg 2003; Hunter, P. J. 2006) has been fervently embraced by the European scientific community, which recognizes that the current partitioning of health science endeavour along traditional lines (i.e. scientific discipline, anatomy, physiology, etc.) is artificial and inefficient with respect to such an all-embracing description of human biology. It is argued that a more effective approach must be sought, encompassing cross-boundary disciplines and integrating them according to the focus of the problem in hand, unconstrained by scientific discipline, anatomical subsystem and temporal or
Q4 dimensional scale (Boyd & Noble 1993; Welsh *et al.* 2006).

This is a radical approach that deserves to be complemented by a radical framework in which observations in laboratories and hospitals across nations can be collected, catalogued, organized and shared in an accessible way so that clinical and non-clinical experts can collaboratively interpret, model, validate and understand the data. It is a framework of technology and methods, and together they form the virtual physiological human (VPH). This vision is complemented by a community of active protagonists, collectively pursuing
Q5 physiome projects across the world (Plasier *et al.* 1998; Bassingthwaighte *et al.*
Q6 1999; Kohl *et al.* 2000; Schafer 2000; Hunter *et al.* 2002, 2005; Bro & Nielsen 2004; Crampin *et al.* 2004, http://www.physiome.org.nz), and through harmonized action, it may be possible to create a coherent and credible VPH infrastructure in Europe within a decade.

2. Role of strategy for the EuroPhysiome and the VPH roadmap

Strategy for the EuroPhysiome (STEP)[1] refers to a project that is characterized as a European Coordination Action, and was funded to consider and recommend effective strategies that promote the development of the VPH. Its deliberations have recently been published (Spring 2007) in an advisory document entitled

[1] STEP—Strategy for The EuroPhysiome FP6-2004-IST-4-027642.

'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' Q7 (http://www.europhysiome.org). This is a policy document that is designed to advise the EU in respect of VPH funding, emphasizing that the VPH is a technological framework that aims to be descriptive, integrative and predictive.

— *Descriptive.*[2] The framework should allow observations made in laboratories, in hospitals and in the field, at a variety of locations situated anywhere in the world, to be collected, catalogued, organized, shared and combined in any possible way.
— *Integrative.*[2] The framework should enable experts to analyse these observations collaboratively, and develop systemic hypotheses that incorporate the knowledge of multiple scientific disciplines.
— *Predictive.*[2] The framework should facilitate the interconnection of predictive models defined at different scales, with different methods and with different levels of detail, producing systemic networks that breathe life into systemic hypotheses; simultaneously, the framework should enable their validity to be verified by comparison with other clinical or laboratory observations.

These themes (among others) are part of a consultative process within STEP that involved the discussion of a broad range of groups and lively debate at conferences, all supported by an advisory board of global physiome experts. Contributions have come from the academic community, industrial and clinical users, professional associations, etc.

The VPH roadmap begins by defining the scope of the VPH, offering justification (motivation) for its existence, based on foreseen needs (research, clinical and industrial). An international perspective is used to give this context, supported by a series of case studies. The importance of a suitable structure for the proposed VPH highlights challenges for its implementation, which are broadly categorized as scientific challenges, challenges in description, challenges of integration, challenges in IT and their solution. The magnitude of the IT challenge is considerable in the light of the data flows involved (petabytes), but carefully evaluated case studies focusing on research, clinical, industrial and societal impact indicate the value of providing infrastructure support for EuroPhysiome activity. Other analyses consider matters of exploitation, dissemination and sustainability, not forgetting political aspects associated with ethical, legal and gender issues. The final chapter recommends actions necessary to secure the future of the VPH. This paper presents a brief summary of the advisory document and allied content.

3. The VPH roadmap: motivation

Justification for the existence of the VPH has its roots in anticipated clinical, industrial and academic needs, underpinned by the conviction that a cross-discipline approach to medical endeavours is the only credible way forward in the twenty-first century (Haygarth *et al.* 2005; Hwa *et al.* 2005; McCallin 2006; Zaenker 2006). Four categories of justification are apparent,

[2] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 7.

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(i) *Clinical*. The clinical justification recognizes the way in which clinical specialization fragments patient management. There are few bridges between clinical specialties (cardiologist, audiologist, neurologist, etc.) and patients of an aetiology requiring a multidisciplinary approach are typically dispatched to various clinical experts for analysis of the numerous aspects of their disease. A more integrated approach could yield many benefits, and the VPH is poised to assist the clinician with the collection, organization, visualization and interpretation of the potentially vast and rich array of data available.

(ii) *Academia*. Justification within the realm of biomedical research comes from the recognition that the expertise of many investigators is quite narrow. For instance, modellers/engineers do not necessarily understand the needs of experimentalists, and neither may be aware of the clinical implications of their work. This is inefficient and impotent in respect of solving clinical problems that could benefit from state-of-the-art knowledge (perhaps most efficiently addressed in a multidisciplinary manner). The solution provided by the VPH is an infrastructure that helps to break down these barriers.

(iii) *Industry*. Within industry, justification arises from anticipation of industrial benefit, because the VPH clearly provides a resource for product design and development. Innovations can be developed more quickly with reduced risk and cost, and recognition of the VPH by regulatory authorities may ease product development and decrease time to market while integrating benefits such as the reduced need for clinical trials or animal testing. At the point of product delivery, there is the promise of relevant, easy-to-create simulation-based training and support. Ultimately, the reward for efforts invested in the VPH is a competitive edge in a global market.[3]

(iv) *Society*. Society plays a vital role in the justification of the VPH, since it is society that will fuel its development and society that it will serve. Benefits accrue from industry (*innovation*, *improved standards*, *low cost production methods*, *etc.*), the clinic (*basic science translated to clinical practice*, *the systemic effects of interventions and side effects, improved decision making*) and cross-disciplinary research. The promise of improved global competitiveness may have far reaching implications for quality of life (*unemployment*, *education*, *social welfare*, etc.).

Motivation summary. Cross-disciplinary clinical, industrial and academic pursuit will benefit society.

4. The VPH roadmap: international context and common objectives

The advocates of the VPH point to the value of such an infrastructure by noting the benefits of their own cross-disciplinary, multi-scale activities. Furthermore, they are plaintiffs for further benefits that could result from harnessing synergies

[3] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 17.

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between projects. Such promotion naturally highlights the objectives common to these apparently disparate activities, which become readily apparent when viewed as a collection of case studies (Bassingthwaighte 2000; Hunter *et al.* 2005).

VPH objectives that would benefit all physiome activities include the following:

- Design of a flexible and logical infrastructure for physiome activities and their implementation.
- Data processing and modelling toolkits.
- Effective access to resources for ontologies and visualization, etc.
- Computing infrastructures (grid, HPC), knowledge management, back-end services, etc.

Objectives summary. The VPH infrastructure must support underlying physiome infrastructure needs.

5. The VPH roadmap: observations on research challenges

Objectives influence architectural design, and the challenges are brought into sharp focus when the specific needs of participating communities are considered. The cross-discipline collaborative nature of the VPH is most evident in this section of the roadmap, since it reflects the diverse opinions of the consultative process. Clinical, industrial and academic experts were engaged, both through e-mail and discussion at conferences. A twofold categorization of the research challenges emerged, identifying broad themes that need to be addressed if the VPH is to become a reality.

(a) It is important to clarify the brief of the VPH (i.e. the nature of the scientific problems and principles to which it relates) and how such issues might be addressed.
Q8 (b) It is necessary to identify the information technologies (ITs) that must be developed to address the challenges raised by the above issues.

In respect of item (a) (and in spite of the apparent variety of challenges that present themselves), it is widely accepted that the true grand challenge lies in understanding biological function. This requires a wealth of data interpreted by models that describe and are informed by the underlying biology. In respect of item (b) it is informative to determine the extent to which (physiome) activities can be truly integrated. This refers to

(i) integration of physiological processes across different length and time scales (multi-scale modelling);
(ii) integration of descriptive data with predictive models; and
(iii) integration across disciplines.[4]

Complementary and concerted effort is needed (Kohl *et al.* 2000; Gavaghan *et al.* 2006) to develop the appropriate infrastructure, frameworks and technologies (computational, organizational and imaging) that can support

[4] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 39.

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these requirements. Databases of models and data at many spatial and temporal levels are required if 'multi-scale' is to fully embrace everything from molecules to organ systems. Software tools are needed for authoring, visualizing and operating models based on widely adopted modelling standards (Hunter, P. J. 2006). There is also a need for the development of ontologies dealing with anatomy, physiology and molecular/cellular biology to uniquely identify and link model components. Finally, data from advances in modelling and imaging should be available to all interested parties through the development of networking databases that keep researchers abreast of relevant progress.[4]

Challenges summary. Construction of a robust and relevant IT foundation for the VPH.

6. The VPH roadmap: scientific challenges

The research challenges above form a backdrop against which specific scientific challenges can be identified. These are categorized as follows: (i) challenges in prediction, (ii) challenges in description, (iii) challenges in integration, and (iv) ICT challenges and their solution.

(i) *Challenges in prediction*. This includes aspects of problem identification, model complexity, understanding interactions (Judex *et al.* 2006), multi-scale modelling, issues of inhomogeneity and intersubject variation, aspects of validation and identification of gaps in modelling or knowledge, human biology and pathology. There are challenges arising from the coupling of models working at difference scales or in different disciplines (e.g. biology/chemistry to mathematics/physics). Fundamental physiological knowledge is also lacking on the effect of genomic information on higher level physiological function.

(ii) *Challenges in description*. It is self-evident that the existence of data is necessary for the development of understanding and the validation of models, but the mere presence of data does not mean that it is complete or accurate. The latter is particularly relevant to model validation and data should be interpreted with care. In fact, it is arguable that all data should be accompanied by a classifier that clarifies the confidence of each measurement. Many sources of data exist (obtained from physical measurement or simulation), but much of it has its origins in instruments/models that introduce their own assumptions and artefacts into the data. Ideally, data collection protocols would accommodate this, ultimately leading to the creation of generic *in vitro* models (appropriately accounting for data quality) or refined customization of *in vitro* models using patient-specific data (characterizing both normal and pathological behaviours). Automated (or semi-) statistical analysis of the final model may be possible using decision algorithms.[5] Models that are developed to answer clinical or industrial questions require accurate anatomical and physiological information (imaging, experimental data, etc), and therefore it is important

[5] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 45.

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to ensure that imaging technology or experimental technique is quality assured to ensure provision of consistent high-quality data.

(iii) *Challenges in integration.* Integration refers to the seamless interfacing of diverse specialties, measurements or models, an obvious example being integration across multiple scales. Integration between disciplines is also important. There is merit in explicitly identifying the need for integration between data that describe biology, and models that can predict and help with the understanding of function. Often simulations are married to particular solvers and too easily, these results in the 'parochialization' of models. There is benefit in describing models independently of the numerical solver, separating them from the numerical methods used to solve them. A flexible arrangement to model implementation or coupling is required and innovative solutions could include the promotion of mark-up language development (in the spirit of CellML, FieldML, etc.; Hedley *et al.* 2001; Cuellar *et al.* 2003; Hucka *et al.* 2003; Lloyd *et al.* 2004) and the encapsulation of models as web services.

(iv) *ICT challenges and their solution.* This concerns the tools needed to address Q9 the scientific challenges discussed above (Hey & Trefethen 2003). A database that collates and classifies models is a core requirement and should include pointers to other modelling efforts around Europe and beyond, thus reducing duplication of effort and facilitating collaboration between researchers (Dao *et al.* 2000; Coyle *et al.* 2003). This could provide a framework for model communication, and would necessitate the development of software tools and standards to facilitate model coupling. Models with greater detail could be combined with low-resolution models, with a consequent reduction in the need to set artificial boundary conditions. The availability of a knowledge management software database could manage such information and integrate it with data from the literature.

The coupling of models is a major challenge in itself and would benefit from a coherent architecture, relying perhaps on a macroscopically functional scaffold within which models of greater or lesser detail can operate and communicate. A federation of predictive services could be used to expose I/O interfaces in a standardized way. Semantic mediation is needed to support interconnection and interpret data spaces. The presence of a standardized data format can ease problems of this kind (e.g. http://medical.nema.org, http://www.hl7.org, http://www.ihe.net), but a robust solution requires both format translation and semantic mediation. Data size (typically gigabytes, but ranging from megabytes to petabytes) needs intelligent strategies for data storage and sharing, recognizing issues associated with bandwidth, latency, caching, etc. (Rio *et al.* 2003). History indicates that we are unlikely to satiate our appetite for data and therefore storage/bandwidth issues require a long-term strategy, recognizing that they are likely to remain perennial problems.

Structural functional data used to build and validate models typically come from the literature or experimental effort. However, data are also generated by simulation and the infrastructure must support the communication, storage and processing of vast quantities of such data. Effective curation (Beagrie 2006) is a core requirement of the VPH. The possibility of distributed computing to solve

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some of these problems is attractive (Woods *et al.* 2005), and a comprehensive VPH resource would facilitate the following:

— Integration of grid computing technologies and middleware into biomedical research demonstrators and applications.
— New architectures and demonstrators for heterogeneous data integration, leveraging current efforts and domain standards.[6]

Unfortunately, IT solutions to many of these problems are not immediately available, but the ongoing development of grid computing projects over recent years (Coveney 2005) has produced many prototype solutions that are Q10 potentially invaluable (Clery 2006). For instance, the Application Hosting Environment (RealityGrid; Cohen *et al.* 2005) is already available in a first release and provides a painless means of interacting with federated Grids. BioSimGrid (Tai *et al.* 2004) offers a template for a suitable VPH architecture since it has developed a prototype, which is designed to act as a repository of simulation data. BioSpice (Garvey *et al.* 2003) is another example and provides a complete molecular infrastructure for life sciences. Through such projects, a wealth of open source biomedical computing software is available and includes the following:

— Middleware/infrastructure resources (http://www.globus.org, http://www.omii.ac.uk).
— The National Library of Medicine Insight Segmentation and Registration Toolkit (http://www.itk.org).
— The visualization toolkit (http://www.vtk.org).
— The National Biomedical Computation Resource (http://nbcr.sdsc.edu/).
— The Multimodal Application Framework (http://openmaf.cineca.it/maf/).

Scientific challenges summary. Pursuit of integration, description and prediction through IT solutions that are native to the VPH.

7. The VPH roadmap: problem sizing and required resources

This section of the roadmap considers the quantity of data associated with multi-participant dialogue, noting that it will be considerable and will require exceptional management. Of course the value of the VPH will be measured by the availability and quality of data that flow to the end-user, but it will also depend upon a steady influx of predictive concepts and robust data if it is to continue to meet the needs of the society it serves. Viability is dependent upon an adaptive infrastructure that can overcome numerous challenges such as the organization and storage of petabytes of data, sustained communication bandwidths exceeding terabytes per day, extensive support for data indexing and data format translation, and all of these embedded within an infrastructure that guarantees secure and transparent access (Seitz *et al.* 2005). Finally, this has to be integrated with quality assurance mechanisms that safeguard the quality of

[6] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 48.

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data accessed by the end-user (Montagnat *et al.* 2004; Middleton *et al.* 2005).[7] Overall, the technology must be immune to obsolescence, with sufficient adaptability to match continuing data growth.

Sizing and resources summary. The VPH requires technology solutions for data storage, data flow and security.

8. The VPH roadmap: impact analysis

The roadmap postulates that the VPH will have significant influence on biomedical research, clinical practice, sectors of industry and society at large. It is presupposed that the VPH will have profound implications for biomedical research by providing an infrastructure that will enable unprecedented collaboration on an international scale. This will extend classic channels of common participation to include contributions from disparate and distant laboratories and accommodate common resources developed by consortia of international teams. Ideally, this will be accompanied by a new era of defined standards and open-source web tools. Such an infrastructure will ensure practical access to the great body of already published experimental data in ways not possible today.

The VPH will impact on clinical practice by facilitating patient-specific tailoring of treatment, better cooperation among the various medical specializations (e.g. it can benefit patient management through improved clinical decision support) and introducing many other benefits not yet envisaged. For instance, anonymized clinical data and published outcomes of clinical trials are critical components of medical endeavour, and together they can significantly contribute to the cataloguing of the human condition. Follow-up data form an invaluable tool for quantifying the efficacy of treatment strategies, clarifying insights and validating predictions. A requirement to return follow-up data to the VPH will encourage a climate of evidence-based medicine and influence future strategies for patient management.[8] Eventually, a successful framework might encourage all activities to be VPH compliant.

With respect to industry, the impact will be measurable as improved technical excellence, reduced development time or streamlined staff numbers. However, ultimately the yardstick used by industry will be financial, and the financial savings that a European-wide scientific initiative might invoke are reliably calculated to be huge, using, where possible, data supplied by industry itself (PriceWaterhouseCoopers 2005). The impact of the VPH on industry will first be felt in the medical device and pharmaceutical industries, but in time will inevitably spread beyond these key areas.

The expected impacts of the VPH on society will be manifold and in general related to interdependent influences. Society will benefit from an improved economy (more turnover and reduced public expenses) and healthier citizens, although societal economic effects due to specific initiatives may be intangible. However, with a large-scaled initiative such as this, several immediate and long-term areas of impact are apparent. At the very least, the VPH will improve

[7] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 51.

[8] Cited from the VPH roadmap, p. 32.

relationships and communication between the industrial, clinical and research communities. This will impact in a number of areas, such as healthcare, industry, research, education and exchange.

Impact analysis summary. A successful VPH will have impact on healthcare, industry and society in general.

9. The VPH roadmap: success stories

Physiome-related activities have contributed significantly to understanding in many areas of the health care sector and there is every expectation that future contributions will be even more significant. A selection of successful physiome projects is listed and potent examples are as follows.

(a) Europe

— LYMFASIM—simulation for modelling lymphatic filariasis and its control (Plaisier *et al.* 1998).
— GEMSS—grid-enabled medical simulation services (http://www.gemss.de, Benkner *et al.* 2005).
— SimBio—a generic environment for bio-numerical simulation (http://www.simbio.de).
Q11 — CHARM—comprehensive human animation resource model (http://ligwww.epfl.ch/~maurel/CHARM/).
— COPHIT—computer-optimized pulmonary delivery in humans of inhaled therapies (http://www-milton.ansys.com/European_Projects//cophit/index.html). Q12
— BloodSim—simulation of cardiovascular and other biomedical problems (http://www-milton.ansys.com/European_Projects//bloodsim/bloodsim.htm). Q13
— HUMOS2—development of a set of human models for safety (http://humos2.inrets.fr/index.php, Tropiano *et al.* 2004).
— GIOME—integrative modelling of physiological and pathophysiological processes in the gastrointestinal tract (http://www.giome.com/, Gregersen 2006).
— LHDL—living human digital library (http://www.biomedtown.org/lhdl).
— SAPHIR—a multi-scale, multi-resolution modelling environment targeting blood pressure regulation and fluid homeostasis (http://saphir.ibisc.fr/, Thomas *et al.* 2007).

(b) USA

— The visible human server—MRI, CT and anatomical images of the human male and female (http://www.nlm.nih.gov/research/visible/).
— BioSim—integrative model of physiology (http://www.biosim.com/).
— VSR—virtual soldier research programme—digital humans in real time (http://www.digital-humans.org/).
— NRCAM—National Resource for Cell Analysis and Modelling—cell simulation (http://www.nrcam.uchc.edu/).

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— AHM—active health management (http://www.activehealthmanagement.com)—predictive modelling for patient benefit.

Success stories summary. The VPH can support physiome activities and augment their success.

10. The VPH roadmap: ethical, legal and gender issues

It is easy to forget that a scientific resource such as the VPH has a wider impact that extends beyond the boundaries of normal scientific influence. The VPH does indeed offer improved healthcare on an international scale, but it also poses significant ethical dilemmas (Bassingthwaighte 2003) that highlight the need for the establishment of intelligent codes of conduct, some of which may require the backing of legislation. In the scientific domain, the promotion of ethical practices is facilitated by key professional groups, and this concept could be rationalized and extended across the entire VPH for the benefit of public confidence and protection.[9]

The ethical dimension includes consideration of the purpose of the VPH and the suitability of the resource to fulfil that purpose. However, ethics does not function in isolation and the VPH should offer opportunities for collaborative sharing of concerns and successes. With respect to intellectual property rights (Maurer *et al.* 2001), a regulatory framework that supports effective data sharing
Q14 and interoperability is required (Ellis & Kalumbi 1998; Charlesworth 2006;
Q15 Philippi & Kohler 2006)—this is an important task that deserves dedicated effort. Data storage and processing must comply with data protection legislation (Directive 95/46/CE of the European Parliament 1995; Herveg 2006), but
Q16 legal anomalies are in evidence across Europe (Herveg & Poullet 2003). The legal component is also necessary to provide guidance in the event of adverse outcomes resulting from inaccurate or incorrectly interpreted VPH data
Q17 (liability; Hureau & Hubinois 2005). Gender is relevant to the circumstances in which VPH data should be used (i.e. are VPH data gender specific and is it appropriate to use such data if gender specificity is not present or apparent?; Singleton *et al.* 2005; Berkley *et al.* 2006) and also considers the extent to which the VPH can be a tool to promote social equality across Europe.

Ethical, legal, gender summary. The VPH has the power to deliver political change.

11. The VPH roadmap: dissemination, exploitation and sustainability

The presence of the VPH will generate numerous opportunities, both scientific and social, and its use may require a cultural shift for many, and may even be regarded as a threat by some, to their current practices.

Q18 It will be important for the rapid and widespread acceptance of this tool so that such perceptions must be reduced as much as possible, both in scale and extent, and that the opportunities provided are seen to be sufficiently rewarding

[9] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 77.

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so that any short-term inconvenience in embracing the technology will be handsomely compensated in long-term gains. This is a matter of education. The dissemination of accurate information, the number and nature of available VPH resources and how they can be accessed, and the provision of supportive educational materials will be critical for this. Effective communication will encourage the present generation to engage and benefit from emerging developments, but should also provoke consideration of longer term initiatives that can equip the scientific community (especially, the young researcher) with a true, multidisciplinary education. It will be a challenge to develop courses that carefully balance and extend breadth, and yet cover topics in sufficient depth. The most important factor, particularly in the initial stages, is that information is consistent and coherent.[10] VPH exploitability and sustainability are largely dependent on the ability of the VPH to influence the health and well-being of ordinary people for the common good (Maojo & Martin-Sanchez 2004). This will be most evident at the interface with the health care system. Case studies are a useful way of communicating such information to the general public and accessible exemplars can help provide strategic focus. In this manner, the benefits and challenges of integrating models over many scales can be illustrated, with individual components giving visible relevance to the clinical and scientific goals (e.g. infection and immunity could be an exemplar that heightens public awareness, providing advanced systems and population level views of disease).

Sustainability summary. A short-term high-profile goal (project) may be an effective vehicle for promoting the VPH in society.

12. The VPH roadmap: recommendations

The final section of the roadmap reviews its content and summarizes key points. In particular, it proffers actions that are deemed to be effective responses to the dilemmas presented by the roadmap and raised by the consultation process. The content is intended to be advisory, clarifying the priority of VPH activities that could be funded under the Seventh Framework Programme of the European Commission (http://cordis.europa.eu/fp7/home_en.html). Tables 1 and 2 summarize the principal issues that deserve attention if the VPH is to benefit from continued development. The key issues are infrastructure, models and data as briefly described below, noting that nothing is possible without the participation of people willing to invest time and effort into VPH development.

(i) *Infrastructure*. The success of the VPH depends heavily on a robust IT infrastructure. In a broader context, there must be support for a VPH community (perhaps as a physical institute?) with structures that can enforce VPH standards and rules. It should provide an environment that supports the execution of commercial codes while safeguarding the quality and ownership of a multiplicity of data. The greatest legal challenge relates to patient ownership of clinical data. Coherent ethical/legal structures that address such problems must be a priority.

[10] Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological human' (www.europhysiome.org), p. 83.

Table 1. In order for the VPH to proceed to its next stage of development, the STEP consortium recommends action in particular areas. (The contents of the tables highlight the infrastructure areas that warrant investment.)

Remit of the VPH:

The grand challenge lies in understanding biological function through
(a) integration of physiological processes across different length and time scale (multi-scale modelling)
(b) integration of descriptive data with predictive models
(c) integration across discipline

Community infrastructure

Support is warranted for
— A recognized central authority that oversees the VPH
— A bridging authority in the short term (NoE)
— Raising the profile of the VPH with the aim of making it a ubiquitous presence in the biomedical arena
— Single sign-on, standardization, interoperability

ICT infrastructure services

Support is warranted for
— A VPH user community
— Data object repositories, federation and management
— Diffuse knowledge management (ontologies etc.)
— Quality assurance of data
— Single sign-in access to VPH resources
— User friendly environments for grid access and applications
— Sharing and distribution of models
— Multi-physics, multi-solver, multi-scale coupling
— Parallelization and job optimization

Technology infrastructure

Support is warranted for
— Middleware development for the VPH
— Interoperability and support for effective standards (DICOM, HL7, etc.)
— Liaison with other interoperabilityinitiatives (e.g. Integrating the Healthcare Enterprise – www.ihe.net)
— Resolution of (grid) security issues, particularly with respect to clinical data

Physical infrastructure

Support is warranted for
— A debate that clarifies whether the VPH should be hosted by few large-scale infrastructures (LSI), or by a loosely coupled, federation of small-to-medium computational resources
— Effort to raise the profile of life sciences as a core customer for grid resources (on a par with the high-energy physics community etc.)

Commercial, Legal and Ethical infrastructure

Support is warranted for
— A commercial infrastructure for the VPH that ensures its financial sustainability (e.g. access charges for VPH resources may apply)
— Execution of commercial code and resolution of distributed platform licensing issues
— Infrastructures that permit data sharing in the context of clearly defined IPR regulations
— Data protection and patient confidentiality
— VPH promotion of social equality

infrastructure

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Table 2. In order for the VPH to proceed to its next stage of development, the STEP consortium recommends action in particular areas. (The contents of the tables highlight the modelling, data and other areas that warrant investment.)

Data

Clinical Observation

Support is warranted for
— Widespread clinical participation
— Accumulation of clinical, observational data and its organization
— Projects that collect relevant experimental data with respect to cell-to-cell and cell-to-tissue interactions

Data Collection

Support is warranted for
— Funding to support organized collection, storage etc. of data for the VPH
— Data curation (e.g. extension of cultural heritage curation expertise to the scientific domain)
— A quality assurance infrastructure that will promote data sharing

Models

Model Accumulation

Support is warranted for
— Developments that enable separation of model definition from the modelling environment
— Development of solver-independent modelling formats (e.g. CellML)
— The offering of models as encapsulated Web services

Model Verification

Support is warranted for
— Methods to quantify model accuracy (i.e. how accurately equations are solved) and verification (i.e. the extent to which the model is an appropriate description of the problem)
— Available reference benchmark problems for the quantitative evaluation of simulation code (e.g. speed, accuracy)
— Development of adaptive algorithms that can be constrained to deliver solutions to specific accuracy across multiple-scale problems

VPH Modelling Challenges

Support is warranted for
— Model preparation (preprocessing, segmentation, mesh generation, derivation of properties from biological data, missing parameters, etc.)
— Model coupling (FSI, lumped parameter and coupled models, changes of dimensionality, boundary conditions etc.)
— Methods to overcome limited computational resources

Model Interconnection

Support is warranted for
— Development of macroscopic 'supermodels' that describe a functional or metabolic sub-system as scaffolds for organizing lower level, higher detail models
— Development of model repositories as a loosely coupled federation of predictive services, exposing an I/O interface that supports model concatenation
— I/O interface standardization/data semantics
— Data redistribution, latency minimization, I/O overhead reduction
— Data standardization and / or format conversion

Miscellaneous

Validation Issues

Support is warranted for
— Efforts directed at experimental data collection against simulation results
— Model verification in the clinical context
— Model certification for clinical use
— Methods to accommodate inter-subject variability
— A VPH dialogue with regulatory authorities

Sustainability Issues

Support is warranted for:
— An infrastructure providing a profitable business model that provides a value-for-money resource and yet sustains VPH development (e.g. Barter, E-commerce models, subscription etc.)
— Continued infrastructure maintenance and development (funding)

People Issues

Support is warranted for
— Recruitment (particularly of younger scientists into the multidisciplinary field of the VPH)
— VPH career support and incentives

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(ii) *Models and data.* The current framework of multi-scale biology has weaknesses that are best addressed by a research focus at cellular length scales, although many of the wider modelling challenges are length-scale independent. These include simulation development, the sharing and coupling of different models and their verification, data standards and quality (Hunter, J. 2006), ontological development and semantic mediation, [Q19] etc. Significant issues relating to data curation (Merali & Giles 2005), storage and data transfer also need to be resolved. Many simulations use different commercial codes and a suitably flexible licensing model (e.g. pay per solve) is needed to encourage occasional or short-term developmental use. The development of models encapsulated as web services may also be advantageous. The VPH must host a repository of reference benchmark problems, for which the solutions are known and by which the quality and performance of emerging simulation tools can be judged.

[Q20] (iii) *People.* A significant barrier to VPH sustainability and consequent realization of benefits to scientific development and public health leads to the current lack of attraction of this field to younger scientists. Gifted young researchers perceive that more promising careers can be found in fields [Q21] such as molecular biology and medicine. Since efforts in interdisciplinary fields are normally under-rewarded, it will be necessary to redress this imbalance by developing a comprehensive career support and incentive system allied to the VPH. Talented young people facing fundamental career decisions must be satisfied that their scientific development and career progression will benefit—rather than being compromised—from involvement with VPH-related activities. Such a strategy is essential if the VPH is to attract the high-quality individuals who are necessary for its rapid and sustained development.

(iv) *Miscellaneous.* Intended use of the VPH in clinical practice imposes numerous responsibilities, including (i) rigour in terms of model design, explicit recognition of assumptions/limitations and (ii) care in the acquiring of validation data, with appropriate recognition of errors and acknowledgement of the limitations of measuring equipment. A mechanism for authorizing clinical application of a model is needed, so that clinical models can be certified for such use. Industrial use of models faces similar challenges, since industrial models are intended for human application—FDA and CE approvals are beginning to acknowledge the value of simulation in the certification process. A link between these authorities and the VPH could benefit both parties and accelerate industrial development, safety and public acceptance of new products.

With respect to society, the benefits of the VPH are perhaps best communicated through concrete examples, and early implementations that demonstrate significant impact in clinical practice are to be strongly encouraged. Politically, the VPH must be managed in such a way that success in the short term guarantees longer term sustainability, independent of contributions from national and European government.

Recommendations summary. Infrastructure funding for IT is an immediate requirement of the VPH.

13. Discussion

The physiome is a long-term vision, one in which *Homo sapiens* is ultimately modelled *in silico*. Although currently unattainable, viable elements are beginning to appear within the scientific domain. The most celebrated example is the genome (describing *H. sapiens* at a genetic level; International Human Genome Mapping Consortium 2001; Venter *et al.* 2001; Little 2005), but many other examples exist, such as the 'heart physiome' (*in silico* description of the heart; Smith *et al.* 2004), the GIOME (*in silico* description of the gastrointestinal tract; Gregersen 2006), the epitheliome (*in silico* description of epithelial cells; Walker *et al.* 2004), the musculoskeletome (*in silico* description of the musculoskeletal system; Viceconti *et al.* 2006; Van Sint Jan *et al.* 2007), the renal physiome (*in silico* description of the kidneys; Chu *et al.* in press; Thomas *et al.* in press), etc. Already these projects are modifying the way we think about human biology, but currently they tend to function as independent entities, operating in isolation from each other. Together, however, they offer the prospect of a grander picture in which information exchange between these *in silico* models enables a description of *H. sapiens* to be formulated (the physiome), based on separate but communicating simulations that describe a whole range of physiological functions across all length scales, from molecules to genes, to cells, to organs to the complete human disposition. An added dimension (with a promise of great reward) is the integration of clinical data, demographics, epidemiology, etc. However, the effective usage of this diversity, usefully augmented by data from modelling, is a challenging exercise, and practical examples, as yet, are few and far between. At the clinical interface, it is perhaps best exemplified by the work of @neurIST (www.aneurist.org), which embraces a rich mixture of data sources (clinical, epidemiological, pharmaceutical, imaging, modelling, etc.) in order to synthesize patient-specific recommendations that are relevant to the clinical management of cerebral aneurysms. This demonstrator is one example of 'personalized medicine'—a concept that is implicit to the VPH. It is a concept that has spawned numerous projects, addressing the specific multidisciplinary challenges that are critical to the success of patient-specific medicine (e.g. the COAST project has a focus on multi-scale issues, see www.complex-automata.org). In principle, the integrated data/modelling framework could revolutionize understanding of diseases and their treatment, aid clinical decision making, accelerate drug design, etc., offering productivity benefits for industry, health benefits in the clinic, educational benefits in schools, research benefits for the academic and economic benefits for the taxpayer. It is not difficult to see why Europe is embracing this vision at the highest level, but in order for it to become a reality, an infrastructure is needed to facilitate information exchange between projects and support their many overlapping activities. Infrastructure is a critical component of physiome design and ultimately needs to be global in extent. This has been recognized by the European Commission, and recommendations to achieve that end are the primary purpose of STEP. The EC is already committed to investing many tens of millions of Euros to kick-start this process, thereby expediting development of the VPH and availing itself of early benefits.

The STEP VPH roadmap is a vehicle for discussion of issues pertinent to the development of the VPH infrastructure and aims to raise problems and pose solutions as a means of guiding VPH funding within FP7. It has been estimated that development and full deployment of the VPH will require approximately 500 million Euros. Approximately 200 million Euros are expected to be invested by national and European research grant agencies, while the remainder is expected to come from the main participants, e.g. industry and medicine. These large figures indicate the magnitude of the challenge to be addressed, pursuing a unifying methodological and technological framework that will allow biomedical scientists from all domains to describe, integrate and predict. The technological component relies on data processing and data modelling tools, storage and computing services, support for community building and collaborative work. This requires the management of knowledge, with innovations that improve access, exploration and understanding of the knowledge accumulated within the VPH by clinical, industrial and societal users. The methodological component involves unified representation of VPH concepts, data and models, development of new processing and modelling methods for the VPH, the development of conceptual frameworks that allow a seamless integration of models, and many other aspects that will emerge during the process. Thus the VPH is manifested as a methodological and technological framework that enables collaborative investigation of the human body as a single complex system.[11]

Europe is not alone in this endeavour, and competing and complementary solutions from the USA and around the world will undoubtedly accelerate scientific advance (Bassingthwaighte *et al.* 2000; Higgins *et al.* 2001; Hunter & Nielsen 2005; Oden 2006). Adequate funding is a universal requirement and the majority of developments can be accommodated within the classic collaborative/competitive models, in which scientists organize themselves in transnational consortia that compete for funding. However, certain activities would benefit from the coordinating influence of an umbrella organization and Europe may be uniquely placed to provide such a supporting infrastructure, coordinating development of standards, interoperability, semantics, quality assurance, etc. This would give Europe a global presence and the power to influence its emerging direction. This is of consequence, because the VPH has considerable potential as a unifying influence in society—its reach extends far beyond science and touches so many aspects that are held dear by the common citizen, such as education, health, social equality, etc. and provides an imperative for fixing some modern ills such as legal harmonization.

Finally, although the VPH might appear to be the offspring of the scientific community, it is important to resist the temptation to think of it purely as a research resource. Close links with industry and the clinic cannot be overemphasized. Enthusiasm from the industry sector, coupled with demonstrable benefit in the clinic, is its most certain route to success, securing the continued benefit and accelerated development of biomedical science (and all its benefits to the citizen) for the foreseeable future.

14. Conclusion

The physiome is a truly global concept that spans many disciplines, involves wide expertise, connects with a diversity of cultures and has the potential to

[11] Cited from the VPH roadmap ‘Seeding the EuroPhysiome: a roadmap to the virtual physiological human’ (www.europhysiome.org), p. 2.

influence the management of many diseases.[12] It is the kind of grand vision that can be a unifying concept and has been adopted by Europe as the VPH, with priority funding under FP7. The purpose of the STEP project is to advise the funding focus through the provision of a roadmap that considers strategies for achieving the VPH over the next decade. The content of the roadmap has been outlined and its implications discussed in the context of a European vision of the physiome.

15. Uncited references

Q25 Levin *et al.* (2002), Jenders *et al.* (2003), Hunter *et al.* (2006) and Pitt-Francis *et al.* (2006).

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Q7 The web link 'http://www.europhysiome.org' has been moved from footnote to its appropriate citation in the text. Please check and approve.

Q8 Please check the edit of the sentence 'It is necessary…'

Q9 Please note that the reference citation Hey et al. (2003) has been changed to Hey & Trefethen (2003) with respect to the reference list provided.

Q10 Please note that the reference citation Clery et al. (2006) has been changed to Clery (2006) with respect to the reference list provided.

Q11 Please suggest whether the web link can be changed to lower case letters (http://ligwww.epfl.ch/∼maurel/charm/).

Q12 Please suggest whether the web link can be changed to lower case letters (http://www-milton.ansys.com/european_projects//cophit/index.html).

Q13 Please suggest whether the web link can be changed to lower case letters (http://www-milton.ansys.com/european_projects//bloodsim/bloodsim.htm).

Q14 Please note that the reference citation Ellis et al. (1998) has been changed to Ellis & Kalumbi (1998) with respect to the reference list provided.

Q15 Please note that the reference citation Philippi et al. (2006) has been changed to Philippi & Kohler (2006) with respect to the reference list provided.

Q16 Please note that the reference citation Herveg et al. (2003) has been changed to Herveg & Poullet (2003) with respect to the reference list provided.

Q17 Please note that the reference citation Hureau et al. (2005) has been changed to Hureau & Hubinois (2005) with respect to the reference list provided.

Q18 Please check the edit of the sentence 'It will be important…'

Q19 Please note that the reference citation Merali et al. (2005) has been changed to Merali & Giles (2005) with respect to the reference list provided.

Q20 Please check the edit of the sentence 'A significant barrier to…'

Q21 Please check the edit of the sentence 'Since efforts in…'

Q22 Reference Bassingthwaighte et al. (2000) has been cited in text but not provided in the list. Please supply reference details or delete the reference citation from the text.

Q23 Please note that the reference citation Hunter et al. (2005b) has been changed to Hunter & Nielsen (2005) with respect to the reference list provided.

Q24 Please note that the reference citation Oden et al. (2006) has been changed to Oden (2006) with respect to the reference list provided.

Q25 References Levin et al. (2002), Jenders et al. (2003), Hunter et al. (2006) and Pitt-Francis et al. (2006) are provided in the list but not cited in the text. Please supply citation details or delete the reference from the reference list.

Q26 Please update publication details in reference Chu et al. (in press).

Q27 Please check the inserted volume and page range details in reference Hunter et al. (2006).

Q28 Please check the page range in reference Judex et al. (2006).

Q29 Please check the details of reference PriceWaterhouseCoopers (2005).

Q30 Please update publication details in reference Thomas et al. (in press).

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