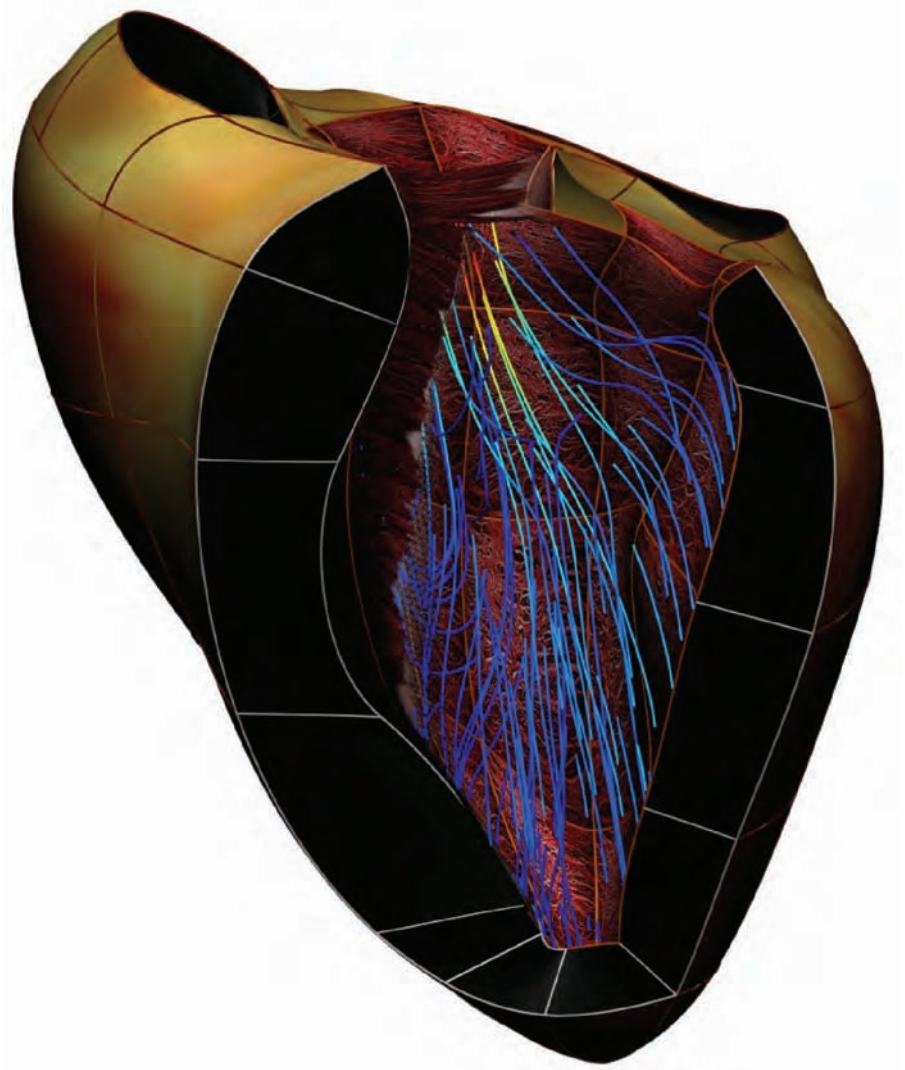
STEP Consortium

Seeding the EuroPhysiome:

A Roadmap to the Virtual Physiological Human



"We zijn nog niet aan de nieuwe patatjes"

"We are not at the new potatoes yet" Traditional Flemish expression

"Adparent rari nantes in gurgite vasto"

"Only the few swim in a rough sea" Virgil, Aeneid, 1, 118

Seeding the EuroPhysiome:
A Roadmap to the Virtual Physiological Human

A research Roadmap for the development of the Virtual Physiological Human

Written by a panel of International experts representing research, industry, clinical practice and society at large

Co-ordinated by the STEP Consortium

Acknowledgement - The STEP project is supported by the European Commission, DG Information Society through the Sixth Framework Programme of Research and Technological Development.

The Virtual Physiological Human (VPH) is a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system. The VPH provides the European research infrastructure that will make it possible for biomedical researchers to complement their conventional reductionist approach with what we call an *integrative* approach, where biological processes are described from a systems point of view.

The present document, compiled through a consensus process that has involved more than 300 stakeholders from research, industry and clinical practice (see Annex #1 for a complete list), aims to provide a research roadmap that will become a blueprint for the realisation of the VPH.

The document discusses in detail all aspects of this endeavour. For a cursory reading, *Chapters 1* and *2* provide a preliminary overview of the VPH concept and an explanation of how the roadmap was produced. *Chapter 12* details recommendations for the concrete implementation of the VPH.

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Editor: Marco Viceconti, Istituti Ortopedici Rizzoli – Bologna (IT)

1.0

Definition: The Virtual Physiological Human (VPH) is a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system. VPH is *not* "the supermodel" that will explain all possible aspects of human physiology or pathology. It is a way to share observations, to derive predictive hypotheses from them, and to integrate them into a constantly improving understanding of human physiology/pathology, by regarding it as a single system.

Scope

A group of genetically identical in-bred mice are stabled under the same conditions; half of them are subjected to mild (0.3g) whole-body mechanical vibrations for a few minutes per day. After a few days, the transcriptional activity of hundreds of genes related to the musculoskeletal apparatus becomes significantly different between the two groups of mice[1]. To explain this observation, we should find the systemic relationship that links the accelerations experienced by the mouse's body with the transcriptional activity of its genes.

Today, biomedical research faces many problems similar to the one above and involves a complexity for which the traditional approach is inadequate. This approach is based on the subdivision of biological systems in some way – by *dimensional scales* (body, organ, tissue, cell, molecule), by *scientific disciplines* (biology, physiology, biophysics, bioengineering), or by *anatomical sub-systems* (cardiovascular, musculoskeletal, gastrointestinal, etc.). But these artificial subdivisions make it impossible to unravel the systemic nature that governs many of the physical manifestations of the human body.

To continue the scientific exploration of the human body that has already so dramatically improved the length and quality of life for a major section of mankind, it has become apparent that it will be necessary to complement this traditional approach with an integrative approach that makes it possible to combine observations, theories and predictions across the temporal and dimensional scales, the scientific disciplines, and anatomical sub-systems, all of which currently create the rather artificial divisions described.

This realisation, shared by the vast majority of experts in the field, has given rise to a number of initiatives such as integrative biology, system biology, physiome, etc.

We[2] believe that this integrative approach requires a radical transformation in the way biomedical research is conducted. It is necessary to create a framework within which observations and measurements from a variety of sources can be collected, shared and combined in many different ways.

This framework should allow experts from a variety of disciplines to work collaboratively to analyse these observations and to develop systemic hypotheses. It should also make it possible to combine predictive models defined at different scales, with different methods or with different levels of detail, in order to make the hypotheses concrete, and to allow their validity to be tested against existing results.

Currently, we are investigating the human body by pretending that it is a jigsaw puzzle made up of a trillion pieces and we are trying to understand the whole picture by looking only at a single piece or, maybe, a few closely interconnected pieces; it is no surprise that we are not finding it easy.

In contrast, the scope of the EuroPhysiome Initiative is to promote the development of the *Virtual Physiological Human (VPH)*, a methodological and technological framework that will enable investigations of the human body as a single (though hugely complex) system.

The VPH is the framework within which we can finally start to put all of the pieces together and it is also the glue that can connect them. The VPH will not represent, *per se*, the whole picture, but it does represent our best pathway towards forming that picture at some time in the future.

We claim that, given sufficient resources, the European Research System can develop, over the next 10 years, the methodological and technological framework that is the VPH. The scope of this roadmap is to identify, explicitly, the essential requirements for developing the VPH and to specify what the objectives of this collective effort should be. In addition, the document describes the current state of knowledge; the challenges that the development of the VPH poses; the material, environmental, societal and other barriers that we shall need to overcome; and the impact that we predict the VPH will make on research, industry, clinical practice and society at large.

Specifically, the framework of methods and technology representing the VPH will have to possess three fundamental attributes:

- **descriptive:** the framework should allow observations made in laboratories, in hospitals and in the field, at a variety of locations situated anywhere in the world, to be collected, catalogued, organised, shared and combined in any possible way;
- **integrative:** the framework should enable experts to analyse these observations collaboratively and to develop systemic hypotheses that involve the knowledge of multiple scientific disciplines;
- **predictive:** the framework should make it possible to interconnect predictive models defined at different scales, with different methods, and with different levels of detail, into systemic networks that solidify those systemic hypotheses; it should also make it possible to verify their validity by comparison with other clinical or laboratory observations.

[1] S. Judex, M. Monaghan, C. Rubin and A. Dhundale. Altered Mechanical Demand of the Skeleton Broadly Changes Transcriptional Activity. *J Biomech* 39(S1):S22, 2006.

[2] This document is the result of a consensus process promoted by the STEP Coordination Action that involved hundreds of experts in biomedical research from academia, industry and clinical practice, representing most scientific disciplines that compose biomedical research and the related technological research. For a detailed list of those that contributed to this document, see Appendix A.

Editor: Gordon Clapworthy, University of Bedfordshire (UK)

2.0

Rationale

The present document has been compiled through a complex consensus process.

At the outset, existing activity that had been encountered tended to be drawn up very much along conventional medical lines, being based mostly on specific organs/bodily systems – heart, kidney, intestine, lung, musculoskeletal, etc.

The first priority, therefore, was to establish a "horizontal" dialogue to identify similarities and differences among the teams working in these areas. It did not appear feasible to make the transition to the entire physiome in one leap, so a two-phase process was adopted. The first move was to establish a set of so-called Strands. These were to have a horizontal perspective, but only a limited span; in this way, it was hoped that their discussions would retain a greater focus and the initial outcomes would emerge more rapidly.

The six Strands created were in Hard Tissues, Soft Tissues, Fluids, Anatomy & Physiology, Multiscale Modelling and ICT Infrastructure. Approximately 100 international experts were invited to join the Strands to provide as broad a range of relevant external opinion as possible; these experts were mostly European but included a significant number from further afield. Serious attempts were made to ensure that the Experts, collectively, were representative of all likely stakeholders, including academic researchers, industrial and clinical users, professional associations, industrial associations, societal users, etc. Industrial representation ranged from large multinational companies to small, niche-market SMEs. Only in this way could we feel confident that the necessary range of input had been acquired for the final roadmap to gain broad acceptance amongst all the necessary groups.

The Strands were each given the task of developing a consensus document, written from the perspective of their own community. The relevant experts were actively engaged in this process by way of active Internet-based discussions.

The six consensus documents then had to be brought together to establish a more universal document reflecting all of the opinion gathered up to that point. This was achieved at STEP Conference 1, which took place in May 2006. The conference started with meetings of the individual Strands, in parallel sessions, to finalise their reports. These reports were presented at the final plenary session of the conference, leading to the first draft of the full roadmap, which was published shortly afterwards. This marked the end of the first phase of the project.

The reports from the Strands were very similar with regard to the technical challenges faced, and to the priorities for, and the approaches to, the future work. So, as no major discrepancies had been identified among the expert groups, it was decided to merge the Strands into a single Expert Panel to comment on the roadmap as a whole. The Expert Panel was augmented with further members who had been identified as providing particular missing expertise or experience, or who were felt, for some other reason, to be able to contribute valuable input into the process. At the same time, the Advisory Board was refined to a core and tasked with editing versions of the roadmap as they appeared.

The first draft of the roadmap was made public on the project website shortly after Conference 1 and comment was invited from all. The content was updated regularly as a result of input received ahead of the second Conference – *Towards the Virtual Physiological Human* – which was held in Brussels on 5-7 November 2006. While Conference 1 had been tightly focused and attended only by invited experts, Conference 2 was more far-reaching and open to wider participation. Circulars to relevant mailing lists, flyers at conferences, focused presentations to interested groups, articles in newspapers and magazines and radio interviews were some of the methods employed to raise awareness of Conference 2 and of the processes involved in creating the roadmap.

Conference 2 provided the first opportunity for large-scale "live" discussion of the issues that had emerged from the earlier STEP activities. A major precept of the conference was that there should be a suitable allocation of time for active participation by delegates – it should not simply be a succession of presentations. The programme was thus designed to ensure that all attendees had opportunities to contribute individually to the process, and many of them took advantage of several lively open sessions to put forward their views.

All input, in whatever form received, was processed after the Conference and this was fed into the following drafts, where appropriate.

The roadmap went through several more editions in the following months, before reaching its final form.

Editor: Serge Van Sint Jan, Université Libre de Bruxelles (BE)

3.0

3.1. Executive Summary

The aim behind the VPH is to help achieve the development of quantitative, integrative and predictive models that describe human life from conception to death, and from genes to whole organism. The main motivation behind the VPH is to provide the necessary infrastructure, including methodologies, databases and tools that will allow scientists working in different fields (at various levels and scales) to communicate, to exchange data and technologies in a standardised way. This also includes training of multidisciplinary individuals and VPH specialists. The sheer scale of data to be generated, processed, and exchanged requires massive computer storage and software tools that are currently not widely available. VPH must define access to computing power and resources available from existing computing centres. Dissemination must also be tackled because the VPH scope is by definition multidisciplinary and only a very limited number of journals might accept physiome-related papers. Reviewers able to deal with multidisciplinary topics are also necessary.

Motivation

Standards and model homogenisation used through all fields of research must be discussed and adopted in order to facilitate data and algorithm distribution for various levels of modelling. Extensive and practical ontologies must allow key information to be allocated to, and retrieved from, knowledge databases, so enabling users (i.e., scientists, but also third persons such as journalists or researchers) to locate relevant information quickly and simply.

Many modelling tools must be developed, standardised or simply made available to the research community. Such tools might facilitate model development (data mining, ontology development, meshing algorithm etc) or perform the modelling itself (i.e. data fusion, visual representation, mathematical/statistical predictions, parameter estimation). Such tools must allow integrating data as disparate and inhomogeneous as data ranging from the molecular level (spatial scale: 10^{-9} m; time scale: 10^{-6} s) to the organism (spatial scale: 10^{0} m; time scale: 10^{9} s) level.

Today, the clinical approach to pathology healing is frequently fragmented because of the very specialised background of clinical specialists. The major motivation behind the VPH effort is to promote better clinical integration of patient-specific data by building technological bridges between areas of specialisation and by promoting the training of a new kind of highly multi-disciplinary clinician. This approach will prove particularly valuable for pathologies that show complex aetiologies (for example, pathologies showing clinical signs related simultaneously to the central nervous system, peripheral nervous system and musculoskeletal). Such pathologies also generate an information overflow including various inhomogeneous data generated from current diagnostic systems. On the other hand, only very few and limited decision-making supports based on knowledge-based algorithms have so far been developed to facilitate the diagnosis process and patient follow-up. Research in such areas is strongly supported by the VPH concept. Once available, these systems will greatly assist our integrative understanding of complex pathologies and will increase the opportunity to develop preventive strategies and alternative therapies. Improved patient customisation should also be achieved thanks to a more integrated processing of the available patient-specific data.

Barriers to this development include a lack of multidisciplinary consensus (on the overall aims, the standards to use, the tools to develop) and poor communication between fields caused by the current lack of scientists with multidisciplinary skills. The above integrative approach will demand an enormous change of mentality in clinical practice and, in order to be better accepted, integrative tools will need to be extensively validated, including in clinics.

The development of the VPH infrastructure will rely strongly on industry (from sectors as diverse as medical imaging, pharmaceuticals, orthopaedic material, IT, computer technology, etc.) that should bring scientific developments to market. The VPH infrastructure and organisation should help industry to develop marketable products in a cost-effective way, thanks to the availability of consensus (scientific and clinical), standardisation, validation tools and trained individuals.

With this VPH framework in place, scientists and industrialists in the field will be better able to answer questions from society at large. Industry, itself, is asking for improved standards, lower production costs, and better access to data and academic knowledge to assist with its own innovation initiatives. VPH could also reduce the need for experiments on animals. Clinicians are increasingly requesting tools for a more integrated approach to solving clinical problems. Advanced integrative tools should help to improve the European healthcare system on a number of different levels that include diagnosis, treatment and care of patients and, in particular, quality of life.

VPH will also help to improve the individual citizen's knowledge of, and confidence in, medicine and medical systems. This will make people more responsible for their own lives and will facilitate the move towards a more holistic approach to medicine in which the body is treated as a single multi-organ system, rather than a collection of individual organs.

3.2. Research needs

Biomedical research is a multi-disciplinary field in which experimentalists, clinicians, engineers and modellers are all involved in working towards the development of *quantitative, integrative* and *predictive* models that describe *human* life from *conception* to *death* and from *genes* to *whole organism*.

This Grand Challenge, i.e. by no means a straightforward endeavour, requires the interaction of and collaboration between numerous different categories of researchers to be successful. Although there is frequent collaboration, it is rare for representatives of those different categories to work in the same research group. Biomedical research would, however, benefit greatly from more interaction between investigators. The sharing of data, expertise, ideas, resources and techniques is in everybody's interest.

We believe that a framework such as the VPH can help in this undertaking by providing a good ***infrastructure***, as well as good ***methodologies***, ***databases*** and ***tools***.

3.2.1. Infrastructure

The multidisciplinary nature of biomedical research can be seen as a strength and as a weakness. It would seem obvious that research is the ultimate beneficiary if you can get people with different areas of expertise to interact.

The problem, however, is that most investigators' expertise is limited to that of their own field of research. This can be counter

productive since, for instance, modellers/engineers do not always understand the needs of experimentalists (they use different terminologies) or modellers/engineers do not fully appreciate what experimentalists are trying to do (the former may not have the right biological background). This may result in modellers developing models that might be of interest to other modellers, but possibly of very little use, if at all, to experimentalists. This is a crucial problem, especially if clinical problems related to patients' health in a similar multidisciplinary context are to be tackled effectively. Furthermore, the time required by modellers with limited biological expertise to develop biological processes can be sometimes out of all proportion to the actual objectives because of a poor appreciation of the overall biological picture.

VPH could help tackle these problems by providing a framework that would facilitate the training of multidisciplinary scientists, as well as support a pan-European exchange of specialists.

Even with multidisciplinary scientists, there will still be a need for additional interaction and collaboration between experts. These interactions, however, can sometimes be limited by the lack of a proper medium for exchanging data and ideas (the limitations of emails, conference workshops too short for extensive consensus work, etc). It may therefore be worth looking, through VPH, into an infrastructure that would facilitate such interactions.

Collaborative projects require an exchange of data. Data generated by experimentalists may, depending on the data modality, range from spreadsheets (low volume) to 3D histo-architectural detail (dozens of gigabytes per sample). The latter type of data is, unlike the former, of major concern because of its size. VPH could help by providing a way of making such data accessible easily, quickly and safely.

Modellers, whose own simulations can also generate gigabytes of data, share this need.

To compute and analyse models and data in general requires specific tools (see below), which can prove computationally intensive (to compute the electrophysiological activity of the heart takes hours if not days, depending on the topic under investigation). Most research groups do not have access to the necessary computing power for solving such modelling problems. The availability of conceptual tools (software, models, ontologies) is also lacking. It is hoped that VPH could help by offering a means of accessing the computing power available within different European organisations and agencies, in a secure, user-friendly and transparent way.

Researchers must, at some point, try to publish their findings. However, the intrinsic multidisciplinary nature of the VPH research means the peer-review process may prove difficult. Indeed, a non-multidisciplinary reviewer might not appreciate parts of such work and ultimately refuse to publish it. On the other hand, however, there is no guarantee that the combined experimental and modelling work described in the manuscript is sound. It is obviously the responsibility of the journal's editor to ensure that it is. Nonetheless, VPH could still help by creating a new generation of reviewers that can assess multidisciplinary research effectively. The same holds true for any kind of review activity (e.g. grant). Next to increasing awareness among reviewers of the VPH vision, journals might be asked to become more involved in VPH-related dissemination by, for example, dedicating a particular section to VPH, or to publish a special issue. A journal entirely dedicated to VPH could be created to facilitate cross-fertilisation of all disciplines requested to address the required objectives. Such a solution would allow the publication of integrative work.

3.2.2. Methodologies

The research at hand is relatively complicated and is therefore both time and resource consuming. It is clear that the development, through VPH, and use of relevant and efficient methodologies could only enhance our research productivity.

There is, for instance, no guarantee that a published mathematical or statistical model is valid. There may be missing information (e.g. equation, initial condition, unit), typographical errors (e.g. a plus instead of a minus, a misplaced parenthesis) etc. Some authors have tried to circumvent this problem by publishing their model online. This may, however, only partially solve the problem as the issue of the format in which the model is made available (e.g. data format, programming languages) still remains. In this case, the user may have to convert the model into another language or, in the best of cases, have to adapt it to his or her modelling environment. In either case, this is time-consuming and a potentially error-prone process. VPH can help by specifying formats that will facilitate the exchange and use of mathematical models (e.g. statistical, differential models), as well as other types of models (e.g. anatomical, histological) or experimental data (e.g. experimental recordings).

To have a model up and running does not, however, mean that everything is fine. In fact, a model may be up and running and may still be inadequate. VPH may provide some model "certification" whereby certain basic characteristics of the model (e.g., existence and uniqueness of solutions, continuous dependence on initial values and on parameters etc.) may be established. Models are usually developed for a very specific purpose. Even if they prove useful for purposes for which they were not originally developed, they may be equally unsuitable for certain tasks. If a user understood a model's limitations and range of applications, it would potentially avoid a lot of frustration (the same applies to the modeller, on being told that his or her model cannot address a given question). Again, it is expected that VPH will be able to help in this context.

Some models may prove too comprehensive for our needs and we may want to homogenise (or even ignore) some low-level details depending on the scope and application of our research, so as for instance to decrease the computational requirements of specific simulations. There are many techniques available to tackle homogenisation problems (e.g. dimensional analysis, Gillespie algorithm, field theories, conceptual graphs, cognitive maps) and VPH could help by making them available to modellers (see database needs below), as well as helping to develop new ones, if needs be (see tools needs below).

Alternatively, the VPH could set up its own standards forum, similar to the OGF, particularly if existing standards bodies are deemed inappropriate for the certification of models.

3.2.3. Databases and Knowledge Repositories

The development and use of models relies on a wide range of data. Patient data may, for instance, be used by modellers for the statistical estimation of parameters and for comparisons against model predictions, while model users may use such data for drug development. Such data may have data associated with them (i.e. metadata, covariates) to, for instance, the patient's age, sex etc. Similarly, data on biological systems may be used to build a model (using data on components and interactions between components, relation of components to cell structures, etc.), as well as evaluating it (using data on signal flow rate, enzyme kinetics, concentration dynamics, molecule turnover rate etc.).

Models need to be validated against experimental data and, once again, data gathering is very important. So it would be more convenient and time efficient to have those data sets available in some agreed formats and in various knowledge databases, which could be queried through a common interface. This, together with a link to the original paper from where the data came, would allow anyone quickly to find out whether the data he or she is after exists or not and, if so, to obtain it in a meaningful and useable format, together with all the background associated with it (i.e. conditions under which the data was collected, how it was analysed etc.).

A model can be of use to others and, like for data sets, would therefore benefit from being accessible through a database. Any potential model user will, however, want some guarantee that the model behaves as claimed by its authors. Unfortunately, there is currently no established way to reassure the model user, which means that he or she may end up getting frustrated and unsatisfied with a model. Neither model developers nor model users benefit from this state of affairs. VPH must address this by, for instance, asking modellers to provide built-in documentation of validation and error checking (through a set of test routines), so as to increase a user's confidence in a model.

But just to have access to the data and models is not sufficient. We need tools to visualise, interpret and process the data. In the same way, we need tools to make sense of the models and run simulations on them. Some of those tools exist (see tools needs below), but as for knowledge databases, a repository of existing tools should be made available.

Developing such databases is not a trivial process, however. VPH could definitely play a major role in this context and not only at the European level (i.e. researchers worldwide could benefit from them).

Standardisation of XML data interchange formats and ontologies are also necessary. Definition and standardisation within the VPH will be done through recognised international standards bodies (e.g. OASIS). This should give greater assurance to industrial and academic entities.

3.2.4. Tools

As mentioned earlier, tools are needed to carry out our research. They can usually be put under one of two categories: a) tools that help developing models; and b) modelling tools themselves. Tools in each of these categories exist, however many require additional refinement or development. The table following lists some of the tools that are needed in bio-medical research.

Tools for model development	– ICT tools for pathway elucidation, integrating proteins, micro arrays and SNP information – Hierarchical parameter transfer methods for the integration of different experimental and/or simulated data (i.e. data fusion) – Tools and techniques for integrating parameter range of experimental values, level of evidence and missing data – Tools for correlating the shape and evolution of anatomical structures (phenotype) with genetic information (genotype) and/or with a certain number of pathologies – Specific computational imaging techniques such as improved spatio-temporal resolution in bio-medical signal and imaging sensors, constrained image reconstruction, statistical image and shape analysis, non-rigid image registration and morphometric tools, efficient geometry modelling and meshing for complex structures, etc. – Knowledge extraction, data mining and bio-medical cross-level ontologies (the need is particularly obvious in, for instance, the coupling of sub-models, particularly at the interface across scales, and the relationships between information, regulation, and the metabolism of living organisms), and – Methods to compute statistics on anatomy and functions from large databases of bio-medical images and signals
Modelling tools	– Mesoscopic modelling, including multi-domain modelling – Hierarchical reconstruction and embedding – Data fusion (i.e. integration of different experimental and/or simulated data) – "Live" modelling (i.e. make models and devices interact with one another) – Numerical methods for the solution of differential models (ODE / PDE / DDE / SDE), e.g. for Pharmacokinetics/Pharmacodynamics (PK/PD) models, and statistical methods for the analysis of correlations, dependencies, dimensional reduction and aggregation – Parameter sweeps (High Throughput Computing), and – Visualisation and virtual reality (interactive/multimodal), and models that combine mathematical/statistical, logical/argumentative, schematic (pathway, tabular) and other visual representations – All middleware and related tools necessary to run and combine models.

Access to these two sets of tools is essential if we are accurately to model a wide range of bio-medical problems in a timely manner, without reinventing the wheel by developing tools that already exist. This is particularly relevant in the current context where we need to integrate information over the whole body, which means having to deal with problems that range from the molecular (spatial scale: 10^{-9} m; time scale: 10^{-6} s) to the organism (spatial scale: 10^{0} m; time scale: 10^{9} s) level. To have access to some of those tools would mean that researchers could, for instance, also reproduce published results and ensure that published data can be safely used.

VPH can help in making current and future tools available to researchers (through a repository of some sort; see databases needs above). The task at hand, however, is not trivial and can only be achieved with the help of multidisciplinary scientists where VPH can, once again, be of help (see infrastructure needs above).

3.3. Clinical Needs

Context – Many clinical fields are in need of advanced tools that would approach complex pathological syndromes using more integrated paradigms. Most contemporary clinical centres adopt a relatively fragmented structure when dealing with pathologies showing aetiology. This fragmentation reflects the high specialisation of most clinicians and the very few bridges that link these specialisations. Such organisational structure is efficient for pathologies, which show straightforward causes: e.g., a fracture will be handled by an orthopaedist, a heart attack by a cardiologist, etc. Unfortunately, many other pathologies show an aetiology that requires a multidisciplinary approach (see below section 5.1 Exemplary Cases) that is rarely met in today's clinical infrastructure. In practice, patients showing such pathologies are often sent to various clinical experts for analysis of their diseases. Redundant analyses are often performed with limited communication between the experts. This leads to longer aetiology analysis, higher health costs, frustrated patients and, sometimes, inadequate treatment. These problems have many sources and could be solved thanks to a more integrated approach as explained below.

Information overflow – Clinicians coping with complex pathologies usually receive information from a range of diagnostic tools and data collected at various scales and anatomical levels. This data is often loosely related, so it is often up to the clinician to integrate it mentally and, based on his/her

experience, to "process" a therapeutic decision. This demands extensive experience in the field on his or her part. Subjective interpretation and human error are reality because currently no advanced tool exists to help clinicians overcome the ever-growing flow of information they frequently receive on their patient. Large areas of the clinical field need tools to allow the integrated analysis of patient cases.

To understand systemic effects – The inability to solve the problems associated with this information overload frequently means that clinical decisions are restricted to reducing the clinical signs shown by the patients (e.g. pains, muscle spasms, fever, blood pressure). The underlying mechanisms of the pathology are often not fully understood and sometimes simply not taken into account because of the lack of integrative tools. As a consequence, the systemic effects of some pathologies on the human anatomy are still poorly understood. In this context, it is hardly surprising that modern medicine mainly concentrates on clinical signs and less on prevention. More advanced tools that combine and analyse the heterogeneous data collected in clinical practice should allow better understanding of the systemic effects of diseases and pathology. Only then can truly predictive tools and preventive health politics be developed. Such an approach should also allow clinicians to develop more cost-effective alternative therapies and reduce health-related social costs.

Bring more basic science to clinical practice – Many results obtained in fundamental biomedical research do not find their way into true clinical practice, mainly because the required bridges between both activities are missing. As a consequence, the conclusions of strict research performed according to validated protocols, and dealing with the more fundamental aspects of pathologies, tend only to be disseminated in scientific journals, and not integrated into clinical practice. This is mainly due to the medicine's own shortcomings (i.e. information overload, no integrated vision) and the frequent lack in most countries of straight collaboration between fundamental research and clinics.

However, it can be expected that the integration of results obtained from academic research concentrating on the fundamental aspects of complex pathologies, and included in an integrated analysis system, should facilitate clinical analysis and lead to a better understanding of the same pathologies.

Invasive therapies alleviation – The execution of invasive therapeutic strategies may be substituted, when possible and appropriate, by the findings from statistical/mathematical model results e.g. the value of an estimated parameter may indicate whether or not to perform a specific therapeutic action, so reducing the patient's discomfort and improving his/her quality of life.

Replace cadaver and animals in teaching – True dissections and practical exercises, both on humans and/or animals, are still the most optimal pedagogical channels to obtain true anatomical and physiological knowledge and expertise. Unfortunately, these channels are not available in some countries for various reasons (political and/or spiritual). Advanced modelling tools should be useful in such context.

Customised therapies – the integration of both fundamental and clinical observations in the above-mentioned integrated analysis system should result in a better understanding of the complex pathological mechanisms of specific diseases and disorders; this is already a major progress on its own. However, the ultimate clinical goal is to integrate patient-specific data into the modelling system to customise results to the particular patient's conditions. Patient specific data integration is often required due to the very individual nature of clinical signs displayed by different patients – even within the same pathology. Customisable systems still require the development of effective and validated registration tools.

Combining therapies and balancing side effects – Sometimes patients present with multiple pathologies. This is particularly true of an aging population like the European one. Each of these pathologies requires specific therapeutic actions, but because of the usually fragmented approach of contemporary medicine combining multiple therapeutic actions, can sometimes lead to conflicting effects (for example, between drugs). A more integrated approach of multiple therapies should help to better balance therapy and reduce their relative side effects on each other.

Fusion of diagnostic information and therapeutic decision – Diagnostic information is often collected at locations/departments other than just the clinical department in charge of the therapeutic decision. Such pipeline is justified by the sharing of common costly resources (e.g. medical imaging infrastructure) between various clinical departments (e.g. rheumatology, neurology, cardiology, etc). On the other hand, this depravation often leads to less efficient communication flow between all individuals involved in the therapeutic decision process. Integrating both diagnostic information and the expert tools necessary to analyse such information to obtain a therapeutic decision would be a more efficient way of handling the current flow of data to process during the various steps of a patient therapy.

Decision-making system – From the above, one can begin to understand the motivations behind the development of an integrated clinical system. Such a system would be based mainly on data collected on a healthy and pathological population during both fundamental research and clinical trials. Patient-specific information must be fused to the generic population model and the results then statistically processed by a decision-making engine built on knowledge-based algorithms. Such algorithms

should integrate, in an objective way, the expertise collected by clinicians on the multiple aspects of their field. The final system, once clinically validated and including extensive risk assessment, should become an effective decision support when dealing with complex pathologies.

3.3.1. Clinical Target

Integrative understanding – From this, it appears that the medical field needs more integrated solutions, particularly for pathologies showing complex and patient-dependent signs. One possible solution is to make available an infrastructure that would allow integrative understanding of whole aspects of complex pathologies. This infrastructure should become a common instrument where all medical specialities are requested in handling a particular patient's case. Components found within the infrastructure would allow clinicians to understand each other's speciality, thanks to tools integrating knowledge and data from those specialities uniting within a common patient-specific framework. Such a solution should help improve the communication pipeline in clinical practice and result in patients with complex pathologies being offered more efficient treatment.

Pre-packaged solutions based on highly innovative technology – The VPH infrastructure will be a container including as many tools and knowledge as is required to develop clinical field solutions. The tools found in the container will be based on highly innovative technology, and would allow all operations necessary to integrate clinical data into the VPH model (a description of such tools can be found in section 5.3. VPH Framework) to obtain predictive patient-specific models. The available tools will be developed and stored in a way that would allow fast development, optimal reusability (to avoid reinventing the wheel) and compatibility with other tools also built from the same paradigm. The latter compatibility will allow development of the multi-level and multi-scale requirements necessary to achieve a true VHP structure aiming towards a physiome-like approach to clinical problems.

Rare diseases – As previously mentioned, not every disease and pathology needs an integrated clinical tool. The development of such a system should focus first on the clinical problems for which the current (fragmented) clinical approach fails to bring satisfactory solutions to both clinicians and patients. Such disorders often shows various heterogeneous clinical signs that are qualified and quantified using heterogeneous technological means (from morphological medical imaging to functional analysis). Tackling such disorders using an integrative technology should lead to major improvements in the field and could be used as a showcase for further developments relating to other disorders. Example of rare diseases as potential candidates can be found in section 5.1. "Exemplary cases" following.

3.3.2. Barriers to development

Multidisciplinary consensus – The EuroPhysiome is a relatively new paradigm not only from a technological point of view, but also because it will gather extremely numerous disciplines that will have to inter-communicate and agree on extremely inhomogeneous topics. Consensus will have to be found on different topics before the development work even starts.

Consensus on standards – Each field of expertise traditionally develops its own habits, vocabulary and standards. Standards from different fields are sometimes (frequently?) incompatible. A solution to increasing interdisciplinary communications is to find a consensus on common standards. Another solution is to carefully describe each field of knowledge in ontologies that would be used by other expertise to access each other's knowledge and data.

Consensus on common tools – As well as standards, different fields often use different tools (algorithms, development tools, hardware). Consensus must be found on these particular topics to ensure compatibility during data exchange and to avoid redundancy of effort.

Understanding each other – A key element of success in a multidisciplinary project is that each discipline involved in turn has an extensive understanding of the other disciplines. Unfortunately, very few professionals have such backgrounds. Indeed, individual experts are often highly specialised and systematically approach a problem from a monolithic perspective. If a similar approach was adopted in a project like the EuroPhysiome, it would end in failure, so a highly multidisciplinary education for all professionals working in the EuroPhysiome is a prerequisite. For example, the Research Training Network could allow bright subjects to spend time at various locations. Such training programmes would also allow individuals to understand each other's cultural differences. Indeed, if one of the strengths of the European Union is its diverse cultural background, it can also be a weakness in a large and complex research project if efforts are not made in that direction.

Acceptance barriers; Change clinical habits – One of the major challenges facing the EuroPhysiome is for clinics to accept it. Besides extensive validation, the way therapeutic teams perform clinical activities must necessitate a change in *modus operandi* to that of the highly multidisciplinary teams. This is frequently not the case, with specialised teams often deployed to deal with a patient's problem from their own vertical perspectives. Rivalries between specialist teams also exist. Ingrained habits will have to change, a task that should certainly not be underestimated, but one that could be solved by proper clinical validation of the proposed paradigm and extensive dissemination of the results. This acceptance will determine the length of the turnaround time required to change the current fragmented therapeutic pipeline into a proper integrated clinical infrastructure.

3.4. Industrial Needs

3.4.1. Introduction

The VPH is an umbrella initiative that presents the opportunity to assemble a diverse range of physiologically relevant data and unify it in a grand endeavour to exploit synergies for the benefit of improved healthcare throughout Europe. The clinical, academic and industrial nature of the anticipated datasets can support optimised healthcare, thus reducing costs and providing a significant commercial opportunity for industry.

By providing a resource to aid product design and development, the VPH offers the prospect of significant industrial benefits. Innovations can be developed more quickly with reduced risk and cost, and with regulatory authority recognition, the VPH may ease product development and decrease time to market – while reducing the need for clinical trials or animal testing. There is also the promise of relevant, easy-to-create simulation-based training and support at the point of product delivery. Ultimately, the reward for investing in the VPH is a competitive edge in a global market.

3.4.2. Industry and the VPH Resource

If the promised relationship with industry is to be effective, clearly a resource such as the VPH must be accessible and cost effective, whilst supporting a host of other needs. We have sought the opinions of industry representatives to document their prioritised responses to the opportunities afforded by a virtual physiological human. Although it would be desirable to engage all relevant industrial parties, this would require contact with several thousand commercial organisations. A representative subset has been identified, using a selection from the published list of suppliers to the UK's National Health Service (NHS[3]) and others known to be working in this area. Companies approached ranged from large multi-nationals, through to specialist Small to Medium-sized Enterprises (SMEs). Industry sectors represented covered a gamut of applications, ranging from basic medical equipment on the one hand, to sophisticated high-power therapeutic devices on the other, and a selection of everything in between. Many companies requested anonymity, and therefore company activity was characterised instead, grouped according to themes indicated in table 3.1.

CATEGORY	INDUSTRY	INTERESTS
Therapeutics	Pharmaceutical	Drug design, manufacture and delivery
	Devices	From small prosthetic devices to Linacs etc.
	Trauma Management	Wound-care, dressings, sutures, surgical instruments etc.
Diagnostics	Imaging	Ultrasound, CT, MRI, X-ray etc.
	Bioelectronics	ECG, EMG, audiology etc.
	Biomechanics	Stethoscope to gait analysis etc.
Other	Other	Data manipulation/storage, modelling, rapid prototyping etc.

Table 3.1. Categorisation of industry representatives

3.4.3. Industrial Consultation

A questionnaire was developed to determine industry responses to issues pertinent to the VPH. A telephone conversation (typically with the head of R&D at the establishment) was used to elicit the views of the company, their requirements and the likely impact of VPH technology on their business outlook. The content of the questionnaire was steered to some extent by information obtained from the STEP conferences, which highlighted several areas of interest, namely that:

- The VPH could address (much needed) access to high-quality, validated data (supplied with some measure of data quality)
- A major impact of the VPH could be the reduction in time-to-market of a new product, and a reduction in (but not removal of) clinical trials
- There is some difficulty in recruiting people with the correct mix of skills and background to fulfil vacancies.

The questionnaire usefully guides the topic of conversation through several areas as outlined below:

- **Introduction:** A brief introduction and outline to the STEP initiative and VPH and a clarification of relevant company activity.
- **Needs:** Information about the type of modelling (if any) the company is working with, and how they use it. We also sought their views on the technology (software and hardware), benefits, costs and savings to be made by using modelling. Their opinions on the limitations of modelling, and their views on the future, were also included. Time was taken to discuss their stance on what the VPH/physiome should and should not include (e.g. modelling of interface between a product and its surroundings, an easy-to-use visualisation toolkit/programming interface etc.).

- **Impacts:** Gleaning information about what industrial motives drive any potential investment in the physiome, and the geographical area that companies cover. Their perceived or expected benefits from this resource, and the associated impact, were also explored. We asked whether they felt there were any disincentives to using the technology.
- **Human Factors:** Examining views on recruitment, the necessity of employing the correct people, training of end-users and their views on the potential of patient-specific medicine.
- **Wrap-up:** Asking whether there was any other organisation that should be taken into consideration and whether there was anything else they would like to raise.

3.4.4. Views Expressed

Several common themes emerged from this research. Echoing views expressed at the STEP conferences, access to high quality, validated data would clearly be of value, and of even greater benefit if it was accompanied by a measure of data quality. The availability of medical grade image data has a profound impact when considering the correlation between a model and the "outside world" or between 3D image data and CAD/FEA models. Current data limitations include material characterisations for the human body. Opportunities to access quality data provided by the VPH, including material characterisations for the human body would be welcomed.

Some companies consider themselves technology leaders – breaking technology bottlenecks is their business. This contrasts with some smaller businesses in which over-reliance on complicated technology makes them vulnerable to technology bottlenecks and could limit the pace of their developments.

Without exception, investment in modelling of a system/device early in the design process was acknowledged as being a method that *could* create substantial savings on the whole product development costs and lower the risks associated with new product development. It could also reduce *but not remove* the need for clinical trials. However, the learning curve associated with modelling is often steep and a user-friendly GUI should not be sacrificed for enhanced model quality. It would be useful if a novice user could get a "first-glimpse" of model results by using the same interface as the experienced user who understands the customisations available. There were also concerns that there is currently little acceptance or trust of modelling results amongst clinicians and regulators.

The idea of a central data and model repository was met with universal enthusiasm. This should house data both for the accepted "normal" physiology and a sub-set for known abnormal physiologies alongside models that can take account of individual differences. During discussions with one organisation, it emerged that their existing modelling environment, developed in-house, can already take account of individual physiologies in the calculations they make, but they acknowledged that this was unusual and welcomed any advancements in this area.

Concerns were raised about the confidentiality and security of patient data, particularly if it was to be passed between organisations and/or countries for processing a patient-specific problem, for example, or to a central storage facility.

3.4.5. Specific Indicators

In each of the main questionnaire categories, specific issues emerged during the conversations. Although few of these have a profound or fundamental impact on the main direction in which the Physiome is expected to evolve, there were some strong opinions presented that highlight particular areas of concern – see table 3.2 and table 3.3. Table 3.3 relates strength of opinion to the numerous indicators highlighted in table 3.2.

TOPIC	MAJOR FINDINGS
Needs	– **Validation** is hugely important; un-validated tools are of almost no value – Obtaining **material properties** for biological materials is a major difficulty – Modelling that can provide **insight** into (and so help to remove) inter-patient variability in results is particularly helpful – **Regulatory and professional bodies** (e.g. NICE and the Royal College of Surgeons) should be kept as informed about new technologies as industrial users. Most companies relish product endorsement by and close ties with leading academics – In general, larger and more sophisticated organisations are happier than smaller ones to examine **simulation tools** in their early stages, before they are fully-polished and ready for the market – Other organisations, in which modelling is not well-established, prefer more **complete systems** requiring less operating skill and lower computing resource requirements – In highly skilled industrial environments, the ambitions of the industry are often less sophisticated than those of collaborating academics
Impacts	– Improving **fundamental understanding** is a popular goal that is rarely achieved at present – Currently gross-scale models are of most benefit, but there is a major move towards **cellular-level and molecular modelling** – The **minimisation of risk** is a key area of simulation applicability. It could also have an effect on the number of clinical trials undertaken (or required) for a product – Faster **time-to-market** and reduced costs are often as important as (perhaps even more important than) improving performance – Larger organisations are investing in modelling technology on the assumption of its worth. Those who have quantified improvements suggest at least a 15% reduction in costs and at least a 25% improvement in **time-to-market** – **Simulation** is seen as a means of reducing the required period of clinical experience prior to full product launch. A reduction from 3 years to 18 months was seen as being typical and of significant benefit
Human Factors	– Special efforts are required to obtain appropriate **skilled staff**. The most successful approach has been to use a special relationship with an academic institute to identify suitable candidates and then train them additionally in industry-specific skills. Contractors are also used occasionally to fill short-term modelling positions – Whilst some companies are driven overwhelmingly by the need for financial success many organisations have a strong sense of **public responsibility** that fits well with the ambitions of the Commission. These organisations would have difficulty with any policy that attempted to favour the provision of health benefits to Europeans before those to other parts of the world. However, no company expressed difficulties with being obliged to favour Europe as its manufacturing base if this was to be a condition of having access to EuroPhysiome resources

Table 3.2. Specific Indicators

CATEGORY	INDUSTRY	VALIDATION	MATERIAL PROPERTIES	MODELLING INSIGHT	REGULATORS/ PROF BODY APPROVAL	FUNDAMENTAL UNDERSTANDING	CELL-LEVEL MODELLING	MINIMIZING RISK	TIME-TO-MARKET
Therapeutics	Pharmaceutical	3	1	3	3	3	3	3	3
	Devices	3	3	2	3	2		3	3
	Trauma Management	2	3	3	2	3	3	3	3
Diagnostics	Imaging	3	1	1	2			3	3
	Bioelectronics	2		1				3	3
	Biomechanics	3	3	2		2		3	3
Other	Other	2		1		2			3

Table 3.3. Views expressed by industry sectors.
Key: 1-Not very important, 2-Important, 3-Very important

3.4.5.1. Critique

The NHS in the UK has a long-standing list of companies with which it does business, using suppliers from Europe that meet tight cost and regulation criteria. The breadth of items ranges from the very small and inexpensive (plasters, bandages, scalpel blades) to sophisticated and expensive equipment (MRI scanners, LINACs). The NHS list of suppliers is comprehensive, able to provide a selection of companies that is representative of commercial health interests across Europe. It was not possible to consult all of these and therefore a pragmatic subset was chosen. All the companies that were consulted have a presence in the UK and Europe and many have dealings with the rest of the world. Making contact with a relevant employee with a suitable background proved to be quite difficult, unless there was a known contact. A number of large companies employ a form of central contact system and it proved difficult to get in touch with a relevant contact through this system. The detail of the questionnaire tended to result in lengthy consultations (not always appreciated by the interviewee!). In the light of experience, a more concise approach would benefit both parties if the exercise were ever to be repeated. A large proportion of respondents stated that, although they were happy to participate in the process, they wanted their responses to be anonymous. In the light of these difficulties, perhaps there is merit in obtaining information through a Web-based consultation, but this option is currently beyond the scope of this project.

3.4.6. Summary/Conclusion

The value of the VPH to industry is clear, but determined effort is required if a closer relationship is to ensue between industry, research and clinicians. Industrial representatives believe access to high quality, validated data, along with a field of experts and a repository of models is highly desirable, as this could have a dramatic effect on the time-to-market and risks associated with the development of a new product. There could also be implications for the number of clinical trials undertaken in this process.

In areas of the industry that are heavily regulated, endorsement of the VPH resources from the regulatory bodies and relevant professional bodies (e.g. the Royal College of Surgeons) could improve the perceived value of the VPH by clinicians, and therefore improve the chances of its widespread use. A resource that is able to accommodate and facilitate the use of patient specific data would be highly applauded.

The VPH initiative has lofty ambitions, which are arguably comparable in concept to sequencing the human genome – something that seems a trivial exercise today. It represents such a tough problem for the many disciplines that will necessarily become involved that the gain to science will inevitably be even greater than the stated aim. It is probable that the gradual improvements associated with pursuing such a goal will be worthwhile in their own right, leading to better small-scale models, improvements in the connections between model systems, and developments in the methodologies for model integration.

The VPH also offers a much-needed focus to the nebulous systems biology domain, which highlights another potential benefit. The development of methodological and technical frameworks, or a common systems biology language, will be

essential in facilitating multidisciplinary community collaboration. Access to standard representations of data and models will, in itself, foster rapid collaborative development. Pharma industries usually make use of data at many different scales: data on molecules (affinity, NMR data, mass spec), their interactions with cells or tissues (cell penetration data, cell toxicity, etc), effects of molecules on whole animals, effects on people.

The benefits that this endeavour could offer to the industry include a reduction in development times, through a number of mechanisms including faster and earlier attrition, and more rapid and directed research cycles. As the understanding of disease and drug interactions improves, it will further highlight the applications of drug repurposing and the identification of related disease-treatment opportunities. The concept of customisable drugs or patient stratification is clearly a driver in today's market, and improvements in prognostics and diagnostics, made through an understanding of how biomarkers relate to disease, are key factors in this. The virtual patient concept also has the potential to draw us closer to reductions in animal experimentation, which is clearly highly desirable.

There might, of course, be some significant barriers – the required technological developments notwithstanding – and significant cultural change will be necessary to support the collaborative environment needed. In industry, consideration of ownership and availability of data, as well as the restrictions placed on the usage of data and models, will prove particularly important. Legal and ethical considerations on the use of data will be significant hurdles at the clinical level.

As there is so much missing from our fundamental understanding of the systems we choose to manipulate, it would be easy to understate the significance of the scientific advances that will be necessary to take us from where we are today to the simulation of the virtual human. This project has a great deal to offer in terms of filling in the gaps and provides us with the motivation for supporting this worthwhile activity as it moves forward.

3.5. Society's Needs

Society's needs are to a large degree reflected in industrial needs (for innovation, improved standards, low cost production methods, knowledge about the human body, better access to data and academic knowledge) and clinical needs (primarily the need to transform basic science into clinical practice, to understand the systemic effects of interventions, including side effects, and to promote decision-making based on risk analysis relating to the individual) and in society's general interest in research. Ethical issues, such as those linked to experimental work on animals, is also a concern of society, which seeks a reduction in animal experiments and invasive studies on humans.

Research, and in particular the type of integrative research that the VPH can offer, strongly supports the clinical and industrial links because the production and commercialisation of products need to be founded on sound research and high-level education.

A basic need of European society, as seen from the perspective of its citizens and global competition, is to improve the economy. For a long time, Europe has moved towards a knowledge-based economy, a trend that is strongly supported by the VPH. An improved economy, with the social welfare system that most European countries favour, will improve healthcare, including the diagnosis, treatment and care of patients, and the quality of life in general. VPH will further improve healthcare by increasing overall awareness and by providing better insights into health and disease, including prevention and regeneration, the impact of better nutrition and better environmental conditions. Prevention and rehabilitation are key to economic improvement and improved quality of life and, in this context, include sports injuries, accidents, and safety issues. Planning and rehearsal of therapeutic interventions using VPH modelling and simulation tools will reduce morbidity and improve outcome.

Education is vital to increasing the population's general knowledge. Education based on VPH tools will improve healthcare as already mentioned, but it will also increase the individual's confidence in medicine and medical systems. Training of healthcare practitioners using Patient Specific and Patient Focused simulation will enhance the quality of care. With a greater level of knowledge, the citizen will facilitate a holistic approach to medicine (treat the whole body – multi-organ systems rather than the single organ). Knowledge and confidence in medicine and computer models will make people more responsible for their own lives.

The needs of society are based on personal needs and expectations. In the post-modern era, citizens expect taxpayers' money to be used in efforts that have a clear and visible impact on their lives. This also includes the need for evidence-based medicine and personalised healthcare.

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4.0

4.1. Premise

The scope of this section is to provide an overview of what is being done in the world to develop integrative research in biomedicine.

International context

4.2. Europe

4.2.1. Reference Documents

VPH White Paper[4]: Final document of the Workshop: "Towards virtual physiological human: Multilevel modelling and simulation of the human anatomy and physiology" Barcelona, Spain, 1-2 June 2005.

The Health Status of the European Union – 2003[5]: The European Community is increasingly concerned with ensuring the physical well-being of its citizens by reinforcing its activities in the field of public health. One of the main pillars for Community action is to review and present accurate data on health status to a wider audience, achieved through the publication of Community Health Status Reports. The aim of these reports is to improve public knowledge and understanding of major health problems in the Community in order to support the appropriate measures at Community, Member State or individual levels.

IMI Strategic Research Agenda (SRA)[6]: The Innovative Medicines Initiative (IMI) is a unique pan-European public and private sector collaboration between large and small biopharmaceutical and healthcare companies, regulators, academia and patients. Its aim is to support the faster discovery and development of better medicines for patients and to enhance Europe's competitiveness by ensuring that its biopharmaceutical industry remains a dynamic high-technology sector. The SRA, whose second version was published on September 2006, repeatedly refers to the use of predictive modelling in general, and of multi-scale modelling in particular, as one fundamental innovation in drug development that will be pursued in the next few years.

SHARE Action initial deliverables: The SHARE coordination action, the STEP twin action aimed at developing the research roadmap for the so-called HealthGrid, produce two early deliverables: "a framework for developing a roadmap for the adoption of Grid technology in healthcare"[7], and "Baseline on technological and security aspects of healthgrids"[8].

Connected Health Report[9]: This report was written with input from both the i2010 sub-group on eHealth and the eHealth stakeholders' group. The paper outlines priority issues which must be pursued in order to reach all of these health systems goals – improve patient safety, encourage well-informed citizens and patients on health matters, and create high-quality health systems and services – while simultaneously facing international competition in the eHealth sector.

4.2.2. Preliminary Implementations of the VPH

In one of the last calls of the FP6, the E-Health Unit of the DGINFSO invited proposals for research projects aiming to integrate information across scale and systems. Among those selected, three projects have a scope particularly consistent with the development of the VPH:

AneurIST: Integrated Biomedical Informatics for the Management of Cerebral Aneurysms. The project, which aims to assist clinicians in the assessment of the risk of rupture in cerebral aneurysms, started on 1 January 2006.

ImmunoGrid: The European Virtual Human Immune System Project. The project, which aims to simulate the human immune system using Grid technologies, started on 1 February 2006.

LHDL: Living Human Digital Library: Interactive digital library services to access collections of complex biomedical data on the musculoskeletal apparatus. The project, which aims to develop one of the first VPH infrastructures for the sharing of data and model on the musculoskeletal apparatus, also started on 1 February 2006.

4.2.3. Complementary projects

The EC is supporting other projects within the FP6 initiative and whose results might have a significant impact in some of the aspects of the VPH:

PRIVIREAL is a EUROPEAN COMMISSION Framework 5 funded project examining the implementation of the Data Protection Directive 95/46/EC in relation to medical research and the role of ethics committees.

SYMBIOmatics: Synergies in Medical Informatics and Bioinformatics. The SYMBIOmatics is a EUROPEAN COMMISSION Framework 6 funded project by the ICT for Health unit in the Directorate General Information Society.

BIOSIM: BioSim is a Network of Excellence established by the European Commission under its 6th Framework Programme. BioSim was initiated on 1 December 2004. The main objective of the Network is to demonstrate how, through a deeper and more qualitative understanding of the underlying biological, pathological and pharmacological processes, the use of modern simulation techniques can lead to a more rational drug development process, improved treatment procedures and a reduction in the need for animal experiments.

BioSapiens Network of Excellence: A European Virtual Institute for Genome Annotation. BioSapiens is a Network of Excellence, funded by the European Union's 6th Framework Programme, and made up of bioinformatics researchers from 25 institutions based in 14 European countries. The objective of the BioSapiens is to provide a large scale, concerted effort to annotate genome data by laboratories distributed around Europe, using both informatics tools and input from experimentalists.

ENFIN: an Experimental Network for Functional INtegration, Network of Excellence EU funded project, contract N. 518254, within the Sixth Framework Programme. The purpose is to provide in the area of bioinformatics a Europe-wide integration of computational approaches in systems biology. This network

[4] http://www.biomedtown.org/biomed_town/STEP/Reception/STEPrelatedprojects/vph-paper

[5] http://www.biomedtown.org/biomed_town/STEP/Reception/STEPrelatedprojects/echealthstatus

[6] http://www.nsmf.org/Attachments/IMI.htm

[7] http://eu-share.org/fileadmin/templates/Document/SHARE-D3.1_Final-1.pdf

[8] http://eu-share.org/fileadmin/templates/Document/SHARE-D3.2_final.pdf

[9] http://ec.europa.eu/information_society/activities/health/docs/policy/connected-health_final-covers18092006.pdf

will be focused on the development and critical assessment of computational approaches in this area, but uniquely will bring together a range of backgrounds and laboratory contexts that will span investigative computer science through to traditional wet-bench molecular biology.

BISTI NIH Roadmap National Centers for Biomedical Computing: The mission of the BISTI Consortium is to make optimal use of computer science and technology to address problems in biology and medicine by fostering new basic understandings, collaborations, and trans-disciplinary initiatives between the computational and biomedical sciences.

HaeMOdel is a recently completed FP6 STRP coordinated by Prof. Alfio Quarteroni and aimed at the development of mathematical and numerical models of the Cardiovascular System.

TUMATHER: Modelling, Mathematical Methods and Computer Simulation for Tumour Growth and Therapy is a Research Training Network funded by the European Commission under its 5th and 6th Framework Programme. The main objective of the Network is to develop mathematical models, algorithms, and computer software for the simulation of multi-scale modelling to describe tumour growth and support therapeutic actions.

MIAS: From Medical Images and Signals to Clinical Information (MIAS – http://www.robots.ox.ac.uk/~irc/) – MIAS is all about transforming the enormous flood of medical data into manageable amounts of useful information that will help doctors and ultimately benefit patients. Funded by the Engineering and Physical Sciences Research Council (EPSRC), the project began in 2001 and is a collaborative effort, with teams from Oxford University, University College London, King's College London, Manchester University and Imperial College, London forming an Inter-disciplinary Research Consortium (IRC). Multiscale modelling is one of the three grand challenges defined by MIAS.

4.3. United States

NSR Physiome Project: The NSR Physiome Project provides comprehensive and downloadable physiological models, many of which were created at The National Simulation Resource for the international Physiome Project collaboration.

WTEC Panel on Systems Biology: The goal of this study is to gather information on the worldwide status and trends in systems biology: "Network Behaviour in Biological Systems" and to disseminate it to government decision makers and the research community.

Virtual Soldier Research: The VSR program is an independent program within the Center for Computer-Aided Design of the College of Engineering at The University of Iowa. VSR's objective is to develop a new generation of digital humans comprising realistic human models including anatomy, biomechanics, physiology and real-time intelligence. VSR's philosophy is based on a novel optimization-based approach for empowering these digital humans to perform, unaided, in a physics-based world. Our objective is to test digital mock-ups of products and systems before they are built, thus reducing significant costs and the amount of time associated with making prototypes. We are a group of 36 researchers from all kinds of disciplines that have come together to create a digital human called SantosTM.

The SimBios Project: The Simbios project aims to establish a National Center for Physics-Based Simulation of Biological Structures (Simbios) to help integrate the field of physics-based modelling in biomedicine and accelerate future research. The main goal is the development of an Open Source toolkit (simTK <https://simtk.org/xml/index.xml>) that will enable biomedical scientists to develop and share accurate models and simulations of biological structures from atoms to organisms.

Digital Human: The Digital Human project is an Open Source Software Consortium using 21st Century information technology tools to represent the body's processes from DNA molecules and proteins to cells, tissues and gross anatomy. Understanding complex biological systems requires an enormous amount of experiments producing considerable amounts of information, all of which are not currently linked. Computers are making it easier to visualise these systems and can also serve as an essential tool to link information. Having a shared framework would allow researchers, medical personnel and engineers to build on each other's work as well as allow biomedical researchers to work effectively together to develop a language that will allow this to happen.

Biomedical Informatics Research Network: The American Biomedical Informatics Research Network is a shared biomedical IT infrastructure to hasten the derivation of new understanding and treatment of disease through the use of distributed knowledge. Drawing upon the expertise and technologies available at numerous institutions, the Biomedical Informatics Research Network (BIRN) is building an infrastructure of networked high-performance computers, data integration standards, and other emerging technologies, to pave the way for medical researchers to transform the treatment of disease.

4.4. Asia-Pacific region

Probably the most relevant initiative in this region is the IUPS Physiome, an international effort coordinated by the University of Auckland, New Zealand. It aims to facilitate the understanding of physiological function in healthy and diseased mammalian tissues by developing a multi-scale modelling framework that can link biological structure and function across all spatial scales. To achieve this requires an open-source internationally collaborative effort to build model databases and computational tools. The roadmap proposed here covers the development of standards for describing mathematical models of biological structure and function and their associated mark-up languages. The development of web-accessible model databases, and the various tools needed for authoring, combining and displaying models, and running simulations with the models, are also considered. A number of examples are given of both current usage of the physiome models and software, and anticipated future end-user requirements.

4.5. Japan

Japan has recently recognised the importance of promoting integrative research among various disciplines, with the Japanese government committing to an official plan for the promotion of science and technology every five years. Last year (2006) marked the first year of the third plan under this policy, which also embraces the concept of fusion research.

One of the targets of this collaborative or fusion research is "Integrative Biology" or "System Biology". Its major theme is the reconstruction of the living organism function, including the human body. This subject, so far the one project funded by the Ministry of Education, Science, Culture, Sports and Technology of Japan to date, is already under way. The project, launched in 2003, is called "Biosimulation" and will conclude next year. It comprises four groups: Keio University team, Kyoto University team, Kobe University team and Osaka University team, each with some rather clinical oriented application objectives as follows:

- Development and Application of Computer-Based Biosimulation Assisted by Metabolome Analyses
- Cell/Biodynamics Simulation Project
- Simulation of anti-diabetic drug action *in vivo*
- Development of Heart and Lung models for *in silico* prediction of drug action and clinical treatment.

The total fund for five years is ¥9,000,000,000 (US$75 million including the initial start up fund). One major project, to develop the fastest computer in the world with funding from the ministry in the order of US$1,000 million over five to seven years, was initiated in 2006 and has reached candidate selection stage. One of the major applications of this new generation super-computer is expected to be in the biosimulation area. The group covering the major research laboratories in Japan to develop applications for this super-computer and has now been formed under the supervision of RIKEN and is receiving funding from the ministry of US$13.3 million a year for four years.

This facility would be offered as a resource for worldwide usage including the EU-VPH project.

4.6. The World Integrative Research Initiative

From this brief and partial summary, it is clear that there is a risk of extreme fragmentation. This is why **the extensors of this roadmap recommend the establishment of a World Integrative Research Initiative (WIRI)**, a lightweight coordination action among all physiome-related projects around the world. What follows is a short list of arguments that could become the responsibility of such an organisation:

Common Objectives

Call the same things by the same name: consensus on definitions

Define and constantly revise the goals of the Integrative Research Initiative

Develop descriptions of the expected results, and of their impact on the life of humanity.

Research Challenges

Promote consensus on the grand challenges Integrative Research poses

Suggest research and technological development objectives considered essential for the success of the Integrative Research Initiative.

Resources Required

Maintain an Integrative Research Investment Monitor, which lists all Integrative Research projects and the relevant resources invested in them

Develop a lobbying strategy that allows the World Integrative Research Initiative to support integrative research within public and private grant agencies

Start a collective open source software project for supporting this integrative research initiative

Promote studies on long-term sustainability and related business models.

Ethical, Legal and Gender Issues

Maintain the GEL (Gender-Legal-Ethical) observatory to monitor the legal barriers to the development of Integrative Research.

Interoperability

Develop standards that ensure the federation of digital libraries and repositories relevant to the Integrative Research Initiative

Create a central repository of Software Tools that list and comment all software that might be useful for an Integrative Research project

Develop, maintain and harmonise semantic representations of the Integrative Research knowledge space.

Community Building

Creating a single website or a federated portal that can provide a single entry point for the whole Integrative Research community

Promote Integrative Research with a top-down approach by ensuring that each major scientific society has an Integrative Research panel (this includes IEEE, IUPS, ASME, IFMBS, EMABES, etc.)

Promote Integrative Research with a bottom-up approach by encouraging initiatives aimed at fostering the creation of new Integrative Research projects, and the idea of team science in biomedical research

Publish Integrative Research News, a monthly electronic newsletter

Promote initiatives that establish a sense of community, such as logos, T-shirts, etc.

Run the World Integrative Research Conference and other similar events.

Editor: Alan Garny, University of Oxford (UK)

5.0

5.1. Executive Summary

There are several cases (vascular – e.g. the @neurIST project – osteoporosis, regenerative medicine, cerebral palsy or spinal fluid circulation, hypertension, cardiac – e.g. heart valve failure, normal and pathological heart – plurimetabolic syndrome, exposure to xenobiotic agents, tumour growth and therapy, etc.) where the need for a VPH-based framework has been clearly demonstrated.

To address all of the complexity of human physiology would not only be unreasonable, but it would simply miss the point that models are "simplified representations of reality", which – by this definition – implies that a multitude of models are required, much like tools in a toolbox. So, which tools should have priority for development? Clearly, the focus should be on clinically relevant physiological aspects, which will inevitably encompass different space and timescales, begging the need for a multi-physics framework. Such a framework will require the efficient flow of information (data and metadata) between VPH-related activities in the health, industrial and academic sectors. VPH must be an *inclusive* framework, not only due to the limited funding, but because of its aims and implementation. It must take into account the 21st Century human environment, in order to determine accurately the relevant boundary conditions required for simulation and to focus on major challenges related to health and well-being.

Common Objectives

We believe that three basic principles should underpin the increased level of co-operation that will characterise the future development of VPH:

1. The establishment of standards for the construction of modelling "services"
2. Adherence to a set of mark-up languages (e.g. AnatML, CellML, FieldML, SBML) for unambiguous description of models, parameters and boundary conditions (in keeping with the approach of the IUPS Physiome)
3. The development of a collection of "core models" at a high level of integration (these would be special instances services, in the sense of Principle 1, or standardised model descriptions, as in Principle 2, or even both, for certain systems).

All of these will be supported by appropriate domain ontologies and semantic annotation techniques to allow for unambiguous interpretation of data, as well as to enforce the use of a common set of terms across separate domains, and to ensure consistency of modelling and logical inferences by means of reasoning techniques.

Implementation of the VPH will occur through different types of efforts, some of which will be EC-funded, while others will be supported from other national and multi-national sources, or even be individual efforts. All of these should share a common vision and have a strong sense of ownership. Some of the features that will need to be implemented include (in no particular order): data processing, modelling, effective access to resources, infrastructures, community building, resource generation and access, knowledge management and backend services.

5.2. Exemplary Cases

5.2.1. Predicting the risk of cerebral aneurysms

It is becoming increasingly common to accidentally detect the presence of cerebral aneurysms during routine examinations. This poses an important problem, since there is no well-established method for assessing the risk of rupture of such aneurysms. Many aneurysms are therefore treated (using a high risk procedure), while they could have perfectly remained asymptomatic for the rest of a patient's life. The @neurIST integrated project[10] aims to unravel this complex problem by combining different types of information (e.g. diagnostic, epidemiological, modelling-based), into a coherent multi-scale representation of the affected vessel, able to compute a risk of rupture that is clinically reliable. At the core of the @neurIST infrastructure will be a VPH representation of cerebral circulation, without which it would be impossible to accumulate all this information in a figure of sense (see also sections *4.2.2* and *8.3*).

5.2.2. Osteoporotic fractures in the bone and joint decade

Osteoporosis is becoming a pandemic disease. While it is marked by a decrease in bone mineral content, it is the occurrence of spontaneous fractures during normal daily life that represents the true index of this disease. The gold standard for osteoporosis assessment, dual X-ray absorptiometry (DXA), is incapable of predicting the risk of fracture, in a given patient, with the necessary level of accuracy. In prospective studies, pure DXA measurements predicted less than 65% of the fractures (tossing a coin would give you 50%). The problem is that we not only need to know how much mineral we have in bones, but also to predict the mechanical stresses induced in bone tissues during daily life. This implies a complex multi-scale modelling that is typical of VPH goals. If we then want to find out what are the behaviours that prevent this pathology, or which treatments are more successful, the need for a VPH-based framework becomes dramatic. There is evidence, for example, to suggest that risk of fracture is more closely related to localised weakening in the skeleton than to a global loss of mineral. So, localised treatment could prove much more effective than drugs that interfere with generalised metabolic processes. But we need to be able to predict where is the weakest point of each patient to be able to use them, and by how much we need to strengthen it. All this is impossible without a framework such as the VPH.

5.2.3. New organs: mechano-biology is the core of regenerative medicine

Hard physical work wears people out. This is probably why organs that absolve the most intense mechanical body work are also those that tend to fail more easily: the heart, the joints, the spine, the gastrointestinal tract, etc. It is hoped that so-called regenerative medicine will help in preventing the catastrophic failure of an organ. The basic idea is to take some biological material from the patient, culture it under very special conditions, eventually in combination with artificial materials, so as to be able to regenerate the whole affected organ or part of it, which can then be replaced with this bio-engineered construct. While we are starting to know a lot about the relation between cells and tissues, we know much less about the relation between cells and tissue function. There is, however, very strong evidence to suggest that, without reproducing the exact mechano-biological conditions, the tissue would find *in vivo*, cellular specialisation and tissue differentiation will not happen correctly inside the bio-reactor. This is especially true for tissues that absolve a mechanical function, such as a cardiac muscle, an articular cartilage, etc. In order to solve this problem, we need to understand how someone's daily physical activity interacts with basic cellular aspects such as gene expression. This involves the creation of models that span three or four-dimensional scales, which once again would require a framework like the VPH.

[10] http://www.aneurist.org/

5.2.4. Understanding cerebral palsy aetiology and predicting clinical actions

Cerebral palsy (CP) is pathology of the central nervous system leading to non-physiological hyperactivity of some muscles that are showing spastic patterns. In non-pathological subjects, limb motion (e.g. during walking) is possible by its alternated contraction/decontraction. In the case of CP patients, and because of muscle spasticity, motion patterns usually show typical limited joint amplitude and frequently severe non-physiological motion patterns. When the patient is a child (as is usually the case, since CP is a congenital pathology) whose skeleton is growing and easily reshaped according to local external constraints, such non-physiological patterns lead to bone deformation and long-term severe joint overuse. Current clinical actions are limited to increasing the patient's comfort by Botox injections, the aim of which is to reduce muscle spasms. The choice of muscle to inject into is still very much empirical and the current literature does not help in understanding the relationships between muscle spasticity, motion patterns, the action of the Botox at the cellular level and the long-term reshaping of the skeleton under non-physiological stress. State-of-the-art improvements will require work at various scales and levels:

- Molecular level: development of pharmacological models allowing the study of the interaction of some drugs (e.g. Botox) on the muscle contraction ionic channels. Only then can we better understand CP mechanisms, predict therapeutic actions and significantly improve CP patients' condition.
- Cellular level: modelling of the bone reshaping mechanism in normal conditions and under non-physiological stresses, and modelling of striated muscle fibre contraction.
- Body and organ level: modelling of the normal musculo-skeletal system physiology of a normal population to increase our understanding of that topic, and customisation of the general population to obtain patient specific models.

5.2.5. Cerebral system: the interplay of cerebrospinal fluid and blood circulation in the brain

Both brain and spinal chord are surrounded by cerebrospinal fluid, partly confined in a complex membrane system. Recent findings have revealed that numerous conditions, some of a very critical nature, are connected with the way in which this system regulates the transport of blood and cerebrospinal fluid. From acute mechanical dysfunction or injury of the upper cervical spine (e.g. whiplash) to chronic and often obscure conditions (like communicating hydrocephalus), the fine balance and interplay of the regulatory mechanisms of the cerebrum are integrative and multi-scale by their very nature. Little data about this multi-level system is available, a scarcity attributed both to the complexity of the system and to the very disparate nature and scales at which the important mechanics are encountered:

- Cellular level: cerebrospinal fluid fluxes are regulated at the tight junction level. Similarly, the water and oxygen exchange at the capillary level play an important role in this system. In effect, entry at the brain cellular level must be modelled to achieve an accurate representation of this all-important system. Only then can predictive tools allowing the visualisation of the relationship between external parameters (e.g. posture, spine position) and system behaviour (e.g. intracranial pressure, the state of the blood-brain barrier) be made available. The association of such predictive models with detailed and multi-modal imaging will lead to patient-specific simulation environments and to better therapeutic decision-making and action.
- Passage level: the complexity of the cerebral vasculature is only complemented by the intricacies of the ventricular/aqueduct system of the cerebrospinal fluid. A multi-scale system by itself, it cannot be viewed in isolation but only connected intimately with the cerebral environment as a whole.
- Organ level: the compartmental nature of neuronal tissue, cerebral blood volume and cerebrospinal fluid leads to very complicated self-regulation behaviour: one must develop accurate models of the spine and skull physiology and account for the relationship with cerebrospinal fluid circulation and blood motion.

5.2.6. Hypertension: channelopathies, diuretic treatment and gene polymorphisms

Hypertension is the result of increased fluid retention due to inadequate salt excretion, i.e. there is an imbalance between salt intake and excretion. The impact of this imbalance on blood pressure (BP) involves many factors and multiple regulatory loops, but the sum total of all these effects may be summarised by consideration of the "pressure-natriuresis" curve, which illustrates the set point of BP and salt excretion. That is, this curve presents, for a given individual, the rate of urinary excretion of NaCl as a function of arterial BP: a shift of the curve implies a resetting of the set point such that excretion of a given amount of NaCl requires higher than normal BP, i.e. hypertension. The actual mechanisms underlying such a shift of the set point are, and have long been, the object of intensive research.

It is well established that essential hypertension (ET: hypertension for which there is no clearly identified cause) is a disease affected by many genetic and environmental factors. Most genes that have been associated with BP regulation (and

thus with hypertension) are genes that code for proteins involved in the regulation of salt and water balance by the kidney, especially transport proteins expressed in the tubular epithelia of the distal part of the nephron. Particularly interesting results have been obtained for genes coding for the sub-units of adducin, a cytoskeleton protein, in relation to salt sensitive arterial hypertension (both experimental and in humans). Adducin polymorphisms have been found to be genetically associated and linked to essential hypertension in humans and to affect the relationship between renal Na^+ excretion and BP (Ferrandi *et al.*, 1999; Am J Physiol, 277: H1338–H1349). The action of thiazide diuretics appears variable depending on the polymorphism of adducin in hypertensive patients, considering either the intermediate criterion of arterial BP or a clinical indicator such as the reduction of cardiovascular risk. Much textbook information covering the relationship between adducin polymorphisms and the action of thiazides on hypertension is available, strongly implicating a role for the NaK-ATPase of the distal nephron (see review by Manunta & Bianchi, 2006; J Am Soc Nephr, 17: S30-S35).

Given these facts, it would be helpful to develop a mathematical modelling environment that would assist quantitative decisions about the treatment of a particular hypertensive patient. Such a model does not currently exist and its development will require the co-operation of experts in many different fields, but we can describe features that it would have to take into account. As an example, one scenario could consider the evaluation of the proper dosage of thiazide diuretic.

In this case, one might begin with a detailed mathematical model of salt and water transport in the renal distal tubule that would allow exploration of the relation between, on the one hand, genetic polymorphisms of adducin and their relation to the effects of thiazides and, on the other, the ensuing implications for net salt uptake from the distal tubule. Although this *local* model would already give much valuable information, it would not directly indicate the *organism level* effect on BP, since the imbalance of salt uptake would trigger a series of compensatory regulations in other parts of the body. Quantitative accounting for these, and for the net impact of the cycle of effect-regulation-compensation, etc., would require implantation of the detailed local model of the distal tubule into a coarser-grained and yet realistic model of the other organ systems and of the regulatory influences involved in the loop. Ideally, thanks to the coarse-grained global context model, such a model would be fast enough (in terms of calculation time) to permit adjustment of key parameters based on clinical signs and test results for individual patients.

5.2.7. Heart valve failure

Cardiac disease is currently the major cause of death in the world, with heart valve failure one of the main afflictions of the cardiovascular system, in particular the aortic valve, since it has to withstand the largest pressure differences. The heart valves can malfunction either by leaking (causing regurgitation) or by not opening adequately (causing stenosis), which can greatly interfere with the heart's ability to pump blood. Both of these pathological conditions reduce the efficiency of the heart and place additional stress and strain upon it. Surgical repair of the diseased valve is the preferred treatment even if there are cases in which its replacement with a heart valve prosthesis is necessary in order to restore proper heart function.

Heart valves can be classified into two broad categories according to the origin of their occluding mechanism: mechanical and biological. Mechanical valves are preferred when a patient is expected to live more than 10 years after implantation. Compared with impressive breakthroughs in many other fields of medicine, artificial heart valve development has progressed only gradually since it started in 1960, when an artificial cage ball valve was implanted. Nowadays, bi-leaflet mechanical valves are the most common, thanks to their reliability and good haemodynamics. Their main drawback, however, is their propensity for haemolysis and thrombus formation. For this reason, mechanical heart valve recipients must take long-life anticoagulant medication, which induces a higher level of haemorrhage risk.

It is generally accepted that the presence of high turbulent shear stresses generated in the flow field of prosthetic valves is partially responsible for the levels of haemolysis and platelet activation. Clinical reports indicate that these artificial heart valves are still unable to eliminate the problems of thrombosis and anticoagulant complications. In fact, red blood cell and platelet damages, which eventually lead to thrombosis, are caused by mechanical stresses of turbulence. More precisely, the largest vortices are generated close to the leaflets and start a cascade of eddies, decreasing in size to the smallest structures. This is the dissipation image of the turbulent spectrum, known as Kolmogorov scales. If the Kolmogorov turbulent eddies are smaller than or similar in size to the blood cells, they then directly interact with and transfer energy to the cells, thus damaging their membranes. In contrast, when the turbulent eddies are much larger than the blood cell diameter, the vortices completely surround the blood cells and rotate or translate them without causing much damage.

A reliable model capable of simulating and predicting the above processes should cope with fluid structure interactions, computational fluid dynamics, turbulence modelling and Lagrangian particle tracking, each factor adding to the complexity of the simulation. Such an effort, however, would be very valuable, since it would allow the testing of several different valve designs and, following an optimisation process, the selection of the shapes that provide the best haemodynamics.

5.2.8. Modelling multi-functional aspects of the normal and pathological heart

Cardiovascular diseases are still a leading cause of mortality in European countries. Among them, ischemic heart diseases, which may lead to myocardial infarct, originate from disequilibrium between different functions of the heart: myocardial perfusion, myocardial metabolism, myocardial fibre architecture and contractile function. Developing techniques for individually modelling these functions and integrating them into a patient specific model would be extremely useful to help clinicians in their decision-making processes. Further, knowledge and modelling of "normality" are key to the detection of abnormal cases.

5.2.9. Plurimetabolic syndrome: insulin resistance, secretion and risk of diabetes

The plurimetabolic syndrome is a cluster of conditions (increased BP, elevated insulin levels, excess body fat and abnormal cholesterol levels) that occur together, increasing the risk of heart disease, stroke and diabetes, and now a real epidemic in Europe (some 33 million people were reported to suffer from diabetes in 2000, a number that is expected to rise to 50 million by 2030).

It is commonly accepted that metabolic syndrome is tied to the body's metabolism, possibly to a condition called insulin resistance. A main component of this syndrome, and of the worse pathologies that derive from it, is the derangement of the glucose insulin system, but abnormal lipids and proteins also play an important role. Organs involved in this pathology are the liver, the kidneys, the gut and the pancreas. Research into the complex processes linking this group of conditions can greatly benefit from the use of models. Specific clinical tests have therefore been developed and particular experimental protocols designed for estimating the required parameters. It follows that the two main metabolic processes (insulin resistance and secretion) have then been the subject of different modelling studies, which have resulted in the availability of various mathematical models.

Though readily available, these models do not offer a common interface that would not only make them easily accessible to anyone, but would also allow them to interact, as well as with other models of specific organs (e.g. liver) and tissues (e.g. muscles and fat). All these goals could be achieved within a VPH-based framework.

5.2.10. Predicting health effects from exposure to xenobiotic agents

The complexity of interactions between the human body and xenobiotic agents (e.g. chemical and physical factors in the environment) has generated a large body of research, especially in toxicology and epidemiology, to assess health effects attributable to exposure to such agents, some of which (e.g. dioxins, electromagnetic fields, pesticides, toxic wastes) have at various times received particular attention from the public. Toxicological studies have greatly contributed to our understanding of the underlying mechanisms, but extrapolation from animal to human scales is proving challenging. Large-scale epidemiologic studies have been undertaken to assess potential or perceived health risks in human populations, but their outcome is often inconclusive, possibly due to the frequent lack of an adequate framework (model) that would be based on the underlying physiological or pathological processes.

Mathematical models have the potential to help improve the transfer of toxicological results to the human domain by, for instance, integrating knowledge. In epidemiology, modelling can help in the identification and estimation of effective doses, so reducing the number of errors in the exposure assessment and in predicting the occurrence of health endpoints. Modelling can also help in clinical situations (e.g. poisoning treatment) by predicting blood levels over time, or by predicting treatment effectiveness.

Mathematical modelling of xenobiotic agents can be studied at different levels:

- Molecular level: genotoxic effects, enzyme induction, metabolic pathways and kinetics, mode of action (toxicodynamics)
- Cellular level: receptor interaction
- Organ and body level: change in processes (pathological range for parameter values), endpoint characterisation and dose-response analysis, customisation to individual patients (poisoning treatment)
- Population level: prediction of population health impact, customisation to specific sub-populations (children, pregnant women, workers).

Simply adapting models of normal body conditions will not suffice. For example, specific modelling efforts are required for metabolic pathways that do not normally exist or are not functional under normal conditions (e.g. for benzene metabolism). In general, specific body responses may be activated only after exposure to a xenobiotic agent (e.g. genotoxic effects).

5.2.11. Tumour growth and therapy

Tumour development involves phenomena that originate from abnormal physiological processes (e.g. tissue renewal and remodelling). These phenomena occur at different levels, in particular:

- Sub-cellular level: altered mechanisms at the DNA level, in gene expression, in the activation of signalling cascades regulating cellular activities (e.g. duplication, motion, adhesion or detachment)
- Cellular level: interactions among tumour cells and other types of cells present in the body (e.g. endothelial cells, macrophages, lymphocytes), inhibitive or destructive interactions, aggregation and disaggregation properties, intravasation and extravasation processes
- Macroscopic level: phenomena that are typical of continuum systems (e.g. cell migration and invasion, diffusion and transport of nutrients and chemical factors, mechanical responses to stress, interactions with external tissues, capsule formation and rupture, diffusion of metastasis).

The development of such models requires the use of a wide range of theoretical and numerical tools (e.g. cellular automata, individual-based models, kinetic theory, stochastic processes, system theory, compartmental models, continuum mechanics, multiphase flows, FEM). Modelling should be done at the relevant scale, while providing a means of interaction with the lower and higher scales.

The challenge is now to interface, in a horizontal fashion, different modelling frameworks operating at the same scale (e.g. individual-based models and PDEs), building hybrid models that combine and exploit the advantages brought by the different frameworks, and to link in a vertical fashion mathematical models operating at different scales (e.g. boolean networks in cellular automata models), building nested models that can be used to transfer information between the different spatial scales.

5.3. Environment

5.3.1. Molecule

The complexity of human physiology is such that a complete description of all interacting entities, including molecules, genes, information networks, etc. needed to produce a holistic model of the physiome cannot realistically be built in the short to medium-term (and certainly not in the lifetime of the VPH project).

Instead, at this stage, the focus must be on isolating specific physiological paths that are alone responsible for clinical conditions, with a key long-term aim of customising drug treatments to human individuals. This invariably involves a need to reach the molecular scale, the level of drugs, in order to get results at the physiological level that include the top and bottom end of physiological processes. Between these levels, information processing biochemical networks modulate the body response to these: molecules, organs, arthritis, etc. define the compartments and transports of products.

Although the question of when efficient customised computational drug design will take place is still open, it is quite certain that it will take place. Moreover, we will be aiming to open the discussion about whether drug agencies will be prepared to accept simulations, at least for part of their certifications. Model integration and validation will be critically important in achieving this objective.

The large space and time scale separation between the molecular and the physiological scales imposes a paradigm shift from single level physical description-based models to multi-scale, multiple-level descriptions. Two kinds of multi-scale modelling and simulation methods may be identified.
A hierarchical simulation is one in which models are used in a loose workflow, where output from a simulation is fed into the adjacent model within the hierarchy as inputs. Hybrid schemes are ones in which different physical descriptions are run concurrently and data is exchanged on-the-fly between the two. Both are amenable to efficient deployment on computational grids.

5.3.2. Body

The VPH is a modelling framework that will operate in a health sector that is renowned for its insatiable appetite for predictive information. This framework will manage the storage and fusion of rich data sets and mathematical models from the clinical, industrial and academic sectors. The value to the clinical domain will be the ability of the VPH to augment decision support, ultimately reducing treatment costs. For the biotechnology and pharmaceutical industries, the VPH will be a modelling and data resource par excellence, able to service the industrial sector extensively. Academia also recognises its potential and will exploit it for the purposes of research and teaching.

5.3.2.1. Information flow

Although a considerable quantity of information will flow from the VPH to the outside world, the VPH will require a steady influx of predictive concepts and robust data if it is to continue to meet the needs of an evolving society. In this regard, the integration of health/academic/industrial interests will be a uniting influence that will create new, previously untapped synergies, generating fresh insights that can be reinvested in the VPH and creating a self-sustaining cycle that offers significant benefits to the participants (clinical, industrial and academic).

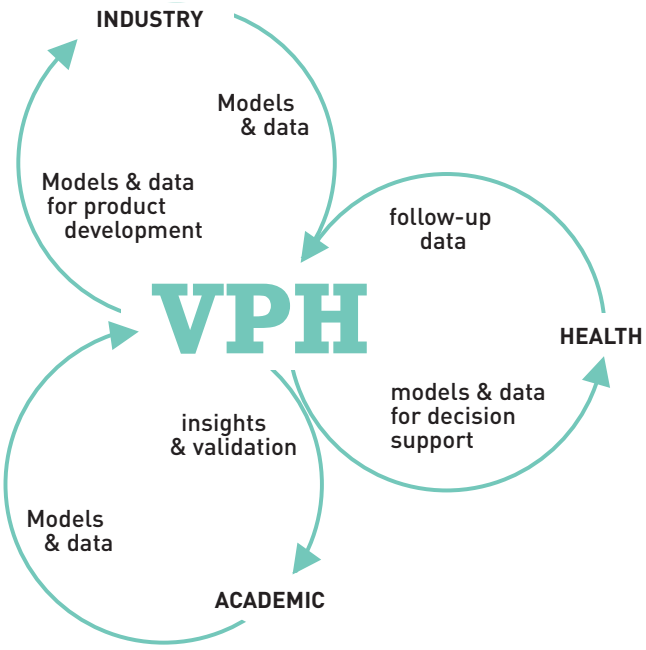

Figure 5.1. Model/data flows to and from the VPH

The health sector stands to benefit from a coherent and organised EuroPhysiome through improved clinical decision support, optimised therapeutic intervention planning, rehearsal and guidance. Anonymous clinical data and published outcomes of clinical trials are critical components, cataloguing the human condition. Follow-up data is a valuable tool for quantifying the efficacy of treatment strategies, clarifying insights and validating predictions. A requirement to return follow-up data to the VPH will encourage a climate of evidence-based medicine and influence patient management in the future.

The industrial sector will reap commercial benefits, using VPH models and data to expedite product development and to add value to their offering (e.g. surgical simulators incorporating pathophysiology). Product safety is an important consideration, and multi-faceted VPH models that integrate data relevant to product acceptance will ease this process. Contributions from industry are expected to populate niche areas, providing valuable information that relates human response to biotechnology and pharmaceutical intervention. The value of this exercise is self-evident and is likely to influence the regulatory pathway that governs device or drug development/acceptance in Europe.

Academic interest is driven by the promise of an expansive and coherent data resource, capable of generating insights into biological processes and validating predictive models that emerge from those insights. The return of augmented data and models to the VPH for storage will naturally encourage future exploitation. Data from academic institutes and associated professional bodies can provide a vast array of complementary data from genomics, to cell biology, pathophysiology, epidemiology, psychology, sociology etc. and yet encompass the major basic scientific disciplines – chemistry, biology, mathematics, physics and statistics.

Central to the success of this initiative will be strict controls on the flow of data into the VPH, such that users will at all times be aware of the quality, scope and limitations of the information available.

5.3.2.2. Boundaries of the VPH?

By its very nature, the VPH is an inclusive entity, built on an extensive knowledge and tool base, but incorporating new developments at the earliest opportunity. Fundamentally, it is driven by the needs of society, but it is also limited by its constraints. In particular, funding imposes practical limitations on its development and for practical purposes, therefore, it is necessary to impose artificial boundaries that clarify the province of the VPH – those areas and disciplines that are eligible for funding under a VPH initiative. This exercise in demarcation will inevitably highlight the cross-boundary nature of the programme and draw attention to the artificial domains present under current funding strategy. The VPH challenges the artificiality of this structure and hints at a more flexible arrangement in which the flexibility of cross-discipline funding matches the bold cross-disciplinary scientific initiatives of the VPH.

The presence of an artificial boundary to VPH activities may seem unduly restrictive, but it is a practical response to a fund-limited dilemma. This mirrors an analogous situation in the domain of simulation, since mathematical boundary conditions are a practical response to a model-limiting dilemma (i.e. a model must have limits), and thus there may be value in aligning the financial and modelling boundaries wherever possible.

5.3.2.3. Boundary conditions, context and simulation

Boundary conditions are an expression of context, and it is important to appreciate that context is critical to the interpretation of physiological data. For example, the pathologies associated with raised haemoglobin concentration and raised pulmonary pressure are well documented but, for indigenous cultures living at high altitude, these are not pathological indicators. Here, normal human physiology has adapted to the environmental conditions. This emphasises that interpretation of physiological data can be dominated by the context (i.e. "boundary conditions") in which the individual finds his or herself. Similarly, the VPH does not exist in isolation. As a representation of Homo sapiens in silico, it must attempt to operate in a virtual context that mirrors the 21st Century human environment. The nature (and flexibility) of the context must be explicitly defined. Such a discussion is a useful vehicle for

clarifying the borders of the VPH. Once determined, the boundaries implicitly define the boundary conditions required for simulation. Contextual factors that influence VPH solutions include environmental conditions (e.g. temperature, humidity), gender, genealogical and genetic factors, the psyche and psychological disposition, pathological status, etc. They are not derived through simulation in the VPH, but are nonetheless important quantities that provide boundary conditions that influence the outcome of a VPH query. These factors provide natural modelling boundaries that can have a role in guiding financial strategy.

VPH boundaries

The boundaries to the VPH are not necessarily physical, but may simply reflect limitations of the simulation environment. For instance, are the genome and molecular biology on a length scale beyond the lower limit of interest? Are quantum interactions to be simulated or do simple lumped parameter models provide for a more effective simulation? At the other end of the scale, is the VPH representative of an average human, or a particular individual? To what extent should populations or population dynamics be employed?

5.4. VPH Framework

5.4.1. Logical structure

5.4.1.1. Introduction

In this section, we consider the logical structure of the VPH implementation. The technical aspects of some possible implementation strategies will be considered in the following section. We believe that three basic principles should underpin the increased level of co-operation that will necessarily characterise the future development of VPH. All of these suppose, in parallel, a concerted effort towards the definition, implementation and adoption of appropriate ontologies (e.g. anatomy & structure, physiology, metabolism), to enforce the use of a common set of terms across traditionally separate domains.

5.4.1.2. Establishment of Standards for the Construction of Modelling "Services"

In this scenario, models and data are made available via execution of the model as Web Services with defined inputs and outputs, allowing models to be used individually or linked as plug-ins for a larger model. The focus is on defining what the *model + data + solution algorithm + computer code + computing platform* delivers as outputs from the inputs. In this approach the model (equations, parameters, initial and boundary conditions, statistical assumptions) is bundled with the solver (solution algorithms and computer code) and the computer hardware to the user of that Web Service. Each service would be identified by its ability to predict certain outputs, given certain inputs. This is achieved by internal process and requires full documentation. Individual services could be implemented with radically different approaches (logical, implementative, of execution), which would be fully documented, but totally transparent in terms of need-to-know for naive users of the service. To provide these services, the VPH framework must assure only that:

- The services can be easily found (e.g. through Universal Description, Discovery and Integration service repositories)
- The data, models, and algorithms can be wrapped, regardless of their logical design and implementation/coding and execution, in such a way as to be exposed as standardised VPH services
- Services can be connected so that the outputs of one are automatically accepted as inputs for others, and one service can become aware of the internal state of another
- The network of interconnected services can be exposed as a new (nested) service.

These apply both to data and to models; in both cases they would be seen as services. A data service, for example, would send a CT dataset written in the format specified by the user as input.

5.4.1.3. Adherence to a Set of Mark-Up Languages for Unambiguous Description of Models, Parameters and Boundary Conditions

This is the approach presently used in the IUPS Physiome. Model descriptions are kept distinct from solution algorithms and must be defined in a structured form that identifies the equations separately from their parameters, initial conditions, etc. via mark-up languages (ML; e.g. AnatML, CellML, SBML, FieldML). This ensures that the models are exposed in a way that makes it clear what the equations, parameters, etc. are, how they relate to other models, and to what extent they satisfy biophysical constraints. Model components can be specified, via the ontological terms in the metadata, using biological databases (e.g. kinetic parameters can be updated for different species, environment conditions (temperature etc), age, disease state etc). The curation processes are being developed to ensure that the biophysical limitations of the models are apparent.

One motivation for this approach is that it allows complex models to be built from separately tested components. Integrative cell models need to link metabolism to signal transduction, ion channel transport mechanisms, pH control, myofilament mechanics, gene regulation etc (and this will be as true for orthopaedic simulations as it is for cardiac simulations). The components of these models at the cellular scale will often be proteins (+ lipids and carbohydrates) where the influence of

mutation, drug binding etc. can be quantified. Most importantly, this approach keeps the models, based on biophysical principles (e.g. physical conservation laws) and the boundary conditions, separate from the algorithms used to solve the equations, and separate from the implementation of the algorithms in a particular code. This is equally important at the organ level where a model of anatomical structure is defined and tested separately from the equations representing the physical laws and the boundary conditions representing the external environmental influences.

The criteria used to judge the correctness and validity of a model are quite different from the criteria used to check that a numerical algorithm is correctly implemented and has achieved a converged solution. If we do not clarify these distinctions and develop the ML encoding standards for models and data (including boundary conditions), as well as make use of computer science coding standards (unit tests, stress testing, etc.), we will have little hope of achieving our goals of integrative, multi-scale, patient-specific modelling.

5.4.1.4. Development of a Collection of "Core Models" at a High Level of Integration

The core models described under this approach would be special instances of the two scenarios described above. The principle of developing a collection of core "supermodels", with low-resolution input-output descriptions of the major components of organism-level systems, is inspired by the 1972 model of Guyton, Coleman & Granger (1972; Annu Rev Physiol, 34: 13-44). This was the first organism level systems model that served, in the hands of its authors, to use knowledge of experimentally verified physiology in the context of prevalent clinical problems to clarify, and in some cases to upset, many widely-held principles. It established a new context in which experimentation and modelling are naturally paired to solve clinically relevant problems.

The Physiome and VPH concepts, by their very nature, evoke the notion of an exhaustive modelling environment in which, in the long-term, all knowledge of human anatomy, physiology and even physiopathology, is accessible through some common interface in such a way as to facilitate personalised medical diagnosis and therapy, to aid in the development of new drugs and to accompany (underpin?) laboratory experimentation. Clearly, this must not be taken as a promise to deliver an all-inclusive mathematical model of the human organism, a goal which is not only unrealistic technically (and will be for the foreseeable future) but also, it can be argued, is unrealisable even in principle – the only complete model is the organism itself. What then can be projected as a realistic logical structure likely to enable practical results within a reasonably short time scale and that will remain flexible and open to continual revision, extension and collaboration on a worldwide scale?

As mentioned elsewhere in this document, it stands to reason that the VPH will be multi-scale both temporally and spatially (molecule, cell, tissue, organ, organism, etc.) and will have to accommodate multi-mode simulation techniques: ODE/PDE/DDE/SDE dynamical systems physiology models, finite element structural models, discrete models such as cellular automata and multi-agent systems models of, for instance, signal transduction, discrete models based on physics (e.g. mass-spring method in computer graphics animation), hybrid models (e.g. ODE/physically-based model using a system of ODEs for chemical reactions and a physically-based model for specific deformable geometry, fluid/structure interaction using a discrete method for the fluid part and FEM for the structure part), hierarchical models (i.e. different levels of representation for global and local behaviours), bio-statistical models (e.g. hierarchical models, PK/PD models), statistical shape and appearance models, and so on. Indeed, examples of such environments exist (especially in engineering applications) and can be drawn upon for VPH development. One striking success in this direction is the Virtual Heart model being developed through collaboration between the universities of Oxford and Auckland.

However, in order to co-ordinate existing projects and, especially, to provide an environment conducive to the future collaborative development of such modelling projects, it would seem propitious to develop a small collection of core models for physiology (like the Guyton model of blood pressure, fluid compartments, flows of principle ions and nutrients, etc.), for bio-mechanics, for the nervous system (currently outside the scope of the present project, as mentioned in the introduction to this roadmap), for cellular metabolism, etc. There will, of course, be overlaps among these core models (and reasons to merge them for certain questions), but the idea is that each would provide an overall, coarse-grained but reliable description of all involved systems, presented as a set of interconnected modules with clearly defined handles (in the sense of the two principles above, i.e. a well-defined list of input/output variables and parameters). These core model collections of modules will, of course, serve on their own as heuristic devices (e.g. for teaching), but more importantly for the long-term VPH goals, they can also furnish *dynamic boundary* conditions for detailed local models when these are called for (see the "Hypertension: channelopathies, diuretic treatment and gene polymorphisms" example in the "Exemplary Cases" section above). This not only makes it possible to predict with a "local" model (at any degree of fine-grained detail down to the molecular level) the effect of some change on an important system variable, but also to extrapolate quantitatively the effect on the implicated organism-level regulatory loops, thus allowing exploration not only of bottom-up effects of, say, a faulty protein but also top-down, possibly compensatory, effects. Indeed, if it is clear that many disease states originate at the genome level, it is also

clear that the robustness of the organism to such perturbations arises from the integrated, sometimes redundant, feedback and other regulatory mechanisms.

The logic of this strategy is to move towards a modelling environment capable of encompassing both ends of the continuum, while simultaneously avoiding the need for extravagant computing resources for system level calculations, and with a view towards the necessarily open-ended and international level of effort and co-operation.

On the technical side (to be discussed elsewhere in this roadmap), success of the core models will of course depend on the development of interdisciplinary standards, ontologies to avoid ambiguity, reliance on mark-up languages (e.g. AnatML, CellML, FieldML, SBML) for model description, as well as scalable numerical analysis techniques, criteria (and committees) for model validation, collections of validated data for benchmarking and model validation, databases for experimentally measured parameter values and so on.

5.4.1.5. Conclusion

The first two principles represent, to a certain extent, alternative strategies. Both approaches would rely on open access to the internal descriptions of models and data, based on a business friendly Open Source license policy.

Consistent with the overarching vision of the VPH/Physiome, the end-point of these three principles will be a large collection of inter-connectable models (or *services*) (modules and sub-modules) describing all aspects of the functioning organism, at all degrees of detail.

The goal, of course, is not to make better models, *per se*, but rather to change the way science is done, taking full advantage of modelling for quantitative exploration of complicated hypotheses/scenarios and to furnish universal access to the legacy of heterogeneous models via a common interface.

5.4.2. Implementation

The road towards the VPH will not be via a single project. We need to construct an umbrella under which many diverse activities can take place, while ensuring their continued coherence and compatibility. Some of these activities will receive Commission funding – for these the issues will be relatively few as normal consensual efforts will take place – but others will arise from self-motivated work by individuals or teams of researchers, or from projects funded from other sources.

It is important, therefore, that the main principles are set out clearly and unambiguously and that the relevant communities have a strong sense of ownership. They should be dynamic and subject to regular review, and researchers should be provided with a strong motivation to engage with them. Only in this way can an initial impetus with a strong motivation and direction be extended into the medium-term.

A number of the features necessary for the development are identified below, but these must be embedded within a structure that is flexible and open to change but which, critically, continues to remain useful for, and retain the trust of, its "citizens".

The precise form and temporal order in which the facilities (described below) are introduced will depend upon the evolving needs of the users they serve. Taken together, they describe a fully supportive structure within which the VPH can grow, but it is clear that they can be developed only by a number of groups, with a variety of expertise, working with a considerable measure of unity.

The establishment of a community that shares a common vision and works collectively can provide an environment for rapid progress across a broad front. The inclusion of clinical and industrial participants is essential for the rapid deployment of results; maintaining the communication links across the "divides" should be a major priority as the initiative progresses. Ongoing, active encouragement from relevant parties on all sides is likely to be needed in the early stages as the full benefits are likely to take a little time to materialise. The provision of relevant fora at which interested groups can exchange views, present results and stimulate interest should be given priority: a high level of inclusiveness is key to avoiding fragmentation.

Implementation of the VPH requires not only the creation of a suitable framework, but also an adjusted approach that implies a willingness to see the "bigger picture" and to engage with others to achieve long-term goals through the collective implementation of a structured succession of short-term measures. Ensuring the continued coherence of these measures is one of the major challenges facing the VPH.

5.4.2.1. Data processing

- Open Source toolkits for the automatic translation between digital storage formats of bio-medical data, and implementations of portable standardised data representation to facilitate data sharing and data fusion
- Methods for the efficient processing of large amount of bio-medical data, including knowledge-based image segmentation and labelling, automatic mesh generation methods, feature extraction algorithms, elastic registration methods, statistical shape modelling and morphometrics, computer-aided diagnosis, pattern recognition and automatic classification methods, filtering algorithms in non-Gaussian framework
- Methods and tools for interoperability of data coming from heterogeneous sources, based on ontologies.

5.4.2.2. Modelling

- Methods to include sources of uncertainty and to compute the range of validity, including tools and techniques for integrating the parameter range of experimental values, level of evidence and missing data
- Toolkits for bio-medical data mining, including advanced methods based on logic programming and neural networks, bio-statistical models and statistical methods for the analysis of correlations, dependencies, dimensional reduction and aggregation, that operate efficiently on large databases of bio-medical images and measurements
- Novel methods for mesoscale modelling, multi-domain modelling, hierarchical reconstruction and embedding, hierarchical parameter transfer methods and data fusion
- Applications of concurrent computing to the modelling of human physiology, including the modelling of massively interacting entities as in the immune system, multi-scale organ functions, of multi-systems metabolic processes, agent-based modelling of cellular processes, multi-level stochastic aggregation models of cellular adaptation
- "Living simulations" (linking simulations to instruments with mutual interaction)
- Methods for the mathematical representation of dynamic systems (ODE/PDE/DDE/SDE).

5.4.2.3. Effective access to resources

- Data representation and bio-medical cross-level ontologies. Projects should include a large scale deployment of these knowledge management methods to existing or newly established large collections of bio-medical data
- Advanced interactive visualisation and exploratory fusion of multi-modal bio-medical data, including virtual reality and augmented reality environments to search and explore large collections of bio-medical data
- New perceptual (visual, tactile, etc.) representations of uncertainty, multiple overlapping spatial fields, and of data sets spanning over multiple dimensional scales, providing effective ways to explore large collections of bio-medical data
- Systematic clinical trials aimed at identifying the most effective representation of complex bio-medical measurements/images as a function of the clinical domain and of the specific clinical task involved
- Cross reference and mapping facilities using semantic web technologies.

5.4.2.4. Infrastructures

- 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 access to distributed data sources, but many hospitals are reluctant to let the information flow outside hospital bounds. For a large-scale deployment of Health Grids, and thus for opening an attractive business, it is important to leverage security to a trustworthy level of confidence that could facilitate generalised access to data from the outside
- Support and infrastructures for large scale collaborations such as deployment studies for testing and validation to ensure user acceptance and collaborative research
- Services to render data from hospital databases anonymous wherever necessary.

5.4.2.5. Community building

- Development and management of a VPH portal
- Open Source software to manage large scientific communities that collaborate on documents, share data and other resources, discuss, etc
- Single sign-on mechanisms that allow access to the whole VPH framework from the main portal with a single authentication session.

5.4.2.6. Resources generation and access

- Frameworks and toolkits for fat client development (e.g. using Eclipse)
- Open Source toolkit for bio-medical data fusion
- Open Source toolkit for bio-medical data processing (i.e. classification, segmentation, interpolation, resampling, partitioning, automatic meshing, etc.)
- Open Source toolkit for the visualisation of bio-medical data allowing the automated transformation of the data set obtained with an imaging modality into the synthetic replica of the data set obtained with another modality over the same target
- Cater to the PC/MAC user community.

5.4.2.7. Knowledge management

- Open Source tools and methodologies to make it possible for large communities to consensually develop and maintain very large ontologies of the VPH resources
- Develop production-strength semantic representations of the VPH and of the infrastructure (Semantic Grid)
- Semantic resource brokers that simplify the construction of complex simulation networks, by connecting simulation resources exposed as Web Services, through semantically based interoperation/reconciliation tools
- Semi-automatic acquisition of knowledge bases from pre-existing sources.

5.4.2.8 Backend services

- User authentication
- Access to VPH resources (i.e. data and simulation services)
- Publication of VPH Resources
- Federation of repositories
- Toolkits for fast wrapping of storage and simulation resources into Web Services
- Software architecture for semantic representation of storage resources
- Software architecture for sharing and re-use of simulation resources
- Global VPH security that makes possible the federation of clinical databases located behind hospital firewalls into the VPH framework; includes the creation of challenges for crackers to demonstrate the strength of the security model
- Interoperability toolkits (i.e. format translators and Web Service mediators) to federate VPH with other worldwide initiatives
- Industrial-strength models for the distribution and the free execution of simulation models based on commercial solvers
- Intermediary Web Services, distinct from simulation codes that could be used to convert data between formats etc.
- Semantic descriptions of simulation models, as well as of data.

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6.0

6.1. Executive Summary

This section attempts to identify the Research Challenges that face researchers in academia, the clinic and industry. These have been categorised into two main topics: (i) what is the nature of the scientific problem and how can this be addressed? (ii) what ICT tools can be developed to help tackle the scientific problems?

The living human is highly complex, with almost limitless interconnections and interactions between systems that are open, responsive and adaptive. A great deal of knowledge from genes to whole systems is becoming available, but many physiological functions are still not understood. The true grand challenge lies in understanding biological function – a multi-faceted approach to research is needed to address this challenge. Data (dynamic biological imaging, genomic and proteomic data, cellular and tissue properties, etc.) provide a wealth of descriptive information. To understand the data and to determine physiological function, models (mathematical, physics-based, computational) are needed that are closely linked to the descriptive data and informed by the underlying biology.

Research Challenges

The key then in tackling the true grand challenge is to determine ways in which the research effort can be made truly integrative. The integrative approach refers to:

(i) integration of physiological processes across different length and time scales (multi-scale modelling)

(ii) integration of descriptive data with predictive models

(iii) integration across disciplines; a model of any system necessitates cross-disciplinary collaboration with the breaking down of traditional barriers between the academic disciplines to bring together mathematical modellers, computer scientists, software engineers and scientists from the life sciences of biology, biochemistry, physiology and medicine.

Challenges in prediction should be met by

(i) identification of the critical problems

(ii) determination of the level of model complexity needed, based on the scope and application of the model (e.g. teaching, understanding mechanisms, for use in the clinic or industry)

(iii) putting greater efforts into understanding the complex biological interactions within the living human

(iv) understanding issues relating to inter-subject variation

(v) careful validation of models as well as model connections

(vi) tackling the challenge of multi-scale modelling. Multi-scale modelling is a quantitative, integrative and experimentally-based approach for studying biological processes and dynamics that span multiple spatial and temporal scales. A framework for this kind of modelling will require standardisation of data formats and modelling approaches to facilitate collaborative practice.

(vii) emphasising model identification and problems of over-parametrisation.

Equally, there are challenges in obtaining descriptive data for both model development and model validation and in making the data easily accessible in formats that can readily be used. The type of data available is a crucial factor in determining the applicability of any model. Challenges here need to be tackled by:

(i) defining data collection standards

(ii) ensuring that imaging technologies or experimental techniques are themselves extensively validated providing accurate data of high quality

(iii) integrating data obtained from different collection technologies in a systematic way thus providing data in more useful formats specific to model development or validation and

(iv) making all end-users (academic, clinical and industrial) aware of the development of new experimental and imaging techniques and the potential they offer within the VPH.

Tackling the grand challenge will be facilitated by a concerted effort running in parallel to develop the appropriate infrastructure, frameworks and technologies (computational, organisational and imaging) that can support the requirements of the anticipated cross-disciplinary collaborations. To span from molecules to organ systems requires databases of models and data at many spatial and temporal levels. It requires software tools for authoring, visualising and running models based on widely adopted modelling standards. It also requires the development of ontologies dealing with anatomy, physiology, and molecular and cellular biology to uniquely identify and link model components. Finally, it requires advances in modelling and imaging to be made readily available to all interested parties through the development of networking databases, keeping researchers abreast of relevant progress.

This chapter ends with an analysis of the problem of accommodating a vast reservoir of physiologically diverse data and modelling tools, whilst supporting robust and effective access to end users and contributors alike. The viability of the VPH is dependent upon its ability to overcome numerous challenges such as the organisation and storage of petabytes of data, sustained communication bandwidths that can transfer terabytes per day, extensive support for data indexing and data format translation, and all of this embedded within an infrastructure that guarantees secure and transparent access, integrated with a quality assurance mechanism that safeguards the quality of data accessed by the end-user.

The magnitude of both data storage and data flows is enormous and, since they must be managed effectively, an estimate of these quantities is key to architectural design. One of a number of possible design solutions is postulated, based on a centralised VPH server, in order to provide a concrete example for which the problem can be sized and the required resources listed. Other options could include a distributed model, where special networking arrangements within a distributed system would ensure that external data transfers for user transactions remained similar.

To engage the scientific community in general, some exemplar or case studies that concentrate on a system with a specific clinical question should be developed. These would showcase current research efforts and highlight the limitations of existing models and validation. The exercise would inevitably be cross-disciplinary and multi-scale, bringing in the importance of molecular and cellular scale effects. Additional issues that relate to the roadmap would also be raised. Such an exercise would perhaps prove to be more effective in defining the problems, the capabilities of the groups and the types of solution that are most effective and beneficial to science and health.

6.2. STEP: A Strategy for the Europhysiome

The European Commission funds STEP under its Information Society Technologies Programme. The term **EuroPhysiome** has been coined to indicate a coherent, integrated European approach to the multiscale modelling of the human physiome[11].

STEP is currently orchestrating consensus building within the relevant European communities – academic, industrial, clinical – to create a sound base on which the EuroPhysiome can be established. It will deliver a roadmap in early 2007 that will define the way in which European work should proceed ultimately to deliver the Virtual Physiological Human (VPH)[12] – the *in silico* human.

The STEP project concentrates mainly on those sub-systems of the human body for which the interpretation mechanisms employ physics-based modelling. These include the cardiovascular, respiratory, musculoskeletal, and digestive apparti, together with the skin, through which the human body exchanges forces with the external environment. But it excludes, for example, the brain and all the perceptual and cognitive aspects of the sensorial apparatus.

Considering the Physiome as a whole would be highly complex. So, to enable fruitful discussion, STEP defined a number of strands within which discussions could take place (Anatomy and Physiology, Hard Tissue, Soft Tissue, Fluids, Multi-scale Modelling and ICT). Initially, the discussion was Internet- and email-based and culminated in a conference in Brussels in May 2006. Here, the consortium and some 100 international experts identified common features among the strands and the important distinctions between them.

The roadmap issues that were discussed were:

(i) Common Objectives (ii) Research Challenges (iii) Resources Required (iv) Ethical, Legal and Gender Issues (v) The Organisational Model (vi) Community Building Initiatives (vii) Impact Analysis (viii) Dissemination Models (ix) Exploitation Models and Long-term Sustainability (x) Recommendations for a Concrete Implementation.

6.2.1. Identified objectives

The Physiome is a truly global concept that spans many disciplines, involves wide expertise, connects with a diversity of cultures and has the potential to influence the management of many diseases. It is the kind of grand vision that can be a unifying concept, bringing together many disparate activities (a valuable exercise in itself).

However, with the breadth of its appeal there is a danger that it attempts to become all things to all people and in the event satisfies no-one. There is value, therefore, in establishing a degree of focus in order to augment its development (e.g. pursuit of the Virtual Physiological Human). Perhaps a suitable first step in this regard is to ask "What is the wider purpose of the Europhysiome?" Certainly, the physiome embraces many things, but how are its developers to view its context? Following consultation at the first STEP conference the views of the experts were noted and their consensus is detailed below.

What is the purpose of the Europhysiome?

It is primarily an opportunity to:

- improve healthcare across Europe (saving money through optimised treatment)
- get industry/science/healthcare to work more closely together
- put in place a robust and flexible IT infrastructure, capable of sustaining an accessible VPH resource that can aid and expedite developments in healthcare (therapies, devices etc.).

Important additional objectives (relating to Research Challenges) that were identified included the opportunity to:

- develop outstanding educational tools
- elucidate biology
- initiate patient-specific healthcare.

To ensure the success of the EuroPhysiome, experts were also asked what they felt should be the priorities of the roadmap, by apportioning funds to a number of categories. The two categories that received the highest average funding were:

- overcoming research challenges
- creating a common shared EuroPhysiome knowledge-base (that included data, models and a people network) and the supporting IT infrastructure that would enable the creation of such a database.

6.2.2. Structure of chapter

So this chapter of the Roadmap attempts to identify the research challenges that face researchers in academia, the clinic and industry. It is inevitable that many of the issues raised were specific to discipline but an attempt has been made where possible to categorise these into general topics that address the nature of the scientific problem. Much of section 6.3 deals with these concerns. There are some issues, however, that remain

[11] The physiome is the quantitative and integrated description of the functional behaviour of the physiological state of an individual or species. The physiome describes the physiological dynamics of the normal intact organism and is built upon information and structure (genome, proteome and morphome). The term comes from "physio-" (life) and "-ome" (as a whole). In its broadest terms, it should define relationships from genome to organism and from functional behaviour to gene regulation. In context of the Physiome Project, it includes integrated models of components of organisms, such as particular organs or cell systems, biochemical, or endocrine systems.

[12] The Virtual Physiological Human is a methodological and technological framework that once established will enable the investigation of the human body as a single complex system.

specific to discipline and in an effort to include as many of the experts comments as possible, these specifics are listed in section (6.3.1.9).

Section 6.4 collates the suggestions that experts have made regarding the ICT tools required to tackle the identified research challenges.

Section 6.5 is a summary from the ICT strand that attempts to put forward some solutions to the challenges highlighted in Section 6.4.

Section 6.6 is a short description of expert recommendations for the discussion in the run up to the second STEP conference.

Section 6.7 deals with how the resources required to solve the problems described above can be quantified.

It should be noted that this document, even in its final form, cannot be comprehensive. The research challenges and how to tackle them will keep evolving as certain problems are solved and others are thrown up.

6.3. Scientific challenges – the nature of the problem

What are the scientific challenges facing us that will enable us to realise the objectives identified above? What are the true Grand Challenges?

The discussion that occurred in the various strands, both in the run-up to the conference and during the conference itself, identified a set of scientific research challenges. The position papers from each of the strands reveal that many of these challenges are specific to a particular discipline or application but an attempt has been made here to categorise them into more general topics that describe the nature of the problem.

From the outset, it has been suggested that the approach we need to take has to be multi-faceted; descriptive, predictive and integrative, so the review in this section attempts to categorise the issues raised by experts into modelling challenges, challenges in data collection and challenges in integration.

6.3.1. Challenges in Prediction

Descriptive data (challenges in obtaining them discussed in Section 2.2) are enormously important but there was overwhelming consensus from all the strand position papers that the major challenge is to determine biological *function*, for which we need models and predictive ability (integrated with descriptive data). Welsh *et al* (2006) [1] suggest that "the ultimate goal is then to develop models which have predictive power – providing virtual cells, tissues, organs and systems that can be used in the development of novel drugs and treatments, and, ultimately, for patient-specific care regimes."

This section examines the challenges faced in producing these models.

6.3.1.1. Problem identification

What are the critical problems and who should identify them?

There is a view that modelling should be driven by the need to answer a specific clinical or scientific question. In trying to understand biological function, first and foremost we need to get insight into mechanisms that are thought to be important in answering that question. A model of the entire human being *in silico* (a virtual physiological human) may not be realistic due to the complexity of the system.

The complexity inherent in the living organism, against the simplicity of models, is discussed in the next section.

6.3.1.2. Model complexity

While the ultimate aim may be the development of fully comprehensive models that try to incorporate as much of the complex reality of the living organism, concerns were aired that fundamental understanding in this process would be obscured. Two important strands in the modelling philosophy have emerged through this consensus-gathering exercise.

In the long term, modelling efforts should not be concerned with immediate impact. The scope should be to understand biological function, which necessarily requires an appreciation of the fundamental science. In the living circulation, there are almost limitless interconnections and interactions with systems being open, responsive and adaptive. The more appropriately complex the model, the more baffling the interrelationships will remain to an individual starting to study it. So there is still an ongoing need for deliberately simplified models to illustrate certain relevant principles more clearly than models that aim for realistic complexity.

The "toy-problems" discussed above, however, may never be used in applications aimed at use in the clinic because they are oversimplified. So in the short-term where immediate impact is of paramount interest, and where a solution to a clinical problem is required, the modelling effort may have to reflect reality as much as possible. In developing these models, it is of crucial importance that the scope, applicability and limitations are made clear.

Easy to use models/simulations that are effective in the clinic or industry are based on good fundamental science. So both approaches need to be supported in parallel with insight from the simplified models informing the more complex models to get an effective high-impact end product.

6.3.1.3. Understanding interactions

Historically, research efforts in physical, mathematical and biological sciences have focused on isolated parts of the jigsaw. Despite biologists' increasing detailed knowledge of dynamic

processes, interdependent regulatory controls and operation of multiple interacting components, the function and malfunction of complex biological processes is still poorly understood (WTEC Panel Report, 2005) [2].

Equally, despite increased modelling efforts, along with great technological innovations that have facilitated enormous advances on isolated components, many physiological mechanisms and clinical problems have not been solved.

It is clear that expertise from a number of different academic disciplines needs to be brought together. The cross-disciplinary nature of the research is what is needed to understand the interactions of the different components within the complex living system. A summary of the crucial interactions that should be included and highlighted by the experts, is given below:

- coupling of biology/chemistry to mathematical/physics-based models
- coupling of solids with fluids
- molecular and cellular scale effects and how they affect macroscale properties/models
- multiphase effects
- effect of nervous control system on other systems
- coupling of musculoskeletal models with tissue adaptation models
- interactions of systems – multi-dimensional interconnectedness
- models of systems or organs need to be bio-chemico-electro-mechanical.

Given the preponderance of comments on the need to include biological (molecular and cellular scale effects), the next section is a discussion on the general modelling approach needed to include such effects.

6.3.1.4. Multi-scale modelling

Multiscale modelling is a quantitative, integrative and experimentally based approach for studying biological processes and dynamics that span multiple spatial (typically nanometers to meters – 10^9) and temporal (typically microseconds to decades – 10^{15}) scales with the view to transfer knowledge and information across scales, as well as support modularity and interactivity.

All the strands made reference to the challenge of extending current models to include multiple-scales and the need for good multi-scale modelling frameworks that allow integration of smaller problems into larger generic or customised models.

In particular, many experts expressed the need for techniques for integration of physiological activity at tissue level to organ level and also from cellular level to tissue level i.e. across *spatial scales*.

Other experts highlighted the need for dealing with a large range of *temporal* scales e.g. in an artery, from tenths of a second (viscoelastic effect due to pressure pulse) to days or weeks for remodelling, to months or years for elastin degradation and ageing effects.

There are currently many approaches available for tackling certain multiple-scale problems e.g.

- probabilistic/stochastic models
- mesoscopic models (e.g. Lattice Boltzmann method)
- agent-based models
- multiphase continuum models
- homogenisation.

A major challenge in the process of developing the models is in deciding on the most suitable approach.

There appears to be a need for the formulation of hybrid approaches that:

- combine agent-based and continuum modelling
- use mesoscale morphology in continuum formulations.

Depending on the scope and application of any model (e.g. teaching, clinical), some low-level details may be homogenised or even ignored, so as to decrease the computational requirements of specific simulations. In a number of specific cases (e.g. therapeutic innovation), this approach may be suitable, but would have to be applied carefully so as not to alter the components which are linked to the problem under investigation (at times, details down to gene expression may prove essential). Typical techniques for the latter include:

- abstracting results into systems models that present lumped parameter approximations of lower scale processes (by, for instance, using formal techniques such as dimensional analysis)
- taking, at a given level, at least one key parameter that can be experimentally validated across levels (i.e. bottom-up/top-down approach)
- mathematical and algorithmic methods for timescale decomposition (e.g. Gillespie algorithm) and spatial averaging (e.g. field theories derived from discrete processes)
- techniques such as conceptual graphs or cognitive maps, or
- using physico-chemical principles to constrain solutions in high-dimensional spaces to ranges that are relevant to larger scale applications.

6.3.1.5. Inhomogeneity issues

Some experts have raised issues surrounding the ability to model inhomogenous or anisotropic tissue. In summary, these relate to:

- accurate characterisation of inhomogeneity and anisotropy of biological
- smarter (or easier) ways to model inhomogeneity and anisotropy.

6.3.1.6. Inter-subject variation

There is an increasing awareness that for usefulness in the clinical setting models/simulations need to be patient-specific. In order to address patient specificity, some types of models (e.g. within musculo-skeletal or fluid mechanics modelling) are developed that require good image processing, segmentation, data fusion and mesh generation. Effort in improving these techniques is needed and is also discussed later in the document.

Other kinds of models (biostatistics, biological network models) may require different patient-specific data that could involve experimental measurements, biological imaging/sensing.

In addition to understanding the effect of variation between normal subjects, insights into normal versus pathological variations are also required. Statistical shape modelling techniques can help elucidate these differences.

6.3.1.7. Model identification and parameter estimation

Once a specific problem has been identified and workable models developed, the issue of estimating parameters becomes important. Where possible these need to come from accurate in-vitro or in-vivo measurements. There are, however, many instances where these are not available. In these cases, model identification is required by which parameters are estimated such that fitness to the available data is maximised. A balance between precision and robustness is required and the process relies on techniques in Data Mining, Optimisation and Statistics including logic and integer programming, and non-linear optimisation such as those applied to Neural Networks.

The problem of over-parametrisation must be addressed within this area. Models of complex biological systems require the integration of multi-scale models. This often leads to models that incorporate a larger number of parameters than required by the problem under investigation that may affect the uniqueness of model predictions (in deterministic models). This issue should be considered with care when defining and integrating mathematical/statistical models in a multi-scale framework.

6.3.1.8. Validation

While it is crucially important for models to be validated against experimental or imaging data, modelling scope can become restricted by lack of validation data. How can this problem be addressed?

Essentially, there appear to be two views on this:

- Simple models allow insight into mechanisms and give freedom to "play". Such models should be developed regardless of whether or not they can be validated purely to enhance understanding of the underlying physiological process.
- On the other hand, complex models that are aimed at clinical use do have to be validated using anatomical and physiological data.

Given these views, it follows that research projects should not be required to have a fixed proportion of funding allocated to validation. Some projects may concentrate on modelling efforts, others on a balance of modelling and validation and yet others may be entirely validation oriented. Although many low-resolution models are simple toy models, some may be validated against system level experimental data, and show good predictive power of system behaviour. It is not improbable that such models may be used in future clinical practice, either as stand-alone models or in combination with high-resolution models.

Other issues that are raised in connection with validation are summarised below:

- paucity of data
- where different models are coupled together validation at each model connection is also required, even if the individual models have been validated independently
- specific examples where validation is particularly difficult and were commented on are given below:
  - in musculoskeletal modelling one can predict muscle forces but true values to compare them with are not available
  - validation of models in different posture, movement and loading situations
  - validation of results from fluid-structure interactions.

6.3.1.9. Gaps in knowledge/modelling effort

There are still many areas where fundamental physiological understanding/knowledge is lacking, for instance:

- quantitative information at the microscopic scale of interactions between cells and matrix
- structural and functional properties of constituent materials
- knowledge of how genomic information maps to higher level physiological function

- experimental assessment of arterial growth and remodelling at the cellular/constituent/functional level
- questions on how newly synthesised/destroyed material is preferentially placed/removed in terms of quantities and spatial directions is fundamental and still unanswered.
- different types of data specific to different systems including:
  - reliable anthropometric data from wide populations
  - quantitative experimental data for parameter setting
  - accurate in-vivo skeletal data
  - quantitative information of tissue histomorphology
  - quantitative information of cellular/extracellular components

Some of the fundamental gaps in modelling efforts to date relate to the coupling of physics-based models with biology (in particular cellular/molecular scale effects) and these were discussed in some detail above. Other gaps in current modelling effort that were fairly specific to the various strands are summarised below:

- urinary system
- cerebral spinal fluids
- microcirculation
- energy metabolism
- flow problems in areas such as lower limbs
- reproductive physiology
- mechano-transduction
- macroscopic models e.g.
- the entire capillary bed down to cellular level
- whole respiratory system
- the creation of a full body musculoskeletal model that can predict the forces exchanged at any dimensional scale from the whole body down to the tissue level, and which is coupled with tissue adaptation models that allow to predict how the apparatus will change under altered conditions
- finite element models of the entire dentition from micro-CT scans
- large displacement modelling (e.g. cardiac mechanics)
- role of pulsatility to flow characteristics under both physiological and pathological conditions
- with regard to the suggestion that effort should be directed towards a fundamental understanding of specialised physical phenomena, such as turbulence, many were of the opinion that this is not justified. Instead, many have suggested that modelling effort should be problem driven and techniques needed should be used or developed as necessary. We lack basic understanding of fundamental *physiological* processes, and that is where the emphasis should be. While progress in technique can be a goal in itself, this should appear in another context and not within physiome-related modelling
- adaptive methods in software, for instance when dealing with models of soft tissue that is highly deformed or tissue that can increase in volume very quickly
- modelling callus and bone growth in realistic 3D geometries
- accurate mechano-biological modelling of cellular process
- the direct visualisation of the constituents to provide hard data of their interaction during loading.
- neuromuscular function
- common ground between organ systems
- statistical methods for handling uncertainty within any model.

There appeared to be consensus within one strand that a well-researched state-of-the-art review is definitely needed. Expert opinion from other strands is not known as this question had not been put to them.

In terms of modelling, such a review would identify what has been achieved to date. Set against a view of the complexity of the actual living organism, the assessment would reveal comprehensively both the gaps in knowledge as well as what should remain beyond the scope of the project.

6.3.2. Challenges in Description

Lack of meaningful input data can be the crucial factor that determines whether a model is a clinically useful tool or a "toy-problem" that allows insight into mechanisms. Accurate anatomical and physiological data that is essentially descriptive is crucial for developing clinically or industrially useful tools.

Many sources of data exist, but it will be difficult to integrate these into one seamless model. With individual organs there have been more systematic attempts to section tissues serially (eg the cardiome project) and this could be extended to other organs. The amount of work involved, however, even to reconstruct a single example, is formidable.

In the following few sections we attempt to categorise the issues that relate to anatomical and physiological data and which have been raised by experts. Much of what follows come directly from the Anatomy and Physiology strand, but every attempt has been made to incorporate comments from other experts that relate to this topic.

6.3.2.1. Data collection standards

Where data does exist it is rarely complete in terms of what is needed for modelling or is inadequate in terms of spatial and temporal resolution. Data is often obtained specifically to validate a particular model, or imaging data obtained is used to inform

particular boundary conditions. The following points were raised in relation to this point:

- there is a need for the modellers and experimentalist to collaborate at very early stages of a project to ensure that what is required is communicated between the two sets of researchers
- additionally, data acquired for a specific project may be more useful to others if particular standards are adhered to. There is clearly a need for setting some form of "gold standard" in this regard.

The development of a data collection protocol should allow

- creation of generic in-vitro models
- customisation of in-vitro models using patient-specific data
- automated (or semi-) statistical analysis of the final model using decision algorithms.

The above should then allow merging of subject-specific and population-based anatomical models.

Knowledge about "normal" and "physiological" needs to be redefined and recollected with the imaging and experimental techniques available today. The motivation for this is that the spectrum of "normal" reactions to any kind of stimulus is broad. The same change in an otherwise healthy person can be "normal" whereas it can be absolutely critical in a person with a certain predisposition or any other underlying disease. Such interactions may need to be incorporated.

6.3.2.2. Accuracy/quality issues

Models that are developed to answer clinical or industrial questions require accurate anatomical and physiological information (imaging, experimental data, etc). Of paramount importance then is to ensure that imaging technology or any experimental technique that is used has been extensively validated thus providing high quality, accurate data. To provide assurance:

- extensive validation protocols are needed to ensure quality of data
- validation protocols should address both scientific and clinical data collection procedures
- accurate, smarter data-reduction algorithms are needed.

6.3.2.3. Data fusion

A great deal of data currently exists in a variety of formats, obtained to address specific problems, across a wide range of disciplines and data collection technologies. The power and usefulness of this data can only be realised if it can be brought together in a systematic way. Many experts have suggest the need for data fusion tools that can:

- integrate data from fundamental and clinical research data
- integrate heterogenous and anisotropic data
- combine whole body MRI with organ-level CT scans and tissue-level microCT data
- merge patient-specific and population-based anatomical data
- combine images from different kinds of imaging technologies.

6.3.2.4. Hardware development/imaging technologies

New imaging systems and experimental techniques for extending the limits of our sensing capabilities across scales and into the structure and function of physiological processes are needed and should include:

- new imaging sensors
- new micro-techniques and other related devices
- protocols and modalities providing new insight into or better spatio-temporal resolution of anatomical structures and patho-physiological processes
- imaging modality simulators can also be extremely relevant to test and optimise the proposed models.

Although urgently required, the improvement of these techniques and the acquisition of accurate clinical measurements may be outside the scope of VPH. They may, however, emerge from general developments in clinical practice (where the resources are greater); the VPH would not be a big enough commercial driver. There is, however, a need to work with hardware manufacturers to extract data from proprietary data formats.

One of the problems modellers face, but which can be addressed within the VPH, is that not enough is known about new experimental techniques or cutting edge imaging technologies and, therefore, what kind of data could become available if this knowledge was harnessed. A networking database (see Section 6.1) that makes connections between the various researchers involved in the whole modelling process (from stakeholders at one end and modellers at the other) would make this kind of information easily available to interested parties who would not normally subscribe to the relevant specialist journals.

6.3.3. Challenges in Integration

The term "integrative" has been used to describe the approach that needs to be adopted to pursue the development of the Virtual Physiological Human. The major challenge in integration was considered by many experts to be that of multi-scale modelling which has already been discussed. Here, we discuss the other forms of integration that would usefully lead to an "integrative" approach.

6.3.3.1. Integration between disciplines

A large number of funding bodies are increasingly recognising the importance of cross-disciplinary research with implementation of funding programmes that address this very issue.

Expertise needs to be brought in from disciplines that traditionally haven't been involved in modelling – e.g. experimental biology, computational biology and stochastic modelling to address uncertainty issues.

Education of people in the early stages (PhD training) should include a good grounding in a variety of disciplines (from the biological and chemical sciences, through to the physical and mathematical sciences) so that a lack of skilled personnel may be addressed.

A number of experts suggested the establishment of:

- networks that brought together different disciplinary experts to solve problems in a particular area
- Europe-wide study groups based on the industrial mathematics study group model that has been running in Oxford.

Indeed, one of the strong recommendations that emerged from the second STEP conference was the need to continue scientific meetings that brought together researchers from the range of disciplines under the Physiome umbrella that this particular endeavour has done.

6.3.3.2. Integration between prediction and description

The second form of integration needed is that between data that describes the biology and models that can predict and help understand function.

Clinical usefulness requires integration of accurate anatomical and physiological information with mathematical or computational models. Descriptive data is often used as a starting point or inputs for models. Such data may provide information about boundary conditions, or high quality accurate imaging data can provide computational geometries for sophisticated models. To achieve this integration the following were highlighted by experts as requiring greater improvement in terms of speed, robustness and reliability:

- data, signal and image processing, multimodality registration, multi-scale approaches, spatio-temporal methods
- automated segmentation
- developing efficient representations for data, signal and images
- mesh generation for soft anatomical structures, deformable models
- integration methods for identifying model parameters according to patient specific data, methods integrating *a priori* information
- descriptive data is also used for validation of models and this was discussed in section 2.1.7.

6.4. ICT Challenges

What ICT tools are needed to help tackle the scientific challenges discussed above? And what are the challenges facing development of those tools?

6.4.1. Database or repository of existing models

There seemed to be considerable consensus on the idea of a database that collated existing models. This could also include a networking database that informed all researchers in the field about other modelling efforts around Europe/the world. Such a database/network would:

- reduce the "reinventing-the-wheel" syndrome and enable people to build on each other's work to make progress in this field
- allow existing knowledge and expertise on well-developed models to be translated into areas where modelling is still in its infancy
- enable collaboration between researchers across the network from the clinician/industrialist to experimentalist and modeller in order to achieve major goals
- databases set up for this purpose should be coherently organised, flexible, up-to-date, well maintained and policed for quality control. Thus actual resources for data processing are needed to populate the developed infostructures (resources are needed not only for building the infostructures and for data acquisition, but also for data processing, curation and annotation)
- one suggestion for the organisation of such a database was some "3D" structure that allowed modellers to search for models according to system (e.g. cardiovascular, respiratory, musculo-skeletal etc.) according to discipline (fluids, soft tissue, etc.) or according to methodology (e.g. numerical techniques, imaging, mathematical or statistical modelling, etc.).

6.4.2. Frameworks for model communication

In terms of the grand challenge – the development of an *in-silico* human – the ultimate aim is to bolt together many detailed models into larger systemic models. This will necessitate the development of software tools to facilitate model coupling. These include:

- efficient multiscale- and multiphysics-oriented computational building blocks (e.g. mesh generation for complex anatomical organs, highly efficient solvers, multiphysics coupling mechanisms etc.)
- new concepts and methods for coupling simulations across scales

- new methods for model reduction and parameter transfer across simulation scales
- new languages (e.g. mark-up) and standards (e.g. simulation API standards) for facilitating exchange of heterogenous models and simulation tools, so that multiphysics and multiscale coupling can be facilitated and promoted
- good engineering software tools. A proper software engineering approach to software development is essential so that it can be maintained as problems and solutions evolve over time.
- Frameworks for multi-level modelling. These include:
  - coupling of spatially distributed models (PDEs – usually 3D) with lumped parameters models (ODEs)
  - coupling of 3D to 2D or 1D models
  - middleware development to allow non-experts use of models/simulation software and to get stakeholders involved and interested
- mathematical tools that could be turned usefully into software tools are summarised below:
  - consistent formulation of a full bottom-up approach starting from sub-cellular processes through individual and population cell behaviour, to tissue and organ function
  - hybrid approaches for combining different mathematical techniques (discussed in Section 2.1.4).

One suggestion for addressing the complex system versus simplified model problem is the development, at a low resolution, of a model of an entire system.

Then, individual models with more detail could be slotted into the low-resolution model. There would be no need to artificially set boundary conditions, but detailed models would fit into the bigger low resolution model. The idea of having a low-resolution model of the entire system would be analogous to a tool or framework that enables integrative research. An example of this is Guyton's circulation model which, although simple, proved to be predictive and applicable within the clinical setting. Such an integrative framework would allow fast enough development but would also allow illumination of required details. In addition, such an integrative approach may complement a reductionist approach whereby deliberately simplified models can still be incorporated in some form.

6.4.3. Knowledge-management software/database

There are three types of data: (structural) data used to build the models, (simulation) data generated by the models and (functional) data used to validate the models. The former and latter types come from the literature or directly linked experimental efforts. The rapid expansion and application of new experimental and imaging techniques have (and we expect this to continue) generated growing volumes of data. The number of publications in the biomedical field has doubled every ten years since the middle of the last century. New knowledge is likely to follow the same growth patterns, so good knowledge management software will become increasingly critical. Depending on the data modality, this can range from spreadsheets (low volume) to 3D histo-architectural detail (dozens of GB per sample). The quality of the data and how easily it can be reproduced should also be recorded.

Simulation data (usually represented in a raw format) ranges from tens to hundreds of GB (Gigabytes), to even a few TB (Terabytes) of data that are usually stored remotely (including the executables for generating the data; metadata is not currently stored, but this ought to change as they could allow for the quick retrieval of simulation data with the appropriate passwords), on geographically-distributed disks (e.g. SRB facilities in the UK), although local storage (i.e. on PCs) has now become affordable.

Across the strands, there was strong consensus that databases or digital libraries of data of various kinds are needed. Examples could include libraries of:

- real bones shapes/dimensions
- affinity of enzymes at molecular level
- rate constants for biochemical reactions
- segmented CT/MRI images
- finite element meshes obtained from segmented images
- anatomical and functional atlases per organ systems and per disease when appropriate.

These libraries or databases would:

- collate the large amount of data available today
- allow easy access in terms of combinations needed
- need to be well-organised and maintained at various levels
- need to be kept updated so that information was current
- need to be policed for quality control
- need also to contain benchmark data and guidelines for evaluating and validating data, methods, tools and simulations.

The above points would also apply to a database of models or simulations.

In relation to data collection the following requirements were also additionally highlighted:

- new methods and tools to provide high-throughput phenotyping from imaging sensors (it is important to realise that new imaging systems/protocols often need new tools and thus need to be developed)

- new techniques and efficient methods for high-throughput image analysis and fusion (e.g. image segmentation, image registration, biometrics, scientific visualisation, etc.)
- new techniques for multidimensional data reduction and exploration
- new tools for better structuring and exploitation of (imaging) information and its integration with clinical variables and genotype (e.g. text mining, ontology building, automatic generation of relational networks etc.)
- novel decision support strategies that seamlessly integrate vertical sources of information or heterogeneous information
- standards and tools for data exchange e.g. formats, ontologies, semantic annotation
- protocols for data processing techniques.

6.4.4. Novel computational and storage technologies

New computational and storage technologies are necessary to extend current IT limitations for modelling in the VPH. The length and timescales involved require storage of information at every level. This information is not only descriptive data from images and other experimental techniques, but also predictive data resulting from simulations. The timescale limitation is particularly strong at the lower scale levels (atomistic and molecular), where modelling starts at femtosecond scale (10E-15 seconds) but needs to reach the timescale of biological processes (micro-milliseconds) [http://arxiv.org/abs/physics/0611201]. Challenges include:

- development of emerging processor technologies which would reduce the timescale gap, including specialized processors like Cell broadband engine architecture (SONY-Toshiba-IBM), stream computing (AMD-ATI) and multi-core processors in general (AMD INTEL) [http://www.hpcwire.com/hpc/1134768.html]
- integration of grid computing technologies and high performance computing solutions into biomedical research to access larger computational capabilities
- new architectures and demonstrators for heterogeneous data integration leveraging from current efforts and domain standards.

6.4.5. Visualisation

Biologists have, for some time, been shifting towards more quantitative models, supported by the fact that increases in computing power allow more complex mathematical models than was previously possible. The introduction of grid technology, and the access to high performance computing and the huge data sets that it promises, means that this trend is likely to accelerate.

In recent years, visualisation has become a standard aid to understanding in many scientific fields, a process that has taken place largely as a result of rapid improvements in graphics capability. Here, the enhanced capability of graphics accelerator boards and the increasing sophistication of relevant algorithms have played even more significant roles than increases in processor power.

As our thinking shifts towards a multi-scale environment, researchers will be faced with the additional demands of conceptualising at multiple levels of detail. Researchers who have traditionally been used to working at different, but fixed, scales will be brought together to work on the same problem – to ensure that communication between them is straightforward and accurate will present a number of challenges. Likewise, the increasing complexity of the models required and the breadth of data under consideration will place ever-greater demands on providing suitable tools with which to analyse and understand the processes involved.

It seems likely that visualisation will play a crucial role here. The over-used, but nonetheless accurate, maxim, "a picture is worth a thousand words", is highly appropriate in this context – visualisation will become a key tool for supporting communication and adding value to the outcomes of multilevel modelling.

In the context of the VPH, it must be emphasised that visualisation will not only be an essential tool for use in research and in industrial and clinical practice, but also a key element in developing the educational materials that will offer insights into this challenging area and enable researchers to adapt readily to the new emerging technologies.

There are two distinct aspects to visualisation that are relevant to VPH – scientific visualisation and information visualisation.

In **scientific visualisation**, physical structures and processes are displayed in ways that can elicit information and behaviour that would otherwise be very difficult to identify. In general, scientific visualisation has been used to investigate problems in which investigators are working at a single scale. In this context, it has become an essential tool in many scientific areas. So, taken in isolation, there are already recognised visualisation approaches at most biological scales.

However, little account has been taken of providing visualisation facilities that can support transition from one scale to another in a seamless and unified way. For example, the NIH/NSF Visualization Research Challenges Report, http://www.sci.utah.edu/cra-nih06/, published in early 2006, gives a good overview of the current issues facing visualisation but, significantly, fails to consider the multiscale problem. It is evident that this problem is still "below the radar" and so there is an urgent need to start discussing approaches that can provide integrated visualisation of data at multiple scales.

Given the additional complexity involved in this work, it is likely that it will benefit even more from the support of appropriate visualisation tools than work at a single level.

It should not be overlooked that differences in temporal scale can also be significant. Phenomena may become apparent only at a specific resolution, but a failure to take account of them at other temporal resolutions can drastically impair the ability to model the process as a whole. This is another area at the early stages of development, so there are currently no guidelines covering how understanding can be improved – by visualisation or by any other means.

Information visualisation is concerned with encapsulating the available data into an overall schema that enables relationships between the various items to be explored. Abstract, non-spatial ("shapeless") data can be organised into a visual form to assist with conceptualisation.

With the explosion of data that is likely to occur as VPH activities expand, keeping track of the available data will be critical. Information visualisation, along with techniques associated with the semantic web will have a great part to play in supporting this.

The sheer biological complexity of the models that are likely to emerge within VPH will tend to make any visualisation somewhat convoluted; it will be a considerable research challenge to develop tools that navigate through the data while avoiding over-simplification.

Both forms of visualisation have, in the past, suffered from a lack of user-friendliness. In general, the user base is already heavily over-committed. The added burden of learning how to manage elaborate software effectively, and how to understand the complex displays produced, is frequently considered "a step too far", with the result that the level of take-up is often disappointingly low. Professionals are often intensely practical people and will not commit time and effort to something unless it demonstrably provides substantial benefits to their daily tasks.

Providing added value to the user by choosing the best visual representation and optimising the user interaction continues to be an active research area.

6.5. ICT challenges – some solutions

This section summarises the suggestions, made by the ICT strand, for providing solutions for some of the requirements highlighted above.

6.5.1. How can transparent access be provided to grid resources?

At UCL, some middleware has been developed – application hosting environment (AHE) – which is a solution for the computational side. The Application Hosting Environment (AHE) – http://www.realitygrid.org/AHE/index.shtml – is already available in its first release, being used on UK NGS and US TG. It provides a facile means of interacting with federated grids and is highly extensible. It is expected to be used interoperably across different middlewares including Globus and Unicore (this is possible via the use or development GridSAM connectors.) Thin clients such as PDAs and cellular phones can also access the AHE. As far as access to databases is concerned, security is a problem, particularly in the medical domain, and one of the main obstacles to safeguarding the confidentiality of medical data and to ensuring that anonymity is preserved. There is also a real problem with the unwillingness of database providers to allow access to and sharing of their data – particularly in a "transparent" manner. It is important to differentiate between the security of data stored in a database (i.e. preventing unauthorised access) and rendering data anonymous, either when it is stored in the database, or as it is retrieved.

Final users should be involved from the very beginning in defining a "reasonable" user interface to the many services that the federate resources will provide. It is not enough to provide "transparent" access, otherwise only a very limited subset of available services will be used.

6.5.2. How can different simulations be coupled in a generic way?

One of the greatest challenges in ICT applied to computational cell biology is to develop standards for defining cell models so that they can:

- communicate with one another in a consistent format
- be analysed for consistency of units and constraint checking
- be read into simulation software in a standard format.

As a first step towards this goal, a framework for modelling cell function has been developed (www.cellml.org) over the past eight years by the Bioengineering Institute at the University of Auckland under the IUPS Physiome Project. The key elements are:

- the development of mark-up languages called CellML and FieldML to standardise mathematical description and model information
- application programming interfaces (APIs) to define the way that information is passed between CellML and FieldML model files and computer programs written in languages such as C, C++, Fortran, Java, Perl, Python and Matlab
- the development of authoring tools to facilitate the creation of computational models from the mathematical description
- the creation of simulation code that reads the chosen CellML files, generates the source code and compiles and links this into an executable that can then be run to generate model results

– the development of ontologies to represent human anatomy and physiological processes.

The CellML language is designed to represent mathematical models of any biological system and:

– is machine readable because it is based on the extensible mark-up language (XML)

– represents concepts from mathematical modelling (model, variable, units and mathematics)

– uses structures in common with object-oriented programming.

Where appropriate, CellML builds on existing XML standards e.g. MathML for the specification of mathematical equations (www.w3.org/Math) and resource description framework (www.w3.org/RDF) for the encapsulation of model information.

Another XML-based standard called systems biology mark-up language (SBML – www.sbml.org) has been developed for describing models of biochemical reaction networks. The modular framework that gave birth to SBML, XML-RPC with an API, is available for main languages, including Java and C# (portability).

UCL have been working on a multiscale model that couples molecular dynamics and fluid dynamics. The coupled code runs as two independent components on different resources and communicates via what is called a hybrid switch service, possibly running on a third machine, which stores and forwards messages between the two. (http://www.biomedtown.org/biomed_town/STEP/Experts/ict/references/coupled_models.pdf). The use of computational steering and coupled models has been investigated in the RealityGrid project (http://www.realitygrid.org).

BioSPICE (www.biospice.org) funded by DARPA, and developed from the largest funding ever given to a software project in life sciences, provides a complete modular infrastructure. It is an open source framework and software toolset for Systems Biology, is intended to assist biological researchers in the modelling and simulation of spatio-temporal processes in living cells. In addition, their goal is to develop and serve a user community committed to using, extending and exploiting these tools towards improving further knowledge of biological processes. In collaboration with other Bio-SPICE Community members, they intend to develop, license, distribute and maintain a comprehensive software environment that integrates a suite of analytical, simulation and visualisation tools and services to aid biological researchers engaged in building computable descriptions of cellular functions. From disparate data analysis and information mining, to experimental validation of computational models of cell systems, their environment intends to offer a comprehensive substrate for efficient research, collaboration and publication.

Information about the Common Component Architecture (CCA) and the current DOE Center for Component Technology can be found at:

http://www.cca-forum.org/scidac/index.html

Other good open source biomedical computing software includes

– ITK – http://www.itk.org/

– VTK – http://www.vtk.org/

– National Biomedical Computation Resource Software Tools

– http://nbcr.sdsc.edu/tools.php

– Scientific Computing and Imaging (SCI) Institute – http://software.sci.utah.edu/.

Another toolkit that could be considered is the Model Coupling Toolkit (http://www-unix.mcs.anl.gov/mct/), a set of open-source software tools for coupling message-passing parallel models to create parallel coupled models. This may be important in resource-hungry simulations such as CFD models coupled to lower level models (3D models coupled to 1D models). The development of this toolkit started in a different application field (climate) but it now provides a general framework for multi-physics coupled models.

6.5.3. How should repositories of simulations be created?

The BioSimGrid (www.biosimgrid.org) UK BBSRC has developed a prototype designed to act as a repository of simulation data specifically for biomolecular dynamics. This could be a good architecture on which to build. Although BioSimGrid is a good example of a solution in a specific field, the fact that the VPH spans many other areas means that it will be necessary to determine whether this architecture is flexible enough to fulfil the requirements of other application fields.

A repository of models based on the CellML format has been developed at the University of Auckland. The goal is to make all published cellular function models available in CellML format and to encourage the authors of these models to ensure that the model parameters and initial conditions available on the CellML site are consistent with the model results published in the paper. The repository is at www.cellml.org/examples/repository and includes models (freely available) in the following categories:

– signal transduction pathway models

– metabolic pathway models

– cardiac electrophysiological models

– calcium dynamics models

– immunology models

– cell cycle models

– electrophysiological models

– smooth and skeletal muscle models

– mechanical models and constitutive laws

6.5.4. Issues in Medical Image Visualisation

Four issues believed to be of great importance in the near future are discussed below:

Medical evaluations. To make the visualisation more beneficial to clinical practice, we shall need to develop methods/tools to evaluate and assess the results of the visualisation in medical terms. A large number of such evaluations have taken place in 2D medical imaging research, in which identified subjects and models are tested through medical experiments and practice. These techniques may be borrowed or extended into 3D visualisation.

Human factors in 2D and 3D image visualisation tools. This is to try to assess the effectiveness of existing imaging and visualisation tools from a user-centred point of view, including the integration of multi-sensorial interfaces (e.g. haptics, stereo vision, etc.). Great efforts have been devoted to developing techniques in terms of improving image quality and processing speed, while the human factors issue, which is concerned with how users (normally the medical professions) view and use the visualisation tools, have been largely ignored. In fact, considerable research effort has been undertaken in the area of Human Computer Interaction, in which human factors have been studied very closely. Again, these techniques can be borrowed.

Feature enhanced visualisation. This is to enhance clinical features during the visualisation process to make it more clinically meaningful. Traditionally, different colours were used to highlight these features. However, with the fast advance of texture techniques from computer graphics, texture based visualisation, which is capable of using a variety of colours to highlight medical features, can become a new alternative. How to provide effective controls to synthesise desired textures to reflect upon the underlying medical features remains a challenging issue.

Large data and information processing. Large medical datasets, especially those involving time series, often contain a large amount of information, which can be retrieved by image feature analysis. However, data analysis techniques such as clustering and data mining techniques will need to be involved to explore further meanings of the data, to discover the links between the large amounts of information and subsequently to identify their patterns.

A number of reports that might be of interest to this group (including the NIH/NSF Visualization Research Challenges Report) can be found at http://www.sci.utah.edu/cra-nih06/. There is an expanding list of references in:

http://www.biomedtown.org/biomed_town/STEP/Experts/ict/references/

6.6. Recommendations for future discussion

Many experts have suggested that the best way forward, and to engage the scientific community in general (e.g in the debate regarding the letter to Nature), is to set up some well-thought exemplars or case-studies that concentrate on certain applications and tell a "story".

Such a case study would begin with a specific clinical or scientific question being asked, go on to showcase current research efforts that are attempting to answer that question and finish with the limitations of existing models and validation. The exercise would inevitably be cross-disciplinary and multi-scale, bringing in the importance of molecular and cellular scale effects. Imaging and other validation technologies would also play a part in telling the "story".

The aim would then be to ask experts to highlight gaps, identify tools needed to fill in those gaps (scientific, experimental, computational or related to infrastructures). Additional issues would also be raised that relate to the roadmap and perhaps prove to be more effective in defining the problems, the capabilities of the groups and the types of solution that are most effective and beneficial to science and health.

6.7. Problem sizing and resources required

6.7.1. Introduction

The VPH presents a significant IT challenge since it is a resource that must accommodate a vast reservoir of physiologically diverse data and modelling tools, whilst supporting robust and effective access to end users and contributors alike. The viability of the VPH is dependent upon its ability to overcome numerous challenges such as the organisation and storage of petabytes of data, sustained communication bandwidths that can transfer terabytes per day, extensive support for data indexing and data format translation – all of this embedded within an infrastructure that guarantees secure and transparent access, and integrated with a quality assurance mechanism that safeguards the quality of data accessed by the end-user. The magnitude of both data storage and data flows is enormous, and an estimate of these quantities is key to architectural design, since they must be managed effectively.

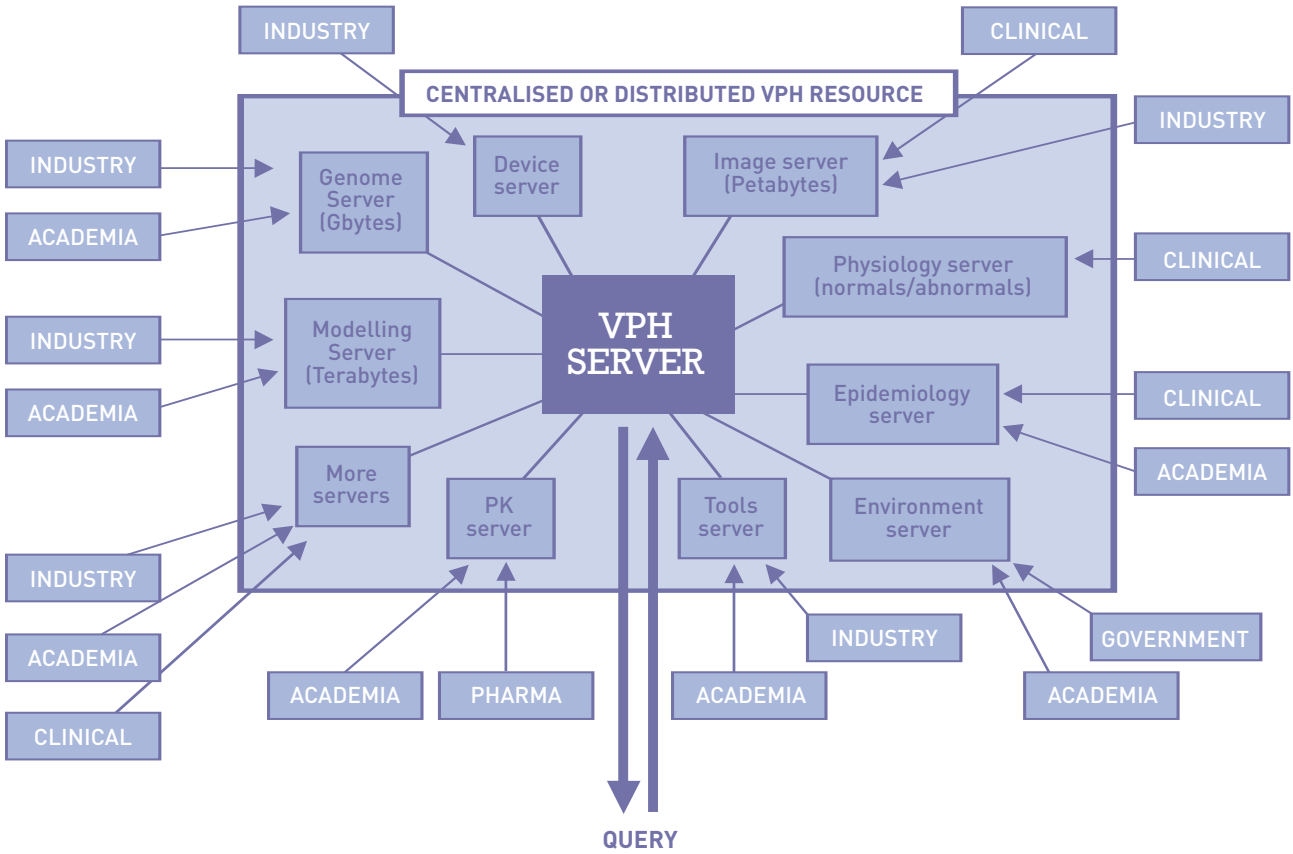


Figure 6.1. The VPH infrastructure is a repository for diverse information access. VPH Central encompasses satellite database servers that service the VPH-server.

Note: For the purposes of this problem sizing exercise the above architectural model is assumed (Fig. 6.1), but this represents just one of a number of possible solutions. Other options could include a distributed model with special networking arrangements etc.

6.7.2. Example Architecture

An example architecture might be a core structure that comprises a collection of contributing data sources that mirror databases across the world, each of which is an established and authoritative entity in its own right (Fig. 6.1). The repository provided by the VPH is a dynamic copy of these resources and is automatically updated at frequent intervals. A consequence of this is that data is naturally categorised according to specialities that have emerged, with the flexibility to accommodate new specialities as they evolve. In the domain of the VPH Resource, these local database copies are queried by a central VPH-server, configured to communicate with each one and also acting as a mediator to facilitate communication between them. On receipt of an end-user request, the query is parsed and forwarded as component requests for data from the satellite servers. The data is collated by the VPH-server in order to service the request. Flags are attached to the data to indicate its status (e.g. validated, published etc.). A utilities server is an integral feature of the VPH Resource and contains libraries of utilities that enable import/export of data between applications. The applications server is a critical component that contains all modelling tools and applications that have been contributed to the VPH.

In response to the query, the end-user receives a cohort of data, tools and applications that can be assembled in such a way as to explore solutions to the query. A VPH-specific graphical programming tool, that allows the user to direct the flow of data through the supplied modelling applications, manages this process. The graphical interface makes use of suitable utilities that hide the complexities of data formats etc. and scripts a series of data/modelling interactions (and invokes the use of shrink-wrapped software) to determine solutions. Thus the user is free to explore the problem in his/her own way.

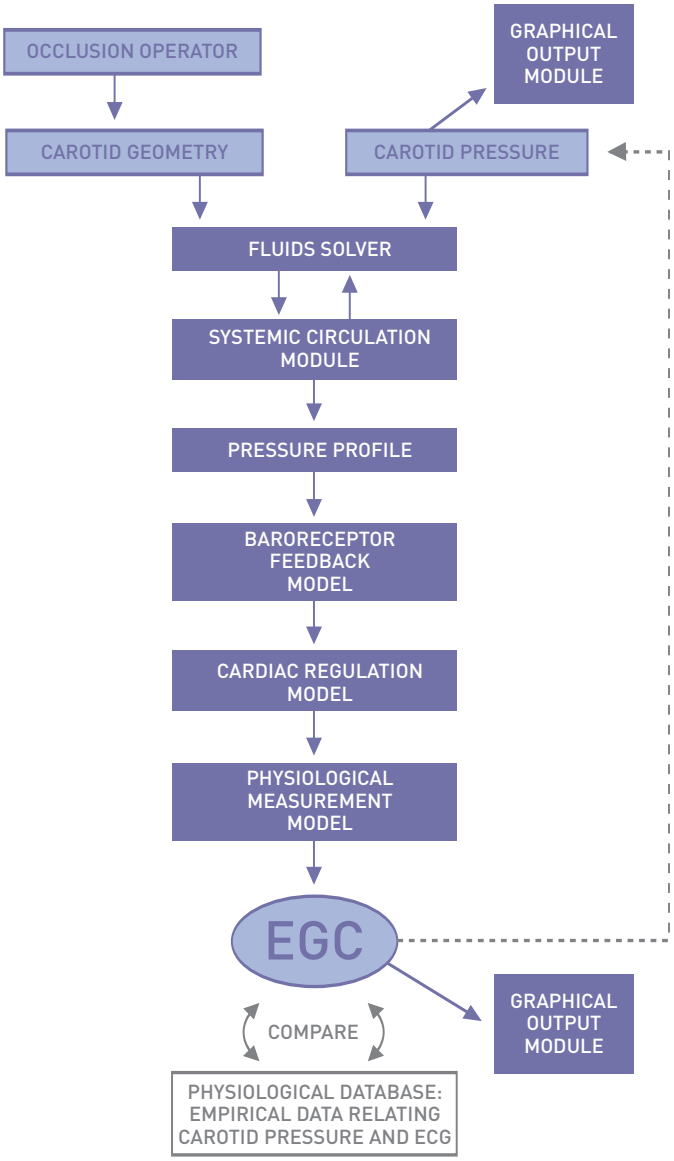


Figure 6.2. Fictional graphical programming environment, illustrating how a query relating to pressure and ECG might be configured.

6.7.3. Example VPH Interaction

A simple example that queries the relationship between blood pressure and ECG is presented below. Note that it exhibits the cross-disciplinary and multiscale nature that is characteristic of such queries.

6.7.3.1. End-user Query

How is the ECG of patient X likely to be affected by partial occlusion of the left carotid artery?

6.7.3.2. VPH-Server response

Data is pulled from the following server libraries, collated and sent to the end-user:

- physiology library (data for typical carotid pressures/flows/ECG)
- pathophysiology library (carotid pressures/flow/ECG response to pathologies)
- mesh library (to model typical carotid geometry)
- utilities library (data format translation utilities)
- tools library (modelling applications linking flow to ECG)
- physiological measurement library (characterises instrumentation response to measurement environment).

6.7.3.3. End-User Action

The VPH graphical interface is used to explore solutions to the query (see figure 6.2).

This example illustrates several characteristics of VPH use. The initial query typically involves negligible data transfer/bandwidth (MBytes). However, the resulting data sets collated by the VPH-server can be substantial, in this case including large data files such as finite element meshes or diagnostic image stacks. Clearly, this stresses the internal bandwidth of the VPH resource, but externally the difficulties are much more pronounced – routine transfer of many GBytes of data to remote users across Europe is problematic. If many users are considered, all independently and simultaneously expecting large data transfers, the magnitude of the challenge becomes even more apparent. Once the VPH files have been successfully transferred, however, the duties of the VPH are complete (with respect to the querying individual). Nevertheless, the end-user may generate terabytes of data on a local computing resource in search of a solution to his query, but this phase does not compromise the functionality of the VPH. In fact the opposite may be true, since the end results may be of sufficient interest and quality that they warrant addition to the VPH resource; they can be added to the satellite servers in due course. Figure 6.3 illustrates a simple scenario that involves transfer of mesh or imaging data and highlights the data loads that may be associated with a single query.

6.7.3.4. Conflicts

The VPH is able to assist in medical decision-making and offers biological insights and predictive outcomes that can be cross-referenced to an exhaustive data resource. As a semi-empirical predictive tool, outcomes can be cross-referenced to known (patho) physiological landmarks and *in vivo/in vitro* data. The use of a sophisticated query computer server will enable speculative queries to be answered through intelligent analysis of all available data, incorporating interpolation/extrapolation mechanisms interfaced to the best modelling tools currently available. Supplemental data contributed by other groups or sectors can extend the knowledge resource and its validity catalogued accordingly. However, the natural growth of such a facility will inevitably provide plenty of opportunity for data conflicts, precipitated by:

– differences in data interpretation

– ambiguities of language/misunderstandings/misinterpretation

– varying assumptions about the context of the data.

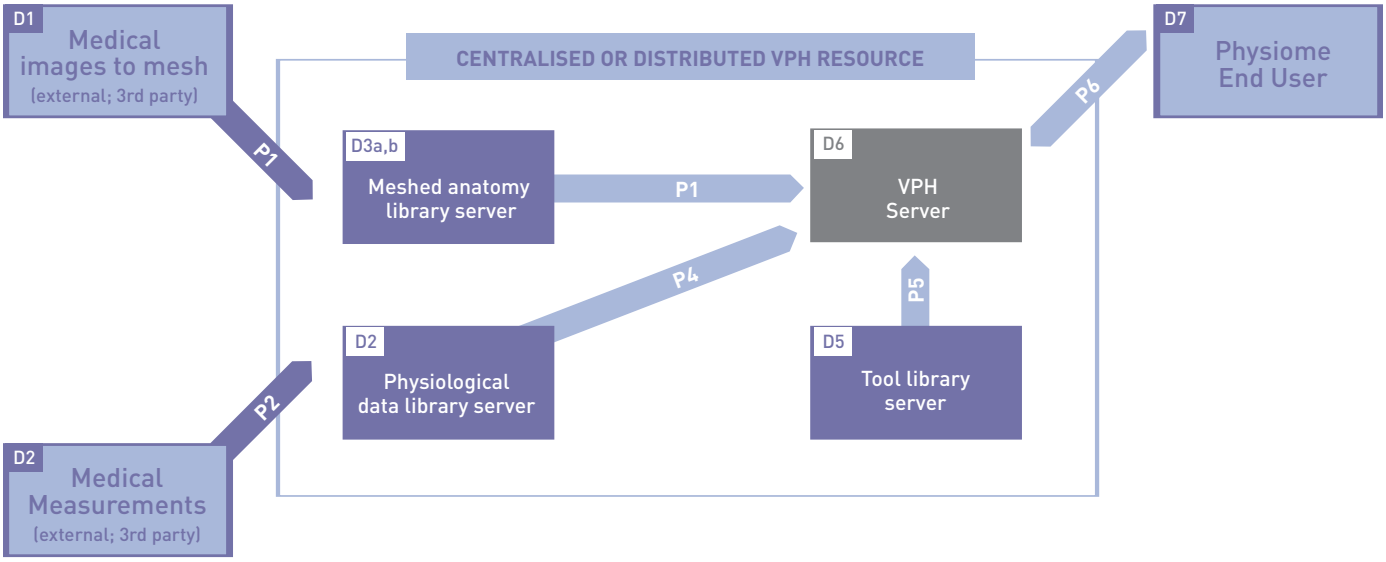
6.7.3.5. Errors

Examples of errors that may exist include:

– modelling inaccuracies

– sensitivity of outcomes to input conditions.

With the current state of the art, it is difficult to envisage automatic resolution of such conflicts. Nonetheless, these can be flagged to inspire debate and expedite correction. Pro forma data entry permits automated data collection linked to the possibility of automatically resolved conflicts, but free form data (e.g. a journal paper) is difficult to categorise automatically (for storage in the appropriate VPH database). This is an opportunity for developments in data-mining and bioinformatics [1], noting that benefits go beyond the VPH. Improvements in information extraction will inevitably profit biomedical research, healthcare and the wider community.



Key:

Data sizes:

D1	– meshes generated by 3rd parties	
D2	– In vivo/vitro measurements obtained by 3rd parties	
D3a	– Mesh server of the VPH	(Many GB)
D3b	– Image server of the VPH	(Petabytes. Note: Hospital PACS for 1yr ~20TB)
D4	– Physiology server of the VPH	(Many MB)
D5	– Tools and utilities server of the VPH	(Many GB)
D6	– Collated data to service user query	(Several GB)
D7	– Storage/processing by the end user	(Potentially many GB)

Data flows:

P1	– Mesh/image data flow to update VPH Central	(GB per day)
P2	– Measurement data flow to update VPH Central	(MB per day)
P3	– Mesh/image data flow to service user request	(GB per request)
P4	– Physiological data flow to service user request	(MB per request)
P5	– Tool data flow to service user request	(Many MB per request)
P6	– Data flow from VPH server to end-user	(Several GB per request)

Figure 6.3. Notional data storage and data flows to service a simple VPH request.

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Editor: Randy Thomas, Laboratory IBISC, CNRS – University of Evry (FR)

7.0

7.1. Executive Summary

VPH will have a significant impact on scientific research, on clinical practice, on industry, and on society in general. Summaries of each now follow:

Impact Analysis

The four principal areas of **impact on scientific research** (section 7.3) are:

- *Research Infrastructure:* centralised access to resources distributed around the globe will both improve collaboration and avoid duplication of effort. It would also help towards what is often referred to as "the three Rs" (Replacement, Reduction and Refinement), i.e. the rationalisation of experimental research and establishment of modelling as a partner to experimental research, to make more intelligent use of the animal experiments that will continue to be necessary. The training of a new generation of multi-disciplinary scientists will, over the medium term, result in more relevant integrated research, better management of time and so more effective use of funding.
- *Methodologies:* the establishment and subsequent adoption of common standards for nomenclature (i.e. ontologies) and mark-up languages for, among other things, description of mathematical models, will greatly facilitate the re-use of published models and the development of new ones. The increased transparency will facilitate evaluation of the limitations of given models and greatly ease comparison of models.
- *Databases/Knowledge Bases:* the cross-discipline ontologies referred to above will provide the common semantic underpinning for databases/data warehouses that are a necessary basis for effective model-development.
- *Software tools:* tools for visualising, interpreting and processing the data will be catalogued, compared and, where possible, made available via a central resource to avoid duplicating effort on tools that already exist. More important for our research will be access to a set of tools that will allow us to do modelling at any appropriate level from the molecular to the organism, which is not presently possible. This will have an impact not only on our research, but also at the clinical, industrial and societal levels. Experimentalists will also benefit from having access to such tools, which will become part of the standard toolbox in the laboratory, facilitating the exploration of new hypotheses during the design of experiments to test their validity, as well as providing a platform for interpreting experimental results, suggesting new experiments, etc.

The **clinical impact of VPH** (section 7.4) will be manifested through improved diagnosis thanks to online access to international multi-discipline knowledge bases and tools for customised patient-based *in silico* disease models. Where simulators are used to rehearse surgical procedures, VPH will significantly help with the coordination of what is currently available and will help establish a common modelling framework that can incorporate function across all relevant scales. It may also become possible to provide efficient access to the results of clinical trials. VPH could involve the organisation of multidisciplinary clinical teams and optimise communication among their members. The VPH infrastructure tools should greatly help to achieve these goals. The VPH would dramatically decrease the number of clinical tests patients have to undergo, avoid redundancy and significantly reduce costs. Finally, the multi-level aspects of the VPH will give a therapeutic team access to highly multidisciplinary tools that would allow them to approach a patient's particular case from different points of view specific to each discipline and at various scales (genetic, cellular, tissue, organ).

Indeed, to establish the necessary multidisciplinary consensus within the clinical community will require an important debate assessing the priorities related to building the EuroPhysiome/VPH: for example, should the problem be approached by analysing the needs for each pathology, and then gather all those needs into one unique system (clinical approach)? Or should the technological aspects of the systems (data, methods, algorithms) be developed first (IT approach)? It is probable that both approaches should be simultaneously conducted to ensure efficient clinical validation and to increase the system's acceptance.

Industrial impact of VPH (section 7.5): The tools developed within the VPH/EuroPhysiome will hasten the introduction of new equipment and techniques by allowing new technologies with potential application to be explored in new ways, generating new knowledge that can be exploited in practical designs and result in improved healthcare services for everyone's benefit. However, in a competitive market place, general technical developments have only a transient effect on industrial performance and fortune, since the competitive nature of industrial enterprise means that all commercial parties absorb technical progress, costs are reduced, performance is improved and the market is realigned. *So, to continue, industrial benefits depend on a continuous stream of innovative ideas,* something which the unlimited scope of physiological modelling can, perhaps uniquely, offer. The areas most likely to benefit are medical device development, the pharmaceutical industry and, conceivably, software development for high-performance computing and the management of massive data warehouses/databases.

The impact of VPH on society (section 7.6): The VPH will improve relationships and communication among the industrial, clinical and research communities. This will impact society in a number of crucial areas. In healthcare, VPH should have impact related to pharmacovigilance, adverse drug effects, streamlined development of medical devices and patient safety. Yet other benefits will be monitoring and initiatives for faster rehabilitation that will reduce the cost to society. As well as the healthcare industry, the automotive industry (vehicle safety and comfort), tools and workplace industry (ergonomics and safety), defence (evaluation of biological damage of weapons) and the leisure and

sports industry (primarily equipment) are among those that will also see an impact from the VPH. This impact will manifest itself in the development of educational tools: for education and healthcare activities, the VPH will provide the basis for development of hands-on simulators for educational and training purposes.

7.2. Research Impact

We are currently witnessing a fair amount of overlap in bio-medical research in terms of the use of infrastructure development, methodologies, databases and/or tools. The multi-disciplinary nature of our research certainly does not help in this context where, for instance, a research team may decide to work on a particular topic and is not aware that another group, from a different field, is already or has already been working on it. This may occur because the two different groups publish in different journals, attend different meetings, etc., and so are unaware of one another's work, the result being that their efforts may overlap partially or, even worse, completely.

This is a problem of infrastructure that, if addressed properly, could facilitate interaction and collaboration among scientists involved in bio-medical research. Not only would this save everyone's time, but it would also allow for better use of human resources and, therefore, of funding. Combined with the development of better methodologies, databases and tools, i.e. VPH, this would directly benefit research as a whole, as well as have an indirect clinical, industrial and societal impact.

7.2.1. Infrastructure

It is not unusual at the moment to spend months without interacting with a fellow researcher. When we eventually do, we may find out that he or she is working on something similar or identical to what we are working on, on something that we were thinking of doing, or on something that is of great interest to us. The development of a better infrastructure will make it possible to find out earlier what our colleagues are doing, allowing us to decide whether to collaborate or to work on something else and avoid a duplication of effort.

The training of multi-disciplinary scientists will bring onboard a new generation of scientists with both special expertise in a particular discipline and an excellent understanding of adjacent disciplines. Unlike most scientists, whose expertise is currently limited to a unique discipline, they will be in a position to fully appreciate how their research in one particular discipline can be of use in another, whether a particular topic at the interface of one or more disciplines is worth investigating or not etc. The end result will be more relevant research, better management of time and, as a consequence, more effective use of funding money.

Our research generates a lot of data. Unfortunately, we may be the only ones who use it, because of the proprietary format in which it is stored. The sheer quantity may also be an issue: how to share gigabytes, if not terabytes, of data efficiently? Although very useful, such data may end up being underused. VPH will help by ensuring that the results of any research can be used by anyone through standard formats and better means of sharing data. This should prompt additional, as well as more advanced and relevant research.

Bio-medical research relies heavily on time consuming computationally intensive simulations, some of them taking literally days to complete. The problem relates frequently to the infrastructure e.g. using simple desktop computers when a supercomputer or a cluster of computers would be more suitable (along with better numerical techniques, as part of a better tools strategy). To make such facilities available to everybody, through the VPH, would mean that the waiting time for the outcome of a simulation would be reduced to a few hours rather than days. That saved time could be used to run more simulations, so improving the quality of our research or even expanding it.

To review a grant or a manuscript that involves several disciplines is difficult. By offering a review system that is more in line with the multi-disciplinary nature of bio-medical research, VPH will improve the quality of our research by getting such projects funded and papers published. Another major consequence of having a better infrastructure – although better methodologies, databases and tools play an equally important role in this context – is that it would help towards what is often referred to as "the three ***R***s" (***R***eplacement, ***R***eduction and ***R***efinement), i.e. the rationalisation of experimental research and establishment of modelling as a partner to experimental research, to make more intelligent use of the animal experiments that will continue to be necessary.

7.2.2. Methodologies

By providing some standard format for publishing and, therefore, exchanging mathematical models, VPH will eliminate, or at least alleviate, the presently laborious and very time-consuming process of re-implementing published models (several months can easily be wasted). Any published model that comes in a well specified and agreed format could be used by any researcher in seconds (literally!). Not only would this save a lot of time (and therefore money) and allow the user to concentrate on more relevant matters, but it would also avoid conflicts between scientists due to real or imagined mistakes in a publication, since published models would be known to be valid, at least with regard to the publication itself.

Another problem with the use of published models is that they often contain no information about their limitations and range of applications. A model user currently spends a fair amount of

time implementing a model and may eventually realise that it is not suitable for his or her research. But with access to this information, the user will know, at a glance, whether or not it is worthwhile using a particular model. Again, the user's time (and the funding body's money) will be better used as a result.

Sometimes, it may happen that we need to model some low-level processes but not necessarily in great detail. By having well defined methodologies for homogenising or even ignoring some of the model's details, the user will be able to take advantage of such low-level models in a way that is not currently available to all. As a consequence, it will be possible to tackle problems that could not be handled before or that would have, for instance, taken too long to compute. Once again, the result of this is more advanced research.

7.2.3. Databases

Datasets (anatomical, histological, experimental recordings, etc.) are needed to build models and usually come in a variety of shapes and forms (e.g. raw, publication, public database). Independent of the shape or form in which the data comes, it may be time consuming to access it. A modeller will have to know or be told about the availability of raw data that may be of use for his or her modelling work. From there, he or she will have to get in touch with the author of the data to get access to it, a process that can be time consuming. In much the same way, searching for published data (using services such as PubMed or Scopus) may not only take time, but may prove unsuccessful. Once its existence is known, data available within a public database is possibly the easiest to access. Still, the problem of the data format remains. In the case of raw data, the format may be proprietary, while published data may contain typographical errors, missing information etc. and the modeller may be unfamiliar with or not equipped to handle the database format.

Through VPH, the modeller will have easy access to such data by querying the relevant knowledge database. As well as the datasets themselves, information on, for example, the conditions under which they were obtained will be available. The availability of such a central repository of data will greatly enhance productivity and minimise the amount of overlooked data, something that can unfortunately happen at the moment.

7.2.4. Tools

Tools for visualising, interpreting and processing the data will also be made available upon request, should, for instance, the data come in a format that the user has never encountered before. This means that time will no longer be spent redeveloping such tools, although some may have to be refined as new needs arise. These tools will also become increasingly more reliable with wider use.

Most important for our research, however, is that we will have access to a set of tools that will allow us to do modelling from the molecular to the organism level, something that simply cannot be done efficiently at the moment. This would greatly speed up model development and have an impact not only on our research, but also at the clinical, industrial and societal level.

Experimentalists will also benefit from having access to such tools at a research level. They will become part of the standard toolbox in the laboratory, facilitating the exploration of new hypotheses during the design of experiments to test their validity, as well as providing a platform for interpretation of experimentally observed phenomenon, suggestion of new experiments, etc.

7.3. Clinical Impact

Currently, patients suffering from rare or complicated illnesses often have to go through numerous clinical examinations performed by multiple clinical teams in various disciplines until their disease is correctly diagnosed and an effective therapeutic programme started. We envisage that the VPH will impact all levels of clinical practice, from diagnosis to treatment and follow-up. The multi-level aspects of the EuroPhysiome will provide a therapeutic team with access to highly multidisciplinary tools, allowing them to approach a patient's particular case from different disciplinary points of view and at various scales (genetic, cellular, tissue, organ). The VPH will not only have an effect on healthcare delivery, but it will also act as a catalyst for the current paradigm shift in medical education.

7.3.1. Diagnosis

The following example is a real case and unfortunately not uncommon. It is given here to demonstrate that, although tremendous progress is being made, the current fragmented clinical approach could be much more comfortable for the patient, more efficient and less expensive if the overall therapeutic scheme were better organised and genuinely multidisciplinary.

"A 39 year-old female patient complains to her family general practitioner (GP) of heavy back pain. This patient leads a "normally and healthy" life: her diet is balanced, she does not smoke, rarely drinks alcohol, engages in moderate physical activity, no recent traumatic occurrences. However, she has a family history of chronic back pain, and complains of stress at work. After a standard examination, her GP advises 30 sessions of physical therapy. These brought some relief but did not solve the problem.

After two months, the GP asked for a standard X-ray that appeared negative, then a CT-Scan, also negative. At about that time, the patient started showing a slight limp. The GP sent the

patient to the private office of an orthopaedics colleague, who requested a new CT-scan of the back (because the first was badly performed), hip joints and knee joints, a Magnetic Resonance Image (MRI) of the same joints and a scintigraphy. All negative. New physical therapy sessions were also given.

More than three months after the initial consultation, the limp was getting worse, as was the back pain. The GP sent the patient to another orthopaedic surgeon for a second opinion. The latter requested a full gait analysis in a university hospital (motion analysis + electromyography of selected muscles). The gait analysis allowed quantification of the gait problem but brought no new information concerning the source of the pathology. The gait analysis team sent the patient to the local rheumatology department to test for joint degenerative diseases; and the patient underwent a new series of MRI. Once again, all tests were negative.

The local neurology department was then contacted to test the patient for a central problem. She underwent a head CT and a PET-Scan. All tests were negative. The same neurology team then performed conduction tests on the peripheral nerves of the lower limbs. These tests showed a reduced conduction speed of some of the shank muscles. Echography of the shank muscles showed that some of them presented a reduced volume. Biopsies and blood tests showed that the patient suffers from a myopathology characterised by nerve degeneration.

After almost four months since she first went to her GP, she's finally receiving the correct therapeutic treatment."

Health systems in Western countries are of higher quality than in other parts of the world but, as this story illustrates, these systems are still far from perfect.

Drawback 1: too much specialisation, too little communication

The above story illustrates how health problems are typically tackled in our health systems. A patient usually goes first to a GP who will redirect the patient to a particular specialist who in turn takes care of the patient according to his/her own area of specialisation and experience. This work scheme works well for easily recognisable health problems.

For more complex problems that are harder to diagnose correctly, the patient will usually have to visit several specialists who often deal with his/her problems using a highly specialised and limited approach. It must be stressed that, even within clinical teams, physicians often work on their own and with little communication with their colleagues, because of time pressure. This lack of efficient, interdisciplinary communication is even more pronounced between different specialities in different locations. It often means that the patient's problem is just seen from one unique and limited point-of-view, without the wider perspective being taken into account. This is a very time-consuming and fragmented approach.

Drawback 2: high personal and societal costs

Patient data is not always passed from one specialist to the other, frequently because of the lack of communication between specialities. As a consequence, some examinations have to be repeated (for example, the CT sessions in the above example) with a resultant increase in costs to the patient and the patient's national health system.

A lack of general perspective and lateral thinking also leads to unnecessary clinical acts. A generalist will first attempt to solve a problem using the tools he/she knows best. If these tools lead to no solution, then other tools will be used and the patient will be sent to a colleague with another speciality. Patients can sometimes undergo several expensive and useless examinations that could have been avoided.

Drawback 3: being a patient might sometimes seem like a never-ending story

For some patients, having to undergo multiple examinations and repeat the same story to various therapists many times over makes them feel that their personal health problems are not taken seriously and that a solution will never be found. They can become depressed, making their health status even worse. Their work absence rate is high and leads to further costs to society as a whole.

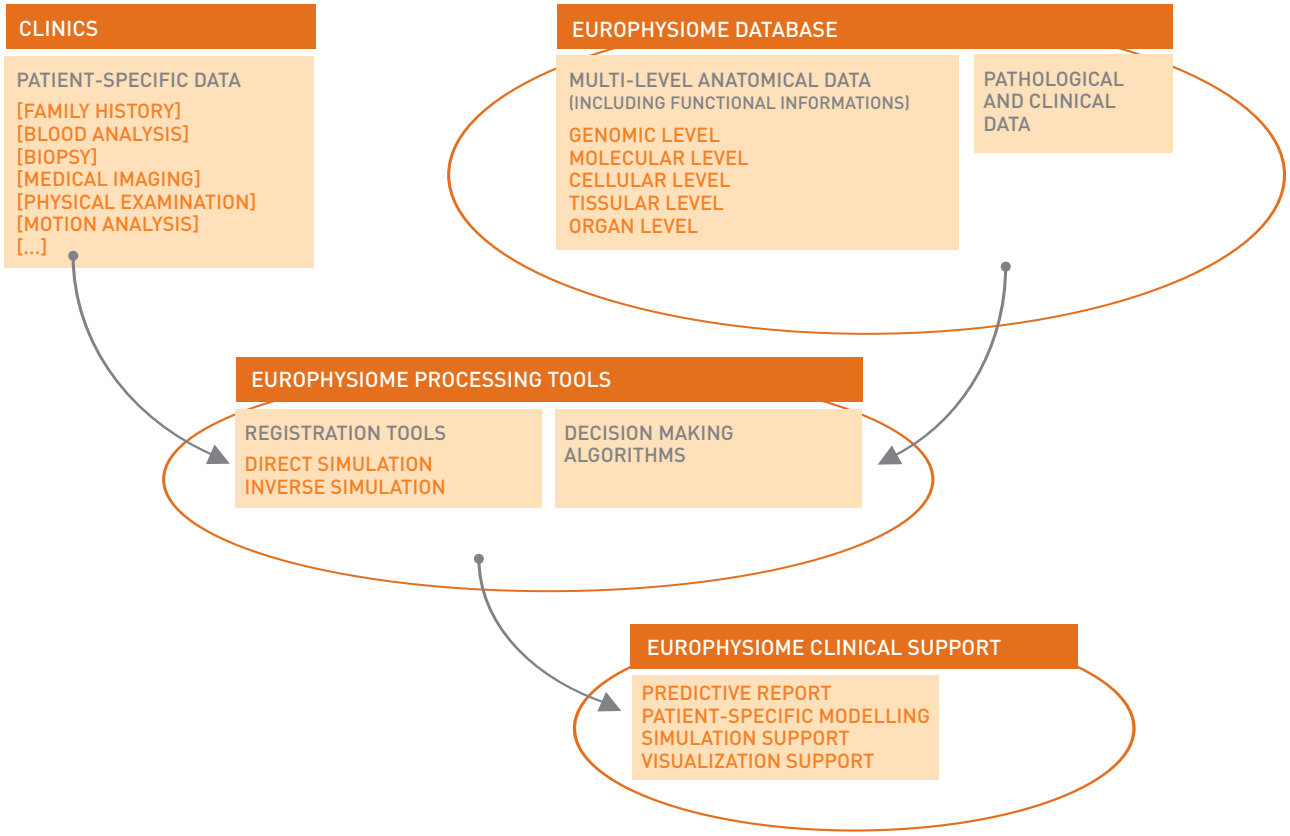
Some of these patients will lose faith in conventional medicine and will try alternative "medicines". This can also lead to lethal situations if the illness continues to progress outside the domain of trained physicians.

A potential solution? Reduce the current fragmentation of the tools used in medicine by integration.

The ideal solution to these problems probably does not exist, because clinical activities and pathologies are so complex both in number and in nature. That said, improving communication between specialities would greatly improve the therapeutic pipeline. The underlying idea is to gather as much information (data, knowledge) from various clinical specialities as possible into a centralised and integrated system, which would offer multidisciplinary teams a common language to analyse a patient's specific status.

The key element of this integrated system, which will be created by the EuroPhysiome initiative, would include multi-level information related to human physiology. The EuroPhysiome infrastructure will be customisable using patient-specific data integrated into general, but anatomically and physiologically correct, population-based models thanks to advanced registration, modelling and simulation protocols. Statistical analysis will also do the anamnesis based on available data in order to offer the therapeutic team extensive decision-making support and predictive models on which therapeutic decisions can be made (see Figure 7.1).

Figure 7.1. The EuroPhysiome (EP). The system will be based on a multilevel architecture. The EP database will contain all data related to both normal and pathological anatomy. The anatomy should be described at all levels: genomic level, molecular level, cellular level, tissue level and organ level. The data available from the database will then be processed through advanced registration and simulation tools (EP processing tools). The level of simulation should be flexible enough to make the necessary connections between the various anatomical levels. Decision-making algorithms will then perform statistical operations of the simulation results. Patient-specific data, collected in clinics, will run through the same EP processing tools in order to obtain a patient-specific clinical model of the patient pathology. The final result will be found in the EP clinical support. The latter will include all tools necessary to analyse and visualise the patient-specific predictive model(s) produced by the EP decision-making support.



Building such systems is a long-term endeavour and will take several decades. The first step is to build the information technology environment that would lead to a reliable anatomical and physiological modelling environment (i.e. the Virtual Physiological Human or VPH) including both normal and pathological information and all the tools allowing the manipulation and combination of inhomogeneous data, as well as extraction of relevant information from the system. Patient specific data could then be combined in order to produce personalised predictive models.

Multilevel EuroPhysiome

The EuroPhysiome infrastructure should include multilevel information for all anatomical systems found in the human body.

The levels are: genomics, molecular, cellular, tissue, and organs. Functional and clinical aspects at each level should not be omitted.

For each anatomical system, the interface should allow medical teams to pass from one level to the other in order to make the necessary connections between all potential pathological sources that could lead to particular clinical signs.

Integration of patient-specific data should be possible at all levels in order to better customise the results and to obtain patient-specific models.

Back to our example

What would a clinical EuroPhysiome change for the patient in the example above? The following is a hypothetical scenario, but it shows the ultimate goals to achieve:

"A 39 year-old female patient complaining of heavy back pain goes to her family general practitioner (GP). This patient leads a "normally and healthy" life: her diet is balanced, she does not smoke, rarely drinks alcohol, engages in moderate physical

activity and has no recent traumatic events. However, she has a family history of chronic back pain and complains of stress at work. After standard examination, her GP realises that this patient shows clinical signs of a serious illness. The patient is sent to a multidisciplinary team; the contact between this team and the patient occurs through a GP attached to the team and coordinating the patient follow-up.

The first test the patient undergoes is an analysis of her personal genome in order to assess whether a genetic cause for her problem can be found. If the test is positive, clinical tests are performed to confirm the genomic diagnosis, and then start therapeutic actions. If the genomic test is negative, then a team meeting is organised between the coordinating GP and the appropriate specialists (in this particular case: orthopaedics, neurologist, rheumatologist and physical therapists). A common set of first clinical analysis is performed: x-ray, CT, MRI. If this leads to nothing, the multidisciplinary team meets again to organise the chronology of more specialised tests.

Thanks to the multidisciplinary approach and consensus, the first specialised test likely to be performed will be an echography, followed by an EMG. The collected data would be registered into the VPH data available from the EuroPhysiome database. The therapeutic team would then be able to run a series of statistical tests at the cellular (muscle cell), tissue (muscle tissue) and organ levels (muscles in their environment and acting on joint motion). Advanced decision-making algorithms would then produce a predictive report on which the clinical team could base its final diagnosis that would be obtained within a week and possibly within days."

Compared to what really happened to this patient, one can make the following remarks concerning the proposed scheme:

By its very nature, EuroPhysiome would request the organisation of multidisciplinary clinical teams and optimise communication within this team. Its infrastructure tools should greatly help in this regard and dramatically decrease the number of clinical tests undergone by patients, so avoiding redundancy. The costs associated with the diagnosis will accordingly be reduced.

The patient will have the feeling that she is following a well-integrated process, thanks to a seriously shortened diagnosis time and the presence of one unique team. The frequent psychological effects observed in patients for whom pathologies have been delayed for various reasons should be reduced.

7.3.2. Intervention

Medical imaging, modelling and visualisation are increasingly combined for adequate **treatment planning** in medicine. Such pre-operative planning typically consists of a range of visualisation facilities, fusion of images, accurate three-dimensional anatomical models, measurement and analysis planning tools and, frequently, facilities for the rehearsal of operations. To date, the focus has been on providing greater precision when targeting treatment. The next challenge is to include functional data that will allow not only improved precision, but also more effective treatment and reduced morbidity.

The last twenty years have witnessed radical changes in surgical techniques. A growing number of procedures are now conducted using a minimally invasive approach in which surgeons operate with instruments passed through small holes in the patient, not much larger than a centimetre in diameter. There are significant benefits associated with minimal invasion, such as reduced patient trauma, reduced blood loss and pain, faster recovery times and lower costs. But by keeping the surgeon's hands out of the patient, we diminish the ability to **navigate** during the procedure through a reduced surgical field of view, lack of depth cues and decreased tactile feedback. A number of different approaches have been used to improve these conditions including dual-camera configurations for stereo-vision capability, instruments with force magnifying sensors and, more recently, mixed or augmented reality facilities providing real time overlays of pre-operatively acquired images and/or models. New and more capable means of guidance are necessary as minimally invasive techniques continue their advance towards replacing open procedures. Current efforts are directed towards improving the accuracy of intra-operative imaging, tracking and image registration. While there has been some success, it is clear that further advances will require integrated multi-scale dynamic models that more closely reflect body activity and responses during the operation.

Personalised treatment planning and operative guidance are complemented by **procedure rehearsal.** The ability to practice before carrying out an operation has been identified as the "holy grail" of surgical simulation. Patient specific models of anatomy are routinely being built for planning and guidance in neurosurgery and orthopaedic surgery. Manufacturers of surgical simulators are working on providing the functionality needed to allow users to load patient-specific anatomy and there are a vast number of research projects working on algorithms, techniques and integrated systems for generating such models. These are all worthwhile efforts, however ***a more coordinated approach is needed*** in order to establish a common modelling framework that allows for the incorporation of function across all relevant scales. Accurately reproducing biomechanical and physiological behaviour to enable realistic procedure rehearsal is one of the key challenges.

The VPH infrastructure will be ideally placed to provide the necessary tools, models and integrative approaches that are required to advance the areas of treatment planning, guidance and procedure rehearsal. The ability to plan therapeutic treatment accurately, to conduct personalised procedure

rehearsals and to provide guidance in the case of interventional procedures will have a very significant impact on healthcare delivery, improving outcomes, reducing morbidity and costs.

7.3.3. Education and Patient Safety

Increasing evidence and studies on **Patient Safety** highlight the need for a coordinated effort to reduce the number and impact of medical errors, and for implementing adequate risk management in the healthcare system. Technological advances permeate secondary and tertiary medical care, making advanced non-invasive imaging, monitoring and complex minimally invasive procedures a reality. The emergence of the genome and physiome and their use in the clinic have the potential to further revolutionise the diagnosis and treatment of a wide range of diseases with tailored drugs and cures. New and emerging technologies and novel information processing/handling paradigms will no doubt continue to influence all levels of healthcare and change the way medicine is prescribed, delivered and monitored. Routine use and integration of the above technologies will bring about safer, tailored, more predictive, actively monitored and adaptive healthcare delivery, which in turn should result in improved patient safety and facilitate proper implementation of risk management strategies. An equally important aspect is that of **education and training.**

It is a well-known fact that many of the recurrent adverse events and critical incidents are the result of improper communication, interpretation of data and/or misuse of medical technologies. Simulation is a powerful tool that can directly address all of these problems by providing a realistic yet safe environment in which existing and future practitioners can rehearse a whole range of procedures and medical care scenarios. Having the freedom to err and explore alternative outcomes can provide a potent learning experience for both novices and experienced practitioners. Observing, analysing and influencing the behaviour of medical teams in a simulated environment offers the possibility of better understanding and promoting the fundamentals of good practice.

Whilst there exist a variety of basic skills, procedural, anaesthetic and physiological simulators in the market, as pointed out above, none of them currently offers the possibility of patient specific simulation and they have very little or no integration of anatomy and function. Moreover, they are focused on a specific physiological function, or on a small number of procedures, or on psychomotor or technical skills, leaving aside very important non-technical skills such as decision making, communication, data interpretation, team interaction and workflow.

The VPH offers the possibility of a truly holistic simulation that incorporates anatomy, function and disease, covering a wider range of interventions, allowing for the training and practice of both technical and non-technical skills. The importance of the ongoing changes to medical education cannot be underestimated. It is vital that these changes are accompanied by adequate training and assessment alternatives that have patient safety and well-being at their core. VPH-enabled simulation training systems will play a key role in establishing simulation as a key component of medical curricula.

As mentioned previously, delivering these clinical improvements will require a long-term effort. Indeed, the multidisciplinary consensus (see below) obtained from the clinical community involved an important debate concerning the priorities related to building the EuroPhysiome: should the problem be approached by analysing the needs for each pathology and then gather all needs in one unique system (clinical approach)? Or should the technological aspects of the systems (data, methods, algorithms) be developed first (IT approach)? It is probable that both approaches should be simultaneously conducted to ensure efficient clinical validation that would increase the system's acceptance.

7.4. Industrial Impact

The EuroPhysiome is a bold endeavour aimed at making available the simulation tools needed to improve physiological understanding, illuminate natural processes and hasten the introduction of new equipment and techniques. It will do this by allowing phenomena with potential application to be explored in new ways, generating new knowledge that can be exploited in practical designs and result in improved healthcare services to the benefit of all members of society.

Whilst it is clearly the case that the impact of any industrial initiative can be felt in improved technical excellence, reduced development time, or streamlined staff numbers, ultimately the yardstick used by industry will be financial. This section of the EuroPhysiome Roadmap attempts to estimate the financial savings that a European-wide scientific initiative might make, relying – where possible – on data supplied by industry itself.

It is worth noting, however, that in a competitive marketplace, general technical developments have only a transient effect on industrial performance and fortune. Ultimately being to the predominant benefit of society and the citizen (since the competitive nature of industrial enterprise means that the technical progress is absorbed by all commercial parties), costs are reduced and performance is improved, and the market is realigned with revised circumstances that usually include lower costs, increased performance and improved design. Continued industrial benefit relies on the availability of a continuous stream of innovative ideas, something that the unlimited scope of physiological modelling can, perhaps uniquely, offer.

7.4.1. Medical device development

It is acknowledged that the introduction of these tools, along with access to models, data and experts, will offer advantages to the entire medical device industry, particularly in reducing occasional duplication of effort. Ideally, this could form an integral part of the new product design process, enabling lower development costs and lowering the risks.

Potential barriers to the widespread industrial adoption of physiome techniques must be vigorously addressed. In discussions with industrial leaders, several concerns have been identified that echo those heard during the two STEP conferences; these include:

- ownership of the data and models along with the associated IP
- legal use of clinical (patient) data for industrial research
- security for confidentiality
- direct take-up by device companies versus use by engineering consultants.

7.4.2. Pharmaceutical Industry

Research and development (R&D) expenditure in the pharmaceutical industry accounts for an impressive 20 per cent (with peaks of 30 per cent) of pharmaceutical sales, corresponding to around 20 billion euro per year within Europe, and exceeding all other technological industries [EFPIA]. Despite a pattern of increased investment over the years, the number of new chemical entities (NCE) has decreased in Europe in recent years, from 93 in the period 1989-1993 to 62 from 1999-2003. In the same period, the USA increased its number of NCE, taking the leading position from Europe in this key benchmark. There are several reasons for Europe's relative decline here. They include the intrinsic nature of the scientific and clinical challenges involved (NCE have become more difficult to find) and the nature of European R&D organisations – improved mechanisms for committing R&D funding is necessary to fully maintain the drug pipelines of European pharmaceutical industries.

Producing a new drug takes in the order of 15 years and costs 1 billion euro, with those that reach the human trial stage failing 6 times out of 7 [RSC]. Most of the costs of R&D go towards clinical trials; therefore, better methodologies and tools to eliminate bad drug candidates before clinical trials would improve the efficiency of the development process and in return free up more resources for the pre-clinical phases of the discovery. These new resources would boost the first phases of the research process, such as basic research, and increase the number of NCEs and potential drugs. A virtuous cycle of better prediction tools = >more efficient pre-clinical to clinical = >more research on basic R&D = >more NCE = >more efficient pre-clinical to clinical would produce large savings and better returns for the entire pharmaceuticals sector, from industries to citizens. The elimination, for instance, of just 5 per cent of bad drug candidates at the pre-clinical stage should produce savings of a hundred million euros per year, which is in the order of magnitude of European research expenditure per year. These savings could be passed on to citizens in the form of less expensive drugs or enhanced R&D to produce more drugs. An example is the vaccines biotechnology industry with the advent of genomic data. Whereas before, the genomic revolution vaccine development took more than 15 years, due to the effectively random search for immunising proteins, the process can now be reversed, and selected proteins from the genome of the bug can be tested directly in *in vivo* experiments, much reducing animal experiments, time to market and associated costs.

Unfortunately, the case of drug discovery still cannot take full advantage of genomic data because the complexity of biochemical interactions in cells makes an integrative approach necessary to the design problem. By making clinical predictions from descriptive and integrative data and modelling, this will be one of the key contributions of the VPH to the pharmaceutical industry.

[EFPIA] European Federation of Pharmaceutical Industries and Associations, www.efpia.org

[RSC] Royal Society of Chemistry, www.rsc.org

7.4.3. Case Studies

It is appropriate to consider some specific examples of industrial processes to develop a view of the financial impact of the technology afforded by the VPH. Having identified the likely benefit in a representative selection of cases, if it is then possible to estimate the number of such developments across Europe, an overall estimate of annual benefits/savings and an assessment of the break-even position on the entire Physiome might be possible. Several examples of projects that might benefit from VPH techniques have been investigated:

- inhaled drug delivery system
- improved prosthetic hip
- more efficient prosthetic heart valve
- wound-suturing and rapid-healing technology
- pharmaceutical product development

Two of these are discussed in detail in the next section of this document:

By combining case-study data on individual product cycle improvements with more general information on the overall rate of product introduction, and the number of organisations engaged in healthcare activities, it will be possible to assess the overall potential for EuroPhysiome exploitation. By applying well-known take-up rate information it should then be possible to derive general figures for the financial impact on European industry.

Case Study 1 – Inhaled Drugs

Background – Drugs delivered to the pulmonary system may be designed, either to act topically to alleviate a local airway condition, or to be transported across the alveolar membrane and into the systemic circulation. The ease with which materials can traverse this boundary makes the lung an attractive route for delivery of systemic medication and this is currently (2006) the fastest-growing area of technology for drug-delivery developments.

The design of equipment to target the alveoli is slightly complex, because the medication should ideally be released early in the breath to be transported quickly and deeply into the lung and avoid upper airway deposition. Approaches vary from sophisticated electronic control to inexpensive mechanical actuation, but the development process always follows a similar path. Crucial to success is the ability to examine the deposition behaviour in human subjects, and the availability of a simulation environment would be a major advance.

Development Process – The typical development process is tabulated below, for both the conventional and the physiome-based approaches. Person-Months are for personnel directly connected with Research and Development only.

This reduction in development effort of around one-third is typical of the improvements to be found where accurate simulation can be used in place of conventional approaches. The key area for improvement is the dramatic reduction in the need for clinical trials and the attendant improvement in the product refinement process.

Case Study 2 – Prosthetic Hip

Background – Partial replacement of the hip joint was first attempted in 1891 using an ivory femoral head. Modern replacement systems using stainless steel and polyethylene result from work carried out in the 1970s and have a success rate of over 90 per cent. The chance of an implant surviving for twenty years is around 80 per cent, but the tendency for patients to live longer means that revision surgery is on the increase.

Cement: Much of today's success derives from improvements in the adhesive used to bind the prosthesis to the patient, and the most commonly used bone cement is now the acrylic polymer polymethylmethacrylate. Patients with cemented total hip replacements can put their full weight on the limb and walk without support almost immediately after surgery, resulting in rapid rehabilitation. Two mechanisms are known to operate to cause prosthetic loosening:

- in the femoral component, fatigue fractures in the cement cause the prosthetic stem to loosen. This is more often the case with patients who are very active or very heavy.
- the action of the metal ball against the polyethylene cup of the acetabular component creates polyethylene wear debris and particles of excess cement may also become loose. The particles may then trigger an inflammatory response that in turn causes further loosening and, sometimes, loss of adjacent bone (osteolysis). As the bone weakens, the instability increases. Bone loss can occur around both the acetabulum and the femur, progressing from the edges of the implant.

	CONVENTIONAL		WITH EUROPHYSIOME	
Item	**Notes**	**PMnths**	**Notes**	**PMnths**
Concept	After detailed research	2		2
Initial design	Assume CAD	12		12
CFD1	Not used	-	In silico	4
Prototype	Uses PC as controller	3		3
Parameterisation	In vitro tests	6		1
CFD2	Not used	-	In silico	3
Clinical trial 1	Scoping	36	Not required	0
Refinement	In vitro tests	6	In silico	1
Clinical trial 2	Detailed performance	36	Corroboration	12
Production design		60		40
Production prototypes		60		60
Clinical trial 3		24		24
TOTALS		**222**		**162**

Cementless: A competing approach is the use of cementless prostheses, where an accurate channel is created into which the implant is inserted using an interference fit. Such designs are larger and longer than those used with cement, and also have a surface topography that is conducive to attracting new bone growth. Most are textured or have a coating around much of the implant such that new bone will grow into the surface. Cementless implants require a longer healing time because they depend on bone growth for stability. Patients with large cementless stems may also experience a higher incidence of mild thigh pain, and joint failure still occurs:

- loosening can occur if a strong bond between bone and stem is not achieved
- polyethylene wear, particulate debris, and the resulting osteolysis remains a problem.

Development Process – it is unlikely that a major redesign of the shape or bulk structure of any of the prosthetic components will now need to be undertaken. Although improvements in the wear characteristics of newer polyethylenes, and the advent of harder bearings, may help resolve some of the problems, manufacturers are continuing to attempt to identify superior surface materials and treatments that may reduce the occurrence of osteolysis and encourage the prosthesis/bone bond. A better understanding of the surface interaction between bone and prosthesis is therefore required, but is proving elusive.

Tabulated below is the financial saving likely to follow from molecular modelling of the interaction that results in surface processing to reduce prosthesis failure by just one per cent.

7.4.4. Industrial Extrapolation and Quantification

Medical Equipment Industry Extrapolation – Extrapolating from the figures given in Case Study #1, if it is considered that the total cost (with indirect personnel taken into account) of a new medical device development is in excess of ?1m, then the cost of fewer than one thousand products will match the intended EuroPhysiome FP7 spend. Across Europe, there are an estimated 600 significant medical device launches per annum, suggesting simplistically that, with full uptake, the declared FP7 VPH budget could be recovered from savings in development costs alone within a three-year period (assuming all developed products benefited).

Generalised Medical Equipment Industry VPH Quantification – A more detailed picture emerges from data supplied by a range of medical equipment manufacturers on their relative development cycle lengths and expected savings from the adoption of VPH techniques. Together with extrapolated data on investment in the establishment and maintenance of the VPH, this has been used to provide a generalised Physiome-quantification analysis that is summarised in the chart opposite.

The chart suggests that, with sustained investment and industrial uptake as estimated, the annual benefits from industrial savings alone will exceed annual VPH investment by around 2018, and the entire system enters profit around 2023.

7.5. Societal impact

7.5.1. Societal impact on industry

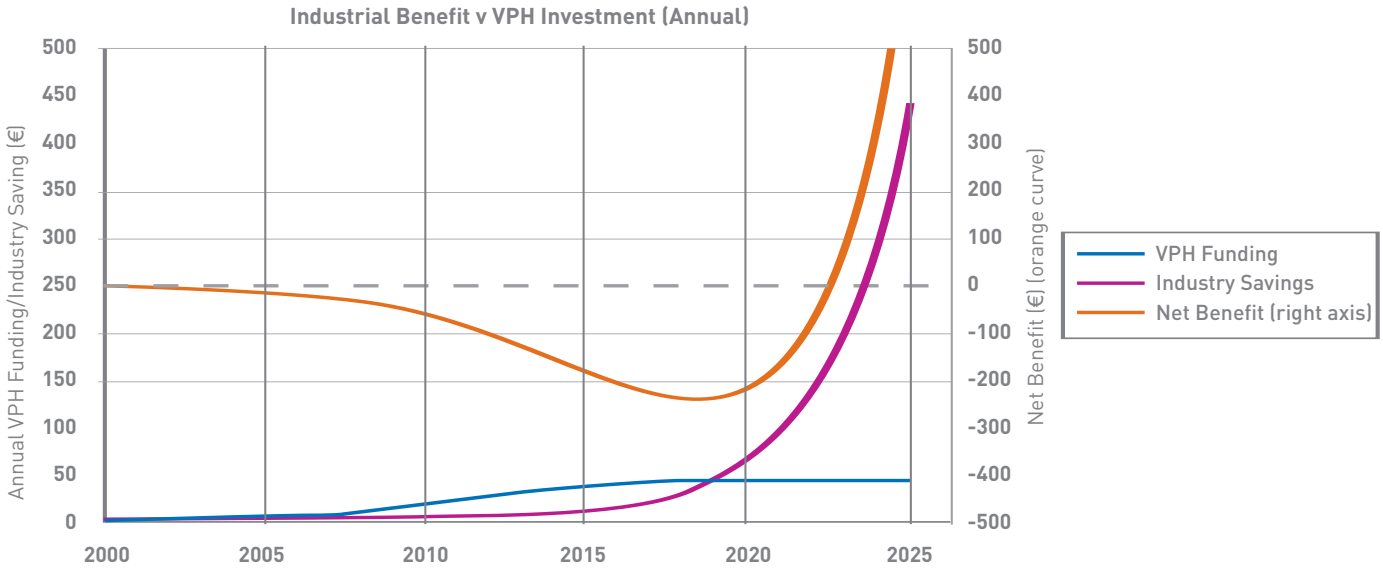
VPH will have an impact on industrial expansion and competitiveness in the global market. This will primarily be in the healthcare industry and relate to the ability of new technology to generate reliable information for diagnosis, planning, treatment, monitoring and rehabilitation, including applications in medical education, medical device design and tools for virtual surgery. The development time for a drug can be reduced by several years as the industry adopts and becomes accustomed to the simulation approach, so there is a strong economic motive for industry to pursue the use of simulation models. Introducing simulation models into the drug development process will also require significant changes in the way the regulatory authorities evaluate new drug candidates. The regulatory authorities must establish their own expertise in the use of simulation models.

In addition to the pharmaceutical industry, industries that will see an impact from the VPH are the automotive industry (vehicle safety and comfort), tools and workplace industry (ergonomics and safety), defence industry (evaluation of biological damage of weapons) and the leisure and sports industry (primarily equipment).

A 2006 report from global experts, Frost and Sullivan, comments usefully on the industrial position: "While the European knowledge base is immense, it is inefficient in exploiting research outcomes. This highlights the importance of the increased participation of small and medium-sized enterprises (SME). The European Commission has taken various initiatives to increase SME participation. Strong industrial partnerships are

Failure consequence	Average EU cost €	EU Procs/yr2	1% saving
Failure-dependent incapacity	30,000	220,000	**€ 182.6M**
Revision procedure	4,500		
Post-operative rehabilitation	3,500		
Post-operative incapacity	20,000		
Societal impact	25,000		

Figure 7.2. Industrial benefits expected over time from VPH investments.



the key to maximise knowledge and expertise, which will result in innovation that can create a knowledge-based economy in Europe" [1].

7.5.2. Societal impact on research, education and exchange.

VPH will have an impact on the development of educational tools, to promote cross-discipline scientific networking and collaboration within and between fields, data sharing, establishing platforms to promote interdisciplinary approaches, and developing demos.

Hands-on experience is important in education and healthcare activities. The VPH will provide simulators for educational and training purposes. It will create IT-systems, providing new ways of understanding and managing human physiology and disease based on the integration of information and tools across disciplines. The VPH will bring health and public health information networks, facilitating greater access to accurate data and information for patients, in order to allow better treatment of European patients using new tools such as telemedicine.

7.6. References

[1]. Life Sciences Funding in Europe (2006) – Phase I M05F- 52 Frost and Sullivan, Pharmaceuticals and Biotechnology

[2]. National Institute of Arthritis, Musculoskeletal and Skin Diseases and Census Bureau national population extrapolation, 2004.

Editors: Hans Gregersen, Liao Donghua, Aalborg Hospital (DK)

8.0

8.1. Executive Summary

Modelling has contributed significantly in a number of areas and it is expected will acquire even greater significance in the future. Numerous interdisciplinary research initiatives are generating excellent research results with regard to modelling, simulation and visualisation of human anatomy and physiology. These initiatives have played important roles in:

Clinic

- data transformation
- treatment optimisation
- diagnosis, operative planning and surgical procedure improvement
- prognosis prediction

Industry

- drugs discovery and development
- medical device design and development
- ergonomics and safety

Academic

- co-operation among multi-disciplinary researchers
- knowledge fusion
- educational tools development

Success Stories

Several modelling study success stories – primarily from Europe and USA – were selected from these initiatives and are based on the best of our knowledge. The examples include simulation models at the cell, organ and whole body level for the transmission, control of disease, device design and drug development; non-traditional educational tools such as a biological storytelling system; animations of biomedical processes and concepts; and interactive virtual laboratories to inspire a user's strategic, creative and innovative thinking.

It is possible to deduce from the stories listed below that, although there are numerous worldwide efforts, modelling and simulation problems are only addressed at the usual interest level of modellers, i.e. on single pieces of the biological process at hand. However, the human diseases affect structure-function relations at many levels. So a model involving multi-scale modelling of human body functions – from the whole body down to sub-cellular level – is needed to provide a more rational basis for diagnosis and treatment than currently exists.

The motivation behind the VPH is to provide a computational framework to facilitate the understanding of the integrative function of cells, organs and organisms. The comprehensive IT-system will provide a new way of understanding and managing the human being, based on the integration of information and tools across scientific and organisational boundaries. It is focused on compiling and providing a central repository of databases, linking experimental information and computational models from many laboratories into a coherent, self-consistent framework. Initiatives can thus be integrated by using mathematical representations based on the VPH platform, which makes it possible to integrate the numerous components of the biological system as well as the quantitative interactions that make the outcome of the system unique. VPH infrastructure will not only support computationally demanding tasks such as complex modelling and simulation, but also enable access to health data distributed in public as well as protected databases distributed all over the world.

A GENERAL OVERVIEW/POSSIBLE SCENARIO

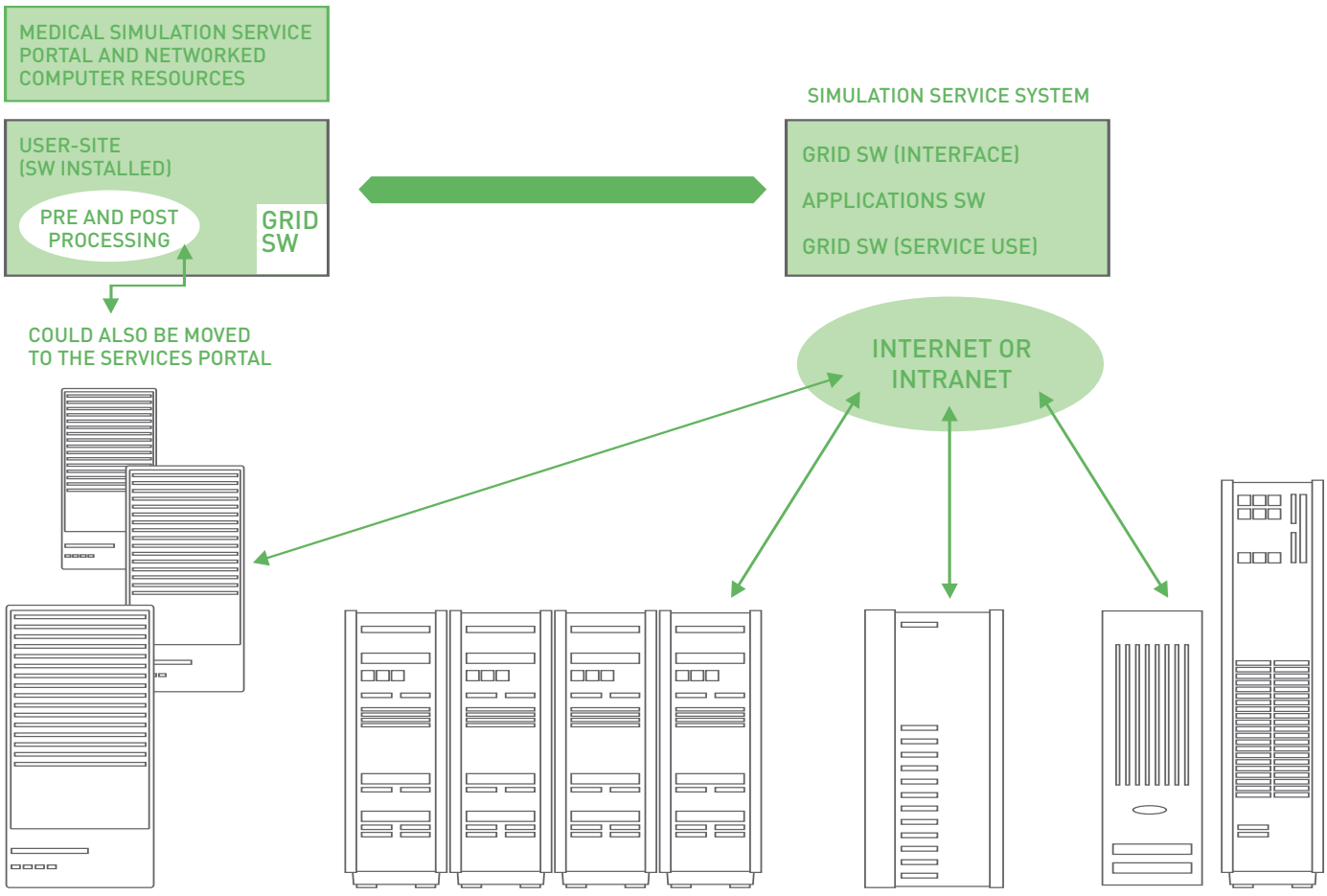


Figure 8.1. Schematic description of GEMSS (cited from: http://www.ccrl-nece.de/gemmss/objectives.shtml)

8.2. European success stories

GEMSS (Grid Enabled Medical Simulation Services, http://www.ccrl-ece.de/gemss/) demonstrated how Grid technologies can be used to transform healthcare and enable Europe to lead that transformation. The GEMSS test-bed renders accessible a multitude of medical computing and resource services in a clinical environment. It provides access to new tools for improved diagnosis, operative planning and surgical procedures in order to create a new way for improved health care. The main results of the GEMSS project consist of an innovative middleware for the secure and lawful provision of a simulation and medical image processing service and a set of medical application services such as:

- Inhaled Drug Delivery Simulation Service
- Cardiovascular System Simulation Service
- Maxillo-facial Surgery Planning Service
- Neurosurgery Support Service
- Monte-Carlo Radiosurgery Planning Service
- Medical Image Reconstruction Service

LYMFASIM (Lymphatic filariasis, http://www.who.int/tdr/research/finalreps/no43.htm) 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.

The Visible Human Server (http://visiblehuman.epfl.ch/) provides a virtual anatomic construction kit on the web using the Visible Human dataset. The applets available on this site provide the features as: 1) Extract slices, curved surfaces, and slice animations from both datasets (male and female); 2) Interactively navigate by slicing through the male dataset in real-time; 3) Construct 3D anatomical scenes using combinations of slices and 3D models of internal structures from the male dataset, and extract 3D animations.

The SimBio project ((www.simbio.de, "SimBio – a generic environment for bio-numerical simulation") aims to improve the clinical and medical practices by the use of numerical simulation for bio-medical problems – "Bio-numerical simulation". A key feature in the SimBio project is the possibility to use individual patient data as input to the modelling and simulation process – in contrast to simulation based on "generic" computational models. Vgrid is an outcome of the SimBio, where it was used to create meshes for head mechanics, knee mechanics and source localisation.

CHARM (Comprehensive Human Animation Resource Model, http://ligwww.epfl.ch/~maurel/CHARM/) is to develop a Comprehensive Human Animation Resource Model allowing the 3D reconstruction of the human body from medical images and the dynamic simulation of its complex musculoskeletal structure, including the simulation of muscular contraction and the finite element deformation of the soft tissues. The final results of CHARM can be used in applications requiring a computer-aided tool for visualising the teaching of the anatomy and physiology of the human body. In the exploitation of the results, CHARM can be potentially used for medical applications (based on the co-operation of medical teams) in the areas of robotised operation and rehabilitation, sport education and training, and for the entertainment industry through computer animation.

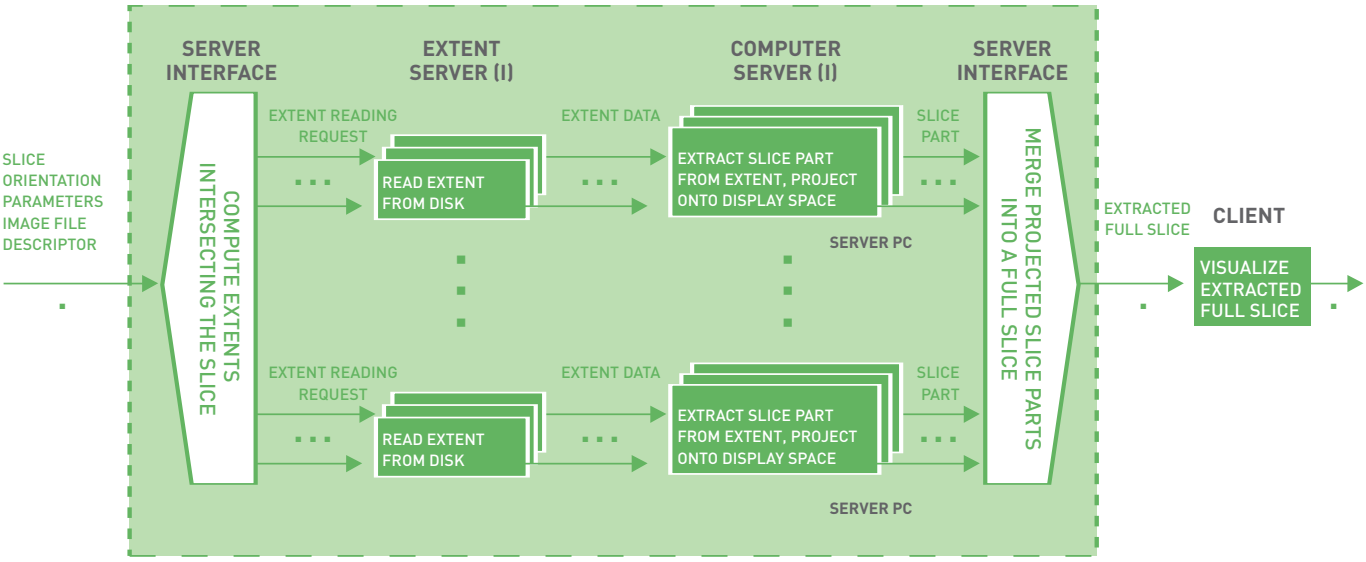


Figure 8.2. Diagram of parallel slice extraction, cited from The Visible Human Server: (http://visiblehuman.epfl.ch/)

COPHIT (Computer-Optimised Pulmonary Delivery in Humans of Inhaled Therapies, http://www-waterloo.ansys.com/European_Projects/cophit/index.html) aims to develop a comprehensive simulation tool for the study of inhaled therapies. COPHIT software is an outcome of the COPHIT project and simulates the entire dynamic drug delivery process for particulate, aerosol and gaseous drug types, from the device, through the lungs to the pulmonary system. The software is designed for use by pharmaceutical companies and clinicians who need to predict and optimise inhaled therapies, and allows deposition and uptake to be customised for particular drugs, delivery devices, diseases and even individual patients. The software is the first known implementation of a fully-coupled 1-D/3-D model of the complete pulmonary drug delivery process.

HUMOS2 (Development of a Set of Human Models for Safety, http://humos2.inrets.fr/about.php), is a European research project for the development of a human model for automobile crash simulation. A human was scanned post mortem in a typical driving position and an anatomically correct three-dimensional representation was created as the basis for the development of a complete Finite-Element model. Detailed material descriptions for the different kinds of biological tissue were obtained by experimental testing. HUMOS2 Project is the continuation of the previous HUMOS project where a human model of a male in a driving position – HUMOS model – was built.

The main exploitable project results will be:

- the definition of the European per centiles: 5th female, 50th male and 95th male
- a tool for the geometrical personalisation of human body numerical models
- the enhanced understanding of biomechanical behaviour and injury mechanisms
- a biomechanical impact experiment database
- new human body models for injury risk assessment.

TUMATHER (Modelling, Mathematical Methods and Computer Simulation for Tumour Growth and Therapy http://calvino.polito.it/~mcrtn) is a Research Training Network funded by the European Commission under its 5th and 6th Framework Programme. As part of its activities, the Network developed several mathematical models, algorithms and computer software aimed at the description of the different phases of tumour growth, including tumorigenesis; the avascular phase; the angiogenic switch; the vascular phase; and the formation of metastases, and the action of specific therapies to combat cancer, e.g. control of angiogenic phenomena, activation of the immune response, hyperthermia through microwave radiation and lasers and optimisation of therapeutic protocols.

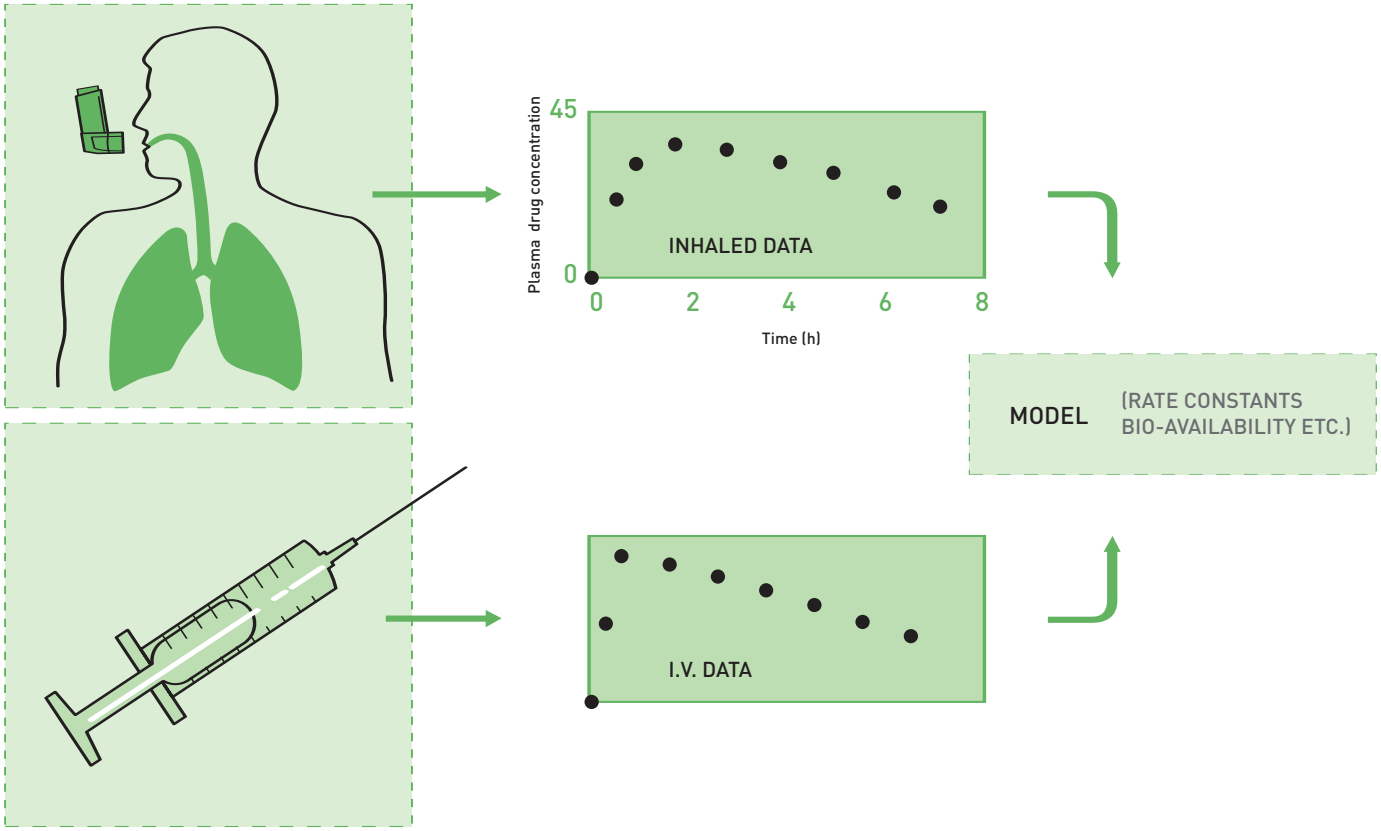


Figure 8.3. Pharmacokinetic models for drug uptake and clearance, cited from COPHIT website: http://www-milton.ansys.com/European_Projects//cophit/results/results.htm

The Network's activity has been coordinated to develop the whole modelling process from phenomenological observation to simulation and validation, through the design of mathematical models and their qualitative and quantitative study, in order to simulate tumour evolution within the full range of scales: from sub-cellular to macroscopic.

The Network is now focusing on linking the mathematical models and simulation tools developed at the single scale level to build multiscale, hybrid and nested models.

@neurIST: Integrated Biomedical Informatics for the Management of Cerebral Aneurysms (http://www.aneurist.org/) is a European initiative within the Sixth Framework Programme Priority 2 of the Information Society Technologies IST. @neurIST is focused on cerebral aneurysms and intends to provide an integrated decision support system to assess the risk of aneurysm rupture in patients and to optimise their treatments. @neurIST will provide an IT infrastructure for the management, integration and processing of data associated with the diagnosis and treatment of cerebral aneurysm and subarachnoid haemorrhage. @neurIST will contribute to a better knowledge of cerebral aneurysms and other diseases by:

- finding evidence of links between genomics and cerebral aneurysms
- helping clinicians to take decisions and select more appropriate treatments.

@neurIST will improve patient care by:

- identifying those patients with high risk of rupture by assessing a personal risk factor, thereby reducing the patient's operation risks and anxiety
- improving personalised design of endovascular devices.

@neurIST will result in major benefits to the healthcare system by:

- reducing healthcare costs through the suppression of an estimated 50 per cent of unnecessary treatments. This will save in the order of thousands millions of euros per year in Europe.

@neurIST will promote and validate:

- a new diagnosis and treatment paradigm extendable to other disease processes using complex data fusion, information extraction, processing and inferential deduction
- the use and development of bioinformatics, medical informatics and medical devices standards and protocols.

Simcyp: Simcyp Limited was founded in 2001 as a spin-out company from the University of Sheffield (http://www.simcyp.com/). Simcyp is a research-based company providing predictive pharmacokinetic software, workshops and consultancy services.

Simcyp develops user-friendly software and databases specifically designed to predict drug absorption, clearance, distribution and metabolic drug-drug interactions from *in vitro* data. Simcyp's software is able to accelerate drug discovery and development by simulating pharmacokinetics in virtual patient populations and identifying individuals at extreme risk.

The company's clients include many of the major global pharmaceutical and bioscience companies, leading academic institutes and regulatory authorities.

The GIOME project (www.giome.com) is the gastrointestinal part of the PHYSIOME that has been mainly developed at the Center of Excellence in Visceral Biomechanics and Pain (www.mech-sense.com) at the University Hospital in Aalborg. The modelling of the anatomy and function of the digestive system has provided a platform for the development of scientific and educational tools, and diagnostic medical devices, for understanding the pathophysiology and pharmacology of symptoms and pain arising from internal organs. Functional disorders of the gastrointestinal tract are very common in the West, with more than 30 per cent of the population affected by symptoms of unknown origin. Success stories from this development are multimodal and functional imaging probes and stimulation techniques that are now being commercialised by European start-up companies and used for clinical drug trials and diagnostic and prognostic clinical studies. A new project, dedicated to creating the virtual stomach and intestine, will be useful for industry in the development of new interventional tools.

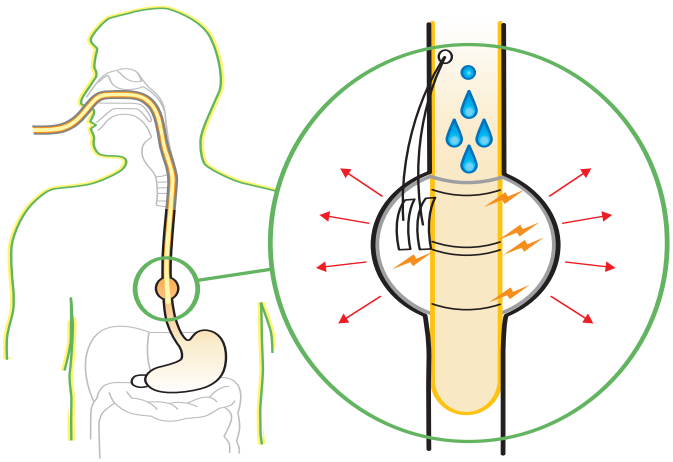


Figure 8.4. Schematic diagram of the multimodal probe. Cited from www.mech-sense.com

8.3. Success stories outside of Europe

BioSim (Interactive Biological Simulation) http://www.biosim.com) 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.

VSR (The Virtual Soldier Research, http://www.digital-humans.org/Report2004/Documents/Accomplishments.htm) is an independent program within the Center for Computer-Aided Design of the College of Engineering at The University of Iowa. It aims to create human-like figures in physics-based environments that are interactive and intelligent. These humans can predict postures and motions and can execute tasks autonomously in response to questions. They respond to real human actions and are sent to places where the real human cannot go. The vision is to deploy these human avatars in vehicles, systems and products, as well as on "virtual" military battlefields, to try out new equipment and assess whether it has been well designed.

NRCAM (The National Resource for Cell Analysis and Modelling, http://www.nrcam.uchc.edu/) is a national resource centre supported by the National Centre for Research Resources (NCRR), at the National Institutes of Health (NIH). NRCAM is the home of the Virtual Cell Modelling and Simulation Framework. It is based at the University of Connecticut Health Centre and is part of the Centre for Cell Analysis and Modelling, CCAM. NRCAM is developing a unique software modelling environment, the Virtual Cell, for quantitative cell biological research. The Virtual Cell has been specifically designed as a tool for a wide range of scientists, from experimental cell biologists to theoretical biophysicists. Likewise, the creation of models can range from the simple, to evaluate hypotheses or to interpret experimental data, to complex multi-layered models used to probe the predicted behaviour of complex, highly non-linear systems. Such models can be based on both experimental data and purely theoretical assumptions.

AHM (Active Health Management, http://www.activehealthmanagement.com/) makes use of the results of Heart Outcomes Prevention Evaluation (HOPE) soon after they were published in 2006 in The 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 from cardiovascular events but who lack evidence of left ventricular systolic dysfunction or heart failure. The benefits observed were additional 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.

Entelos, Inc. (http://www.entelos.com/) was founded in 1996 by Alex Bangs, Jill Fujisaki, Samuel Holtzman, Cathy Crane Moley and Tom Paterson. The company builds *in silico* disease models – called PhysioLab® systems – and creates "virtual patients" to significantly reduce the time, cost and risk required to discover and develop new drugs. The company collaborates with global pharmaceutical and biotechnology companies in the areas of metabolic and inflammatory diseases such as asthma, obesity, diabetes and rheumatoid arthritis. Its biosimulation systems have been used to validate novel drug targets, select and develop compounds, optimise clinical trials and combination therapies, reprofile drugs, evaluate in-licensing candidates and better position existing products in competitive markets. The company employs life scientists with expertise spanning molecular biology to clinical medicine in fields related to metabolism, inflammation and immunology, and engineers with backgrounds in whole-system control dynamics, including chemical, electrical, mechanical and aeronautical engineering.

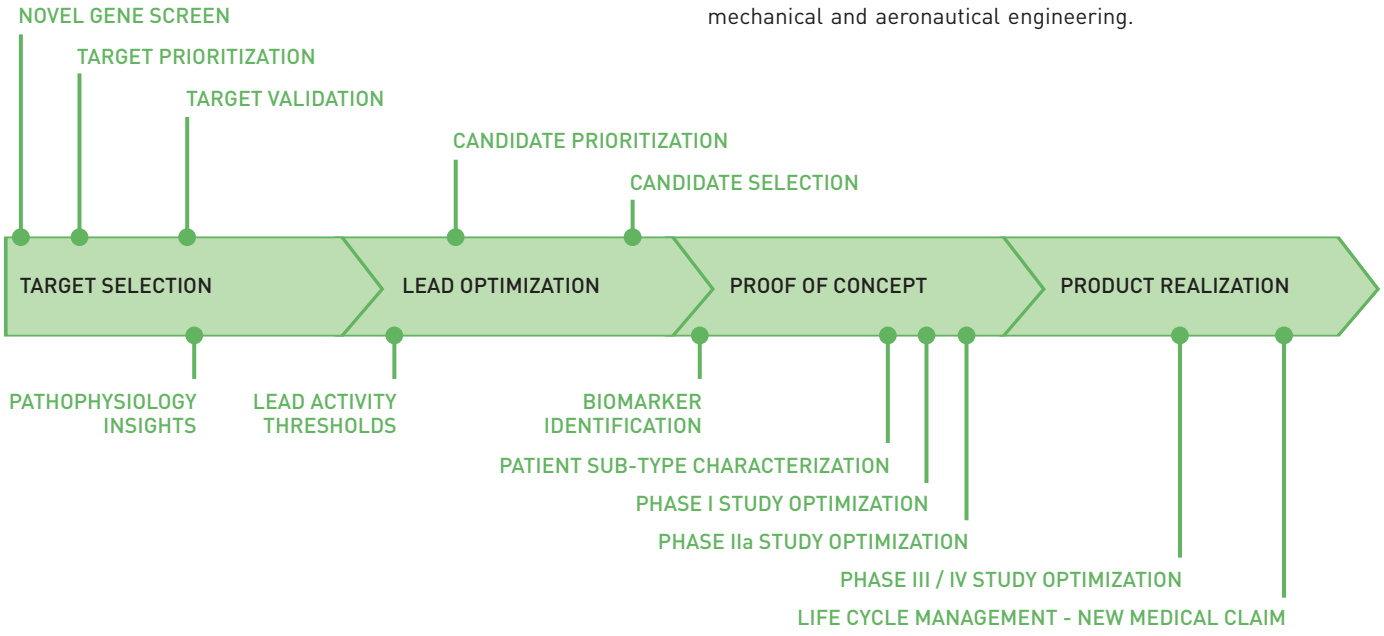


Figure 8.5. Applications of PhysioLab technology in pharmaceutical R&D (Alex Bangs, 2005)

Teranode (http://www.teranode.com) was founded in 2002. Teranode evolved from a team of scientists and professors from the University of Washington. Its goal has been to change the role computing plays in Life Sciences by providing flexible, scientist-driven technology that automates experiment workflow, manages experiment and biological data, unifies data into user specific views and manages product lifecycle. Teranode's products are used to integrate chemical and biological knowledge enterprise-wide and improve the speed and value of experimentation in R&D. TERANODE Design Suite (TDS) is a collaborative tool for designing, managing, analysing and reporting experiment data. Unlike traditional informatics, TERANODE Design Suite eliminates the need for custom programming by integrating visual experiment design with lab automation and analytics. TERANODE Design Suite has three applications (Protocol modeller, Protocol player and biological modeller) to meet specific needs throughout the lifecycle of experimentation.

POINTONE (http://www.pointonesystems.com) is a privately held firm pioneering intelligent clinical-genetic information systems for enhanced healthcare practice with molecular medicine at the point of care. Clinical System incorporates valuable new genetic-based results to improve healthcare. Collectively, this area of "Molecular Medicine" applies the knowledge in genomics, gene expression, proteomics and pharmacogenomics to the clinical care of patients. Molecular Medicine is a broad term for more effective healthcare treatment at a personal level and which includes clinical diagnosis and treatment based on understanding the molecular basis of health and disease. The product: POINTONE Clinical System (PCS) is a clinical decision support platform that provides physicians with the tools and information necessary to consistently apply best practice guidelines. PCS consists of modules to assist physicians in identifying patients at high risk for disease, and to apply appropriate screening and risk reduction strategies (Risk Profile) and modules to assist physicians managing patients with chronic diseases (ChroniCare). These two product suites are integrated to support managing patients through the continuum of care from risk stratification, diagnosis and prognosis, to treatment monitoring and outcome tracking.

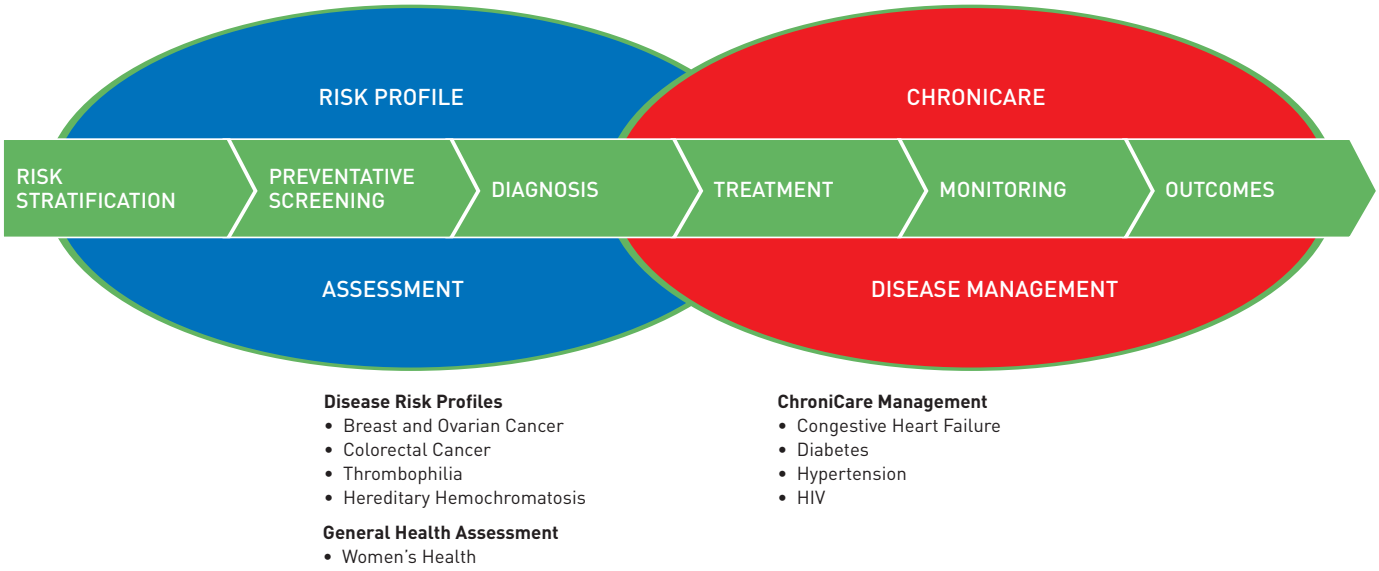


Figure 8.6. Schematic diagram of POINTONE Clinical System. Cited from POINTONE Systems Information (http://www.pointonesystems.com/pdf/06%2011%2003%20POINTONE%20Sell%20Sheet.pdf)

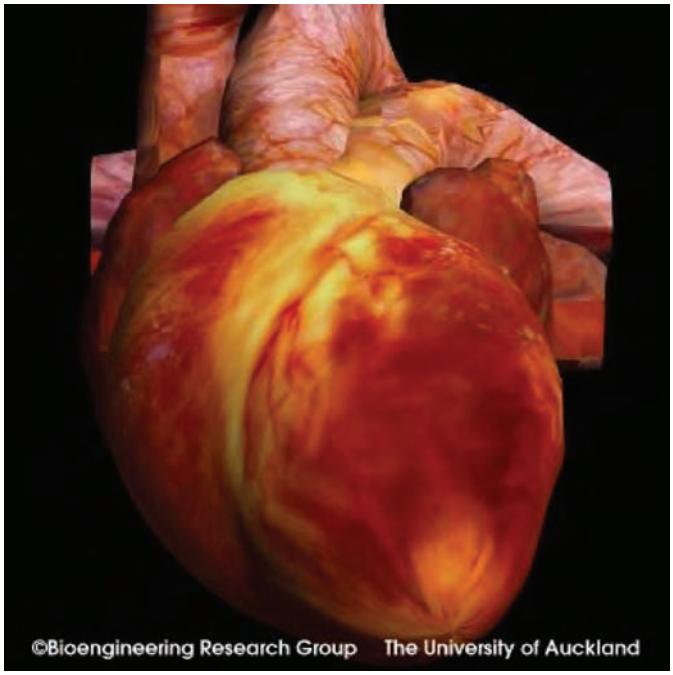


Figure 8.7. Textured model of the heart cited from: http://www.bioeng.auckland.a.c.nz/projects/heart/heart.php

Heart Physiome Project (http://www.physiome.org.nz/heart) models how the heart works as an integrated organ, and what processes lead to arrhythmias. Data was gathered on cell processes and mathematical models were established that represent these processes. The project is a collaboration between five professors: Denis Noble, David Paterson, Mark Sansom and Richard Vaughan-Jones from the University of Oxford and Peter Hunter from the University of Auckland in New Zealand. One of the team's key aims is to use the models to help understand different mechanisms of arrhythmias. A simple change in a computer file can replicate a mutation in a channel protein, for example, and the impact of that change can be followed in the model of the whole organ. This approach has already shed light on a key problem for clinicians: why arrhythmias that look very similar when recorded on an electrocardiogram (ECG) can have many possible underlying causes.

Editors: John Fenner, David Pinney, Keith McCormack, University of Sheffield (UK)

9.0

9.1. Executive Summary

Although the VPH promises improved healthcare on an international scale, it also presents some ethical dilemmas, and demonstrates the need for intelligent legislation. The ethical dimension requires consideration of the purpose of the VPH and the suitability of its resources to fulfil that purpose. A legal component is necessary to provide guidance in the event of adverse outcomes resulting from inaccurate or incorrectly interpreted VPH data, and to safeguard public privacy and freedom of information. Gender is another relevant social issue and includes aspects of social equality as well as those circumstances in which gender-specific VPH data may be of particular value.

Ethical, Legal and Gender Issues

9.1.1. Ethical Issues

An ethical focus is necessary to ensure that, in the enthusiasm to make use of emerging techniques, the approaches chosen are those that are configured to sustain and support patient rights, promote positive societal values and remain consistent with the latest ethico-legal environment. Respectful consideration of individuals and their protection through well-defined patient rights are key elements of this approach and the VPH should not compromise the ethically-driven values accepted by healthcare professionals. A significant effort directed at ensuring that sound ethical principles are upheld is a prerequisite for the success of the VPH.

9.1.2. Legal Issues

The VPH is a repository of health data that may be used to influence patient management, through both clinical decision support and the industrial development of new devices; the principal legislative aspects can therefore be identified as:

Data Protection – privacy concerning the holding and processing of an individual's personal data, balanced with freedom of access to that information by those who seek to benefit society. The VPH initiative will succeed only if it has access to the fullest possible range of patient data, but individuals have a clearly established right to protection from exploitation. Conformity with existing legislation must therefore be verified at each stage of VPH development, and the possible need for additional clarification kept under scrutiny.

Intellectual Property Rights (IPR) – protection of intellectual property, typically via patent or copyright, and the influence of such protection on development of the VPH. Comprehensive specification of IPR policies will encourage information exchange with third parties and promote an atmosphere of trust. Industrial involvement would be hampered by any uncertainty over ownership. The IP framework must be clear and free from ambiguity so that the rights of participants are not in doubt.

Liability – responsibility for compensating an individual for injury or mismanagement as a result of interaction with the VPH. Use of the VPH will influence individuals' healthcare, and issues of liability arising from inappropriate VPH application must be considered. An environment in which VPH usage is reduced because of uncertainty over legal liability must be avoided.

In all cases, existing legislation may differ between EU Member States, and a harmonised approach should be identified to avoid confusion or conflict across national boundaries.

9.1.3. Gender Issues

Aspects of age, race and gender are clearly important to the progress, treatment and outcome of some diseases. The VPH is expected to uncover gender-sensitive behaviour of a quite subtle nature, with further research ultimately leading to superior gender-specific treatment regimens and improved therapeutic effectiveness, possibly even at reduced cost. In the context of gender, there is also a social dimension, and the VPH must be seen to adopt best practice and demonstrate even-handedness; it is an opportunity for the scientific domain to influence social values and promote social equality across Europe.

9.1.4. Conclusion

The influence of the virtual physiological human extends beyond the scientific arena, and a commitment to the success of the VPH requires a commitment to the resolution of numerous social issues that are inextricably interwoven with this technology.

9.2. Introduction

A centralised health computing resource available to the health, industry and academic sectors throughout Europe is an innovation that offers the prospect of improved healthcare on an international scale. However, it also poses significant ethical dilemmas that highlight the need for the establishment of intelligent codes of conduct, some of which may require the backing of legislation. In the scientific domain, key professional groups facilitate the promotion of ethical practices, and this concept could be rationalised and extended across the entire VPH for the benefit of public confidence and protection:

- the ethical dimension includes consideration of the purposes of the VPH and the suitability of its various resources for the fulfilment of those purposes
- the legal component is necessary in respect of freedom of information and the protection of Intellectual Property Rights (IPR), and provides guidance in the event of adverse outcomes resulting from inaccurate or incorrectly interpreted VPH data
- gender is relevant to the circumstances in which VPH data should be used (for example, whether VPH data is gender-specific and under what circumstances data usage is appropriate in the absence of this information) and also introduces consideration of the extent to which the VPH could be a tool to promote gender equality across Europe.

9.3. Ethical Considerations

There are significant ethical considerations associated with the introduction of new technologies in healthcare, both at the fundamental level of human rights as they apply to all individuals, and at the cultural and community level where sensitivities towards issues of race, sexual orientation or religion may be heightened. Respectful consideration of individuals and their protection through well-defined rights, both as citizens and as patients, are key elements. For the VPH to be credible it must be consistent with the current ethico-legal environment and be sufficiently adaptable that it can overcome differences of interpretation that are characteristic of new initiatives. However, it should remain true to established principles, and should not compromise the ethically-driven mores accepted by healthcare professionals, that include:

- beneficence – practitioners should act in the best interest of their patients

- non-maleficence – the principle of "first, do no harm"
- autonomy – acknowledgement that patients have a right to accept or refuse treatment
- justice – concerned with the fair distribution of health resources
- dignity – recognition that patients have a right to dignity
- honesty – recognition that patients can expect to be told the truth about their condition and treatment.

The VPH needs to be demonstrably and transparently a force for good in society, both to avoid alienating prospective beneficiaries and to win over sceptics. It should promote positive societal values, and be configured to sustain and support citizens' rights, such as their right to:

- have access to healthcare. Transport and financial capacity are important factors in this context, since it is desirable that the disadvantaged in society are able to access adequate health services. It can be argued that the Internet increases accessibility but, equally, the Internet is not available to all, and it is important that a VPH reliant on such technology does not become a divisive force in society. Note that this is relevant to more than just physical access, since the mentally disabled can face considerable problems when accessing information services.
- be accurately informed about the status of their health, and the nature of any therapies. It is desirable that relevant information be presented in such a way as to be comprehensible to patients. The VPH has profound potential for education and raising awareness of issues pertinent to public and personal health.
- informed consent. This recognises their rights to self-determination and their freedom to choose paths of action based on the facts before them. Patients may choose to proceed with medical procedures as advised by medical practitioners, or may withdraw consent at any moment without justification and yet still expect full and continued healthcare support. The VPH has a role in predicting the outcomes of informed choice and may influence the patient management pathway for a range of ailments.
- expect sufficient education to allow them to make informed choices about procedures that affect them. Patients with inadequate understanding are unable to make informed choices and identify needs. VPH structures should be transparent, so that patients are clear about the role of the VPH in their contexts.
- expect that health data should be pertinent, correct and secure. These are important ethical principles and European legislation is available to support them. The VPH must be seen to promote public privacy and be recognised as advocating freedom of information. Data protection presents many challenges to the VPH and highlights the need for substantial financial investment if it is to be effectively managed. Adverse publicity in this area could prove fatal, since it may precipitate a loss of public confidence.
- be treated with dignity, irrespective of sexual, racial or religious affiliation. There may be advantages in demonstrating the neutrality of the VPH, as a means of improving public awareness and confidence in the initiative.
- expect that care will be undertaken according to acknowledged best practice and the state of the art. With appropriate maintenance the VPH is potentially permanently state of the art, and its use will encourage best practice. It is interesting to speculate that "VPH" may become a badge of quality in the future clinical environment.

Ethics is informed by practice, so it follows that ethical assessment should be integrated within each VPH project. In this way sensitivity to ethical dilemmas will be significantly enhanced and ethical issues will be addressed at the earliest opportunity. Valuable outcomes would be the production of ethics manuals and codes of practice to aid transparency and provide a basis for recognised best practice in particular areas.

Ethics does not function in isolation and there should be opportunities for collaborative sharing of concerns and successes. At the very least this could occur through dedicated sessions at conferences but ideally there should be support for a more formal body whose purpose would be to facilitate links between the ethical components of different projects and provide a consolidated ethical view on strategic issues.

In summary, consideration of ethical issues can be viewed not only as a necessity, but as an opportunity for politically-astute positive promotion, since the ethical perspective is a powerful means of securing public support. Equally, failure in this area would be a failure to take advantage of an opportunity for the public good – the latter is arguably a suitable metric by which the value of the VPH can be assessed. A significant effort directed at the ethical considerations of the VPH is a prerequisite for success.

9.4. Legal Considerations

The value that society places on the ethical objectives can be measured to some extent by the legislative structure designed to protect and support them. Since the VPH is a repository of health data that may be used to influence patient management (either through clinical decision support or development of new devices by industry [1]) the principal legislative aspects can be identified as:

- data protection – privacy concerning the holding and processing of an individual's personal data
- intellectual property rights – protection of intellectual property (data and methods) through copyright and the influence on development of the VPH
- liability – responsibility for compensating an individual for injury or mismanagement as a result of interaction with the VPH.

These are discussed below; similar issues were considered in the GEMSS project (IST-2001-37153) – see http://www.gemms.de.

9.4.1. Data Protection

Privacy of personal data is a fundamental right, supported by legislation whose presence is designed to ensure that computers are used ethically within society (e.g. European Directive 95/46). Freedom of information is protected by registration with a data protection registrar. The register holds information about the system, the nature of the data held and its use, where the data comes from and to where it may be passed. The compiler of the data must ensure that it is:

- obtained and processed fairly and lawfully
- held and processed only for those lawful purposes described in the register
- disclosed only to those people specified in the register
- adequate, relevant and not excessive in relation to the purpose
- accurate, complete and up to date
- held no longer than necessary in an identifiable form
- accessible to the individual concerned
- properly secured.

Rules and Regulations Pertinent to Data Protection in Europe

- Article 8 of the European Convention on Human Rights and the judgements of the European Court of Human Rights
- Article 7 & 8 of the Charter of Fundamental Rights of the European Union
- OECD 1980 Guidelines on Privacy
- Council of Europe 1981 Convention for the Protection of Individuals with Regard to Automatic Processing of Personal Data
- Recommendation (97) 5 of the Council of Europe on the protection of medical data
- Recommendation (83) 10 of the Council of Europe on the protection of personal data used for scientific research and statistics
- Directive 95/46 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Directive 2002/58 concerning the processing of personal data and the protection of privacy in the electronic communications sector
- Opinion no. 13 of the European Group on Ethics on Ethical Issues of Healthcare in the Information Society
- Declarations, Considerations and Guidelines from the World Medical Association on Patient's Rights, Telemedicine, Health Databases, and Medical research involving Human subjects.

The individual has a right to be informed, to rectification, erasure or blocking, to object, and not to be subject to an automatic decision producing legal effects. Although privacy of personal data held on a computer (and in filed manual records) is enshrined in data protection law, the European Privacy Legal Framework permits differences between the national policies of the Member States.

Despite a significant volume of material considering data protection (see box) there is clearly an opportunity for legal conflict for those involved with a cross-European initiative such as the VPH. This is complicated further by a VPH data repository that may be centralised within a virtual institute (i.e. not physically located in one place, but split across several countries). The differences in privacy rules cannot prevent the transfer of personal data between Member States if they have transposed the European Privacy Directives into their national laws. However, the legislation focuses only on privacy protection and does not cover activities beyond its well-defined scope, such as personal data processing or data transfer between states for reasons of public health, social security, or other obligations. Since countries implement the data protection directive in their own specific ways, such operations may conflict with data protection law. There is no legal solution to these anomalies currently, so the situation with respect to the VPH is unclear.

A short-term solution is to establish Codes of Conduct specific to the VPH, but ideally a longer-term solution should be sought, in the form of harmonisation that identifies potential obstacles in each of the Member States and proposes effective European solutions [2]. A pragmatic response is to abide by the European data protection law of the country that has the strictest requirements, but ultimately legal opinion could be consolidated through a legal forum designed for the purpose. In addition to issues of data protection, it must be recognised that countries differ with respect to medical confidentiality or general privacy clauses in their law/common law/constitutions. They may also contain provisions on the use of data in medical research in legislation on medical research. A systematic review of such differences would be invaluable and would aid the production of codes of conduct.

9.4.2. Intellectual Property Rights

Pan-European medical research projects must consider a breadth of legal requirements, such as data protection, medical confidentiality and liability – and this also includes intellectual property rights (IPR). These rights protect patents, copyright, trademarks etc and, taken together, reflect the value that society places on creativity. Ironically, it is the regulation of the sharing of this type of information that secures freedom for information exchange, such freedoms being essential for satisfactory function of the VPH.

Copyright secures an individual's right to prevent the copying ("theft") of original material without the author's permission. Its honourable history includes the protection of literary and artistic work and now encompasses computer programmes and databases, with rights that cover copying, adaptation and distribution. Clearly, this has implications for the VPH since it is explicitly designed to store and share data and facilitate the processing of such data. Unfortunately, the IPR climate within which the VPH will operate is not yet clearly defined, even though the importance of a legal framework for data sharing and database interoperability is widely acknowledged [3]. The regulatory framework must be clarified and sufficiently well defined so that contributors and users alike are not intimidated by punitive vagaries that might lead to legal action.

Specification of clear IPR policies will encourage information exchange with third parties and promote an atmosphere of trust that is beneficial to the VPH (and could be one of its distinguishing features). This important aspect extends beyond patient data to include commercial concerns (vulnerable to exploitation) and even the databases themselves (e.g. database metadata). The current climate reflects the sensitivity of data providers to abuse of their IPR – some databases are not publicly available and require licensed access, others demand that origin of the data is transparent, or that data integration is not allowed, whilst some request explicit acknowledgement when used [4-7]. A solution that promotes effective data sharing and interoperability is feasible, but it is an important task that deserves dedicated effort. The final goal is a viable and clear IPR framework in which information exchange can thrive, precipitating the anticipated benefits of the virtual physiological human.

9.4.3. Liability

It is a tribute to the potential of the VPH and its ability to influence healthcare that issues of liability must be given high priority, so that the inevitable circumstances in which the outcome of a VPH interaction adversely affects an individual, can be addressed. There may be many reasons for an unforeseen adverse outcome:

- patient variability
- databases populated with incorrect data
- inappropriate use of data
- the use of a flawed model
- a misunderstanding of the assumptions associated with a model etc.

Clarification is needed on the circumstances under which it is appropriate for an individual to seek compensation, the apportioning of blame and responsibilities for compensation [8]. As with data protection, the laws and their interpretation may differ between EU Member States and it is difficult to envisage a harmonised legal environment in which the VPH would operate. That said, it may prove informative to turn to legal instruments that have parallels with the issues raised here.

In the realm of industrially produced movables, a producer is liable for damage caused by a product defect as indicated in European Directive 85/374. The injured person needs proof of the damage, the defect responsible and their causal relationship. In the case of damage to an individual wrought by several contributors, the injured person is entitled to full compensation for the damage from any of them. Defects can be evaluated in the context of public expectations of safety. Compensation may be sought in the event of death, personal injury or damage to property (limited to goods for private use or consumption). Conversely, the producer of the product is not liable when the product could not have been identified as defective in accordance with the objective state of knowledge at the time it was introduced. Liability requires that the knowledge must have been accessible at the time the product was put into circulation. Under European Directive 85/372 there may be no compensation for pain or suffering if directed by the law applicable to the case.

These are factors that illustrate the climate of liability in which the VPH is likely to operate and draws attention to some of the issues that must be addressed if the virtual physiological human is to be a viable growing resource. All legal possibilities pertaining to VPH-induced damage should be explored in order to quantify the vulnerability of practitioners and patients and disentangle the cross-border conflicts associated with the resource's legal aspects. An example strategy might consider the jurisdiction of a member state (forum convenience), the nature of lawsuits that might be filed and analysis of the law applicable to the suit. This is an expensive process of course, so perhaps the adoption of a Regulation dedicated to the VPH might be a solution. Numerous studies have examined the disharmonies between national Tort Laws in Europe, notably the European Centre of Tort and Insurance Law (www.ectil.org) which edits the series "PRINCIPLES OF EUROPEAN TORT LAW":

Vol. 1: J. Spier (ed.), The Limits of Liability: Keeping the Floodgates Shut (1996);

Vol. 2: J. Spier (ed.), The Limits of Expanding Liability: Eight Fundamental Cases in a Comparative Perspective (1998);

Vol. 3: H. Koziol (ed.), Unification of Tort Law: Wrongfulness (1998);

Vol. 4: J. Spier (ed.), Unification of Tort Law: Causation (2000);

Vol. 5: U. Magnus (ed.), Unification of Tort Law: Damages (2001);

Vol. 6: B. A. Koch/H. Koziol (eds.), Unification of Tort Law: Strict Liability (2002);

Vol. 7: J. Spier (ed.), Unification of Tort Law: Liability for Damage Caused by Others (2003);

Vol. 8: U. Magnus/M. Martín-Casals (eds.), Unification of Tort Law: Contributory Negligence (2004);

Vol. 9: W. V. H. Rogers (ed.), Unification of Tort Law: Multiple Tortfeasors (2004).

The complexities of tort law are considerable. Effective utilisation of the VPH requires that the rules governing its use are transparent and well defined, and that it operates in an environment that protects both practitioner and patient alike. This will engender confidence in all who use it (directly or indirectly).

9.4.4. The Legal Imperative

A minimalist approach to the legal issues is wholly untenable, since this will inevitably jeopardise public confidence and compromise development of the VPH. A targeted legal effort is a necessity, therefore, and is an incentive to harmonise important legislative principles across Europe. An analysis of the ethical, legal and IPR issues that arise from the many physiome-related projects across Europe might usefully highlight areas in which future problems can be anticipated (and resolved?). An in-depth examination and assessment of these requirements could determine, either a) best practice or b) whether there needs to be additional European legislation to facilitate medical research. Whatever the outcome, it is essential to recognise that ethical and legal matters are given due consideration in all VPH-associated activities.

9.5. Gender

Aspects of age, race and gender etc. are clearly important to the progress and treatment outcomes of particular diseases, such as breast cancer. Although these have scientific relevance to the virtual physiological human, they also highlight a social dimension, and since a successful VPH will have widespread impact, the positive benefits can be applauded, whilst negative aspects should be addressed. A mature approach involves recognising the sphere of influence of the virtual physiological human and managing its development in such a way that its inertia is used to positive effect. Legal harmonisation is an example already cited and gender equality is another opportunity for progress that crosses European borders. The VPH must be seen to adopt best practice and demonstrate even-handedness in matters of gender. Although women are largely underrepresented in the scientific domain, positive discrimination is not necessarily a viable or desirable solution (a clear message that came from gender discussions hosted under various STEP forums). It is important for the dignity of the female scientist that she is afforded the space to make her mark, so that the respect she earns is recognition of scientific merit rather than the efficacy of a quota system.

The tension of balancing life at work and home is responsible for many of the stresses of 21st Century family life. Noting that the VPH is a 21st Century tool, it should be well placed to provide 21st Century assistance in the face of such problems and illustrate how some of these difficulties can be resolved. For instance, it can readily accommodate remote access and could be a vehicle for promoting effective "telecommuting", indirectly contributing to the solution of child-care problems. Many parents would welcome the opportunity to work part-time, and this degree of flexibility may be well suited to ventures that involve the VPH, hopefully leading to greater fulfilment at work and contentment at home. It is possible, too, that such initiatives will promote a more equal gender distribution amongst those beginning or pursuing a career in this area and may even positively influence staff retention. The VPH has great potential as an educational resource, so personnel taking a career break may find their return to full time employment eased by the ready availability of material that is both of high quality and reflects state-of-the-art developments.

In the scientific domain, the biological sciences are a female stronghold. By its very nature, however, the VPH crosses discipline boundaries and it is inevitable that cross-gender initiatives will result. Men and women will have the opportunity to mix (and integrate?) with environments in which they are normally under-represented. This gender mixing will not only promote respect and encourage gender equality but will tend to introduce very different perspectives that can be a catalyst for new insights and ideas.

As well as the social impact that accompanies the inter-disciplinary nature of the VPH, there are significant gender-specific scientific benefits. Many classes of disease are not overtly gender sensitive and typically a gender-neutral approach to patient management is profitable and frequently the norm for current medical practice. However, the power of the VPH will highlight gender sensitive behaviours that are much more subtle than diseases such as osteoporosis, offering the prospect of superior gender-specific treatment regimens, leading to improved therapeutic effectiveness at reduced cost [9,10]. This is an incremental step towards the lofty goal of patient-specific treatment in which optimised therapy will benefit all, including the health budget.

Clearly, gender sensitive issues need to be recognised and accommodated within the VPH framework, both socially and scientifically. Attention to gender specificity will produce outcomes that can help to clarify gender related components of disease processes, their associated risks and the modes and success of therapies. It is also an opportunity to influence social values and promote the importance of gender equality throughout Europe.

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10.0

10.1. Executive Summary

The success of the emerging VPH will be highly dependent upon the information provided to the potential user community. While it appears that a sizeable proportion of the work will be performed within projects funded by the European Commission that will be subject to some overall co-ordination, there will remain a significant level of activity outside these projects.

Thus, there is a danger that a centralised, but inclusive, resource such as that provided by STEP will cease to exist and that the EuroPhysiome will become diffused as its identity is subsumed into individual projects.

The early days of the VPH will see constant change as new resources become available at an increasing rate. The existence of some co-ordinating body will ensure that resource providers can find an easy way of ensuring that the user base becomes aware of their materials at an early stage, assisting rapid uptake. It is anticipated that the proposed Network of Excellence, to be funded at Call 2 of the Framework 7 ICT Programme, will play a major part in this process.

It is also clear that early engagement of industrial and clinical participants is essential for the successful development of the VPH.

Dissemination Models

10.2. Introduction

The availability of the VPH will present a number of new opportunities, and its use will require a cultural shift for many. As a result, it is possible that the VPH will regarded by some as a threat to their current practices, which may lead to a degree of resistance to its introduction.

For the rapid and widespread acceptance of the VPH, it will be important that this view of the VPH as a threat should be reduced as much as possible, both in scale and in extent. Acceptance of the VPH will be accelerated by ensuring that early users are provided with considerable assistance, so that any short-term inconvenience they may experience in embracing VPH technology is more than compensated for by the benefits they receive from its use. These users will become a valuable vehicle for disseminating the usefulness of the VPH and for creating a positive perception about its future impact.

The dissemination of accurate information, clear and complete indications of the number and nature of the available VPH resources and how they can be accessed, and the provision of supportive educational materials will be critical to this process. The most important factors, particularly in the initial stages, will be that information is consistent and coherent and that researchers will be able to gain a full picture of the contemporary situation in a straightforward way.

10.3. Provision of VPH resources and information

Particular VPH resources will be produced by a number of independent projects, some funded by sources such as the European Commission, others from independent work of individuals or groups. In all such cases, there will be little motivation to provide the comprehensive and regularly updated overview that is seen as essential for creating the vibrant "VPH community" that can sustain the VPH as an integrated resource in the long term, unless there is a specific brief to do so.

There is, therefore, some danger that the centralised momentum produced by STEP and activities aligned to it will be rapidly dissipated as a result of the internal pressures of the individual projects that will be taking place. Each of these will have its own specific priorities, but none will have the care of the VPH as a whole on its agenda.

Call 2 of the FP7 ICT Programme allows for a single Network of Excellence (NoE) in the area of the Virtual Physiological Human. The VPH straddles many intellectual domains and, because of this, there is no organisation that it can immediately look to as its "champion". Once the VPH community has become mature, it is likely that such organisations will emerge, with the consent of the overall VPH community, to provide leadership, coordination and standardisation, but this will take some time.

In the meantime and in the absence of an alternative coordinating body, the future of the VPH will rely heavily on the NoE taking a large responsibility for ensuring the continued momentum of work both within and outside the NoE consortium.

Clearly, this NoE must establish credibility and ownership at an early stage; it must be embedded within the VPH community, but its role should be restricted to supporting the community, rather than directing or managing it. It will be important that it retains the active consent of all of the stakeholders – academic, clinical, industrial and societal – and that each of these sees that its interests continue to be supported.

The NoE will commence at about April 2008, creating a concern that in the 12 months between the conclusion of STEP and the start of the NoE, there may be some loss of momentum and a degree of fragmentation. The first few months of the NoE are thus seen as a critical period for establishing the future plans for the VPH and for ensuring that the various other VPH projects funded in Call 2 are assimilated into a coherent whole.

It is also to be hoped that some arrangements can be made by parties interested in the VPH concept to provide a focus for the VPH during the hiatus that will follow the end of STEP, though no candidates have yet come forward.

One of the most critical features of VPH development will be the creation of a portal or other centralised resource containing comprehensive information on VPH-related projects (coordinators could be regularly polled to provide updated information), relevant conferences, press briefings, product releases, etc. The Biomed Town initiative, http://www.biomedtown.org, which provided considerable support to STEP, is a good example of what can be achieved using a relatively low level of resource.

Other measures likely to foster the VPH community would be an annual conference and a regular newsletter to subscribers – these could be managed by the NoE. Summer schools or other activities for developing broad insights and assisting a new generation of researchers well versed in VPH technology to emerge should also be priorities.

While STEP has worked closely with professional and industrial associations, the transition to the next level by ensuring that dissemination percolates to individual companies and clinical departments will be a considerable challenge that is likely to demand sustained actions over an extended period. However, it should not be forgotten that, ultimately, the major impetus for them to gain interest in the VPH is the promise of benefits that can be gained by doing so.

For industrial companies, it must be demonstrated at an early stage that assimilating the ideas of the VPH and using them in novel ways conveys a competitive advantage or opens up possible new markets. This will encourage further investment and the

probable emergence of small, dynamic companies, possibly spin-offs from larger corporations, which will form the vanguard for future industrial exploitation.

The same applies to clinicians – if the VPH bears early promise of rewards in terms of more effective, more cost-effective or more efficient treatment, then its uptake will not be in question. If benefits are delayed or over-hyped at an early stage, then it will become considerably more difficult for the VPH to gain acceptance later.

Thus, the early provision of VPH resources of proven usefulness and usability, and accurate descriptions of their status and worth, should be seen as the most important dissemination vehicles that can be produced. And once the usefulness is proven, it will be essential to continue a programme of dissemination, not only in scientific circles but also amongst politicians and health service administrators, in order to ensure that the VPH continues to flourish and to receive its due proportion of future investment. It is incumbent on all VPH researchers to take some responsibility in this area while the VPH continues fully to establish itself amongst competing endeavours.

Finally, it will be important to ensure that the general public is not overlooked in the dissemination process. STEP has demonstrated that there is an appetite in the press and in magazines for stories related to VPH, if they are presented appropriately. Articles associated with STEP have reported interviews with consortium members fairly accurately during the project. Interviewees should take care to avoid raising unrealistic expectations of the speed of uptake of the technology or else the credibility of the VPH initiative may be damaged, but the area will certainly benefit if a wide range of VPH researchers continue to reach out to the media and so keep the VPH firmly in the public eye.

10.4 Priorities for a coordinating body for the VPH

Whichever coordinating body emerges for the VPH should consider the needs of the various stakeholders and ensure that appropriate information is supplied to them on a regular basis. Priorities for this coordinating body should include the following:

(a) General

- providing a comprehensive and current information resource about all aspects of VPH development to all stakeholders: researchers, industrialists, clinicians, the general public, etc.
- regularly eliciting information, viewpoints, perspectives from the VPH community and communicating these to appropriate recipients
- reviewing overall progress and providing an accurate and increasingly respected overview of the contemporary situation
- adjusting existing goals and defining new ones, in consultation with the VPH community and ensuring that these are clearly enunciated.

(b) For the scientific community

- ensuring that information about new resources (such as data or software), conferences and events, or other relevant items is brought to the attention of VPH researchers in an accessible way
- ensuring that publicly funded VPH projects communicate fully with each other to avoid duplication of effort and to ensure greater compatibility amongst the outcomes of the projects
- providing a means by which consensual opinion within the VPH scientific community can be broadcast to relevant organisations
- organising regular fora for the VPH community, such as an annual conference at which both scientific and organisational aspects of the VPH can be discussed
- providing educational support to assist existing researchers rapidly to develop new skills that may be necessary for successful adoption of VPH technology
- providing opportunities to assist with the education of a new generation of VPH researchers possessing skills across a suitable breadth of technology, possibly by summer schools, etc.
- providing a European "voice" on the world stage and encouraging increased activity worldwide
- providing an organisation that can coordinate the early development of relevant standards.

(c) For industry

- providing a link between academic researchers and industry in terms of both scientific progress and in terms of suitable applications
- providing support for the development of spin-off companies either from academic departments or from large corporations
- monitoring exploitation of VPH technology and ensuring that bottlenecks and technological barriers are addressed at an early stage

(d) For clinical practice

- encouraging projects to include clinical practitioners during the development and implementation so that successful clinical adoption occurs at an early stage
- ensuring that "success stories" of the practical application of VPH are broadcast rapidly and widely to relevant audiences

(e) For the public

- supplying materials to the media which clearly outline the benefits associated with the development of the VPH
- ensuring that such materials are accurate and avoiding content that may later be discredited as this would severely damage the credibility of the VPH
- ensuring that the approach is pitched at a suitable level for the targeted audience
- consideration should seriously be given to employing professional help from experts in public relations.

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11.0

11.1. Executive Summary

We favour a Network of Excellence (NoE) to permit coordination of all activities across the VPH programme within the 7th FP. Without such a single coordinating entity, there is a serious risk that the multitude of separate projects will progress independently and, although no doubt productively, would not then be amenable to linkage in the later stages of the programme or beyond its lifetime. The NoE will take on this responsibility and will ensure that common standards are adopted for model development and interoperability.

Exploitation Models & Long-term Sustainability

A means to ensure that VPH will be both exploitable and sustainable over the long term is the development of exemplar case studies that tell a story which directly impacts on the health and well-being of ordinary people. These studies will provide strategic focus and, in requiring the integration of models from different VPH partners over different length and time scales, and between different models, will ensure multiscale integration within the context of very specific clinical goals. For example, pilot projects involving 3-5 partner teams will draw on the expertise of each member. The use of existing data resources, together with novel approaches, will enable the building of models at different levels of abstraction to answer global and pressing clinical questions. These projects will interface with the core activities of the VPH NoE, which will have overarching responsibility for coordination of many other projects funded within the initiative. Through this framework of interaction and a set of guiding principles, therefore, the VPH can achieve high visibility within scientific and clinical disciplines with the ability to use generic methods for other projects. The VPH exemplars will be able to define practical minimum data standards, data types and model parameters integrating with other model resources.

We propose that infectious disease represents the ideal cross-cutting exemplar to drive integration of models across all scales and between systems. The dynamic, multi-organ, multi-factorial biology of an infectious disease such as HIV/AIDS, upon which we would focus, and the pharmacodynamics of anti-infective drugs, would be an ideal project. Such an approach will not only advance both systems and population level views of disease, but will also be of direct clinical relevance. This represents a unique "middle out" approach (as opposed to top down/bottom up) which combines computer simulation and modelling with data from physical experiments and clinical observations under the premise that the rules by which parts of the system and external influences upon it are governed are more important than a description of these parts and that which prevails upon them.

Another key element of the success and ultimate sustainability of the VPH programme will be its ability to exploit the associated e-infrastructure which has been developed by the EU in the 6th FP and which will continue to evolve in the 7th FP. In anticipation of the development of a European petascale computing infrastructure, policy must be developed whereby EU projects have guaranteed access to such EU infrastructure – something currently lacking. It is proposed that the NoE assume overall responsibility for ensuring that the capabilities and access mechanisms for this e-infrastructure, including security requirements, are in place, and that this should be aligned to meet the scientific and clinical objectives of the VPH programme. Of particular importance is the unification of software and middleware standards, and security models, such that separate "grids" currently available may become usefully interoperable.

The NoE will evolve a unified VPH community over the period of the 7th FP, and will plan the instrument(s) by means of which its longevity can be assured subsequently, possibly via the establishment of a VPH Institute.

11.2. Introduction

The VPH will only be exploitable and sustainable over the long term if it directly affects the health and well-being of ordinary people. The place this will happen is where people interface with the health care system. The VPH roadmap makes comment on the fact that the project should be driven by exemplar or case studies that tell a story. More importantly, these "stories" should be clinically relevant. The exemplars, therefore, should provide strategic focus. Moreover, the case studies should be used to evolve the VPH in certain directions and to guard against generic platform technology solutions that do not address the specifics of the clinical goals. Finally, the case studies should aim to integrate models from different components of VPH partners, both over different length and time scales and between different models. For example, the case studies should be able to integrate not only horizontally with exciting projects such as the Cardiome, Epitheliome, Giome and Renal Physiome within the VPH, but also with other EU funded activity, for example BioSim, ViroLab and ImmunoGrid. Outputs from one modelling scenario should serve as input parameters for the next model. Strategic focus for the VPH will be provided by the careful choice of case studies. It is essential that, although the VPH will integrate and model over multiple scales, each component of the case study should have a direct application and relevance to the clinical and scientific goals. Finally, the case study components, when combined in a true multi-scale environment, through enabling hierarchical and/or hybrid modelling and simulation, will produce a combined insight of direct clinical relevance.

There needs to be within the VPH the introduction of new ideas on the coupling of complexity modelling and simulation to the biological and clinical data, as well as to existing knowledge. Traditionally, research has been divided into "top down" models and simulations that aim to provide insights into the detail of the system, and "bottom up" approaches that aim to study individual components in great depth and then assimilate this knowledge into a holistic view. We propose a more radical "middle out" approach that mixes the computer simulation and modelling with data from physical experiments under the premise that the rules by which parts of the system are governed are more important than a description of the parts.

We propose that a 7th FP VPH Network of Excellence (NoE) should aim to support and fund a limited number of pilot projects which exemplify themes involving 3-5 partner teams orientated around such case studies, an example of which is given below. These would interface with the core activities of the VPH NoE, which will coordinate the many other projects funded within the initiative and ensure their adherence to common standards for model and computational interoperability, thereby providing added value as well as representing a practical interface to the VPH. We propose that infectious disease represents an ideal opportunity to advance systems and population level views of disease. Infection and immunity should be one such exemplar project as it provides a dynamic environment where disease is played out over widely varying, yet tractable timescales. Infectious disease is relevant to everybody as it affects every country in the world. Infectious

diseases mechanisms are accessible through patient samples and detailed molecular biology. Population and epidemiological level insights into infection are available from the clinical management of diseases. Finally, intervention strategies through anti-microbial agents provide a means of altering disease states and of assessing the evolutionary escape of the pathogen from drug selective pressure. This provides a framework in which individual levels within the system can provide models that integrate in a multi-scale environment, both vertically from gene dynamics to population dynamics, or horizontally from organ systems such as the Giome to Epitheliome.

11.3. Exemplar: Infectious disease pilot project within the VPH Network of Excellence

The vast majority of global disease burden can be attributed to infectious diseases, of which the largest killers are Malaria, Tuberculosis and HIV/AIDS. The effect of diagnosis and treatment on infectious disease morbidity burden can be calculated through disability-adjusted life years (DALYs), for example, identification of HIV infection and treatment in children under 12 months of age would save ~2.5 million DALYs. Infectious diseases are of continuing importance in the developed world with HIV/AIDS, Hepatitis C virus infection induced hepatocellular carcinoma and nosocomial infections representing significant causes of ill health. Many of these infections are difficult to treat by drug therapy or through vaccination. The dynamic, multi-organ, multi-factorial biology of infectious disease and the pharmacodynamics of anti-infective drugs make this an ideal exemplar project, as outlined below. We would focus on HIV/AIDS.

The aim of the infectious disease pilot project would be to investigate three questions, as follows:

i) How do the integrated gene and cellular networks of host and pathogen lead to persistent infections and reactivation during immunodeficiency?

All pathogens modulate host cell gene expression during infection. Viruses, which are obligate intracellular pathogens, utilise host cell processes for their replication. Understanding and modelling the dynamic and co-ordinated nature of infected cell and surrounding non-infected cell gene expression programmes, together with alterations in the gene expression programmes of immune cells, will provide a detailed basic biological view of an infection process at the cellular level. Although much gene expression data exists for different pathogens relatively little is of time series in nature and as such there is a paucity of data for such modelling. This component of the mini-project would therefore involve both the collection and modelling of gene expression changes to important medical pathogens, together with developing methods for data integration between existing disparate datasets. Overall this will allow: (a) the measurement and modelling of gene expression dynamics during cellular infection, (b) the measurement and modelling of intercellular communication in the infected and non-infected cellular state, (c) the measurement and modelling of intercellular communication between the innate and adaptive immune system. The outcomes of this integrated modelling project would be (a) the identification of biomarkers that evolve over the dynamic stages of infection, (b) the identification of gene/protein targets for therapeutic intervention using existing drugs, (c) the efficient integration of diverse high dimensional gene expression datasets and (d) through the use of multi-scale modelling and simulation, an understanding of cellular communication and intercellular gene expression relay circuits.

ii) How do host and pathogen population biology, genetics and environmental variations affect the dynamics of these networks?

The modelling of cellular-based changes in gene expression must be scaled to provide a cellular level model of virus spread within a tissue and organ, the dissemination to other target cells and organs and how innate and adaptive immune responses limit and then fail to contain the spread of the virus with the host. Models that can account for the effect of variation in the response of the host and of variation in the fitness of viral variants on the dynamics of these processes will be required, with the aim of elucidating mechanisms that describe the anisotropic properties of infection. Ultimately, these integrated models must provide a cellular level abstraction, with the models lying somewhere between the individual detail of gene expression networks and the higher level abstraction of organ function. These models must link the initial infection, namely infection of dendritic cells in the mucosal epithelium, the initial spread of infection to secondary lymphoid organs, especially within the gut, the establishment of persistent viral replication and, finally, the loss of immune control. This will involve multi-scale models and will link directly VPH projects on the Epitheliome and Giome together with other EU projects such as ImmunoGrid and models of circulation. The aim of this research will be to demonstrate how the integration of diverse models can build a picture of infection in a complex, multi-organ multi-cell type system.

iii) How do models and computational simulations improve treatment of infectious disease?

Models of infection processes do not necessarily improve therapeutic options. Issues of virus drug resistance, intrinsic differences in host susceptibility and population dynamics all affect the spread of a virus in a population. Through using molecular dynamics models of HIV proteins and drug resistant variants, we will predict drug-binding affinities as a surrogate for clinical drug resistance and determine the utility of such models in predicting drug treatment outcomes. We will utilise models of drug delivery, metabolism and other pharmacodynamic properties to assess how the contribution of host variation in drug metabolism can influence the development of HIV drug resistance. We will make use of extensive HIV sequence, phenotype and patient clinical detail databases to assess these models. Similarly, we will determine how models of variation in virus fitness, both within a host in response to immune and drug selective pressures and within a population, alter the spread of the virus within a population. The aim of this work is to model how drug therapies and population dynamics alter the course of a virus infection both within a single person and within a global population.

iv) Understanding the dynamics of other pathogenic viruses in the context of immunodeficiency.

Epstein Barr virus (EBV) is usually acquired in early childhood and infects almost all adults. In most cases infection is without symptoms, the exception being primary infection in teenage years that results in mononucleosis, or glandular fever. When not causing illness the virus resides as a latent infection in B cells, the cells of the immune system that make antibodies. Under certain circumstances, however, EBV can trigger the cells it infects to multiply rapidly, resulting in several kinds of cancers, the two most common being Burkitt's lymphoma (a B cell cancer common in Africa) and nasopharyngeal carcinoma (a tumour of the nasopharynx which is prominent among cancers affecting men in many parts of Asia). In addition the virus has been linked to, amongst others, lymphomas in immunocompromised patients, cancer of the lining of the stomach, and breast cancer. EBV therefore represents the other side of virus persistence relative to HIV—in the case of EBV the human host and virus co-exist until the immune system is compromised. EBV therefore represents a counterpoint for the investigation of the same human virus system but representing two different states, control in immune competent and disease in the immune compromised.

Currently clinical actions in terms of the pathological manifestations of EBV infection are responsive: it is the pathological outcome which is treated, as opposed to the malignant cause. If a greater understanding could be obtained with regard to how EBV infection and associated environmental, genetic and coincident factors can lead to specific disease end-points, in different people, a more proactive and patient-specific approach to managing the EBV associated disease burden may be uncovered. In order to address these issues, several models must be realised to investigate the complex disease aetiology. Various types of data are available: genetic/genomic (relating to host genetics and the interaction between EBV and its host cell at the level of viral and cellular genes), cellular (relating to the dynamics of B- and other -cell populations during EBV infection, reactivation and EBV-associated disease); and organ and body level (relating to the disease processes and outcomes in several body compartments and on various scales). We would use and integrate new data into the understanding of EBV infection in healthy and immunodeficient individuals.

Other NoE pilot projects, IPs and STREPs can be co-ordinated using this framework of interaction within the VPH both for other important infectious diseases and other pathological processes. In each case the exemplar project will take the expertise of a group of investigators and a defined set of clinically relevant questions, produce novel approaches and co-ordinate the use of existing data resources, utilise and build models to address defined questions and integrate models at different levels of abstraction to answer global and pressing clinical questions. Through these guiding principles the VPH can achieve high visibility within scientific and clinical disciplines with the ability for the utilisation of generic methods for other projects. The VPH exemplars will be able to define practical minimum data standards, data types and model parameters integrating with other model resources.

11.4. Alignment of EU e-infrastructure with VPH

There is a major task to be undertaken in ensuring the alignment of the European computational grid infrastructure with the needs of the VPH programme. The major EU infrastructures already in existence include EGEE and DEISA. Within the 7th FP, it is expected that the EU will also aim to build a European petascale computing infrastructure. In particular, until now, there has been no policy by means of which EU projects which may require access to such EU infrastructure are guaranteed access to it at the time their projects are submitted and reviewed. This must be changed, and it is a responsibility of the NoE to help to ensure that this happens. Access to such resources is one thing, another is whether they really meet the needs and requirements of the scientists and clinicians involved in VPH related research. In this respect, easy access to the resources is an essential requirement. In the first few years of grid computing, this has been very far from the case. The situation is gradually improving, but significant effort will be required within VPH, again partially performed and broadly overseen by the NoE, to ensure that appropriate middleware and client tools are developed and made available to users.

The existing resources, amongst other things available from EGEE and DEISA, are expected to provide only a partial solution rather than a total one. EGEE offers persistent low end, high throughput cluster computing resources, storage and some relevant services (though new projects are expected to contribute hardware to the EGEE grid), while DEISA currently provides access to very high-end resources across the EU, time-sliced with their use by national partners, so access is currently intermittent at best. In general, however, VPH users are expected to require access to a much more heterogeneous grid, comprising low, intermediate and high-end compute resources, but also visualisation, storage and networking capabilities. Compounding the current problem of separate "grids" for EGEE and DEISA is the fact that they run different basic software stacks: EGEE has Globus as its underlying middleware, whilst DEISA uses Unicore. This causes significant impediments in terms of interoperability since, for example, their security models are quite distinct; like different gauges on a railway system, seamless interoperability (so that users are unaware of these differences) has proved a challenge. Progress is now being made in this direction, and is supported by high priority activities in the EU 6th FP OMII-Europe project. It will also be necessary to dedicate a major effort to addressing the key issue of security—any clinical activity comes with legal requirements to assure patient anonymity, so it is of the utmost importance that these requirements of confidentiality are upheld.

We expect, therefore, that some aspects of VPH funding must involve collaborations with EGEE, DEISA, OMII-Europe and the EU Commission itself, in order to ensure that genuinely usable infrastructure is provided to the VPH community. These issues, being of such central concern to the overall VPH programme, will need to be organised centrally by the NoE.

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12.0

12.1. The Infrastructure

Concrete Implementation: recommendations

12.1.1. The VPH needs

The ICT infrastructure should provide these services to the VPH:

- support for the creation, the management and the federation of users' communities
- support for the creation, the management and the federation of repositories of data objects, characterised by sizes ranging from Mb to Gb each (the effective deployment of solutions mostly based on web services, but which involve the transfer of large binary objects, pose a particular problem)
- diffuse knowledge management, including the ability for a community to maintain its own ontology, and to promote the curation of its own data
- support for the deployment of quality scoring services, designed to evaluate the quality of the shared data automatically or by human intervention
- single sign-on independent from the front-end applications
- software environments that make it easier to deploy grid-based end-user applications that totally hide the grid complexity
- sharing model objects as data objects (which involve the problem of the solver, which is required to re-run the model; if the solver is custom-made there is an issue of easy porting; if it is commercial there are licensing issues)
- multi-physics, multi-solver, multi-scale model solutions involving coupling and data transfer between the model components
- use of highly parallel architectures in "Burst" mode: use parallelisation to obtain medium-sized solutions in quasi-real time.

12.1.2. Community infrastructures

- VPH needs a single entry point, a single sign-on and the minimum standardisation framework that ensures interoperability; this implies a central authority. However, in the first stages of the VPH development there is consensus that a lightweight organisation, such as EuroPhysiome, could be sufficient to ensure the minimal level of standardisation and consensus for the early prototypes to interoperate; Europhysiome could be managed through a Network of Excellence, or other similar networking initiative.
- In parallel, the community should explore all possible collaboration with existing standardisation bodies. One option is STEP, the international standard for interoperability in computer aided engineering services; some of the STEP standards already aim to standardise the storage format of multiphysics simulation models. Another option is a dedicated section of the DICOM standard, similarly to the "DICOM for Surgery" effort. One option could also be the presentation of small STRP proposals, aimed at exploring the usability of such existing standards and/or their further development.
- "It is the community, stupid" should become the VPH slogan. Every activity should be placed in a collaborative context. A typical example is the collaborative and consensual development of domain ontologies, which is hardly possible with the tools currently available.

12.1.3. Physical infrastructures

- This remains an open question: the **VPH should be hosted by a few Large Scale Infrastructures (LSI), or by a loosely coupled federation of small/medium computational resources?**
- A major problem is the recognition of Life Sciences as a core customer for grid infrastructures, and on an equal footing with more traditional customers such as high-energy physics, environmental sciences, astrophysics etc. This probably also involves the revision of national policies and the allocation of structural funding.

12.1.4. Technological infrastructures

- It is necessary to develop middleware that is specifically aimed at the development and deployment of the VPH. A key factor is that the users of these software packages will be much less expert in computer science than is normal in other grid application domains, so attention will have to be paid to usability and other related factors, such as user interfaces.
- A fundamental requirement towards the deployment of VPH solutions in clinical practice is adherence to the two main emerging standards in healthcare: DICOM[13] and HL7[14]. An even stronger commitment towards interoperability is that emerging from the Integrating Health Enterprise Initiative[15] (IHE), an initiative by healthcare professionals and industry to improve the way computer systems in healthcare share information. IHE promotes the coordinated use of established standards such as DICOM and HL7 to address specific clinical needs in support of optimal patient care. Systems developed in accordance with IHE communicate with one another better, are easier to implement and enable care providers to use information more effectively. The most important event for IHE is the so-called *Connectathon*, which provides the most detailed validation of the participants' integration work. Participating companies prepare for the event using testing software – the MESA test tools – developed for this purpose. During the Connectathon, systems exchange information with complementary systems from multiple vendors, performing all of the transactions required for the roles they have selected, called IHE Actors, in support of defined clinical use cases, called IHE Integration Profiles.

[13] http://medical.nema.org

[14] http://www.h17.org/

[15] http://www.ihe.net/

– The Medical Data Management Technical Coordination Group[16] of EGEE is working on a secured service dedicated to access and manipulate medical images and associated metadata from the grid. The working group's mandate is to refine medical application needs for data management, in particular critical security requirements, and to provide a service compatible with the DICOM medical standard for storing, and accessing in a controlled manner to the data, via integration with the Storage Resource Manager of GLite.

12.1.5. Commercial, Legal and Ethical frameworks

– Even if VPH is recognised as a core customer for LSI, the business model(s) that makes VPH sustainable in the long term remains to be defined, also in terms of ICT resources. This must be analysed in the context of a complex exploitation scenario where multiple actors with very different exploitation perspectives act as potential users (e.g. from the clinician studying rare diseases, to the big pharmaceutical company needing to develop a new drug).
– Executing commercial codes. The licensing models of companies developing engineering software that is used also in the VPH context (finite element analysis, CFD, optimisation, etc.) need to be revised and sustainable in the context of a totally different business model, where the intense use of the models, and of the parallel architectures, poses new perspectives.
– Confidentiality. Since the national legal frameworks differ, it will be necessary to ensure the highest level of technological flexibility in order to ensure a reasonable take-up in all countries. In particular, it will be necessary to separate the physical location of the confidential data from the possibility to access them, since simple anonymisation might not be sufficient in certain cases.
– As defined in various national legislations, the biggest legal challenge comes from the patient's ownership of his own clinical data. While in many cases this rule is rarely enforced, and while for many VPH projects simply collecting extended informed consent can circumvent the problem, we should start to develop architectures where the authorisation process includes the patient in the loop.
– Although gender issues were debated extensively, no specific VPH gender issues emerged. The VPH initiatives should actively promote and support policies of substantial equality in opportunities for both genders, while recognising the differences and specificities of genders.

12.2. The Data

12.2.1. Accumulating clinical observations

There are many definitions of integrative biology and of systems biology, some cleverly designed to protect the territory of a few well-established research labs. However, all the work done during the STEP action indicates that there cannot be any systemic look that does not involve the analysis of what happens outside the cell. **It is necessary to favour projects that aim to collect relevant experimental data with respect to cell to cell and cell to tissue interaction.**

12.2.2. Challenges in data collection

The most critical challenge in data collection is funding. There are no grant opportunities at the European level that support the collection of data for the VPH. The VPH data cannot be considered a by-product that comes for free from other activities (clinical, experimental, etc.) so a dataset must be collected specifically for this purpose in 90 per cent of cases to be of use to the VPH. The experimenter needs to design the data collection, the data organisation, the storage, and the documentation, knowing in advance that the dataset will be shared. This imposes a significant overhead, whose costs must somehow be covered.

A related issue is that of curation. According to the DCC[17] "Digital curation, broadly interpreted, is about maintaining and adding value to a trusted body of digital information for current and future use". Again, one could conclude that no funding is available for curation activities, but this is not entirely true. Actions such as e-Content Plus[18] specifically support curation of large scientific collections. However, this is currently strongly limited to the cultural heritage context. We recommend that in FP7 these actions are explicitly extended to all those collections that have not only a cultural, but also a scientific value.

A related challenge is that of quality insurance on the shared data. If we plan to use a certain dataset for subsequent activities, we had better be sure that it has been collected in an accurate, methodologically thorough way. However, this general statement finds a huge number of different incarnations in different sub-communities. We recommend the development of mechanisms that delegate to the communities the development and the operation of quality insurance services for specific types of data. This poses an organisational and technological challenge that must be addressed.

12.3. The Models

12.3.1. Challenges in VPH modelling

Due to the complexity of the applications, numerical modelling in biomedicine always poses major challenges in pre-processing, e.g. in the activities that prepare the model. Some examples are:

– segmentation and automatic mesh generation
– derivation of dishomogeneity and anisotropy properties from the biomedical data, and their inclusion in the models
– model identification, and probabilistic representation of the input parameters.

[16] http://egee-intranet.web.cern.ch/egee-intranet/NA1/TCG/wgs/mdm.htm

[17] http://www.dcc.ac.uk/about/what

[18] http://europa.eu.int/information_society/activities/econtentplus/index_en.htm

Strongly coupled multiple models are always a challenge in simulation. In biomedicine, some examples are fluid-structure interaction, the dynamics of multiple deformable bodies, bone remodelling and other adaptation processes, meso-scale modelling involving coupling between lumped-parameters and continuum field problems, etc. We need further research on how to create these models, how to solve them in reasonable time, and how to verify and validate them.

Some problems are simply related to brute computational power. Today, I can make a full 3D hyper-elastic model of the passive deformation of one muscle, but the idea of running such a model simultaneously on all skeletal muscles during a passive movement poses huge problems of scalability of the current solutions.

12.3.2. Accumulating models

We need to solve some significant problems in order to share and accumulate predictive models.

One relevant issue is the use of commercial solvers to develop VPH models. Ideally, we should be able to develop a model representation that is totally independent from the specific application used to create and solve the model. While the direction can and must be pursued, it is true that in some cases, the advantage of sharing a model written in a solver-specific format is significant, e.g. when the solver we used exposes a unique feature that is not available in other solvers. If we accept that solver-specific models have to be shared, there must be a support mechanism to access them using the commercial solvers. This would be possible if the licensing model these companies use, which is currently based on paying to have the software, moves to models where a small fee is collected each time the solver is run.

A second problem is the interdependency between the theoretical/mathematical description of a model and its concrete numerical implementation (which involve pre-processing and solution). Ideally, we should be able to describe our models independently from the numerical method, and even more from the numerical code we use to solve them. This appears possible in a number of cases, and this separation is present in concrete implementations such as the CellML mark-up language, or the JSim software. However, in other contexts such as continuum modelling, this separation becomes more difficult. Because of this, and while we recognise the superiority of any approach that keeps the model and its solutions methods separate, we recommend that VPH research also targets the development of models as fully encapsulated web services, where the model and its numerical implementation are totally coherent.

12.3.3. Interconnecting models

There are two paradigms that emerged from the discussion. The first is to use *supermodels*, global models that describe macroscopically a functional or a metabolic sub-system, as scaffolds for organising lower level, higher detail models. The second is to avoid any mandatory structure, and to organise the model's repository as a loosely coupled *federation of predictive services*, each exposing an I/O interface described in a standardised way that makes it technically possible to concatenate them.

Consensus was reached that VPH needs both approaches. A federation of predictive services loosely coupled should form the VPH; some of the services should be metabolic or functional supermodels, which can be used as scaffolding to keep some other lower level models organised and structured. The first makes possible the development of the second.

We can separate the problem in *services* that take input data and give output data, and the *data*, the information that travels back and forth.

We need shared semantics for the data; while it is always possible to develop layers of semantic mediation to interconnect data spaces where the same thing is called by two different names, at least at a European level, it would be much simpler to share common data semantics. In this sense, the mark-up languages developed by the IUPS Physiome, while insufficient to solve the whole problem, could provide a starting point to define the types of data objects that VPH should manage. It is less clear if we also need a shared semantics for services, as these would be quite challenging to develop, and until the number of services is moderate, we can probably live without it. However, in the long run, we will face the same problems for the services that we face now with the data, so services semantics are a long-term need.

Once we share a common representation of the knowledge, we need to find ways to develop, collect, organise and interconnect predictive services. The name we chose already contains the solution: we do not believe it would be possible to make a repository of predictive models, as in most cases, the model definition is inseparable from the solver that is used to run it. I can create a data object that contains my mesh, my boundary conditions, my materials properties, etc. but sharing it would not give any advantage. Firstly, the model is defined with respect to a solver, and if another user does not own that solver, it becomes useless. This is not a file format problem, but rather relates to the fact that each solver has its own modelling concepts. In addition, the point is not to share the model, but rather to share the predictive service, so when I have my own inputs, I can run your model and get my own outputs. We believe that it would be much more convenient to develop simulation services that, through standardised interfaces (e.g. WSDL web services interfaces) would accept a list of inputs and generate a list of outputs. If the inputs also involve user interaction, the service should expose its own web interface. A better solution would be to expose the interactive inputs, and to incorporate them as remote-execution services in fat clients running locally. The highly standardised I/O interface would make it possible to develop generic queue services that allow a generic user to create his model by simply interconnecting inputs and outputs of various predictive services.

A related problem is data vicinity. Considering that the data objects entering end exiting from these services can be some Gb in size, the classic web service paradigm based on messages that travel back and forth needs to be revised. The first point is

that any application that uses these services should be designed without any assumption on the service latency, e.g. by using fully de-coupled interfaces, a la Ajax[19]. The second point is that the data should probably better stay closer to the service execution point than to the client. This suggests the need for a data grid architecture, where each data object has a universal path, and a client can pass it as an input to a service simply by sending such a path. Similarly, the services outputs would be stored on the data grid and the invoking client would receive back the universal path of the output. Clever caching policies would make the whole architecture more efficient: although the medical images are stored in data grid nodes located in hospitals, it would be useful also to pre-cache them near the segmentation service server. As the output data is usually much smaller, this would make the I/O overhead minimal. All this caching, of course, should not breach security and privacy policies.

The last aspect regards the format used to store the data. Following the IUPS Physiome approach, one could consider developing standard mark-up languages and using them to store any VPH data. Any service should read and write those standardised formats. This, however, appears unrealistic. Even assuming total support for these VPH standards, general-purpose simulation packages that may be used to develop services would not support such formats. A possible solution could be agreed on common data formats, but to implement them only as mediation services, that we invoke when we need to interconnect our service to another, and we want to use a *lingua franca*. The data format mediation services could be VPH services themselves; centralised services to which I can add my own translator so as to accumulate value. The data mediation services could be pure format translators, or true semantic mediators when the differences are not only in the format, but also in the logic we use to represent the data.

12.3.4. Model verification

It is now a classic treatment to assess the accuracy of a numerical model in two distinct parts: model verification (assessing the accuracy with which the model solves the mathematical problem, e.g. solving the equations correctly) and validation (assessing the accuracy with which the model predicts the physical reality, e.g. solving the right equations).

The VPH infrastructure should provide facilities for model verification. VPH should host specific datasets defining so-called benchmark problems, problems for which an analytic solution is known. These independent benchmarks (and their exact solution) would let us run verification tests on every new code, and to compare the numerical accuracy of different codes in different situations.

A more advanced evolution would be a numerical modelling environment that works at imposed accuracy. In this case it would be the user that, on the basis of the specific application, requires a certain upper boundary for numerical accuracy. The system should completely automate any pre-processing step influencing the model's numerical accuracy (e.g. mesh refinement, which involved automatic mesh generation) and should incorporate the numerical analysis methods that make it possible to adjust the solutions parameters automatically so as to achieve the required accuracy.

12.4. The Validation

12.4.1. Challenges in validation

If we plan to use the VPH in clinical practice, validation becomes paramount. We need to know what level of accuracy we can expect from our model. However, this is a complex issue for certain types of model. Once the model is fully verified, we need to explore its validation.

The VPH infrastructure should also collect experimental results, properly connected to the modelling information, so as to provide a true validation problem that can be used to assess the accuracy of a model in predicting the physical reality. These would not be benchmarks, but rather challenge problems for which a set of validating measurements obtained with a controlled experiment is available. It must be noted that the validation is a continuous process. As the experimental methods improve, we end up with new challenges. Ideally, the VPH infrastructure should make it possible to rerun all pertinent models against a new challenge problem when this is published.

A second type of validation process is that considered by the scientific method. Following that approach, each hypothesis should be used to predict other independent, but correlated phenomena that are also confirmed experimentally after it has been validated against direct measurements. This second type of validation is very difficult, and applies only to certain models. However, such interdependencies should be incorporated in the automated validation process, whenever they emerge in the literature. The possibility to interconnect different VPH models might also be used in this sense.

12.4.2. Validating for the clinic

The VPH repositories could be used to generate significant distributions of the inter-subject or inter-treatment variability of certain input parameters, which would give us a realistic framework within which to assess the sensitivity of our models to the uncertainty of the input parameters.

VPH infrastructure should be designed so as to make the running of retrospective and prospective validation studies for predictive models relatively easy.

In all cases, it is unlikely that the final clinical user can appreciate the adequacy of the validation process for a certain model, so it will be necessary to create mechanisms that provide to the final user a sort of "certification" of the model that the user can trust. This certification mechanism should be sufficiently flexible to accommodate the most informal to the most formal processes because of the huge difference in maturity, development and the needs of the various sub-domains.

[19] http://en.wikipedia.org/wiki/Ajax_%28programming%29

12.4.3. Validating for the industry

Industrial users have problems similar to those facing clinical users. However, there is an additional factor: certification. The role of simulation in certification has been strongly underestimated in the past. Now both FDA and the CE mark systems are starting to acknowledge the role of computer simulations in the certification process. The VPH community should establish a dialogue with the certification bodies, to explore how the existence of the VPH infrastructure could help the certification authority, and possibly further expand the role of simulation in the development of new products.

12.5. Long term sustainability models

12.5.1. General context

On the basis of the current state of the discussion, we can identify three roles: the *Provider*, who is the researcher or the institution that develops and makes available a VPH resource; the *User*, who can be a person or an institution (both for-profit or non-profit); and the *marketplace*, which is the logical and physical infrastructure that supports these transactions.

The marketplace must absolve two types of duty: i) provide the technological services that makes it possible and easy for the providers to share their resources, and for the users to locate and access the resources they need; ii) ensure that all resources are stored, organised and annotated in a standardised way, so as to ensure the total interoperability of any pair of resources, and to make easier the development of added-value tools for the creation, organisation and curation of resources. These two functions can be absolved by a single entity, by two separate entities, or by multiple marketplaces steered by a standardisation organisation.

With the term resource we indicate any result of VPH-related research that may have a value for a user. Currently the two typical types of resources we can identify are *data resources*, and *service resources*.

12.5.2. Barter model

The simplest model we can imagine for our communities is the barter model. Within a closed VPH marketplace, we can develop a credit/debit system that makes it possible for a user to access a provider's resource only if the user is himself or herself a provider. Each new user would receive some free credits at the beginning, which would let him use a few available resources. After that, he would get new credits only if he makes new resources available, and if others use these resources. This model makes sense in the early phases of development of the VPH, when the main goal is to consolidate the infrastructures and to enlarge the amount and quality of the available resources. It relies on two implicit assumptions: all authorised users are equally allowed to use resources (which probably implies the restriction of the community to non-profit users), and the infrastructural costs for the development and the maintenance of the marketplace are supported with external resources. This could be possible when the creation and maintenance of a marketplace is part of funded project, or under a more complex model where the Standardisation Body is run on a voluntary basis, and a federation of backend services – again provided on a voluntary basis – forms the infrastructure. If these costs are moderated, some research institutions might decide to invest in such support as a way of gaining visibility and recognition.

12.5.3. E-Commerce model

This is an evolution of the barter model, and can eventually incorporate it to regulate the relationship between non-profit users. The idea is that some users are willing to pay to access some resources. The entity that operates the marketplace becomes a broker between the providers and the paying users, and retains a transaction fee. Each provider sets a price tag for its resources; the marketplace operator collects a fee from the users of that resource, retains a fraction, and makes available the rest to the resources' provider. This model requires a number of additional infrastructural services, mostly relating to security. If different types of users see different pricing policies, the correct authentication and categorisation of users becomes very important. If a user is going to pay money for a resource, he will probably want some assurance that the resource is of good quality. This might be addressed with the Quality Scoring services mentioned above.

12.5.4. Subscription support

This model becomes realistic only when the VPH contains enough added value to justify a company paying for it. The idea is to organise the VPH as a service rather than a product, and to ask for-profit users to pay a subscription to access the VPH resources. It could be implemented by a single VPH resource provider (who would provide the access to all its resources to a for-profit user in exchange for a monthly fee), or as a global support model for the VPH portal. In this second case, the subscription income could be used to cover the infrastructure expenses; the remaining funds would be distributed among the providers in direct proportion to the frequency with which each provider's resources have been accessed in the past.

12.6. The People

A major problem in the sustainable implementation of the ideas behind VPH, and the realisation of the corresponding benefits with respect to scientific development and public health, is the attraction of this field to younger scientists. Currently, it is much more promising for gifted young researchers to go directly into fields such as molecular biology and medicine. Efforts in interdisciplinary fields are usually under-rewarded, so it will be necessary to develop around VPH research a comprehensive career support and incentive system. The most talented young people facing fundamental career decisions have to see a real chance for their own scientific development when entering VPH-related activities. Only then, will we be able to recruit top quality people and to achieve fast and sustained scientific development.

Annex 1: Experts that contributed to the consensus process

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110	Goodship	Allen	The Royal Veterinary College (RVC)	UK	Research
111	Goodwin	Brian	Schumacher College	USA	Research
112	Graichen	Kurt	Berlin Heart	DE	Research
113	Granville	Nick	Smith-Nephew Research Centre	UK	Research
114	Gronchi	Tessa	CF Consulting	IT	Industry
115	Guillard	Gwenaël	Università di Genève	CH	Research
116	Harris	Peter	University of Melbourne	AUS	Research
117	Hasenkam	Michael	Aarhus Universitet	DK	Research
118	Hege	Hans-Christian	Zuse Institute Berlin	DE	Research
119	Heller	Markus	Charité University of Berlin	DE	Research
120	Hellingwerf	Klaas	Biocetrum	NL	Research
121	Hernández	Alfredo	INSERM – Université de Rennes 1	FR	Research
122	Herveg	Jean	Facultes Universitaires Notre-Dame de la Paix Namur (FUNDP)	BE	Research
123	Hilbers	Peter A.J.	Eindhoven University of Technology	NL	Research
124	Hobatho	Marie Christine	Université de Technologie de Compiègne	FR	Research
125	Hocking	Neil	LSBDS	UK	Research
126	Hoekstra	Alphonse	University of Amsterdam	NL	Research
127	Hofmann	Martin	Fraunhofer Institute – SCAI	DE	Research
128	Holt	Cathy	Cardiff University	UK	Research

129	Holzapfel	Gerhard	Graz University of Technology	A	Research
130	Horrevoets	Anton	Academic Medical Center, University of Amsterdam	NL	Research
131	Howard	David	University of Salford	UK	Research
132	Huberson	Joël	NewPhenix	FR	Industry
133	Huijing	Peter	Vrije University	NL	Research
134	Hukins	David WL	University of Birmingham	UK	Research
135	Inchingolo	Paolo	Università di Trieste	IT	Research
136	Ito	Keita	AO Foundation	CH	Research
137	Janssen	Dennis	EORS	NL	Research
138	Jeneson	Jeroen A.L.	Eindhoven University of Technology	NL	Research
139	Jensen	Oliver	University of Nottingham	UK	Research
140	Jijakli	Hassan	Université Libre de Bruxelles	BE	Research
141	Johnson	Chris	University of Utah	USA	Research
142	Jones	Bob	CERN	CH	Research
143	Jordan Rodriguez	Blanca	Atos Origin Spain	ES	Industry
144	Kaandorp	Jaap	University of Amsterdam	NL	Research
145	Karniadakis	George	Brown University	USA	Research
146	Kauczor	Hans Ulrich	German Cancer Research Center	DE	Research
147	Kelly	Daniel	Trinity College	IRL	Research
148	Kilner	Philip	Royal Brompton Hospital	UK	Research
149	Klingmüller	Ursula	DKFZ	DE	Research
150	Kofránek	Jiri	Charles University	CZ	Research
151	Krams	Rob	Erasmus Medical Centre	NL	Research
152	Kroschewski	Ruth	Swiss Federal Institute of Technology Zurich (ETH Zurich)	CH	Research
153	Kuiper	Jan Herman	Keele University	UK	Research
154	Lackovic	Igor	University of Zagreb	HR	Research
155	Lacroix	Damien	Technical University of Catalonia	ES	Research
156	Lam	Dave	Telemedicine and Advanced Technology Research Center (TATRC)	BE	Research
157	Lanucara	Piero	Consorzio interuniversitario per le applicazioni di supercalcolo per università e ricerca (CASPUR)	IT	Research
158	Lavignon	Jean-François	BULL	FR	Industry
159	Le Novere	Nicolas	EMBL – European Bioinformatics Institute	UK	Research
160	Leardini	Alberto	Istituti Ortopedici Rizzoli	IT	Research
161	Lefevre	Jacques	Ecole Centrale de Lille IDEA-SIM	FR	Research
162	Legré	Yannick	CNRS/IN2P3	FR	Research
163	Lerski	Richard	University of Dundee	UK	Research
164	Lin	Hai	Zhejiang University	CN	Research
165	Linehan	John H.	Stanford University	USA	Research
166	Lonsdale	Guy	C&C Research Laboratories, NEC Europe Ltd.	UK	Research
167	Lorenz	Cristian	Philips Research Europe	DE	Industry

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168	Macellari	Velio	Istituto Superiore di Sanità	IT	Research
169	Macerata	Alberto	Università di Pisa	IT	Research
170	Maglaveras	Nicos	Aristotle University	GR	Research
171	Maglogiannis	Ilias	University of Aegean	GR	Research
172	Magnin	Isabelle	Creatis Lyon	FR	Research
173	Mancino	Giorgio	Università degli Studi di Roma TorVergata	IT	Research
174	Marchesi	Carlo	DSI – Università di Firenze – BimLab	IT	Research
175	Marcus	J.T.	VU University Medical Center	NL	Research
176	Marias	Kostas	FORTH – Institute of Computer Science	GR	Research
177	Martinez Barca	Miguel Angel	Universitad de Saragoza	ES	Research
178	Martin-Sánchez	Fernando	National Institute of Health Carlos III Madrid	ES	Research
179	Matthys	Koen	Imperial College London	UK	Research
180	Mazzà	Claudia	Istituto Universitario di Scienze Motorie (IUSM)	IT	Research
181	McCulloch	Andrew	University of California San Diego	USA	Research
182	McMahon	Barry	Tallaght Hospital	IRL	Clinical
183	Meijer	Kenneth	University of Maastricht	NL	Research
184	Meinzer	Hans-Peter	DKFS	DE	Research
185	Merloz	Philippe	University Department of Orthopaedic Surgery CHU A. Michallon	FR	Clinical
186	Mickaily-Huber	Elizabeth	CFS Engineering	CH	Industry
187	Middleton	John	Cardiff University	UK	Research
188	Mihalas	George I.	European Federation for Medical Informatics	RO	Research
189	Milanesi	Luciano	Institute for Biomedical Technologies ITB – CNR	IT	Research
190	Molenaers	Guy	University of Leuven	BE	Research
191	Montagnat	Johan	Centre National de la Recherche Scientifique	FR	Research
192	Moore	Richard	Eucomed Trade Organisation	BE	Industry
193	Moss	David	Birkbeck College	UK	Research
194	Mueller	Ralph	Swiss Federal Institute of Technology Zurich (ETH)	CH	Research
195	Mulhall	Kevin	Mater Misericordiae University Hospital	IRL	Clinical
196	Nash	Martyn	University of Auckland	NZ	Research
197	Nester	Christopher	University of Salford	UK	Research
198	Nicolini	Linda	Cordis Neuro Vascular	BE	Industry
199	Nikolaos	Papandrianos	University Hospital Maastricht	GR	Research
200	Noble	Denis	Oxford University	UK	Research
201	Nolte	Lutz	University of Bern	CH	Research
202	Nuesser	Peter	Berlin Heart	DE	Research
203	Oomens	Cees. W.J.	Eindhoven University of Technology	NL	Research
204	Oresic	Matej	VTT Technical Research Centre of Finland	FIN	Research
205	Pacini	Giovanni	Metabolic Unit, Institute of Biomedical Engineering, CNR, Padova	IT	Research
206	Pagano	Grazia	CF Consulting	IT	Industry
207	Paiva	Manual	Université Libre de Bruxelles	BE	Research

208	Panfilov	Sasha	Utrecht University	NL	Research
209	Pankoke	Steffen	Wölfel Beratende Ingenieure GmbH + Co. KG	DE	Industry
210	Panunzi	Simona	BiomathLab	IT	Research
211	Paoluzzi	Alberto	Università di Roma Tre	IT	Research
212	Papageorgiou	Elpiniki	Technological Education Institute of Lamia	GR	Research
213	Payne	Stephen	Oxford University	UK	Research
214	Pedley	Tim	Cambridge University	UK	Research
215	Petrella	Anthony	Colorado School of Mines	USA	Research
216	Petrone	Marco	Cineca	IT	Research
217	Philippens	Mat	TNO	NL	Industry
218	Picchini	Umberto	BioMatLab IASI-CNR	IT	Research
219	Piechnik	Stefan	FMRIB	UK	Research
220	Piero	Lanucara	Consorzio interuniversitario per le applicazioni di supercalcolo per università e ricerca (CASPUR)	IT	Research
221	Pioletti	Dominique	Laboratory of Biomechanical Orthopedics	CH	Research
222	Plank	Gernot	Medical University of Graz	A	Research
223	Poelmann	Robert	Leiden University Medical Center	NL	Research
224	Poli	Samantha	Università di Roma La Sapienza	IT	Research
225	Pomiankowski	Andrew	Complex UCL	UK	Research
226	Potapov	Aleksej	BioMedTech FUND	RUS	Research
227	Preziosi	Luigi	Politecnico di Torino	IT	Research
228	Pries	Axel	Free University of Berlin	DE	Research
229	Promayon	Emmanuel	Université Joseph Fourier – Grenoble	FR	Research
230	Pulkkinen	Pasi	University of Oulu	FIN	Research
231	Quadrani	Paolo	Cineca	IT	Research
232	Quarteroni	Alfio	EPFL	CH	Research
233	Rafiriou	Dan	Cluj-Napoca Technical University	RO	Research
234	Raja	Vinesh	Warwick University	UK	Research
235	Razavi	Reza	King's College	UK	Research
236	Reneman	Robert	University of Maastricht	NL	Research
237	Rinderu	Paul	University Craiova	RO	Research
238	Rizzoli	René	Université de Genève	CH	Research
239	Rocaries	François	ESIEE	FR	Research
240	Rochette	Michel	Ansys France	FR	Industry
241	Ronchaud	Rémi	European Research Consortium for Informatics and Mathematics (ERCIM)	FR	Research
242	Rooze	Marcel	Université Libre de Bruxelles	BE	Research
243	Roux	Christian	ENST – Bretagne	FR	Research
244	Ruefenacht	Daniel	Hopital Universitaire Cantonal Geneve	CH	Research
245	Ruggiero	Carmelina	Università di Genova	IT	Research
246	Ruiz	Aurelio	Universitat Pompeu Fabra	ES	Research

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247	Rusanen	Leena	Snowpolis	FIN	Research
248	Said	Rajab	Simpleware	UK	Industry
249	Saiz	Javier	Universitad Politecnica de Valencia	ES	Research
250	Salvan	Alberto	ISIB-CNR	IT	Research
251	Sanz	Ferran	IMIM – Universitat Pompeu Fabra	ES	Research
252	Sauro	Herbert	Keck Graduate Institute	USA	Research
253	Schenone	Andrea	Università di Genova	IT	Research
254	Schima	Heinrich	Medical University of Vienna	A	Research
255	Schwen	Ole	University of Bonn	DE	Research
256	Secomb	Timothy W.	University of Arizona	USA	Research
257	Seemann	Gunnar	Universitaet Karlsruhe	GE	Research
258	Serrano	Luis	EMBL Heildelberg	DE	Research
259	Severi	Stefano	Università di Bologna	IT	Research
260	Shepherd	Adrian	Birkbeck College	UK	Research
261	Sherwin	Spencer	Imperial College London	UK	Research
262	Shulgin	Boris	Warwick University	UK	Research
263	Sidemann	Sam	University of Haifa	IL	Research
264	Skår	John	Karolinska Institutet	S	Research
265	Slegers	Linda	Philips	NL	Industry
266	Sloot	Peter	University of Amsterdam	NL	Research
267	Smallwood	Rod	University of Sheffield	UK	Research
268	Smith	Nicolas	Oxford University	UK	Research
269	Solovyova	Olga	Institute of Immunology and Physiology, Ural Branch of Russian Academy of Sciences	RUS	Research
270	Sorine	Michel	INRIA	FR	Research
271	Soukane	Assia	IBISC/LaMI UMR 8042 CNRS	FR	Research
272	Spaan	Jos	University of Amsterdam	NL	Research
273	Stanski	Donald	Novartis	USA	Industry
274	Stergiopulos	Nikos	Swiss Federal Institute of Technology Zurich (ETH)	CH	Research
275	Stroetmann	Veli	Empirica Communication & Technology Research	DE	Research
276	Sundnes	Joakim	Simula Research Laboratory	NO	Research
277	Taylor	William R.	University Medicine Berline	DE	Research
278	Tegnér	Jesper	Karolinska Institutet	S	Research
279	Teillac	Pierre	European Patient Forum	CH	EC liason
280	Testi	Debora	B3C Biocomputing Competence Centre	IT	Industry
281	Theunis	Laurens	EuropaBio Trade Organisation	BE	Industry
282	Thiopoulos	Constantinos	ININOVATION	DE	Industry
283	Thomaseth	Karl	Institute of Biomedical Engineering ISIB-CNR	IT	Research
284	Thornton	Janet	EMBL- European Bioinformatics Institute	UK	Research
285	Tollis	Ioannis (Yanni) G.	FORTH – Institute of Computer Science	GR	Research

286	Tomberg	Claude	University of Brussels	BE	Research
287	Vallée	Jearn-Paul	Geneve University Hospital	CH	Clinical
288	van Beeck	Hans	Vrije University	NL	Research
289	van de Vosse	Frans	Eindhoven University of Technology	NL	Research
290	van der Vusse	Ger J.	University of Maastricht	NL	Research
291	van Lenthe	Harry	KU Leuven	BE	Research
292	van Riel	Natal	Eindhoven University of Technology	NL	Research
293	van Vaerenbergh	Stéfan	Université Libre de Bruxelles	BE	Research
294	Vatta	Federica	Università di Trieste	IT	Research
295	Veeckmans	Bart	Materialise	NL	Industry
296	Vehí	Josep	Universitad de Girona	ES	Research
297	Ventikos	Yiannis	Oxford University	UK	Research
298	Verdonck	Pascal	Universiteit Gent	BE	Research
299	Verdonschot	Nico	EORS	NL	Research
300	Villà i Freixa	Jordi	Parc de Recerca Biomèdica de Barcelona	ES	Research
301	Wade	Rebecca	EML Research	DE	Research
302	Wang	Chengtao	Chinese VMH	CN	Research
303	Waniewski	Jacek	Institute of Biocybernetics and Biomedical Engineering (IBIB)	PL	Research
304	Weinans	Harrie	Universitait Medisch Centrum Rotterdam (EMCR)	NL	Research
305	Wiederhold	Brenda K.	Virtual Reality Medical Institute, Virtual Reality Medical Center, Interactive Media Institute, IMI-Europe	BE	Industry
306	Winlove	Peter	University Exeter	UK	Research
307	Wismans	Jac	TNO	NL	Industry
308	Wright	Jessica	University of Sheffield	UK	Research
309	Young	Philippe	Simpleware	UK	Industry
310	Zachow	Stefan	Zuse Institute Berlin	DE	Research
311	Zambarbieri	Daniela	Università di Pavia	IT	Research
312	Zanchi	Vlasta	FESB-University of Split	HR	Research
313	Zannoni	Cinzia	Cineca	IT	Research
314	Zasada	Stefan	University College London	UK	Research
315	Zemek	Deborah	University of Utah	USA	Research
316	Zervides	Constantinos	University of Sheffield	UK	Industry
317	Zhang	Henggui	The University of Manchester	UK	Research
318	Zue	Yue-Min	Creatis Insa Lyon	FR	Research