Digital Human Modelling: A Global Vision and a European Perspective

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Abstract. The Physiome is an umbrella term that refers to human modelling with mathematics and computational methods, accommodating cross-disciplinary science (chemistry, biology, physics) and a breadth of dimensional and temporal scale (sub-cellular to organs, sub-microsecond to tens-of-years). The Virtual Physiological Human is a European initiative that is intended to provide a unifying architecture for the integration and cooperation of multi-scale physiome models, thereby creating a predictive platform for the description of human beings *in silico*. Unlike the Genome, the challenge of the Physiome may be almost unbounded, as the desire for increased detail imposes a continuing pressure for ever-finer data granularity, and the necessary Information Technology (IT) infrastructure spawns innovations that surpass conventional solutions. It is foreseen that maturing physiome activities will increasingly influence medicine, biomedical research and commercial developments, and the central role of IT highlights the need for a specific and robust IT infrastructure.

The European Commission has experience of supporting challenging technical endeavours through its Framework Programmes of research, and in the forthcoming 7th Framework Programme, it will invite researchers from within and outside Europe to unite in seeking solutions to key issues of the Physiome. The Virtual Physiological Human (VPH) investment programme will establish the necessary infrastructure and address the grand technical challenges identified by experts. This paper examines the background to the strategy and the ways in which the programme's structure has been determined.

Keywords: Physiome, Virtual Physiological Human, infrastructure, modelling.

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1 Introduction

The Virtual Physiological Human (VPH) is a methodological and technological framework that once established, will enable collaborative investigation of the human body as a single, complex system. It will be a tool to facilitate the sharing of observations, an environment for the investigation of hypotheses, supporting the development and validation of theories, integrating all observations and hypotheses into a dynamic understanding of human physiology and pathology. The VPH refers to the supporting infrastructure that makes this possible but it is not the model itself.

The need for such an architecture has emerged from the European scientific community, which has eagerly embraced the concept of the Physiome, as described by Hunter et al [1]. The current partitioning of health science along traditional lines (scientific discipline, anatomy, physiology etc) is considered an artificial and inefficient framework for such an integrated and dynamic description of human biology. In contrast, the VPH is tendered as a comprehensive solution to this disparate challenge, and the first steps of its development are the subject of this paper.

2 The First STEPs to the VPH

Development of the VPH requires scientific focus, funding and forethought, and consequently the European Commission (EC) has instigated a think-tank that operates as a European Coordination Action, funded by the e-health unit of the EC as part of the 6^{th} Framework Programme. It has the acronym STEP (**S**trategy for **T**he **E**uro**P**hysiome) and is tasked with considering and recommending strategies that promote the development of the VPH, providing focus for VPH activities within the 7^{th} Framework Programme (FP7) between 2007 and 2013. STEP will publish its report [2] in spring 2007 ("*Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human*"). It is intended to inform the decisions of the EC with respect to the funding of VPH and physiome research, and will emphasise the need for efforts that are descriptive, integrative and predictive across scientific disciplines and physical measurement scales. Contributions to this roadmap have been critiqued through a consensus process that has involved the broadest of groupings, from the academic community, industry, clinical experts and a wide range of professional associations.

By reference to the emerging STEP roadmap, this paper outlines the EC commitment to digital human modelling and simulation, highlighting its interest in developing an infrastructure capable of supporting global physiome activity. Critically, the EC recognises that the influence of the VPH extends beyond the scientific domain, and inevitably, will have an impact on society as a whole.

3 The VPH and Its Motivation

Dissatisfaction with current modelling approaches from clinical, industrial and academic quarters offers strong justification for the development of the VPH and emphasises the belief that a cross-discipline approach is the only credible way forward in the 21st century [3]. Anticipated societal benefits also add significant support to the endeavour.

Clinical: A feature of current medical practice is specialization, and bridges between clinical disciplines are weak. Consequently, western medicine struggles with the management of multi-system or multi-organ pathologies and the VPH offers a means of breaking down these barriers by providing an inherently cross-disciplinary tool that can alter the way in which we approach physiology and pathology. Ideally, close integration with the healthcare system will encourage its adoption as an effective clinical decision support tool.

Industry: The VPH will be a resource to aid product design and development, reducing risk and cost. Innovative resources will accelerate time-to-market, with the potential to strengthen the medical related industries. Approval of the VPH by regulatory authorities will help to reduce (but not totally remove) the need for clinical trials and animal testing.

Academia: The narrow expertise of individual researchers is characteristic of scientific focus, which all too often, produces modellers, engineers and experimentalists who do not understand each other; frequently none of them appreciates the clinical impact of their joint work. This is an impediment to the development and understanding of science and healthcare, and again the VPH offers a means of crossing these barriers, expanding horizons and facilitating communication between those participating in biomedical science.

Society: Societal needs are a conglomeration of personal needs and expectations, which includes ambitions for quality of life and an anticipation that taxes are used to improve the lives of citizens. This is consistent with a vision of the VPH as a tool that can have far-reaching effects on the breadth of human experience, from improved healthcare to enhanced quality of life.

In essence, motivation for VPH development is justified by the pervasive nature of the technology and its benefits, reinforced by the international perspective on the VPH as presented below.

4 International Context and Common Objectives

Numerous examples can be cited that illustrate the relevance of the VPH to a diversity of current projects. These extend beyond Europe, and include the USA and the Asia-Pacific region. Activities that have resonance with the VPH (funded under EC FP6) include AneurIST, ImmunoGrid and the Living Human Digital Library (LHDL). Alongside EuroPhysiome activities, there are a number of other Physiome projects around the world, the major ones being the National Simulation Resource (NSR) Physiome project from the USA and the IUPS Physiome, coordinated by the University of Auckland, NZ. Numerous successful initiatives are present across the globe [2] (e.g. LYMFASIM, the Virtual Soldier Research programme, Heart Physiome etc.), and to reduce the risk of fragmentation, the authors of the STEP roadmap recommend the establishment of a World Physiome initiative – a lightweight coordinated action among all physiome-related projects around the globe.

It is important to recognize that there are many fundamental activities common to these projects that need not be reinvented with each project but could usefully be developed and administered through a single infrastructure platform or resource such as the VPH. Overlap with VPH objectives is particularly apparent in the health computing and health-grid arena (e.g. the SHARE initiative for Health-Grid computing). There is a growing belief that the VPH can only be successfully implemented by using the resource-sharing mechanisms provided by a Grid computing infrastructure, but barriers within current Grid technologies need to be overcome before full-scale VPH implementation becomes possible.

5 Research Challenges

The vision for the VPH is the result of a complex consultation and consensus-building exercise involving a large number of internationally recognised experts. This cross-discipline complementarity comes to the fore when the challenges for VPH implementation are considered. The two principal research challenges are identified as:

1. Clarifying the nature of the scientific problems and principles pertinent to the VPH and how they might be solved, and
2. Identifying the ICT tools that should be developed to address these problems.

It is widely accepted that the true, grand research challenge lies in understanding biological function. This is the focus of the first point, and requires a multi-faceted approach to biomedical endeavours, since the complexity of a human being allows for almost limitless inter-connections and interactions between systems that can be open, responsive and adaptive. An abundance of data provides a wealth of descriptive information, but to understand it fully and determine physiological function, models are needed that closely link descriptive data with underlying biology.

The pivotal role of information technology as a solution to this challenge is self evident, and leads to consideration of the second research challenge (point 2 above). This is predominantly a challenge of integration: not only the integration of processes spanning large temporal and spatial scales and the integration of descriptive data with predictive models, but also integration across disciplines. A concerted effort is required [4], [5] to ensure that adequately supportive and appropriate infrastructures, frameworks and technologies are developed. To address the multi-scale aspect of the VPH, a collection of large databases, accommodating models and data at the various scales, is required. A variety of software tools is also needed to author, run and visualise these models, along with a defined common language to address the disparate components.

6 Scientific Challenges

The VPH research challenges discussed above can be further dissected into Challenges in Prediction, Description, Integration and Information, each examined below:

6.1 Challenges in Prediction

Model interaction and complexity, and issues of inhomogeneity and inter-subject variation, fall into this area, as does the difficulty of problem identification and boundary setting. The identification of gaps in our knowledge of human biology and pathology is also important, along with the clinically essential area of model and data validation.

6.2 Challenges in Description

It is prudent to recognise that the presence of data should not be taken to mean it is accurate or complete. Instruments, models and systems that produce data introduce artefacts and set limits that translate to uncertainties in measurement. The introduction of data collection protocols could limit these effects, as detailed records of data collection methods would avoid misinterpretation. A solution is the inclusion of appropriate metadata, with consequences for all those involved in data collection. However, this rigour has advantages, for if high quality data is traceable to source, there may be justification for its use in physiological and clinically applicable models.

6.3 Challenges in Integration

Integration in this context refers to the establishing of appropriate connections at the interfaces between differing temporal and spatial scales, for both models and data, and to the integration between academic and clinical specialties. The interface between a model and an appropriate data set is an important link for validation, and demonstrates the need for comprehensive, flexible and extensible mark-up languages such as CellML[6] and FieldML etc.

6.4 Challenges in Information and Communications Technology (ICT)

The primary challenge for ICT is to develop a coherent suite of tools capable of addressing the scientific challenges described above. One of the core requirements is for complex databases that collect and classify models and data and act as guides to modelling efforts in Europe and beyond. This requirement illustrates the need for a standard framework that can support the coupling of different models. Since the VPH will involve very large amounts of data (petabytes, at 2007 standards) smart strategies will be needed for cataloguing, storage and sharing.

A dedicated and distributed VPH computing resource is an attractive solution and would expedite the integration of grid computing technologies and middleware (amongst other things) with biomedical research. However, since the VPH by its very nature operates at the forefront of technology, many solutions do not yet exist, but there are prototypes – such as the Application Hosting Environment (RealityGrid [7]) – that can already act as an interface with federated grids. The template provided by the BioSimGrid is another example, since this is designed to act as a repository of simulation data specifically for biomolecular dynamics. BioSPICE also has a similar, open-source, modular infrastructure.

7 Impact Analysis

The roadmap speculates about the future impact of the VPH. Effects will be not only on biomedical research and clinical practice but also in the associated industry sectors and society at large.

Impact on biomedical research will be evident through the provision of an unprecedented collaborative architecture on an international scale. The main benefit for the clinical arena will be the facilitating of patient-specific treatment, along with better cooperation between the various clinical specialisations. Indirectly this will also have an impact on the cataloguing of human physiology and pathology through the collation of studies and data gathered under the VPH umbrella.

The most immediate impact to industry will come in the medical devices sector where the VPH will offer improved technical excellence, a reduction in the development time of new products and amelioration of the risks associated with their introduction.

Societal impacts would take longer to manifest themselves, reliant on the postulated outcomes described above. Reduced public expense and healthier citizens will be the primary anticipated effects, but other less-obvious consequences (workforce size, educational diversity, vehicle safety, ergonomics etc) will follow.

8 Ethical, Legal and Gender Issues

Since the impact of the VPH will spread beyond the realms of normal scientific influence, it is perhaps more important than usual that these wider aspects are addressed comprehensively. The VPH poses numerous ethical [8] and legal dilemmas that need explicit attention. For instance, guidance in the event of an adverse clinical outcome resulting from the VPH is a very important legal area to consider alongside the balance between freedom of information and the security and privacy of patient data. Copyright and the sharing of data (IPR) is a topic in need of urgent and specific legal clarification.

Social and political dilemmas are also a feature of the VPH since it must not compromise ethical ideals valued by society. Indeed, the VPH could influence perennial issues such as social equality because it may identify race and gender characteristics that challenge our preconceptions. Typically, a gender-neutral approach to patient care is currently used in modern medicine since there are comparatively few gender specific diseases such as osteoporosis. However the VPH has the potential to identify gender-sensitive behaviours that are much more subtle, creating the prospect of gender-specific treatments and improved outcomes.

9 Dissemination, Exploitation and Sustainability

Some of the consequences of the VPH could require a shift in cultural behaviour, for example in the working practices of clinicians; the VPH may therefore be viewed by some as a threat. As with any other major change, the VPH requires sensitive and comprehensive education in its use and benefits. Dissemination and profile-raising campaigns need careful planning so that developers and end-users alike may be engaged. Ultimately the long-term sustainability of the VPH will be dependent upon its ability to influence the health and well being of all citizens.

10 VPH Recommendations That Issue from the Roadmap

Following consideration of the many issues raised, the STEP roadmap offers a number of recommendations for the concrete implementation [2] of the VPH in each of the following areas: Infrastructure, Data, Models, Validation, Dissemination and Sustainability. Firstly, it is suggested that continued funding for a network of experts is confirmed so that the available momentum generated by the STEP action can be sustained and translated into VPH success. A suitable instrument might be an FP7 'Network of Excellence' (NoE) that would track all physiome-related projects and facilitate dialogue to encourage cross-fertilisation of ideas.

10.1 Infrastructure

A scalable but resilient infrastructure should be designed as a priority. The VPH will harness very large quantities of information, and its sustainability will be dependent upon its ability to accommodate this data. An adaptive infrastructure that can deal with the challenges of transfer, organisation, indexing and storage at the rate of terabytes per day is required. Success is critically dependent upon the development of a suitably robust IT infrastructure. More widely, a 'VPH community' should be formalised, willing to help develop and enforce the standards to which the VPH should be built.

10.2 Data

Standards for data-collection should be established as a priority. Projects for the collection of data for cell-cell and cell-tissue interaction could be favoured since this will enhance the understanding of the underlying biology. Ideally, data should be collected in a manner consistent with written protocols. This would provide data that is traceable so that the quality of the information can be assured enabling separation of high quality data from that obtained as a by-product of some other activity, unlikely to carry the same levels of assurance.

Data curation (storage, protocols and standards) is critical to the success of this venture and requires specific attention and clarification of IPR issues for data sharing if the VPH is to be successful. The brief of the VPH includes dealing with patient data gained from a clinical setting. The utmost care must be given to the creation of relevant security protocols. Rigorous mechanisms for quality assurance are a necessity when considering integration of clinical and non-clinical data.

10.3 Models

Standards for the interconnection of models should be established as a priority. Development of simulation tools and models is to be encouraged, however the output of these activities needs to be validated to ensure their suitability. Sharing and coupling of models also requires support, with dedicated effort directed at support for physiome mark-up languages.

10.4 Validation

Standards for model validation are also an early necessity. Since it is envisaged that the VPH will be used in a clinical setting, this imposes a strict requirement for validation. Methods are needed to ensure that models are consistent with their claims, accompanied by explicit statements concerning assumptions and limitations along with care in the acquisition of validation data and acknowledgement of errors and limitations.

10.5 Dissemination

A number of strategies are required for the effective dissemination of the VPH concept. There is a recognised need for:

- Continued 'evangelisation' for the VPH through effective channels
- Representation at conferences to cement the VPH community
- Representation of the VPH in education
- Standardisation
- Coordinated action to endorse and disseminate the VPH vision
- European and global harmonisation of the Physiome effort

10.6 Sustainability

Undoubtedly interim effort (and finance) demonstrating the viability of VPH concepts in the short term will be needed before the VPH gains sufficient credibility to become sustainable in the long-term. Suitable EC vehicles include the aforementioned Network of Excellence (NoE), but also Integrated Projects (industrial involvement with short-term impact) and STRePs (Specific Targeted Research Project – smaller consortia with focused outcomes). A mechanism for accommodating non-government finance and sponsorship (e.g. industry) is also a necessity.

11 Discussion

The Physiome is a long-term vision, one in which eventually, an integrated multi-scale model describes all aspects of human biology from genes and molecules through cells to organs and the whole organism, all acting as one. Functional elements of this mosaic are beginning to appear, such as the genome (genes), heart physiome, etc. However, these currently operate as ‘stand-alone’ models and do not interact with one another. If they were to interact, a much better picture of the entirety of human biology could be gained to enhance understanding of diseases and their treatment. The Physiome will therefore comprise a kit of parts, together with assembly tools, that will allow the investigator to construct models matched to the tasks in hand, and to output data in forms appropriate to the interventions, investigations or designs required. This has implications for the clinical decision-making process along with much wider benefits to health, industry and society. This paper postulates that a suitably robust and adaptive infrastructure is a critical part of the endeavour and needs to be available to all users worldwide if it is to be a success.

The grandest challenge of the Physiome lies therefore not in the construction of a single model of enormous complexity, but in the need to establish a vast, expandable IT framework. Within this, models of any complexity can be constructed from available quality-assured sub-components and data, such that reliable results can be obtained with the minimum of effort. A secondary goal is to begin to populate this framework with the raw content (tools and data) that users will require. The final element will be the inclusion of proven, documented and validated models of physiological subsystems that can offer immediate benefit. The vision of the European Community (EC) is that over the next ten years a suitable infrastructure is built to accommodate the framework of technology and methods supporting Physiome efforts worldwide. The technological component is primarily focused on information and communications technology and the management of knowledge, with innovations that improve access, exploration and understanding of the content accumulated within the VPH. The methodological component relates to a unified representation of concepts, data and models, development of new methods of processing and modelling and the integration of models across all scales.

The roadmap to the EuroPhysiome[2] was crafted by those working daily in the field, assisted by information from a wide range of potential industrial and clinical users. Many components with which the Physiome will be populated are already available from specialists: Cardiome, Epitheliome, GIOME etc. The challenge is now to establish the framework that will allow the mutual interaction of these components, and to extract their true potential to improve the health and well being of the world's citizens. The principal European mechanism by which VPH developments can occur is through the funding instruments available within FP7, arranged around four 'work-programmes': Cooperation, Ideas, People and Capacities, each with a number of themes. EC funding for VPH activities exceeds 70 million euros, and can complement external sources of funding (e.g. grants that are available from national agencies and industry). It is expected that the health and ICT areas will account for approximately 50% of all EC research spending in the FP7 Cooperation programme with ICT being the largest priority theme for FP7. An estimated 500million euros will be required to fund the development and deployment of the VPH. These are substantial sums and indicate the magnitude of the challenges to be addressed.

The creation of the VPH poses a number of challenges across multiple disciplines, from mathematics and ethics to genetics and clinical integration. Unquestionably, the VPH is a grand challenge for the European research system as a whole. However, this challenge is larger than any human subset, whether European, American or Asian; it is a truly global endeavour, and the EC is inviting global participation as it seeks to add European resources to the quest to understand humankind.

12 Conclusion

The Physiome concept is simultaneously intriguing and challenging, and it has profound implications for the future of human modelling and biomedical science. The European response presented in this paper, is to invest in the VPH as an underpinning IT infrastructure designed to unify disparate projects and expertise, creating a platform that offers the functionality of a multi-component Physiome. The challenge is technological and methodological, and Europe recognises the necessity for international cooperation, seeking collaboration within and beyond its borders as a means of consolidating the vision that is the Virtual Physiological Human.

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