VIRTUAL PHYSIOLOGICAL HUMAN

White paper

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TOWARDS VIRTUAL PHYSIOLOGICAL HUMAN: MULTILEVEL MODELLING AND SIMULATION OF THE HUMAN ANATOMY AND PHYSIOLOGY

Research challenges and intermediate steps to be addressed by future interdisciplinary research programs

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KEYWORDS

MODELLING: To construct a mathematical description of a system. The model can then be used for simulation or optimization. All models are predictive in the meaning that simulation output predict what could occur in the real world where the system is operating.

SIMULATION: The imitation of the reality for studying the effect of changing parameters in a model as a means of preparing a decision or predicting experiment results. It can be seen as the numerical evaluation of the model of a system, to estimate the true characteristics of the system. A simulation is an experiment run as a model of reality.

COMPLEXITY: A recently identified property of living systems that makes these systems more potent than just the sum of their components. Among other, complex systems are redundant (i.e. able to maintain their outcome despite alterations in some of their components), quantitative (i.e. the quantitative dimension of between component interactions is of great importance in the outcome), recursive (i.e. a change in a single component can lead to backward changes in other components).

BIOINFORMATICS: Research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioural or health data, including those to acquire, store, organize, archive, analyze, or visualize such data.

BIOMATHEMATICS: The area of mathematics which deals with the mathematical representation of biological phenomena.

MEDICAL INFORMATICS: Methods and systems for the storage, retrieval, sharing and optimal use of biomedical data, information, and knowledge.

COMPUTATIONAL BIOLOGY: The development and application of data-analytical and theoretical methods, mathematical modelling and computational simulation techniques to the study of biological, behavioural and social systems, extended to the behavioural and social aspects of health care systems.

SEMANTICS: The study of meaning in language.

ONTOLOGY: An explicit formal specification of how to represent the objects, concepts, and other entities that are assumed to exist in some area of interest and the relationships that holds among them.

GRID: Grid technologies emerged from specific needs in particle physics for high-computing intensive applications and from the availability of high-speed high-bandwidth networks. Rapidly, the term Grid evolved towards a concept of ubiquitous and transparent computing and encompassed the vision of intensive computing as well as of automated knowledge discovery. Today technologies are able to provide increased computing power and large scale distributed storage facilities, with the development towards the semantic GRID capable of processing and managing heterogeneous data thus enabling new automated knowledge discovery.

HPC: High Performance Computing. HPC brings enormous amounts of computing power to bear over relatively short time.

HTC: High Throughput Computing. HTC employs large computing power for very lengthy periods.

XML: Short for E**X**tensible **M**arkup **L**anguage, a specification developed by the W3C. XML is a pared-down version of SGML, designed especially for Web documents. It allows designers to create their own customized tags, enabling definition, transmission, validation, and interpretation of data between applications and between organizations.

VPH: Virtual Physiological Human

INTRODUCTION AND SUMMARY

Developing the computational framework and ICT based tools for the multilevel modelling and simulation of the human anatomy and physiology - here referred to as the ***Virtual Physiological Human*** *(VPH)*- is, perhaps, the 'grand challenge' for several disciplines at the cross-road of ICT and the biosciences. The VPH will have impact on the way health knowledge is formalised, acquired, understood, represented, analysed, communicated and validated. It will create a new basis for research and healthcare and will open up new opportunities for industrial development. Examples of topics in which rapid impact is expected can be described as;

- understanding of physiology and its dysfunctions (diseases),
- the identification of relevant biomarkers for diagnosis and in the optimisation of screening,
- to allow individualised medical decision,
- the discovery of innovative medicines and the interaction between personalized drugs and individual humans,
- validation (in silico versus in vivo data), multi-physics multi-resolution data acquisition,
- design of more targeted implants and artificial organs and
- possibly also in areas where reverse-engineering of human organisms are important, such as in robotics and artificial intelligence.

The decision to write this White Paper was made at the expert workshop held on 1st June 2005 in Barcelona (visit reference link above). The goal of this paper is to shape a clear overview of on-going relevant activities, to build a consensus on how they can be complemented by new initiatives for researchers in the EU and to identify possible mid-term and long term research challenges. This initiative is an add-on to the existing scientific areas already supported by the European Commission. Activities identified span from better use of existing data and tools to the development of new methods, libraries and tools. Some of the main aspects of the VPH are the need to further development of numerical modelling and simulation and of innovative imaging processing methods to make use of them, the multidisciplinary dimension, the infrastructure needed and finally the acceptance issue. It is important to underline that these areas are being developed also in a more specific content but new needs are identified in the realm of the VPH.

An evolving trend will be that towards **personalised healthcare**, based on the use of simulation to predict the outcome of interventions, including surgical and pharmacological, on the individual. Last, but not least, *in silico* modelling and simulation complement modern biomedical signal and image acquisition systems where *in vivo* and *non-invasive* measurements are not yet available or feasible to provide virtual signal or image acquisition strategies.

To realise this long-term vision numerous challenges will have to be overcome, representing efforts that must build on advances in many different scientific disciplines. Careful planning of the intermediate steps is needed, to enhance Europe's presence in the field, and enable better economic exploitation and more rapid application development in healthcare and health related research as well as identification and exploitation of the elements of the approach which can bring early social and economic returns.

Numerous interdisciplinary research initiatives are generating excellent research results with regards to modelling, simulation and visualisation of human anatomy and physiology. These research initiatives focus on different (biological) levels; molecular and cellular levels, tissue and organ levels, and system and human (organism) levels. The complexity is immense on each of the individual levels, requiring highly interdisciplinary approaches. A list of examples can be found in chapter 1.2 and in the Annex.

The current paper builds on the results and experiences to-date and proposes challenges for the multidisciplinary research community in Europe and beyond.

The recent understanding that complexity is a leading property of living systems[1] has led to realise that the use of information technology (IT) might be the way to tackle with the barriers of managing and understanding complicated diseases such as cancer or schizophrenia[2]. By using mathematical representations, it is possible to integrate the numerous components of a biological system as well as the quantitative interactions that make the outcome(s) of the system unique.

The wealth of data now available from many years of clinical research and informatics, advances in high-throughput genomics and bio-informatics, coupled with recent developments in computational modelling and simulation, presents a wonderful opportunity to understand the physiology of the human body across the relevant 10^9 (nm to m) range of spatial scales and 10^{15} (μs to human lifetime) range of temporal scales and, in combination with the existing grid infrastructure and other HPC platforms, to apply this understanding to the clinic. Human diseases affect structure-function relations at many levels (gene, protein, cell, tissue, organ, and organism) and a multi-scale modelling framework could provide a more rational basis for diagnosis and treatment than currently exists. In modelling and simulating a VPH the link between the genotype, phenotype and environmental must be considered. To effectively perform such a link, a continuum of overlapping models on different biological levels and with different levels of complexity is needed. It is not obvious how to achieve continuity in the models and simulations across biological levels, each of which is normally governed by specific rules and assumptions.

The challenge is to develop mathematical and computational models of structure-function relations appropriate to each (limited) spatial and temporal domain and then to link the parameters of a model at one scale to a more detailed description of structure and function on the adjacent levels. To span from molecules to organ systems requires databases of models at many spatial and temporal levels and software tools for authoring, visualizing and running models based on widely adopted modelling standards. To be trustful, such mathematical models mimicking human physiology, namely "physiologic models" must behave realistically and fit reality as close as possible. This implies two folds.

First, "physiologic models" need to be fed by meaningful and interpretable parameters: that implies the elaboration of virtual data formation models. Indeed, "physiologic models" must be based on an adequate and accurate observation of the living world. The exploration of the living tissues must be optimised by selecting the best physical sensors adapted to the physical nature of what has to be measured (temperature, pressure, biochemical, electro-magnetic processes, motion, mechanical dynamics, fluid dynamics, metabolism,..) providing data signals and images. Specifically for images, the interaction between the exploring wave and the medium is of major importance for getting meaningful measurements. Consequently, an optimal measurement of *in vivo* data, needs dedicated "data formation models" coupling *virtual physical waves propagation models* (US, MRI, X-Rays, TEP) with virtual *human models* including anatomy (complex 3D deformable moving shapes), tissue properties and as far as possible physiology (from the molecular level to the organ). Such models would help to provide virtual reference data bases including both the human tissue properties and the possible physical means to measure it. As a second interest, such simulators would be very useful for teaching young medical doctors showing them for example both the US and the MRI slices of the same region of interest within the body so enhancing their complementary (and very different) content. The "data formation models" would also help the clinician for selecting the best adapted exploring imaging technique by simulating various imaging modalities for his patient, possibly mimicking pathology, in different acquisition conditions (sequences in MRI, angle of view in X-Rays, RF in US, etc) so optimising quality and pertinence of real data acquired while limiting cost and patient irradiation.

Second, a solid validation and clinical evaluation of the "physiologic models" (resp. "pathologic models") outputs versus actual physiological (resp. pathological) data is a necessary condition for the adoption of virtual anatomo-functional human models by the medical community. A reliable confrontation between the simulated data and the real ones is unavoidable and truly challenging. To do so, both virtual and real data have to be available (reference data bases and individualized patient data) and there is a need to define adequate similarity criteria between virtual and real data, the final criterion, from a clinical point of view, being a similar interpretation of those data in terms of diagnosis

[1] Wheng G, Bhalla US, Iyengar R. Complexity in biological signaling systems. Science 1999;284:92-6
[2] Sawa A, Snyder SH. Schizophrenia: diverse approaches to a complex disease. Science 2002; 296:692-5

or therapy. In practice, the main challenge concerns images comparisons in the wide sense: i.e. comparing multidimensional temporal sequences provided by any modality, using any contrast agent and representing any pathology. In practice this means a crucial need for efficient (global, local, temporal, multimodal) segmentation techniques that still remains an open problem. Finally dedicated protocols for clinical evaluation, comparing the virtual model outputs and real data, will help to close the loop by refining models from the measured distortions with reality and improve those models towards truly realistic and helpful "physiologic models".

Furthermore, there is a necessity to create a common language able to accurately describe all the complex structures and functions encountered in understanding and simulating living humans. This requires the development of ontologies, dealing with anatomy, physiology, and molecular and cellular biology, to identify and link model components. A further requirement is the availability of knowledge-banks structured upon the ontologies. These knowledgebanks would gather all knowledge acquired form observational and experimental biology and medicine that might be relevant to modelling of human systems. Each piece of information in these kowledgebases should be marked by its level of evidence and linked with the original report it was extracted from.

In addition to the "technological challenges", there are also major methodological, infrastructural and multidisciplinary challenges that need to be addressed for such a project to be viable and successful.

Finally, the added value of the results has to be carefully examined and communicated. For example, the variations between individuals, and time dependent variations of biological processes of each individual need to be considered in setting achievable goals and milestones in this great endeavour. The most important aspect of all is availability of high quality biomedical data for parameterisation, validation and verification of the models. A key issue is how to convert noisy, often incomplete biomedical data, into knowledge which can be sued to examine and validate models and simulations. Not only the ontological issues related to the semantic coherence, but also the legal and ethical issues related to patient identifiable data and their use must be addressed.

The European Commission (EC) proposes to encourage collaboration across Europe to further explore the research challenges and needs of the VPH idea. In addition to numerous projects dealing with modelling and simulation, the IST programme managed by DG Information Society and Media (DG INFSO) has since 2001 supported activities under the area of biomedical-informatics (BMI). This is a multidisciplinary field that arises from the synergy of biomathematics, medical informatics and bioinformatics. The main mission of BMI is to provide a framework for developing, integrating and sharing biomedical knowledge related to human health from very different research disciplines such as genomics, proteomics, clinical research and epidemiology. BMI deals not only with the integration of health related data on different levels (molecular, cellular, tissue, organ, person and population), but also with computationally demanding tasks of data mining, modelling, simulation and visualisation. More information about projects in this area can be found on the ICT for Health website[3]. Some of the challenges mentioned above are already addressed in the FP6 IST Call 4, *Integrated Biomedical Information for Better Health.* While many proposals to this call probably address specific disorders or diseases, the goal of the *Virtual Physiological Human* has to be much more ambitious: it has to tackle all areas of the human anatomy, integrate data from all levels, provide predictive simulations with almost infinite resolution to let scientists and medical practitioners know as much as possible about the *Real Physiological Human*.

Advanced research projects on related topics such as complex systems[4] are being supported under the Future and Emerging Technologies[5] area of the IST programme. In particular, projects under the complex systems initiative, such as the Programmable Artificial Cell Evolution (PACE) project, address upstream topics. A limited call for proposals is planned under IST Call 5 on the simulation of complex systems[6]. Furthermore, survey initiatives focusing on bioinformatics and systems biology have been supported by the European Commission, DG Research. See, for example, the workshop on systems

[3] http://www.cordis.lu/ist/directorate_c/ehealth/index.html
[4] http://www.cordis.lu/ist/fet/co-6.htm
[5] http://www.cordis.lu/ist/fet/home.html
[6] http://www.cordis.lu/ist/fet/co.htm#cs2005

biology[7] held on December 8th, 2004. Recently a workshop was organised by the DG INFSO Grid Technologies unit entitled "Workshop on Simulation, Visualisation and mixed reality."[8]

The VPH has a precursor initiative: the EuroPhysiome, which reflects a grouping of researchers connected to the IUPS Physiome at the European level. This grouping represents a wish for a stronger and more co-ordinated representation of European research on the international scene.

Short summary of identified challenges

The challenges and activities identified in this paper span from better use of existing data, methods and tools to the development of new methods, standards, libraries and tools for future research.

As a new and ambitious research area, one of the fundamental needs that have been identified is that of **methodology**. Indeed, **modelling complex systems** (biology and diseases are complex systems) is a quite complicated, multidimensional, endeavour. As such, in order to achieve the goal of the modelling process and further to optimize a rather time and resource consuming process, a relevant and easy to practice and flexible methodology is required, including guidance for validation.

Libraries, databanks and data collections are considered essential resources to be built. Further to gene, protein, tissue and medical records databanks, there is an urgent need for biomedical-knowledge banks showing levels of evidence and range of observed variation and reference sources. This needs proper ontologies, fill-in and quality control procedures. The issue of governance of such trusted resources could include guaranteed access governed by Service Level Agreements (peer review access to shared resources is insufficient).

The **infrastructures** needed, will most likely require Grid-enabled algorithms capable to exploit distributed resources in specific European networks, with a specific difficulty associated to the federation of databases that are owned by hospitals and clinical centres. Large scale deployment of distributed computing and storage resources should facilitate data integration and support computationally expensive simulation tasks.

Several **tools** needed **for modeling and simulation** have been identified. They are either basic tools needed to process basic issues underlying the VPH or related to specific modeling and simulation issues. Examples of the first category are mathematical models, data fusion tools, informatics for pathway elucidation, cross-level ontologies, navigation tools, novel in vivo and non-invasive imaging systems, image computing techniques and how to deal with missing data or data uncertainty. In the second category examples such as model learning and hypothesis generation from integrated medical and genetic data, predictive models of disease and drug effects under different conditions of genetic inheritance and environmental interaction, models of human organs including new paradigms to approach multi-level spatio-temporal changes such as, for instance multi-agent based modelling.

Standards, interoperability, proofs of concept, as well as **pilot and deployment projects** are identified as major challenges. Benchmark datasets, standards for validated models and methods for performance evaluation will be needed if models are to be used by other than their designers. But also the method for their use should be validated and easy to apply. Proofs of concept, i.e. *in silico* developments dealing with practical issues, are needed to show that the aim is achieved or at least achievable in well chosen and meaningful cases. Many developments are in the transition between research use and clinical use. Therefore pilot studies performed by the technology/software developers in close collaboration with biologists and clinicians interested in leading edge developments pave the way for research-to-clinical use transition. The biggest related challenge seems to be developing clinically-friendly user interfaces in close collaboration with end-users.

Of **policy** relevance are several fundamental open questions that need to be addressed to produce a framework for the development of the VPH. These questions are perhaps inherent to every collaborative internationally wide project, but remain crucial to ensure the implementation in a sustainable, synergistic and consensual way from the earliest phase. For instance defining the user needs for the various groups of users will be a challenge. Similarly, the question on what the VPH should contain needs to be answered in advance. Perhaps less obvious questions to be answered are

[7] ftp://ftp.cordis.lu/pub/lifescihealth/docs/systems_biology_worskhop_report_jan2005.pdf
[8] http://www.cordis.lu/ist/grids/pub-report.htm

those of ownership and maintenance. Databases will need to be mirrored at multiple sites with daily updating via global high-speed research networks. The question of long-term support to maintain the databases is, therefore, important. Other considerations are that of the use of open-access resource and the supposed advantages versus the possibility that the system be compromised because it might come to be seen as unreliable. Much thought and debate is needed on this issue. To make the VPH commercially attractive, it is important to develop methods for sharing models and simulations while preserving the intellectual property rights of authors/developers.

Finally, we have to face the question of **funding**. Adequate funding systems for multidisciplinary innovative research across scientific communities will be needed. Although unprecedented, there seems to be an unavoidable need for joint research initiatives and funding schemes at the interface between the European funded IST and LIFE thematic areas. The different funding systems for health within European countries pose their own boundary conditions for the introduction of the Virtual Physiological Human as a healthcare and research tool.

1. THE NEED FOR PREDICTIVE MODELS

1.1. The Potential for Predictive Models

Predictive modelling is actually late to come to health care, having long been used in financial services, automobile design, meteorology, and air traffic control. Whereas disease management programs tend to focus on patients already diagnosed with specific high-cost conditions such as heart failure, diabetes, and asthma in an attempt to control utilization, predictive modelling often casts a broader net, focusing on patient populations and outcomes, not a handful of diseases, where information from models must be authoritative, reliable, timely, accessible and relevant[9]. It's widely expected that within the next ten years we will select, train, credential, remediate and recredential physicians and surgeons using simulation, virtual reality, and web-based electronic learning. The world leaders in these technologies will emerge in the next 5 to 10 years.[10]

A challenging case

Large-scale retrospective clinical studies indicate that approximately 80% of the total hip replacements that need to be replaced fail because of aseptic loosening. This term indicates that the prosthetic components lose their mechanical stability with respect to the host bone, and this is not due to infection. When we can exclude problems of massive wear, or adverse immune reactions, or mechanical failure of the artificial materials – failure scenarios that are becoming increasingly rare – this lack of mechanical stability can be explained only with a complex mechano-biological process that, because of adverse biomechanical conditions, erodes the bone tissue at the interface with the prosthesis, replacing it with mechanically unstable soft tissue. These adverse biomechanical conditions are due to the interaction between the design of the prosthesis, the anatomy of the host bone, the mechanical properties of the tissue that form it, and the forces that the joints, ligaments and muscles transfer to the bone-implant interface. These forces depend on the anatomy of the patient, his/her height, his/her weight, the type of movements he/she performs during his/her life, and the neuro-motor strategy he/she adopts to perform them. If we want to understand why, in some patients, the implant becomes loose, while in many others it does not, we need to take into account all of these factors.

But this is currently impossible. Professionals in the field can measure how a particular patient walks, sits down, climbs the stairs, etc. Some advanced musculo-skeletal models can predict the muscle forces required to perform a certain movement. Finite-element analysis models can predict the stresses, strains and relative micro-movements that the muscle loading induces in the bone-implant complex. There are also some mechano-biological models that predict the tissue differentiation and adaptation when the micro-mechanical interface conditions are known. In the near future, we may have imaging technologies that can visualise the concentration in some tissue of a gene or of a protein whose presence may be prognostic. But we cannot yet put together all of these pieces. And, more importantly, we cannot do it for a specific patient or for a population of patients.

Ref: Pancanti et al. (2003) J. Biomech, 36(6):777-85.

The use of numerical models in healthcare are justified by the complexity of the problems at hand which is not amendable with current approaches, leaving these problems unsolved despite we know enough to solve them provided we can recourse to an appropriate method. A few examples are: prediction of individual response to treatment (to optimise therapeutic decision, save money and prevent undue burden for the patients); choose the best strategy for a patient (combination of treatments); decrease the failure rate in drug development (*in silico* proof of concept: prediction of the pleïotropic effects – at the sub-cellular, cellular, tissue, organ, whole body level – of a new chemical binding to a site of action); identifying the target that potentially leads to the most effective searched for effect; understanding the mechanism of multi-genic, complex diseases; identifying treatments for rare diseases. But the real potential seems to be in predictive modelling combined with secondary prevention measures.

1.2. Success Stories on Modelling and Simulation in the area of healthcare[11]

There are a number of success, high-impact stories that have emerged in the last couple of years, mostly in the US and Europe. The main examples include simulation models for the transmission and

[9] It is interesting to note that Virtual environment training systems are at the same stage of development as airplane simulators were in the late 1930's, and airplane simulators were not accepted as valid training devices until 1955.

[10] PJ Gorman et al, Center for Advanced Technology in Surgery, Stanford. Am J Surg Nov 2000.

[11] The list of projects presented in this paper should by no means be considered as representative of all ongoing activities, but is merely a very first collection of examples. They were simply collected through input from the participants and without any extensive search or specific selection criteria. The follow up activities to this paper will include the compilation of a more extensive and structured list.

control of disease, as well as non-traditional educational tools which have been developed such as a biological storytelling system, animations of biomedical processes and concepts, and interactive virtual laboratories to inspire user's strategic, creative and innovative thinking. Some examples are mentioned here below, others can be found in the annexes.

- In Europe, LYMFASIM[12] is a simulation model of the transmission and control of lymphatic filariasis that has been developed to predict the long-term impact of intervention strategies based on vector control and chemotherapy. The current LYMFASIM model was used for a sensitivity analysis to estimate the number of treatment rounds and the treatment coverage that are needed to achieve elimination of bancroftian filariasis through annual mass treatment with either diethylcarbamazine (DEC) or ivermectin.
- Supported by the BIOMED IV project, the dose-effect relation (DER) on the prevention of angina pectoris of a substance acting solely on a potassium current of the sino-atrial node cells has been predicted. The observed DER, after hundreds of patients have been included and followed-up in three randomised trials, fitted very well the predicted DER. If the prediction had been accepted by the pharma developing the compound, time and money would have been saved by performing a single confirmatory phase II trial[13].
- The relation between the spontaneous evolution of a disease and the treatment evolution is predictable through a modelling of the mode of action of the treatment (effect model); the relation is specific to a treatment, a disease and a given marker of the evolution. The use of this approach has shown that the relation is not always linear, and that it is possible, through this model, to predict the response to the treatment for a given patient. One of the many consequences of the reality of this relation and the possibility of estimating it through modelling is a change in the decision making process of the doctors[14]. An effect model for the assessment of drug benefit: example of antiarrhythmic drugs in post-myocardial infarction patients[15].
- More than 300 compounds, that have been demonstrated to decrease the size of cerebral infarction in animal models of human stroke, failed once they were tested in real human patients with evolving stroke (actually some increased the size of the MRI infarct); nobody understood why such a gap between animal and human findings does occur; as a result, around year 2000, big pharmas abandoned the search for treatments of this condition, despite acute stroke is quite prevalent in Europe and represents for patient and for the community an enormous burden. From simulation with a model of ischemic stroke it was possible to sort out plausible explanations (in short: differences in cortex anatomy, white/grey matter ratios and neurons over astrocytes ratios between rodents and humans) that cannot be sorted out by other methods than simulation[16].
- In the US, Interactive Biological Simulation - BioSim[17] is an educational approach at Carnegie Mellon University (USA). This is an interactive and visual problem-solving environment for the biomedical domain. They designed a biological world model, in which users can explore biological interactions by role-playing "characters" such as cells and molecules or as an observer in a "shielded vessel", both with the option of networked collaboration between simultaneous users.

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[12] Supported by the WHO, Principal Investigator Prof. J D F Habbema, Erasmus University, Rotterdam; Methods Inf Med. 1998 Jan;37(1):97-108

[13] Partly published in Chabaud S, Girard P, Nony P, Boissel JP on behalf of the THERMOS group. Clinical trial simulation using therapeutic effect modelling: application to ivabradine efficacy in patients with angina pectoris. J Pharmacokinetics Pharmacodynamics 2002; 29: 339-63.

[14] Basis published in Boissel JP, Collet JP, Lièvre M, Girard P. An effect model for the assessment of drug benefit: example of antiarrhythmic drugs in post-myocardial infarction patients. J Cardiovasc Pharmacol 1993; 22: 356-63

[15] J Cardiovasc Pharmacol 1993; 22: 356-363; however, in this article only the empirical basis was tackled with in a special case; the model approach article is under preparation.

[16] These results are not yet published. However, the main aspects of the model used have been published .Duval V, Chabaud S, Girard P, Cucherat M, Hommel M, Boissel JP. Physiologically based model of acute ischemic stroke. J Cereb Blood Flow Metab 2002;8:1010-8; Dronne MA, Boissel JP, Grenier E, Gilquin H, Cucherat M, Hommel M, Barbier E, Bricca G. Mathematical modelling of an ischemic stroke: an integrative approach. Acta Biotheoretica 2004; 52:255-72.

[17] http://www.biosim.com

- CIIT Centers for Health Research in North Carolina constructs biologically-based simulation models. These pharmacokinetic models using tools like Simulink[18] have important potential applications in the prediction of human health risk from exposure to manmade chemicals and in the development of new pharmaceuticals. The Simulink model confirmed that predicted levels of nasal mucosal DPX for a given inhaled concentration of formaldehyde in rats and monkeys, when extrapolated to humans, would enable researchers to predict human risk. Government agencies, including Health Canada and the US Environmental Protection Agency, will use these findings to help establish environmental standards for formaldehyde usage.

- Active Health Management (AHM)[19] makes use of the results of Heart Outcomes Prevention Evaluation (HOPE) soon after they were published last year in Lancet and the New England Journal of Medicine. The study showed that an ACE inhibitor, Ramipril, is beneficial in a broad range of patients who are at high risk for cardiovascular events but who lack evidence of left ventricular systolic dysfunction or heart failure. The benefits observed were in addition to those achieved via proven secondary prevention measures, such as aspirin, beta blockers, and lipid-lowering agents. The US federal government has expressed interest in these predictive models, and AHM has two pilot programs under way with the Federal Employee Health Benefits program and Medicaid.

From these and other projects referenced in the annexes, one can deduce that the efforts are numerous albeit fragmented all over the world, addressing modelling and simulation problems under the usual interest of modellers, i.e. on single pieces of the biological process at hand. Taking into account these efforts would therefore mean that building multilevel and multi-process models imply either the re-modelling of the single pieces or the re-using, when possible, of available models. Re-usability of and communication between models are evident issues requiring co-operation efforts.

2. REALISING THE VIRTUAL PHYSIOLOGICAL HUMAN: RESEARCH NEEDS AND CHALLENGES

Realising the VPH will be an effort that must build on advances in many different scientific disciplines. Although a number of research initiatives have advanced the possibilities in many directions - including bio-informatics, medical informatics, biomathematics, bio-medical modelling, predictive simulation, and visualisation - the combination of information from all levels ranging from molecules to systems and patient levels creates a new level of complexity. Perpendicular to the research direction, the acceptance and every-day-use of this new technology in clinical and general healthcare might be the biggest challenge. Demonstration of the benefits of VPH is needed to open a longer term perspective for commercial exploitation of its resources.

The VPH needs to be integrated in an IT infrastructure (sometimes called a Grid) that links all the necessary resources. The goal in Europe would be the creation of a single Health Grid, i.e. a Grid comprising all relevant resources, naturally including security and authorisation features to handle subsidiary independent nodes. If this IT infrastructure is to support healthcare, it needs to be constructed on a backbone of reliable, maintained, supported resources. The set of resources will need to include both the academic/scientific shared repositories and IT systems and commercial services.

Enormous progress has been made in recent years aided by the increases in performance of computing platforms in numerical modelling providing realistic and validated predictions of many very complex phenomena. However, it should also be mentioned that there is a real need for the continued development of numerical modelling and simulation technology to address the future challenges of multi-scale, multi-physics problems that arise naturally and automatically in virtual human modelling. That need is justified by the strongly held belief that the clearly documented advantages of numerical modelling in the engineering industries, for example, can be brought to the health sector. However, the adoption to biomedical-problems will take new developments at the core of this technology (for example efficient iterative solvers designed for this class of problems).

[18] http://www.mathworks.com/products/simulink/
[19] http://www.activehealthmanagement.com/

Although image analysis is a developing area in medicine, the point is that new efficient and reliable methods must be designed to automatically instantiate these models to a given individual from the available biomedical signals, in particular from medical images, and also from anatomical and genetic information. Image computing technology will also mediate the process of integrating in personalised anatomical coordinates information gathered from different imaging systems that provide in vivo and structural or functional measurements at various scales of observation. Building such personalized models is a challenging goal which requires, in particular, the development of new computational imaging and data assimilation methods coping with massive numbers of measurements and unknowns. These developments will usually go hand in hand with developments in medical imaging systems that will unveil either structural or functional aspects of the observed entities or improved observational resolution both in spatial or temporal dimensions.

The challenges and activities identified in this paper span from better use of existing data, methods and tools to the development of new methods, standards, libraries and tools for future research. Particularly related to the available data it is important to find a balance between the quality and quantity of existing sources and the needs for new data gatherings.

2.1. Methodologies

Modelling complex systems (biology and diseases are complex systems) is a quite complicated, multidimensional, endeavour. As such, in order to achieve the goal of the modelling process and further to optimize a rather time and resource consuming process, a relevant and easy to practice methodology is required. This includes guidance for validation. It should be flexible enough to meet every case. Mathematics should meet the complexity of the living system to model. This requires to improve available mathematical tools and to invent new tools. This will be achieved through a support of targeted research in biomathematics based on a tight cooperation between mathematicians and life and health scientists.

Also, there is a need for methodology (and techniques as well) for integrating models in activities. Two examples: 1) using numerical therapeutic models would help new drug innovation and guide the course of a development; however, for development, although we need it, we do not have a process which, by integrating new data from *in vitro* and *in vivo* experiments with the new chemical entity in the evolving model would permit through a Bayesian approach a more precise and rapid go-no-go decision taking; 2) predictive medicine: prediction tools are not used because (among other reasons) there is no methodology for integrating them into the decision making process of the doctors.

Different methods to approach the VPH which were suggested are:

- An integrated approach of systems biology and systems epidemiology could provide a unified vision and help to overcome the existing gaps. This would allow both the data on molecular basis and on the patterns of individual genetic variation and environmental exposition to be incorporated into the same models.
- The use of specific paradigms to better understand a desired level of the human body in detail and subsequently relate the information and data with specific pathologies.
- The simulation can be approached through a first phase in which a model representing the individual's anatomy is constructed. The internal anatomy is almost always recovered through 3D medical images. The first step in this process is the segmentation of the image, which consists of labelling each of the voxels to identify its material (bone, articular cartilage, artery wall, etc.). In addition, several biomedical signal and imaging sources can provide complementary functional information from where boundary conditions for personalised simulation can be derived. Signal and image registration will therefore play an essential role in spatio-temporal normalisation and alignment of all available data.

2.2. Libraries, Databanks and Data Collection

On one hand, generic techniques for data representation, acquisition, storage, sharing, processing and integration, that are disease and "level" independent, and on the other, very specific context dependent data processing and integration techniques, are needed. Further to gene and protein databases, there is an urgent need for bio-knowledge banks where model designers (and users) would find the knowledge and data they need, with their level of evidence and range of observed variation, their sources (references) and other information as well. This needs proper ontologies, fill-in and quality control procedures. Guaranteed access to trusted resources governed by Service Level Agreements (SLA) is needed (peer review access to shared resources is insufficient).

Some examples of databanks/libraries needed are:

- Patient data banks/Biobanks. Simulation requires real data; a depository of patient data would be helpful for model designers (parameterisation, validation) and model users (in certain fields, e.g. drug development). An important milestone to make progress in these directions is the development of these large databases of subjects and patients including biomedical signals and images as well as genetic information. The collection of both medical and genetic information of same patients would enable verification of some of the models and assumptions as well as provide inspiration based on new knowledge obtained by the data mining techniques.
- Database of the biomechanical properties of tissues and organs, for applications such as medical simulation (there is a need to identify existing sources of physical and physiological data for building more accurate and realistic models and simulations).
- Digital atlases that contain dynamic information across spatial and temporal scales of abstraction.
- Libraries of anatomical images with functional imaging data, of tools for processing observational data, and of tools for modelling or simulation to produce predictive measures of performance or outcome, going beyond the observational measures described previously.
- Data on biological systems: 1) components and between component interactions, relation of components to cell structures, etc. 2) signal flow rate, enzyme kinetics, concentration, molecule turn-over rate, etc. Former data are necessary to built the model, later data are necessary to value the model parameters.

2.3. Infrastructures

Huge computing power is already required to run advanced computational models in their direct mode (for prediction) or inverse mode (to adjust to a specific patient from biomedical measurements). The amount of required computing power to process large databases will require the development of grid-enabled algorithms capable to exploit distributed computing power and data in specific European networks. Although data storage is a responsibility for hospitals, many business opportunities can arise from data sharing and processing applications. However, federation of databases requires additional complex structures and computing effort. Large scale deployment of distributed computing and storage resources should facilitate data integration and support computationally expensive simulation tasks. The VPH Grid requirements are for large scale deployment studies allowing evaluation of a larger range of requirements, including local deployment aspects, and practical experience with production Grid use. Specific challenges identified are:

- Grid infrastructures for High Performance Computing (HPC) (for mesoscopic simulations), High Throughput Computing (HTC) (for parameter space explorations), Database federation and integration (for data disclosure), problem solving environments (for complex systems) simulations.
- Health Grids represent an access to distributed data sources, but many hospitals are reluctant to let the information flow outside the hospital bounds. For a large-scale deployment of Health Grids, and thus for opening an attractive business, it is important to leverage security up to a trustworthy level of confidence that could release a generalized access to data from the outside.

- Support and infrastructures for large scale collaborations such as deployments studies for testing and validation to ensure user acceptance and collaborative research. The leading centres in Europe could combine complementary data to create and to manage an anatomical data resource, spanning the modalities and including functional data.

2.4. Tools

There is also a need for tools, some of them endorsed by strong evidences. They can be divided into two classes, the first being connected to tools needed to prepare the starting conditions, the second related to specific tools for modelling and simulation.

Tools for preparing the basis for the VPH

- Not all the biological sub-systems have a mathematical counterpart fully meeting all its component interactions (number, functionalities).
- There is a need for informatics for pathway elucidation, integrating proteins, micro arrays & SNP information for understanding pathway mechanisms in relation to specific diseases; integrated system biology and genomic epidemiology; and sound knowledge representation systems for phenomes and genomes. Informatics tools will be needed to navigate over computer simulations of the genome, proteome, metabolome and their dynamic representations.
- The development of hierarchical parameter transfer methods for the integration of different experimental and/or simulated data (i.e. data fusion, which is a fundamental tool needed by users).
- Not all available knowledge the model is designed to incorporate has the same level of evidence and, further, there is a large variability of the values of all parameters (e.g. affinity constant) across the literature. In addition, in a complex biological system there are always values lacking regarding a few or sometimes many between component interaction parameters; all these three aspects a source of uncertainty on the range of validity of the models and raise unsolved problems for designing a relevant model. Tools and techniques for integrating parameter range of experimental values, level of evidence and missing data are needed. For models aimed at predicting individual patient disease behaviour or response to treatment, integration in the model between and intra-individual variability needs to merge deterministic and/or stochastic multiscale machine learning and statistical (regression) solutions.
- There is a need for development of specific tools to correlate for instance the shape and evolution of anatomical structures (phenotype) with the genetic information (genotype) and/or with a certain number of pathologies. In this context, the modelling of the imaging process can be seen as a precursor to coupling anatomical models to individual patient data.
- Specific computational imaging techniques are needed. These include improved spatio-temporal resolution in biomedical signal and imaging sensors; constrained image reconstruction; statistical image and shape analysis; non-rigid image registration and morphometric tools; knowledge based image segmentation and labelling; efficient geometry modelling and meshing for complex structures; statistical shape modelling and morphometrics, computer aided diagnosis and pattern recognition, data mining tools and advanced visualisation and fusion of multimodal data as well as tools to extract specific image features which can be related to some important model parameters in order to constrain the model to the observations.
- Obviously, but importantly, biomedical cross-level ontologies will need to be generated. This need can clearly be seen if we think of further needs like the coupling of sub-models, particularly at the interface across scales, and the (to be scientifically elucidated) relationships between information (signals); regulation (control), and the metabolism (biophysics/biochemistry) of living organisms.
- Last but not least, it is necessary to develop methods to compute statistics on anatomy and functions from large databases of biomedical images and signals. This is a difficult problem because it requires the development of robust inter-subject registration methods and also the development of new mathematical tools to compute statistics on manifolds which are not vector spaces.

Tools for modelling and simulation

Novel (hierarchical) modelling techniques will have to be developed as to perform intermediate modelling (mesoscopic modelling), including multi-domain modelling; hierarchical reconstruction and embedding (linking different levels of models); data fusion (integration of different experimental and/or simulated data); 'living simulations' (linking simulations to instruments with mutual interaction); parameter extraction (biostatistics); parameter sweeps (high throughput computing); and visualization and Virtual Reality (Interactive/multimodal) and models that combine mathematical/statistical, logical/argumentative, schematic (pathway, tabular) and other visual representations.

Specific challenges are:

- Model learning and hypothesis generation from integrated medical and genetic data will have to be conceived.
- Realistic, robust and predictive models of disease and drugs under different conditions of genetic inheritance and environmental interaction.
- Modelling of the function of the human organs using spatio-temporal information on the changes of the functions and the parameters regulating the mechanisms at the cellular and the cellular communication level.
- 3-D models of the body, combining anatomic and functional details, where metabolic pathways and processes can be implemented, linking structural information, will have to be developed.
- Development of a common modelling language for creation of biomedical models. Current examples include AnatML, CellML, SBML and the Common Anatomical Modelling Language (CAML).
- The development of multi-level stochastic aggregation models that would account for evolutionary adaptations from the molecular/cellular levels to the higher processing levels of tissue and organ physiology will be needed.
- Modelling massively interacting entities as in the immune system. Full-scale computational models of the entire immune system are not simple, but will rely on integration of many different interacting components. However, many of these components may be much simpler models of how immune systems – step by step – deal with pathogenic organisms. These simpler models may therefore successfully model essential subcomponents of the immune system, provided that the biological mechanisms controlling these steps are sufficiently simple.
- Agent-based modelling: The vision of a multi-agent approach is that the behaviour and evolution of an ensemble of cells is computed in such a way that each cell is represented as an agent interacting with its environment. This environment includes the neighbouring cells. A rule set is developed that describes signalling, interaction and response processes (see brief description of the Epitheliome project below).

2.5. Standards, Proof of Concept, Pilot and Deployment Projects

Standards for validated models are needed if models are to be used by other than their designers. They should have their validity guaranteed. Also, the method for their use should be validated and easy to apply.

In each of the potential field where numerical models in biomedicine are considered, we need **proof of concept**, i.e. *in silico* developments dealing with a practical issue, such as better

GEMSS: an example of a pilot study.

Pilot studies are ongoing, recently within the GEMSS project (http://www.ccrl-nece.de/gemss/), in the area of simulation tools for reconstructive maxillo-facial surgery. The target is to provide a tool built around a computational Grid service (simulation service) that allows the surgeon to optimise the operational procedure, by virtual try-out, and at the same time provides a visualisation of the final result, which can be used within consultation with the patient.

medicine innovation or more relevant and precise prediction of response to treatment, showing that the aim is achieved or at least achievable in well chosen and meaningful cases. The related challenges identified are the following:

- The biggest one will be developing clinically-friendly user interfaces in close collaboration with end-users. Any consortium should include the clinical services, which can collect the data with informed consent, advice on its interpretation, and ultimately test and exploit the resulting tools.

- It will be very important to determine the normal physiological range of variation of a model parameter (at the gene, protein, cell, tissue and organ levels) and how this range is affected by specific diseases. As stated previously these values must be included in the biobanks and libraries.

- Benchmark datasets including ground-truth information and evaluation protocols that can be used to catalyze the development of the VPH as well as to standardise performance evaluation.

- For some applications, it may be necessary to develop an animal model for gathering additional data and testing predictive models. Suggested species include the pig, because of the similarity in cardiovascular characteristics between pigs and humans, and the mouse, which is used extensively for genetic analysis.

Finally, it is important to note that many developments are in the transition between research use and clinical use. Pilot studies performed by the technology/software developers in close collaboration with clinicians interested in leading edge developments pave the way for research-to-clinical use transition.

3. A EUROPEAN INITIATIVE: THE EUROPHYSIOME

3.1. A Prime Initiative

The European Physiome initiative reflects a grouping of researchers in Europe all, in one way or another, connected to the IUPS Physiome[20]. The underlying idea is to enhance collaborations in Europe and position European research more strongly and united in the international context. It will enable its subscribers to access material provided by many users, sites and authorities, and to exploit this material in the context of their own requirements.

To gain acceptance this EuroPhysiome project will need to be strongly linked into techniques used in clinical assessment and to clinical decision support systems. As well as their use in research and clinical diagnostics the Physiome models have applications in medical education, the design of medical devices, tools for virtual surgery and surgical training and, drug design and toxicity testing. A long term plan is needed in co-ordination with non-European Physiome projects and which has milestones for research and implementation.

In its original position, the promoters suggested that the EuroPhysiome should include:

- *A library of anatomical images, both static and dynamic, complemented by functional imaging data.*
- *A library of tools for processing, in the most general sense, raw observational data to derive additional information. This might include image processing operations and data fusion operations, but will extend to the integration of heterogeneous data formats, for example from imaging combined with the electronic health record, with data from epidemiological studies and with genotype and/or phenotype data. It might include data-mining tools for identification and extraction of relevant information from heterogeneous data sources. Any or all of these tools have the potential to contribute significantly to the development of knowledge, of treatment protocols, to diagnosis and to risk assessment.*

[20] http://www.physiome.org/, http://www.physiome.org.nz

- *A library of tools for modelling or simulation to produce predictive measures of performance or outcome, going beyond the observational measures described previously. These tools might operate at any or all of the length scales from molecular up to patient levels.*

Before starting the actual development work, a considerable number of consensuses will have to be found. Each field of expertise traditionally develops on its habits, vocabulary and standards.

But standards from different fields are often incompatible. A way to increase interdisciplinary communication is finding a consensus on common standards. A number of standards, such as the DICOM standard for medical images, are clearly established and represent the obvious choice for the EuroPhysiome. Alignment with and adoption of the ML standards developed within the International Physiome project is also considered to be self-evidently worthwhile. The development of database standards, for example for the electronic health record, is well-advanced, at least at national levels.

Beside standards, different fields are often using different tools (algorithms, development tools, hardware). Alternatively, carefully describing each field of knowledge by means of ontologies could be considered. The vision of open-source and open-access software and environments is shared, although it is recognised that some users will add data or functionality that they might need to exploit commercially in a business model. Consequently, and given that often clinical data from physiological measurement systems is in proprietary format, and that extracting data from these systems for further processing is not always straightforward, EuroPhysiome considers separating out raw and unprocessed data libraries, whether image, time-series or other, from those embedded within the models.

A key element of success for multidisciplinary projects is the extensive understanding the involved disciplines may have of each other. Unfortunately, very few professionals have such a multidisciplinary background, and often individual experts are highly specialized and systematically approach research issues from a monolithic perspective. A necessary measure is, therefore, the multidisciplinary education of professionals. For example, Research Training Network could allow bright subjects to spend times at various locations. These successive stays would allow them to better understand each field vocabulary, approach and organizations. With this knowledge, these multidisciplinary researchers should be better prepared to make the necessary connections between fields. Such training programs would also allow individuals to understand each other's cultural differences. Indeed, if difference of cultural background is one of the strengths of the European Union, it can also be a weakness in a large and complex research project if efforts are not made.

One of the big challenges of the EuroPhysiome is to be accepted in Clinics. Beside extensive validation, the way of performing clinical activities will request from therapeutic teams to change their daily way of working, and organize themselves around highly multidisciplinary teams. This is often not the case, and specialized teams are often used to deal with a patient's problem from their own limited perspectives. Frequently, some competitions also exist between specialties. This will request an important change of daily habits. This effort, certainly not be underestimated, might be solved (at least partly), through political decisions.

An example for the implementation of Step #1: The LHDL (Living human digital library) proposal

A community server will be established using off-the-shelf software for community building and collaborative working. Three software frameworks will be developed, independent but strongly integrated, that will provide all the infrastructural services that the available software cannot provide:

- An *application framework* for management, fusion and exchange of biomedical digital data. The single researcher should be able to combine into a single archive CT and MRI datasets, EMG registrations, motion capture data, results from finite element and multi-body dynamics modelling software. The framework should also provide core capabilities for remote collaboration, in particular for collaborative exploration of the data.
- A *service framework* for the development, the sharing and the choreography of biomedical software services, possibly organised as web services, that let you visualise and process the 2D, 3D, and 4D datasets stored in the repository.
- A *knowledge management framework* that enables users to develop semantic web services that keep all the data and algorithmic resources of the repository organised in agreement with a dynamically defined ontology, and services for advanced resource discovery and retrieval, web services choreography, and maintenance of the metadata and of the ontology.

3.2. Achieving the EuroPhysiome: a Roadmap

A suggested roadmap to achieve the ambitious objective could be pursued in three steps:

- **Step #1:** Creation of a virtual research organization for community building, collaborative working, resource sharing and resource assembly that takes advantage of the services offered by the grid infrastructures deployed in Europe. (e.g Digital Library)
- **Step #2:** Establishment of a large community of researchers and prospective users that create a large repository of data and algorithms, organise it around a consensually defined ontology, and define the interface specifications for the various clinical, industrial and societal use cases (community building and digital content enrichment).
- **Step #3:** Development of vertical projects aimed to solve specific use cases and establishment of a long-term sustainability model (*in silico* humans research).

An example of implementing Step #2: The Living Human Project (www.tecno.ior.it/VRLAB/LHP/):

The Biomechanics European Laboratory (BEL), after an extensive preparatory discussion among the 4,500 researchers on the BIOMCH-L mailing list, condensed into a list of statements that were discussed extensively during the BioNet Event by more than 100 delegates from the most prestigious European research institutions, launched in late 2002 the *Living Human Project* (LHP).

The *Living Human Project* will develop a worldwide, distributed repository of anatomic-functional data and of simulation algorithms, fully integrated into a seamless simulation environment and directly accessible by any researcher in the world. This will establish Europe as the leader in the area of human functional modelling, directly challenging the Visible Human Project and related American initiatives.

The further development of this roadmap will be taken up by the project STEP resulting from the 4th call for projects for IST in FP6. The project is currently under negotiation.

4. POLICY ISSUES

There are several fundamental open questions that need to be addressed to produce a framework for the development of the virtual physiological human.

Who will be the users?

The first target users include not only **clinicians and researchers** but also the IT, pharmaceutical and medical device **industry**. The researchers should not be only clinical researchers but also researchers from many different areas such as medical-, bio- and neuro-informatics, medical device designers and manufacturers, pharmaceutical developers and/or those involved in biomedical education including students. Each of these groups will have their own specific requirements. Some might require just a few sample datasets to use as input to their own processing procedures: many of these will have very prescriptive input data requirements. Others might require facilities for data-mining, for data fusion, data combination of data, for representation of epidemiological information, and/or for data mining.

What should it contain?

An overview from our perspective of what the virtual physiological human might encompass is presented in this paper. This glosses over the huge issue of the detail of the coverage. For the data library alone, how many samples should it offer? The Visible Human has proved an enormously valuable resource; nevertheless this resource is very limited in that it represents only post-mortem anatomical information, and for just two individuals. The VPH should offer a much more comprehensive library of data, but the definition of the extent of this library is a challenge in itself. A complete description of even a single individual under a wide range of physiological loading conditions is already impractical, so what will be the boundaries of the data collection? What is the degree of continuity required between data structures? Is it necessary, for example, that organ-level image data should always be complemented by functional data, by molecular imaging, by genetic profiling, by histological examination results, etc? For many purposes this would be most desirable (if impractical!), but for others completely unnecessary and restrictive. Is it appropriate to include individual (anonymised) data at all, or should all data be 'averaged'- and if so, how? Most teaching hospitals now have data storage facilities running into Terabytes, and even these contain relatively little information compared with that which might be required for the libraries of the virtual physiological human. With respect to processing tools, what should be offered? Certainly many potential users will have their own specific tools, often not shared in the public domain, but others would welcome access to a whole battery of processing and simulation tools.

There is a need to form a coordinating team, working groups and other commonly shared resources such as a web site that can provide information about biomedical models, simulations and images. This may require professional staff and coordination that require additional funding.

The creation of a web-based journal with a focus on medical modelling and simulation in medicine was suggested. Although there is currently a number of high quality scientific journals publishing from time to time articles on this topic, there is not a well identified journal devoted to publication of high quality research papers in this specific domain exclusively.

Who will 'own' it, and how will it be maintained?

We might first ask the question as to whether we want or need, and whether it is practical to maintain, a central resource at all. As mentioned earlier, each hospital maintains an increasingly large database that contains much of the information that we might wish to access, and there is a lot to be said (particularly in terms of practicality) for distribution of data storage facilities. The sheer size might make anything but distributed storage impractical, but we have all experienced the frustration of useful data disappearing from the web as sites come and go and links are broken. There will be massive, and probably insurmountable, security issues with external access to the primary hospital databases. Export of specific and anonymised data might, however, be possible, and is, indeed, a fundamental tenet of many current research programmes. There will be major issues of how data qualifies to become part of the physiological human libraries, and of how access to the data is funded and supported.

Governance is therefore a critical issue. The research community would probably prefer to have access to the widest possible range of resource material from which it can choose those elements that might be useful for any particular application. It would probably consider that the time taken to sift and sort the material would be a fair price to pay for the availability of the resource. At the other end of the spectrum, the regulatory authorities would probably not entertain adoption of any of the resource unless it had been subjected to rigorous peer review and validation procedures. Industry would probably sit somewhere between these positions. Even if the risk associated with the use of the resource will always remain the responsibility of the user, there should be some quality control at all on the elements that contribute to the VPH.

Databases will need to be mirrored at multiple sites (Europe, US, Asia-Pacific) with daily updating via global high-speed research networks. The question of long-term support to maintain the databases is important.

Although we all have the utopian vision of an open-access resource, freely downloadable, usable and extendable, there might be an argument for controls on data, tools or models qualifying for inclusion. Otherwise clinical and industrial take-up and adoption might be compromised because the system might come to be seen as unreliable. Unfortunately any form of policing is likely to provoke argument, and there will be the question of who is qualified to judge the quality of any candidate material. It is reasonably common practice to make databases available to a limited group of users for a period long enough to iron out the bugs - but with a policy of opening up more and more as we gain confidence in the applicability of the models & data and the range of potential users therefore expanded. Much thought & debate is needed on this issue. It is important to develop methods for sharing models and simulations while preserving the intellectual property rights of authors/developers

The associated legal and ethical issues such as medical-financial considerations and data collection possibilities must be identified and handled.

How will this be funded?

Adequate funding systems for multidisciplinary innovative research across scientific communities, including maintenance costs ex. see libraries mentioned above and testing and validation costs are needed. There is an unprecedented and increasingly unavoidable need for joint research initiatives and funding schemes at the interface between the current and future IST[21] and LIFE[22] thematic areas.

[21] http://www.cordis.lu/ist/

These should promote, and practically allow, designing disease-oriented acquisition protocols and collection of multiscale biobanks developed in synergy with integrative computational modelling and simulation toolboxes, computational resources, and data integration infrastructures.

The different regulatory frameworks and funding for healthcare delivery systems and approach eHealth related research and deployment in EU pose their own boundary conditions for the introduction of the tools related to *Virtual Physiological Human* in clinical practice. In some countries, the decisions as to which mechanisms can be employed are taken within the particular institute, based on a combination of medical-financial considerations. In other countries, a centralised decision - perhaps the authorisation/specification by health insurers - on allowable tools is taken. The eHealth action plan[23] adopted by the European Commission on 30 April 2004 and the associated roadmap should both contribute to facilitate these aspects. It is clear that it will not be sufficient to demonstrate the medical impact of Grid-based simulation tools, but also the economic impact – and that demonstration needs to be made to the appropriate decision makers.

Other suggestions for funding and maintenance structures are:

- Through the use of a private (non-governmental), non-academic, non-profit entity if possible
- An initiative jointly funded by several Governments with institutions like EBI, NIH, Welcome Trust, etc. having an oversight role or the set-up of a permanent and publicly-funded institution
- At European level, to develop, to support and to maintain this resource to the benefit of the whole of the European (and indeed worldwide) community.

[22] http://www.cordis.lu/lifescihealth/home.html
[23] http://europa.eu.int/information_society/activities/health/policy_action_plan/index_en.htm

ANNEX 1: Specific Projects, Topics and Related Initiatives

A list of other similar or related initiatives to the VPH are given below:

1. International Initiatives:

1. The **IUPS Physiome Project**[24] is an internationally collaborative open source project to define the physiome by providing a computational framework to facilitate the understanding of the integrative function of cells, organs, and organisms. The Project is focused on compiling and providing a central repository of databases, linking experimental information and computational models from many laboratories into a single, self-consistent framework. It aims to develop an infrastructure for linking models of biological structure and function in human and other eukaryotic physiology across multiple levels of spatial organization and multiple time scales. The levels of biological organisation, from genes to the whole organism, includes gene regulatory networks, protein-protein and protein-ligand interactions, protein pathways, integrative cell function, tissue and whole organ structure function relations, and finally the integrative function of the whole organism. This conjunction of research effort will promote comprehensive databases and an integrative, analytical approach to the study of medicine and physiology. It can thus be seen to be fulfilling the missing link between the Genome project and human physiology, by creating an exhaustive in silico model of the human physiology. The Physiome Project is a truly international undertaking, organised under the auspices of the International Union of Physiological Sciences (IUPS), with co-chairs in New Zealand, the USA, Australia, Japan, the United Kingdom, Germany, the Netherlands and Israel. In the context of the Physiome Project, are included integrated models of components of organisms, such as particular organs or cell systems, biochemical, or endocrine systems. The **CellML** language is designed to represent mathematical models of biological systems

2. European Initiatives

1. The **Living Human Project**[25] (LHP) will develop a worldwide, distributed repository of anatomo-functional data and of simulation algorithms, fully integrated into a seamless simulation environment and directly accessible by any researcher in the world. The objective is patient-specific bio-numerics (-mechanics, -electromagnetics, etc.) and image-processing (both for pre-processing & visualisation) for the complete human body, with integration of individual systems through hierarchical approaches at the algorithmic level and through middleware operating across distributed systems for Grid computing, using a semantic web to manage the information. The focus of the Grid approach is to provide services to medical or clinical users, removing any need for them to have to handle the details of the computing systems or simulation methods.

2. The **Epitheliome initiative**[26] proposes an original modelling paradigm constructed on the idea that the social behaviour of cells can be represented by the interaction of software agents and, more particularly, that the rules that govern the behaviour of agents can be replaced by the underlying mechanisms to give a biologically determined model.

3. **SimBio**[27] **and GEMSS**[28] are examples of systemic modelling and simulation developed for the systemic and organ levels. The SimBio project targeted bio-physics problems related to human body parts of interest for specific medical treatment – as a means to realize patient-specific bio-numerical modelling. The key distinguishing factor, compared with image processing or image reconstruction in the same applications arena, is the use of computational methods for predictive purposes. The GEMSS project has developed a Grid middleware for medical simulation services building on common Grid standards. The focus was on innovative extensions that support complex simulation and medical image processing applications including security models

[24] http://www.physiome.org/ , http://www.physiome.org.nz/
[25] http://www.tecno.ior.it/VRLAB/LHP/
[26] http://www.dcs.shef.ac.uk/~rod/Integrative_Systems_Biology.html#The_Epitheliome_Project
[27] http://www.simbio.de/
[28] http://www.ccrl-nece.de/gemss/

compliant with European legal issues, fail-over and recovery from errors as well as workflow and service orchestration techniques for time-critical processes.

4. **@neurIST**[29] is a recently funded European Integrated Project that will develop an IT infrastructure for the management and processing of heterogeneous data associated with the diagnosis and treatment of cerebral aneurysm and subarachnoid haemorrhage. The data span all length scales, from molecular, through cellular to tissue, organ and patient representations. These data are heterogeneous in form, including textual, image and other symbolic structures, and are also diverse in context, from global guidelines based on the broadest epidemiological studies, through knowledge gained from disease-specific scientific studies, to patient-specific data from electronic health records. New methods are required to manage, integrate and interrogate the breadth of data and to present it in a form that is accessible to the end user. @neurIST seeks to provide channels for the integration of all data sources on cerebral aneurysm. Two platforms will be developed that will exploit directly the IT infrastructure and will provide immediate application to other disease processes. The primary theme of @neurIST is to develop vertical integration across data structures and across length scales, but horizontal integration at every level of abstraction, from access to information sources, to complex information processing, knowledge representation, structuring and fusion will cement the collaboration between the disciplines. @neurIST will transform the management of cerebral aneurysm by providing new insight, personalised risk assessment and methods for the design of improved medical devices and treatment protocols. Furthermore the approach will be extendable to other disease processes and scalable to federate a large number of clinical centres and public databases. A total of 29 EU partners participate in @neurIST as well as 4 non EU external collaborators; the project will be coordinated with IUPS Physiome project. The project was submitted to the 4th call of FP6.

5. **CARDIOSENSE3D**[30] (Images of Cardiac Electro-Mechanical Activity) is a cooperative research action at INRIA to build a generic dynamic model of the beating heart and a procedure to automatically identify its parameters for any specific patient. Once the generic model is adapted to a specific patient, it becomes possible to derive a set of quantitative and objective parameters useful in helping clinicians and physiologists to better understand the electro-mechanical coupling and diagnose pathological conditions. Our approach combines a 3D model of the electric wave propagation with a 3D biomechanical model of the cardiac muscle. The two models are explicitly coupled into simulations to generate the dynamic behaviour of the heart. The model for electric wave propagation is derived from Fitz-Hugh Nagumo equations, while the mechanical model is based on the classical Hill-Maxwell rheological law. These models are expected to reflect on a macroscopic scale the coupling acting on the cellular scale. To provide a realistic motion of a standard beating heart, the highly anisotropic nature of the muscle fibres in standard anatomy is taken into account.

6. The **Integrative Biology**[31] project aims to realise this potential by developing multi-scale models of the heart and cancer tumours spanning the range from genes to whole organs and by enabling the coordinated use of supercomputing resources to run simulations of these models with a spatial and temporal resolution not practically possible before the UK e-Science Programme. The long term goal driving the project is development of an underpinning theory of biology and biological function capable of sufficiently accurate computational analysis that it can produce clinically useful results.
7. The following projects where presented by the University of Amsterdam[32]:

   - The **Modelling of HIV infection** and drug therapy of HIV project specifically addresses a few research items data fusion, intermediated modelling and parameter extraction.

   - **Detecting malign leukocytes** in peripheral blood uses the Simulation of Elastic Light Scattering (ELS) of small arbitrary shaped particles by means of the Discrete Dipole

[29] http://www.aneurist.org/
[30] http://www-sop.inria.fr/CardioSense3D
[31] http://www.integrativebiology.ac.uk/
[32] http://www.science.uva.nl/research/s cs/

Approximation (DDA) method. The developed computational model has been used to calculate the complete scattering matrices of humane leukocytes.

- **Simulated Vascular Reconstruction** in a Grid based Virtual Operating Theatre has developed a virtual reality environment which combines interactive visualization of patient specific vascular medical data (MRI/MRA scans) with a flow simulation environment into an interactive exploration environments that provides a virtual operating theatre in which vascular reconstruction procedures can be simulated. In this environment, the mesoscopic lattice Boltzman flow simulation technique (a particle-based simulation using cellular automata) is used to simulate blood flow through human vascular geometry obtained from patients with vascular disease.

- **Modelling of Growth and Form** is a project where three-dimensional models have been developed for the morphogenesis of organisms with a relatively simple developmental biology, as for example sponges and stony corals. A method has been developed for modelling the growth process regulated by gradients of morphogens or other chemical agents and the availability of nutrients in the environment.

- **Modelling biochemical pathways** is developing and comparing computational models of parts of the living cell that can calculate in detail system properties from experimentally obtained molecular and physical-chemical data. Such a model is as close as possible to the biological experiments and therefore can be used not only for understanding the principles of function but also to steer further biological experiments.

- **Modelling and inferring of developmental regulatory networks** is developing a model for simulating regulatory networks that are capable of quantitatively reproducing spatial and temporal expression patterns in developmental processes. The model is a generalization of the standard connectionist model used for modelling genetic interactions. The model will be coupled with a biomechanical model of cell aggregates and used to study the formation of spatial and temporal expression patterns of gene products during development in cellular systems. As a case study the body plan formation in relatively simple multi-cellular organisms are used.

8. **STEP** (A Strategy for the EuroPhysiome). The project is designed to provide coherence to European Physiome-related activities by creating an integrated framework, the EuroPhysiome, which, while remaining true to the Physiome concept, can accelerate the progress of the European teams by avoiding redundancy, enhancing compatibility, etc. STEP has gathered the existing European projects that are working under the Physiome umbrella into the current consortium. The STEP proposal was submitted to the IST call 4 for proposal of the 6th Framework programme of the European Commission evaluation.

9. **Microsoft Research, University of Trento: Centre for Computational and Systems Biology**[33] The objectives are to advance the state of knowledge of biological information processing, the aetiology of disease, and potentially new therapies through the creation of a new research centre that will bring together scientists from multiple disciplines to focus on conducting leading research into advanced computational modeling of biological systems. To conduct novel research into defining new computational and communication paradigms that are 'biomimetic' in nature, i.e., based on new principles learned from the research into biological information processing and to exploit the research. This is expected to take the form of the development of new computational tools for enabling the predictive modeling of biological systems and processes for basic and applied research. These tools will help improving health-care, environment monitoring and protection, quality of food as well as developing better therapies and treatments by the pharmaceutical industries. To disseminate and communicate the results of this research for the benefit of the scientific community globally, including publications, open conferences and workshops, and provide freely available, the tools developed in the course of the research for (non-commercial) science.

[33] http://dit.unitn.it/~bioinfo/index.php?option=com_content&task=view&id=17&Itemid=46

10. **Integrative Physiology @ Oxford/Cambridge**[34] Obesity and Type 2 diabetes are major and growing public health problems. Whilst advances in genetics and molecular cell biology have made major contributions to enhancing the understanding of these diseases, they are fundamentally disorders of whole-organism homeostasis. To forward our understanding of these diseases is to improve, they are developing a cadre of basic and clinical scientists armed with skills and knowledge in both molecular and cell biology and in the study of whole organisms. The Integrative Physiology Initiative provides the opportunity of creating an entity in which such individuals can be fostered. The research involves the study of both humans and rodent models and involves a network of collaborations between groups of investigators, including both younger scientists and more established researchers at the forefront of obesity and diabetes research internationally.

11. **ImmunoGrid** is a European consortium which focuses on the development of a Virtual Human Immune System, a simulator of the physical immune system and immune processes. The human immune system is simulated across multiple nodes and includes definitions of immune organs - both primary and secondary - immune cells, and various nodes representing physical locations in the human body. Immune cells are, for example, represented as agents (in the Agent-Based Modelling sense) and their circulation is represented as a diffusion process and/or chemotaxis. Antigens will be represented as agents as well. The project focus is on the distribution of bone marrow, thymus, lymph nodes, spleen, and other immune peripheral system organs across the grid nodes. The ImmunoGrid proposal was submitted to the IST call 4 for proposal of the 6th Framework programme of the European Commission evaluation

12. **BioSim**[35] The purpose of the network is to develop in silico simulation models of cellular, physiological and pharmacological processes to provide a deeper understanding of the biological processes and help the pharmaceutical industry maintain its competitive power.

13. The **SIMRI**[36] project aims at developing a realistic Interactive 3D Magnetic Resonance Imaging simulator. **SIMRI** simulator allows computing the virtual 3D MRI of an organ (excitation sequences, proton relaxation, T1, T2) solving the Bloch equations in interaction with the virtual human Body. It provides realistic 3D simulation as far as the shape and the tissue physical parameters are available. See for example a virtual brain MRI slice (address below). It can simulate MR artefacts such as chemical shifts or local field inhomogeneities. Time needed to compute 3D realistic volumes is huge. The software is implemented on the grid (***EGEE project***) and a web version of the software is available.

3. US-based initiatives

1. **Biomedical Information Sciences Initiative (BISTI), National Centres for Biomedical Computing**[37]**.** The centres bring together researchers in computation, biology, and behavioural science to collaborate on a number of projects, including:

   - The Physics-Based Simulation of Biological Structures Center, led by Russ Altman, M.D., Ph.D., and Scott Delp, Ph.D., of Stanford University in California, which will develop a simulation toolkit that enables scientists worldwide to model and simulate biological systems from single atoms to entire organisms. More information is available at http://simbios.stanford.edu/.

   - The National Alliance for Medical Image Computing led by Ron Kikinis, M.D., of Brigham and Women's Hospital in Boston, Massachusetts, a multi-institutional effort to develop software programs that integrate analysis and imaging data from a variety of sources, including MRI scans, to better understand a broad range of human diseases. Collaborating organizations include Dartmouth Medical School; General Electric Global Research; Georgia Institute of Technology; Harvard Medical School; Kitware, Inc.; Massachusetts General Hospital; Massachusetts Institute of Technology; University of California, Irvine; University of California,

[34] http://www.int-phys.org/
[35] http://chaos.fys.dtu.dk/biosim/?action=home
[36] http://www-creatis.insa-lyon.fr/menu/ivolumique/segmentation/simri-hbc/index-us.html
[37] http://www.bisti.nih.gov/ncbc/

Los Angeles; University of California, San Diego; University of North Carolina, Chapel Hill; and University of Utah. For more information, visit http://www.na-mic.org/.

- The Center for Computational Biology, led by Arthur Toga, Ph.D., of the University of California, Los Angeles, which will join computational and mathematical approaches to study genes, cells, systems, and the whole brain. By combining this information, the center will create "computational atlases," sets of maps featuring different biological data and serving as platforms for detailed, large-scale modeling projects to study biological processes and human diseases. For more information, visit http://www.loni.ucla.edu/CCB/.

- The Informatics for Integrating Biology and the Bedside Center, led by Boston-based researchers Isaac Kohane, M.D., Ph.D., of Brigham and Women's Hospital and Children's Hospital, and John Glaser, Ph.D., Vice President and CIO at Partners HealthCare System, which will develop computational tools that enable clinical researchers to capitalize on the gains of the genomic revolution to understand the basic biology of diseases such as diabetes, neurological disorders, and high blood pressure. Collaborating organizations include Children's Hospital Boston, Harvard Medical School, Harvard School of Public Health, Joslin Diabetes Center, Massachusetts General Hospital, Massachusetts Institute of Technology, and Partners Healthcare Systems, Inc. The center's web site is www.partners.org/i2b2.

2. **ASPIRE**[38] allows surgeons to perform several 3-D virtual surgeries and choose the one that is most appropriate for a particular patient before they go to the operating room. The purpose of vascular reconstruction is to redirect and augment blood flow, or perhaps repair a weakened or aneurysmal vessel. Many times the optimal procedure is obvious, but this is not always the case, for example, in a patient with complicated or multi-level disease. Pre-operative surgical planning will allow evaluation of different procedures *a priori*, under various physiologic states such as rest and exercise, thereby increasing the chances of a positive outcome for the patient.
3. **MARS, CART, TreeNet/MART**[39] for Epidemiological Research: Identifying relationships that cannot be identified in any other way. E.g.: The association between vitamin E and the development of myocardial infarction, exploring the association between regional heart function and coronary calcification classification of study participants; Shenghan Lai[40], Johns Hopkins Medical School. Discern models in genetics for Alzheimer, alcoholism and cocaine addiction, Marsha Wilcox[41], Boston University Medical School.
4. **BioPSE**[42] is a specialization package for SCIRun[43], a Problem Solving Environment (PSE), for simulation, modeling, and visualization of scientific problems, which expands it's capabilities for modelling bioelectric field problems.
5. **CMISS**[44] is a mathematical modelling environment that allows the application of finite element analysis, boundary element and collocation techniques to a variety of complex bioengineering problems. It consists of a number of modules including a graphical front end with advanced 3D display and modelling capabilities, and a computational backend that may be run remotely on powerful workstations or supercomputers.
6. **CONTINUITY**[45] 6 is a computational tool for continuum problems in bioengineering and physiology, especially those related to cardiac mechanics and electrocardiology research. In addition to continuum modeling, Continuity 6.0 has facilities for least-squares fitting of parametric models to experimental measurements from diverse sources including gross anatomy, histomorphology, 3-D medical imaging, and physiological and biomechanical testing.

[38] http://www-med.stanford.edu/aspire/
[39] http://www.salford-systems.com/
[40] http://www.reynolds.jhmi.edu/personnel/core_profile/lai.html
[41] http://genetics.bumc.bu.edu/people/faculty/wilcox.htm
[42] http://www.sci.utah.edu/ncrr/software/biopse.html
[43] http://software.sci.utah.edu/scirun.html
[44] http://www.cmiss.org
[45] http://www.continuity.ucsd.edu/

7. The **VIRTUAL CELL**[46] is an online Cell Biology textbook. It provides students with an interactive journey through the cell.
8. **GEPASI**[47] is a software package for modeling biochemical systems. It simulates the kinetics of systems of biochemical reactions and provides a number of tools to fit models to data, optimize any function of the model, perform metabolic control analysis and linear stability analysis. Gepasi simplifies the task of model building by assisting the user in translating the language of chemistry (reactions) to mathematics (matrices and differential equations) in a transparent way. This is combined with a set of sophisticated numerical algorithms that assure the results are obtained fast and accurate.
9. **AMBER**[48] refers to two things: a set of molecular mechanical force fields for the simulation of biomolecules (which are in the public domain, and are used in a variety of simulation programs); and a package of molecular simulation programs which includes source code and demos.
10. **SIMBIOS**[49] Physics based simulation of biological structures. Physics-based simulation provides a powerful framework for understanding biological form and function. Simulations may be used by biologists to study macromolecular assemblies and by clinicians to examine disease mechanisms. Although individual investigators have made elegant contributions to physics-based modelling in biomedicine, the field is fragmented. Modeling applications are typically limited to a single physical scale, and individual investigators frequently must create their own software. These conditions create a major barrier to advancing simulation capabilities. We propose to establish a National Center for Physics-Based Simulation of Biological Structures (Simbios) to help integrate the field and accelerate future research. This Center will develop, disseminate, and support a simulation tool kit (SimTK) that will enable biomedical scientists to develop and share accurate models and simulations of biological structures from atoms to organisms
11. The **Virtual Human**[50] The Virtual Human (VH) will be a research/testing environment having an integrated system of biophysical and other models, data and advanced computational algorithms coupled with a computational (engineering) solid-body model of the anatomy. VH will have a Web-based interface for easy, rapid access from several points of entry. VH will serve as a platform for national and international users from governments, academia, and industry to investigate the widest range of human biological and physical responses to stimuli, be they biological, chemical, or physical. This effort goes far beyond the visualization of anatomy to incorporate physics, such as mechanical and electrical tissue properties, and biology from physiology to biochemical information, into the platform so that responses to varied stimuli can be predicted mechanistically and results viewed three-dimensionally.
12. The DARPA **Virtual Soldier**[51] will investigate methods that will revolutionize medical care for the soldier. The project will produce complex mathematical models to create physiological representations of individual soldiers. These holographic medical representations (known as Holomers) can be used to improve medical diagnosis on and off the battlefield. The Holomers coupled with predictive modeling software, will facilitate a new level of integration in medical procedures. The Virtual Soldier will provide multiple capabilities, including automatic diagnosis of battlefield injuries,prediction of soldier performance, evaluation of non-lethal weapons, and virtual clinical trials.

4. Other initiatives

1. The goal of the **CyberCell**[52] is project to create an accurate dynamic model of a simple living organism within 5 years using a molecular-level population dynamics approach. The overarching premise of Project CyberCell is the integration of experiment and theory, where directed, high-resolution biological and biomolecular measurements are used to drive and validate combinatorial

[46] http://www.ibiblio.org/virtualcell/index.htm
[47] http://www.gepasi.org/
[48] http://amber.scripps.edu/
[49] http://cbmc-web.stanford.edu/simbios/summary.htm
[50] http://www.ornl.gov/sci/virtualhuman/
[51] http://www.virtualsoldier.net/
[52] http://www.projectcybercell.ca/

numerical analysis and systems modelling. Project CyberCell is a founding member of the International E.Coli Alliance, an evolving international collaboration aimed at creating a life-like computer model of a living cell through its Project Gemini initiative.

2. The **Leading Project for Biosimulation**[53] aims at establishing computer-based simulations of cell functions and biodynamics through model applications by integrating data obtained from genomic analyses and the analyses of cell/biomolecule movement and locomotion. Moreover, this simulation aims at deepening the understanding of biological phenomena and directing toward the promotion of efficiency in the development of new medicines and techniques in the medical field.

[53] http://www.lp-biosimulation.com/english/index.shtml

ANNEX 2: R&D programs and efforts outside Europe related to the VPH

The following table represents a collection of funding given to topics related to the VPH outside Europe. It is purely based on the intrinsic knowledge of the workshop participants and does not represent a complete picture, just a starting point.

Country	Duration and/or funding year	Indicative amounts
US		
National Centres for Biomedical Computing	5 years grants from September 2004	$15.7 million year 1 projected total $79.7 million
NIH supporting numerical modelling	Per year	$80 million
Allen Brain Atlas project		$100 million
NIH & MNI (MRI pediatrics database)		$25 million
NIH & Alzheimer (MRI)	5 years	$60 million
National Cancer Institute, In Vivo Cellular and Molecular Imaging Centers grants		$4 million
National Institute of Biomedical Imaging and Bioengineering (NIBIB)	2004	$289 million
Pacific Northwest National Laboratory (3-D imaging and computational models)	5 years	$10 million
Australia		
Funding to independent medical research institutions for IST costs	2004, seven years	$200 million
Japan		
Biosimulation project	2003	$70 million