A Vision and Strategy for the VPH

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Summary

European funding under Framework 7 (FP7) for the Virtual Physiological Human (VPH) project has been in place now for nearly three years. The VPH Network of Excellence (NoE) is helping to develop common standards, open source software, freely accessible data and model repositories, and various training and dissemination activities for the project. It is also helping to coordinate the many clinically targeted projects that have been funded under the FP7 calls. An initial vision for the VPH was defined by FP6 STEP project in 2006. A year ago we wrote an assessment of the accomplishments of the first two years of the VPH in which we considered the biomedical science, healthcare and ICT challenges facing the project [1]. We proposed the VPH Institute as a means of sustaining the VPH vision beyond the time frame of the NoE. Here we update and extend this assessment and in particular address the following issues raised in response to [1]: (i) a clearer vision for the VPH, (ii) the external changes needed in regulatory policy and business models, and (iii) a discussion on how the VPH should link to molecular systems biology.

Keywords

virtual physiological human, physiome, computational physiology, systems biology, multi-scale modelling

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1. The VPH vision

The Physiome, Systems Biology, the Virtual Physiological Human, Personal Health Systems, Biomedical Informatics, Life Science e-Infrastructures, Systems Pharmacology. All of these domains share one common issue: the need for integration. To implement biomedical research outputs into clinical practice and healthcare industries we need to integrate data, information, knowledge and wisdom. We need to integrate data of the same patient stored in different hospitals in different member states or in clinical research databases; we need to integrate patient-specific knowledge with domain-specific knowledge; we need to integrate the information related to various parts and processes of the human body into a systemic understanding of pathophysiology; we need to integrate the knowledge digitally captured via metadata, ontologies and models in order to respond to the combinatorial explosion of complexity that integrative research is producing; and we need to integrate the wisdom produced in the research laboratories and in clinical practice, which will be formalised in guidelines, standards and protocols and used to promote translation of basic science and integrative models into healthcare benefits.

Our vision for the VPH/Physiome project is: ***To establish an ICT and computational science framework for digital, personalised, and predictive medicine in the 21st Century. To link discoveries in molecular biology with clinical imaging and other technologies using computational physiology based on the mathematical and engineering sciences. And to link genotype to phenotype for human and other animal tissues through anatomically and biophysically based multiscale models of physiological structure and function, at the levels of cells, tissues, organs and organ systems.***

This is a huge challenge that, if met, will have a tremendous impact on the life of our citizens, and on the European and international economy. For the general public the vision of a 'Digital Me' or, in a clinical setting, a 'Digital Patient' that contains all my healthcare information, is a powerful concept. But the challenges are immense: ***Data must be safely managed for access by the various biomedical professionals with my approval, communicated with all my wearable and implanted technology to constantly monitor my health status and to inform me, my family and friends, or my trusted healthcare providers of alarming events, supporting the collaboration of various trusted specialists around my complex systemic diseases, and used with all my data to predict the future development of my health in order to facilitate disease prevention and a fully self-aware lifestyle and health management.***

The Virtual Physiological Human (VPH) FP7 project is addressing this challenge by promoting and facilitating the use of computational models, software tools and web services. The goal is to achieve a more efficient and effective 21st century healthcare system and to create new economic opportunities for European healthcare industries. In common with other areas of application of modern scientific methods, medical practice will benefit from technologies in which digital data enables predictable outcomes through quantitative models that integrate physical processes across spatial scales down to the molecular level. We need to promote personalised, predictive, integrative, scientifically based approaches to medicine. These will use computational tools to link individual patient data with virtual population databases via the knowledge of biological processes encoded in mathematical models. The biomedical community also now has the opportunity, thanks to the adoption of new model and data standards and a common set of reference ontologies, to assemble the molecular pieces from 50 years of reductionist science in order to understand genotype-phenotype relationships by linking databases of genetic and proteomic data to anatomy and function at the cell, tissue and organ levels. Biophysically based computational modelling of the human body, applied to human physiology and the diagnosis and treatment of disease, will revolutionise 21st century bio-sciences and medicine. The success of this exciting opportunity is highly dependent both on the development, adoption and integration of ICT and eHealth

infrastructures throughout Europe, and on the coordination of this effort with other related international initiatives such as the IUPS[1] Physiome Project.

Note that the NoE is concerned primarily with ICT infrastructure, coordination and training for the VPH and the VPH-I projects themselves are primarily focussed on developing and implementing biophysically based computational models into clinical environments via industrial partners. The success of all of these endeavours is of course dependent on the continued progress of (separately funded) biomedical science in revealing the biophysical mechanisms underlying structure and function at all spatial scales.

A Roadmap for the VPH project was laid out in 2006 by the STEP coordinated action [2]. The outcome of the first FP7 VPH funding round in 2007 (Call 2) was the VPH Network of Excellence (NoE), three Integrated Projects (IPs), nine Specific Targeted Research Projects (STREPs) and two Cooperative Actions (CAs), all of which form the initial core of the European VPH Initiative (VPH-I). The second and third funding rounds (Calls 4 & 6) have added 4 more IPs and six more STREPs. With nearly four years of experience behind us (including STEP), it is time to assess our achievements and plan for the short, medium and long term future of the VPH and the NoE.

2. What have we achieved so far?

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

Standards, tools and services

The first stage of the NoE project has been largely concerned with establishing standards for models and data, building model and data repositories for published models, and assembling a toolbox of existing software programmes (many, but not all, open source) that are relevant to the VPH. A key role for the NoE has been writing the Application Programming Interfaces (APIs) for the markup languages that allow the application software packages to read models and data from the repositories. These developments are described in detail in the accompanying report. The markup languages provide the *syntax* (the grammar) for encoding models and data. Equally important are the *semantic* 'metadata' that give biological and biophysical meaning to the models and data via biological and biophysical *ontologies* (structured vocabularies). Mapping a number of existing ontologies onto the modelling framework is therefore another important thread in the immediate future, since it will enable unambiguous links to gene, metabolic and protein databases. Note that considerable progress has been made over the last two years in coordinating the development of VPH standards such as CellML and FieldML with those of the molecular systems biology community, in particular SBML.

Dissemination, training and outreach

Many communities will be impacted by the VPH, including: in the short term, biomedical researchers and students; in the medium term, healthcare workers and European industry; and, in the longer term, patients and the general public. Dissemination and training is therefore a major responsibility and one that has to be tailored separately for these various audiences. The initial focus for the NoE was the website containing full descriptions of the VPH projects and giving access to the VPH modelling and data resources and training programs, suitable for the first target community. The NoE website is now receiving 13,000 visits per month and the newsletters, which are published at 6

[1] International Union of Physiological Sciences.

monthly intervals, continue to be well received. Interest in the VPH continues to grow as evidenced by the successful VPH-Industry Day hosted in Barcelona in September 2010, and new, developing, collaborations with other communities such as the International Association for Medical Education (AMEE). Training remains a fundamental part of the dissemination strategy, where the VPH NoE will target young and experienced researchers alike. VPH training should be embedded in basic and applied research methods courses for higher degree students and as part of informatics education and training for the health workforce. The important contribution that such initiatives can make in the context of the long-term sustainability of the VPH initiative has been recognised by the VPH Community, leading to a number of successful initiatives. For example, a consortium of core and associate VPH NoE partners have been awarded funding over the next two years, under the ERASMUS life-long learning programme, to support the development of VPH-focussed, Master's level, training modules. This necessity for a qualified VPH-formed workforce has been further backed up by the preliminary analysis of a questionnaire sent to Industrial, Clinical and Academic partners to investigate the requirements in terms of training future professionals in highly-skilled jobs in the pharma and medical devices industry as well as regulatory bodies. An essential and urgent step identified in the last Vision Document was the implementation of a workshop and summer schools to train people in the use of the VPH models and software. Such activities were recognised as an important part of a wider, pan-European process directed towards the introduction of systematic educational activities with the aim of ensuring that academia, medicine and industry throughout Europe have a workforce that is appropriately equipped to meet the possibilities offered by this new and important discipline. Over the last 24 months two study groups and one workshop have been successfully convened. In study groups, individuals (including clinicians) with different levels of experience and types of expertise, focus on a collective problem. In contrast, the workshop brought together modellers and tool developers to address interoperability and the combination of models to address a common purpose.

Aside from training initiatives many other efforts are contributing to the formation of the VPH community: the BiomedTown on-line community, which hosted the consensus process of the STEP action, has been constantly growing since then and now has nearly 2000 members. Also, the larger VPH projects are contributing to the dissemination of the VPH vision. In addition to their project web sites, projects like VPHOP or euHEART are publishing periodic newsletters that reach thousands of stakeholders worldwide.

International linkages

Internationally the WIRI agreement [3] and the Osaka Accord [4] have established a worldwide agenda for physiome research under the patronage of the European VPH initiative and the IUPS Physiome Project. Other important events in the last 12 months have been the participation of a European delegation at the IMAG[2] symposium in Washington in 2010; the SBML/CellML [5] combined meeting in Edinburgh in October 2010, or the *Virtual Tissue* conference organised by the USA Environmental Protection Agency and the European Commission in Spring 2009. These and similar earlier events have been of considerable political relevance, and have strengthened the role of the European VPH community on the international research scene. Note that many of the VPH-I projects have international partners and the NoE itself has 'International General Members'. This formal recognition of international membership is also important for VPH-linked co-funding arrangements in countries outside Europe. The five 'International Cooperation projects' funded under VPH are; RICORDO, TUMOR, NMS, Sim-e-Child and MSV (see below under VPH-I projects for further details). The ARGOS project, to promote common methods for responding to global eHealth challenges in the EU and the US [6], is another opportunity to encourage US input to the VPH as well as VPH input to IMAG.

[2] The Interagency Modelling and Analysis Group (IMAG) coordinates multi-scale modelling initiatives from various United States agencies including the National Institutes of Health, National Science Foundation, National Aeronautics and Space Administration, Department of Energy, Department of Defence, United States Department of Agriculture, and Unites States Department of Veteran Affairs.

VPH-I projects

The goals of the current 21 VPH projects are summarised briefly below. There are major technological achievements in various areas, including: data collection, management and integration; processing and curation of data into information; reductionist and integrative modelling of pathophysiological processes; presentation, deployment and end-user applications. It is also notable that there is already an active involvement of companies participating in the VPH consortia, both SME and large corporations, and that the involvement is moving from their R&D departments to their strategic management as the first business scenarios emerge. The clinical partners are providing a vital contribution to many of the VPH projects, participating enthusiastically and with considerable commitment. Note that the NoE clinical advisory board is now playing a more active role and provides a mechanism for generalising the lessons learned from the clinical partners of the individual VPH-I projects.

The VPH-I projects have made significant contributions to the NoE Toolkit, providing a wide range of content relevant to the wider VPH community. Major technological contributions include tools for collection, management and integration of data, processing and curation of data into information, reductionist and integrative modelling of pathophysiological processes and presentation, deployment and end-user applications. Even at this embryonic stage of the Toolkit, it is clear that the community is nurturing a wealth of potentially powerful and relevant tools. The Toolkit portal - in conjunction with its requirement to annotate content with limited metadata - can usefully bring some order and structure into this collection, with the NoE clarifying direction and recommending strategies that promote interoperability and sustainability.

Example tools range from software for data exchange (e.g., ArchFTP client) to physiological modelling (e.g., the euHeart software framework) and also include database and analysis support. Many imaging related tools are being developed, which reflects the importance of imaging to the VPH community, but perhaps, also increases the danger of overlapping functionality. Standards are not widely professed, but they are in evidence, from the use of XML to structure data (e.g., HAMAM) to the use of CellML/FieldML/SBML in the modelling work. Also, it is encouraging to see active uptake of underpinning technology frameworks like MAF, GIMIAS, ITK, VTK, cmGUI and OpenCMISS. Deployment of these tools helps to consolidate the respective user communities, accelerates tool development and encourages standardisation. Some of these frameworks, although initiated before the VPH-I was started, are being actively adopted and used in running VPH-I projects (e.g., MAF in VPHOP, MSV and NMS Physiome; GIMIAS, cmGUI and OpenCMISS in euHeart, RICORDO, MSV and VPHShare; ITK/VTK underpinning both MAF and GIMIAS).

Various centres of expertise are emerging, focused around expert groups that can assist new users, helping those in difficulty and clarifying the merits of the technologies to potentially interested parties. This might be considered a pragmatic approach to standardisation because experts tend to offer opinions that are necessarily biased towards data formats that have been effective for their own use. Naturally, this encourages uptake of a subset of available formats.

The current VPH projects (listed here in alphabetical order) are targeted as follows:

ACTION-Grid (CA) is promoting collaboration in medical/biomedical Informatics and grid technologies to promote the interface between ICT and nanotechnology.

ARCH (STREP) is developing clinical decision support tools based on patient-specific predictive modelling of vascular pathologies.

ARTreat (IP) is developing an interventional decision support system for stenting procedures based on multiscale patient specific models of atherosclerotic disease.

CONTRACANCRUM (STREP) is using multiscale modelling techniques to simulate patient specific cancer treatment outcomes.

euHeart (IP) is developing open source codes and multiscale/multi-physics models of heart electromechanics for clinical cardiac diagnostic and device development applications.

HAMAM (STREP) is establishing a database of curated and annotated imaging data and software tools for breast cancer diagnosis.

IMPPACT (STREP) is developing minimally invasive, patient-specific treatment strategies for liver cancer based on bioengineering multiscale modelling principles.

MSV (STREP) is developing visualization of multiscale data through open-source extension to the visualization toolkit (vtk).

NeoMARK (STREP) is implementing collaborative research networks and tools for the early detection of oral squamous cell carcinoma.

NMS Physiome (STREP) is a transcontinent NeuroMusculoSkeletal physiome activity in pursuit of personalized, predictive and integrative musculoskeletal medicine.

PASSPORT is developing an open source multiscale framework for diagnostics and surgical training in the liver, based on modelling liver cell regeneration.

preDiCT (STREP) is developing models of cardiac electrophysiology for drug design and toxicity testing.

PredictAD (STREP) is developing an evidence based statistical framework for diagnosis of Alzheimer's disease.

RADICAL (CA) is investigating security and privacy issues for VPH applications and best practices for medical and genetic data protection in distributed environments.

RICORDO (STREP) aims to support VPH resource sharing by providing a semantic interoperability framework that links physiology-related data and model resources (www.ricordo.eu).

Sim-e-Child (STREP) is a grid-enabled platform for large-scale simulations in paediatric cardiology.

SYNERGY (STREP) is a modelling and simulation environment for systems medicine and decision support for clinicians using chronic obstructive pulmonary disease as a demonstration case.

TUMOR (STREP) is an interoperable, clinically oriented, semantic-layered cancer digital model repository.

VPH2 (STREP) is developing decision support tools for heart disease.

VPHOP (IP) is developing a patient-specific, multiscale modelling framework for predicting osteoporotic fracture in elderly patients.

VPH-SHARE (IP) is developing of an organizational framework for the widespread integration of VPH services.

Two further FP7 projects that link strongly to the VPH-I projects are:

p-Medicine will create an infrastructure that will facilitate the translation from current practice to personalized medicine. The project is designed to bring VPH methods to three sets of clinical trials treating various cancers (leukaemia, breast cancer, Wilms' tumour).

INBIOMEDVision - aims to become a European-wide initiative intended to monitor the evolution of the Biomedical Informatics field and address its scientific challenges by means of collaborative efforts performed by a broad group of experts with complementary perspectives on the field.

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

DEISA[3] VPH virtual community

The VPH-NoE has also taken steps to build a relationship between the NoE and the VPH-I research projects through the development of a DEISA (www.deisa.eu) VPH Virtual Community. The Virtual Community, applied for and managed by the VPH-NoE on behalf of the VPH-I, provides access to high performance computing facilities for any VPH-I research and allied projects which require such a facility. Currently, over 50% of the projects are being supported in this manner. Moreover, additional EU funded projects working in e-Health related domains are also being supported. The Virtual Community has been renewed by DEISA for the last two years, with a total of 5.6 million CPU hours being allocated between the start of the community in 2008 and the end of DEISA in early 2011. In the future the VPH will require access to the petascale resources available within the new PRACE infrastructure (www.prace-project.eu). Overall, the requirements include seamless access to such high-end computing resources and distributed heterogenous patient data, facilitated by high quality-of-service high bandwidth networks. In this respect, the VPH is supported by the new EU FP7 project called MAPPER (www.mapper-project.eu).

3. Sustaining the VPH

Currently, the only coordination of the VPH-I projects is via the VPH NoE, which is also pursuing its own specific goals such as the VPH toolkit. In order to transform the VPH vision into a reality for European industries and healthcare services, a long-term coordination action is needed in order to:

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

These activities cannot be maintained in the long term by the NoE or by any other initiative that has funding for a limited period. They require the attention of a permanent organisation, capable of ensuring continuity over actions that may last for decades. This requires that the issue of sustainability of the VPH initiative be addressed. In our view, the best way to achieve this will be to establish a non-profit European 'VPH Institute' with a mandate to support the maintenance of VPH databases and the continued development of standards and business-friendly open source software.

A VPH Institute

In the 2009 document, we stressed that in order to ensure long-term sustainability of the VPH initiative, it is necessary to establish a collective identity in the form of an international, non-governmental, not-for-profit organisation, hereafter referred to as the *VPH Institute*. A *pro tempore* Board was established in 2010 by invitation to nine leading figures in our community. This group elaborated a draft statute that was publicly discussed on Biomed Town, and then formally approved during the Strategic Consensus Meeting held in Brussels on 29 September 2010. General consensus was found around the statute and the governance model it describes. Thus, the VPH Institute has entered its foundational phase, with the call for founding supporting members, and legal incorporation as a private not-for-profit organisation according to Belgian law. It is expected that the process will be completed by early 2011.

The need for a formal definition of the mission and vision of the institute was stressed during the meeting. This was included in a preamble to the statute, and says:

The mission of the VPH Institute is to ensure that the Virtual Physiological Human is fully realised, universally adopted, and effectively used both in research and the clinic.

[3] Distributed European Infrastructure for Supercomputing Applications - see www.deisa.eu

<u>The vision of the VPH Institute</u> for the first five years is to realise the VPH to the largest possible extent. To achieve this objective the VPH institute will work to:

- *Ensure that VPH-related research receives an adequate level of funding all over the world;*
- *Ensure that this funded research contributes with a high degree of synergy to the realisation of the VPH.*

In the next ten years the priority is to make sure that the VPH framework is:

- *Universally adopted;*
- *Deployed into research and clinical settings so as to produce the highest possible benefits.*

It is recommended that as soon as the Institute is formed, an international board is formed, to which the VPH Institute will provide the secretariat, to represent all scientific societies that worldwide are interested in the VPH, such as IUPS, IEEE, EAMBES, IFMBE, etc. This activity should also reconnect with the initiatives and the projects targeting the internationalisation of VPH, such as those described under 'international linkages' in Section 2.

VPH conference series

The ICT-Bio meeting [7] held in Brussels in October 2008 was the kick-off meeting for the VPH. The ICCB2009 meeting held in Bologna in September 2009 [8] was a second integrative biosciences VPH meeting. The NoE steering group is now planning a VPH conference series that will provide an annual event for the VPH community and also help to coordinate international physiome activities.

The first conference of the series, VPH2010, took place in the Université Libre de Bruxelles in Belgium on 30th September to 1st October, 2010. The meeting, which was opened by Zoran Stancic, Deputy Director General (DG Information), was devoted to the VPH Initiative and attracted 250 participants from VPH groups, Industry and Clinics. There were also representatives from countries such as Australia, Japan, New Zealand, Singapore and South Korea .

Over 95% of respondents stated that VPH2010 met with their primary objectives and 90% stated that VPH2010 was relevant to their practice, research or work. 73% of respondents from the feedback forms stated that they came to VPH2010 because of networking opportunities. This demonstrates a real need to continue with dissemination activities and VPH NoE will be continuing to host VPH events throughout 2011 and 2012.

Training and dissemination

With its broad multidisciplinarity and diversity, no single academic institution is likely to be able to (or indeed want to) provide specialist training for all aspects of the VPH. Cooperative training offers a potential solution, exposing students to leading experts who are specialists in their respective fields. Over the last twelve months, formal agreements have been drawn up between a number of educational institutions. These form the basis of VPH-focused ERASMUS collaborations. The next twelve months will see the first cohort of students benefiting from exchanges under this initiative with the NoE working to encourage further collaborations across the EU.

A critical mass of young and enthusiastic researchers is vital to the future of the VPH but other groups must not be neglected; it is essential that training activities also reflect the needs of the wider VPH Community. Translation of VPH models and tools to industry and the clinic will stimulate new and increasing demands for both trainees and trainers. It is critically important that the exploitation and rate of uptake of VPH technology not be held back by the lack of appropriately-skilled personnel. As mentioned previously, surveys are being conducted amongst potential clinical and industrial end users, exploring current attitudes to training, levels of training provision and investment and projected future requirements. This will define current practice and inform forward planning.

As highlighted above, external funding has been secured via the ERASMUS LL Programme to develop joint educational resources for generic VPH activities. This project, the VPH Masters Initiative Programme (VPH-MIP) will extend beyond the life-time of the NoE and it is envisaged that students will access the educational materials developed as part of a VPH community resource.

In this context, consideration should be given to the provision of a web-based facility, accessed by a portal, to provide a focus for interaction between training providers, course developers, young researchers wishing to develop a career in physiological modelling, established researchers seeking training as part of a commitment to Life-Long Learning, and representatives from the major employment sectors. VPH training will need to be responsive to the changing needs of employers, and an on-line resource would provide an environment to engage with and obtain feedback from industry, healthcare, and professional bodies. The mechanism by which this would be achieved is still under discussion, but the BiomedTown VPH portal, using Web 2.0 technologies and approaches, could be used to engage and build these communities.

4. What are the biomedical science challenges?

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

An important task is to identify and connect with other communities who are already working on standards and data-repositories within their fields. This is most pressing for molecular data such as protein-protein interactions, protein structure databases, gene expression and metabolic databases. New technologies based on second and third generation sequencing instruments (DNAseq, RNAseq, CHiPseq, etc) are now producing terabytes of data. VPH models increasingly incorporate the signalling, metabolic and gene regulatory networks needed to explain physiological function. Given the large role of signalling, metabolism and gene regulation in human disease processes such as cancer, diabetes, neurodegeneration, heart failure, etc, a description of these 'molecular systems biology' networks within multiscale VPH models is indispensable. There are a number of active communities within Bioinformatics and Molecular Systems Biology facing similar challenges to the VPH community, and it is important for scientific advancement in these areas to increase the communication between the communities dealing with different data types, ranging from molecules to models as well as clinical data [9].

We discuss these requirements below under (i) genomic networks, (ii) metabolic networks, and (iii) physiological databases. Issues to do with clinical data are discussed in the next section.

(i) Genomic networks – models and databases

The term 'genomic networks' often includes three levels of data: First, at the DNA level, there is the raw DNA sequence, promoter regions, enhancer regions and genetics variants (SNPs and CNVs). The major effort within the biomedical community during the last 5 years has been the genome wide association study (GWAS) monitoring a selected set of putative SNPs. However, this is only the beginning and within the next 5 year period an exponential increase is expected in data production. The requirements for standards and databases are active research areas in bioinformatics that, within Europe, are exemplified by efforts such as ELIXIR (www.elixir-europe.org), a European effort to develop an infrastructure for the life sciences.

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

This is one of the fastest developing areas in biomedicine and raises significant challenges on standardisation regarding storage, annotation and analysis.

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

There are significant challenges in how to integrate this variety of molecular information as well on standards and storage [10]. It is important that the VPH community establish links to these ongoing efforts in one of the most active areas in biomedical research of clear relevance for understanding diseases and therefore important for the health. Moreover, the challenge of relating genomic networks with multiscale physiological models, such that one can address and understand the genomic networks of complex diseases in a population context, defines a large and ambitious research topic that needs to be given specific attention in the coming years if we are to hope for tailored clinical treatments based on simulation studies of the genetic profile of the individual requiring treatment. Many challenges in personalized medicine reflect a lack of understanding of what is called the genotype-phenotype map (GP map), i.e. the aggregated phenotypic effects across different length and time scales of different constellations of genetic networks and related information on the DNA, RNA and protein level. The biomedical genetics community is now facing serious challenges concerning the overall applicability of the genome wide association study (GWAS) approach when it comes to drug development and personalized medicine. The VPH initiative may be of substantial help by providing mechanistic model descriptions of the phenotypic effects originating from genomic network variation. Such causally cohesive genotype-phenotype (cGP) models are very advanced multiscale physiological models with an explicit link to molecular information and with the capacity to describe, for example, how genetic variation manifests in phenotypic variation at various systemic levels up to the tissue, organ and whole-organism level.

Gaining a quantitative understanding of the phenotypic variation in humans as a function of genes and environment in a mechanistic sense, i.e. understanding the GP map, in both the explanatory and predictive sense, is a tremendous challenge that awaits technological, conceptual and methodological breakthroughs [11]. The impact on biomedicine of such an understanding, capable of linking genes, phenotypes and population level genetic phenomena through a causal understanding of the GP map can hardly be overstated. One of the three new exemplar projects in the VPH NoE in 2010 is specifically targeted to the development of such cGP models.

(ii) Human metabolic networks – models and databases

Metabolism provides the energy for all physiological processes and biochemical processes are therefore closely coupled to the physiological functioning of cells and organs. Molecular networks for intracellular signalling networks link extracellular stimuli such as hormones to the adaptive responses of the cell. Intracellular signalling networks and metabolism are not separated but interact very extensively thereby providing a strong link to the physiological databases and models. Note that modelling human physiology requires not only consideration of metabolic networks inside the cell, but also the exchange of metabolites among various cell types in a tissue (for instance between astrocytes and neurons in the brain) and transport processes of metabolites between organs in the body.

A large body of biochemical literature on human metabolism is available, and metabolic genes in the human genome have been partially characterized. With regard to the reconstruction of human metabolic networks, initial reconstruction efforts were made and are available in databases. There are several tools available for reconstruction of metabolic networks including KEGG (www.genome.jp/kegg) and BioCyc (biocyc.org). Efforts to merge the existing databases on human metabolism and provide common standards have begun, but progress is slow and is hindered by lack of a strong unifying organisation. While data on human metabolism are perhaps somewhat more

ambiguous than genome sequences, the benefits of having a well-organised database of human metabolic pathways would be substantial. The content of such a database can be formed based on all genes in the human genome which are known to be linked to metabolism. This can be complemented and augmented by incorporating knowledge from the vast biochemical literature.

It is advisable that the VPH community take an active role in an organisational structure for a joint effort with molecular systems biology to establish and improve a unified database of the human metabolic system. A discussion of current databasing initiatives that the VPH could link to is given in Section 7.

In addition to the reconstruction of the human metabolic system, an inventory and standardization of modelling approaches and modelling tools especially suited for metabolic network simulation, analysis and visualization should be undertaken. The development and adoption of generally accepted standards for metabolite nomenclature and identification, reaction stoichiometry, kinetic equations, etc, should form the basis of databases of all metabolites, reactions, kinetic equations and analysis tools relevant to human metabolism. Metabolic models could be readily exchanged and interlinked if based on these standards and databases.

(ii) ***Physiology – models and databases***

A further significant gap is the lack of comprehensive web-accessible databases of physiological data, encoded with well-established data and metadata standards. Such data provides numerical parameters for use in computational models. This need was expressed in section 3.2.3 of the VPH STEP roadmap. One standard, DICOM, does exist for medical image data. Others such as C3D (www.c3d.org) are well established binary data formats for specialist communities (biomechanics, animation and gait analysis in the case of C3D). A more general purpose metadata standard (BioSignalML [29]) is being developed for annotating physiological time-dependent signals encoded in a wide variety of existing specialist standards. But even this represents a small fraction of what is needed. A major effort is now needed by the physiology community to identify the types of physiological data that are available and to begin the development of a broad range of data standards and data repositories; as a first step, example datasets are being collected from the VPH-I and VPH NoE-Exemplar projects. The tools for interpreting these data are being developed by the VPH and Physiome Projects. These data resources have to be aligned to corresponding efforts on physiological models (Section 6).

5. What are the healthcare challenges?

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

The needs

The European healthcare system, including its biomedical research and technological development component, is a huge, complex, and highly articulated system. Due to the peculiar political history of the European Union, it is not a surprise that such a system is highly fragmented, not only between members states, but also between regions, districts, and even single hospitals. However, in spite of this extreme heterogeneity, there are some common requirements that are emerging in a number of analysis documents produced by very different sources [12-15]. Such requirements can be summarised in three keywords: *Personalised*, *Predictive*, and *Integrative* healthcare. A fourth keyword, *affordable*, is implicit, as the sustainability of healthcare systems is becoming the number one issue in a number of member states dealing with a constantly aging population.

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

The 'Digital Me' vision

The vision we have is of a 'Digital Me', a coherent digital representation of each patient that is used as an integrative framework for the consolidation within the European research system of fundamental and translational Integrative Biomedical Research and the provision to European Citizens of an affordable Personalised, Predictive, and Integrative Medicine.

This vision and the currently open call for a support action targeting the so-called 'Digital Patient', have three major challenges:

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

From this description, one might see a risk of overlapping with the VPH Research roadmap, but this risk is only apparent. In our opinion the Digital Patient roadmap should focus on problems closer to the deployment of the VPH vision, i.e. on problems such as user interface, information systems interoperability and integrability, generalisation and wide use deployment of the concept of integrative model.

Personalised, predictive and integrative healthcare

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

Clinical data

The re-use of clinical data remains a key challenge. As pointed out in the STEP roadmap, there is a need for "Global VPH security that makes possible the federation of clinical databases located behind hospital firewalls into the VPH framework" (VPH Research Roadmap section 12.1.5). In a recent report [15], Deloitte writes: "Most Life Sciences (LS) Research & Development functions are under increasing pressure to improve innovation, reduce development inefficiencies and advance product safety. Patient-level data, collected through Electronic Health Record (EHR) systems, offers one promising avenue for redefining Research & Development (R&D) and revolutionizing the LS value chain. Globally–aggregated, patient-level data could support the identification of disease mechanisms and new discovery areas, accelerate the termination of unsuccessful compounds, decrease patient recruitment cycle times for clinical trials, and improve drug safety surveillance

through continuous monitoring". In conclusion, there would be significant value in federating these databases. However, it is important to recognize that the majority of the 'clinical databases' behind the firewalls are poorly structured and annotated, according to an ICT perspective. This remains a serious hurdle for medical informatics in realizing the full potential of the VPH vision.

Interoperability is the key to the effective re-use of clinical data. Currently, data exchange tends to be *ad hoc,* and no facility exists to support organised data exchange between multiple independent repositories (clinical, industrial and research). Candidate technologies capable of providing a data infrastructure that can facilitate VPH-wide data exploration, exchange and interoperability need to be explored and evaluated. A viable data infrastructure must support many activities (curation etc) giving data prospectors the freedom to revolutionise clinical procedures from the data they obtain, and yet issuing data providers with necessary assurances that their data will not be abused. Facilities for secure download/upload must be supported and data providers require further assurances that data users are appropriately authenticated and authorised to use the data. The VPH Institute is one mechanism by which formal authorisation procedures could be managed and policed whilst also providing guidance on recommended procedures (e.g., anonymisation) that are important to the clinic. The VPH Institute is also well placed to be at the vanguard of standardisation efforts, since it will be astutely aware of the needs of the community and could recommend appropriate strategies that maximise opportunities for data interoperability. For instance, SNOMED CT is a comprehensive clinical terminology that is starting to become a standard in many clinical communities, including adoption as the language of the Care Records Service of the NHS in the UK, and is thus a target for adoption by the VPH initiative. This is but one aspect of a wider initiative, which includes such fundamental efforts as the harmonisation of nomenclature (modelling and clinical) through adoption of formalised ontologies, recommendations for data formats and data interchange (eg. DICOM) and suitable representation on international standards committees (e.g., HL7). The standards activity is necessarily multifaceted, and must recognise the competing demands of research, industry and the clinic. This is an opportunity for VPH advancement which would be sensitive to the dangers of over-regulation.

Finally, there are important legal issues to be tackled. By its very nature, the VPH crosses scientific and national boundaries. Differing interpretations of data protection law (eg. EU directive 95/46/EC) between member states discourage collaborative sharing of data for patient benefit. This is compounded by jurisdictional uncertainty due to a lack of legal precedents in this area. The ethical considerations relating to sharing of patient data are also formidable and could easily become a stumbling block to the progress of the VPH. The VPH Institute would be a proponent for change, guiding and focusing effort in both areas, ensuring that these issues are given the priority they deserve in order to secure the vision of personalised and integrative medicine that is the goal of the virtual physiological human.

EC regulatory policy

Translation of predictive modelling technology to the clinic is an exciting prospect and a leading driver for many researchers. However, clinical uptake is associated with greatly increased responsibility and essential regulation. Few researchers have the knowledge and experience required to undertake this final step. In the next twelve months, the VPH must plan the development of an environment to foster translation. Industry will be a critical partner in the translation process but, whilst industry has ready access to regulatory guidance in support of the introduction of a new pharmaceuticals or medical devices to market in the EU, this is not the case for software. The emergence of VPH technology in the clinic comes at a time of significant regulatory change; since the revision of the European Medical Device Directive which came into force in March 2010, the definition of a Medical Device now includes software used for diagnostic and medical purposes. Such software, if intended for sale or distribution for clinical use, must first be CE marked. Only software produced and used in a clinical institution is exempt from CE marking, although in practice all issues of conformity should still be addressed. The Commission has published a guidance

document to help identify software which is categorised as a Medical Device, but at this early stage of implementation, many European States differ in their interpretation of the Directives.

The VPH Community has a responsibility to raise awareness of these issues and, towards this goal, is extending its current programme of industrial engagement to include the regulatory community. As a first step, the NoE organised a regulatory and standards event as part of the September 2010 Industry Day. Invited speakers included representation from the FDA, the DICOM standards working group and COCIR the trade association, representing European Radiological, Electromedical and Healthcare IT Industry. COCIR is particularly active in the context of EU software regulation and has set up a Medical Software Task Force. Continued involvement with these groups must be a strategic aim and will help to guide researchers through the regulatory minefield.

VPH technology will have to meet two further key challenges en route to routine clinical application: it has to prove both its clinical and socio-economic benefits, and it needs sustainable business models. More and more, funding agencies require such activities as an integral part of ongoing research to ensure that the output will indeed meet the needs of clinical users, the health system, industry and society.

Impact analysis

In biomedical research, methods assessing the clinical and socio-economic impact of complex technologies such as multiscale computer modelling of human physiology have rarely, if ever, been applied. Whereas conventional health technology assessment (HTA) is usually applied only to incremental, almost established, technological innovations (which are studied as a well-defined alternative intervention at specific decision-points in a treatment algorithm), VPH technology may lead to the complete transformation of diagnosis and treatment pathways and thereby of the respective clinical guidelines. The assessment of such complex, multi-faceted health technology innovations already during their early phases of development requires innovations also in clinical and socio-economic impact assessment [17]. A new, multilevel generic methodological framework will have to be developed, built on a method-mix of socio-economic cost benefit analysis, the comparative analysis of healthcare pathways, and disease cost simulation models based on health economic theory. In order to guide the research process itself, and to help focus it on the most promising and realistic development path, a prospective, formative approach is mandatory.

Business models

Such approaches will, at the same time, ensure a well-founded and structured framework for collecting key data needed to develop the business case and sustainable business models for healthcare provider organisations as well as industry. When leaving the academic and laboratory development stage, industry will have to take over and deliver the complex integrated systems that will in the end be needed to render VPH technology not only a viable, but also a highly beneficial alternative to present medico-technical solutions. The reliable, theory-guided collection of financial and non-financial data on benefits, costs and risks, on impacts perceived by clinical users, patients, healthcare providers and payers, on required organisational and behavioural changes etc, and their acceptance to key participants will pave the way towards defining the business case and identifying appropriate business models.

Market analyses to assess the longer term business potential and the development of exploitation strategies will support the translation, commercialisation and diffusion of ‘disruptive’ VPH technologies. To extract value from an innovation, a project needs an appropriate business model. At this stage, it is too early to specify distinct business models which deliver added value to the customers or clients. But business modelling will need to become an inherent dimension in the socio-economic impact assessment framework of future activities. The involvement of industrial partners in research consortia will strongly support such a perspective and facilitate eventual exploitation.

A further analytical dimension concerns the ‘business’ case at the societal level. Empirical evidence [18] shows that in many, if not most, instances new system technologies do not necessarily imply a

win-win situation for all participants, but rather that some of them may lose, and (if they have a powerful position within the healthcare system) may even act as so-called 'veto players' being able to block innovations in spite of their overall convincing return to society. It is to be expected that highly disruptive VPH technologies may fall into such a category, requiring complex interventions at the health system level and compensation for those who otherwise may be able to block diffusion.

6. What are the ICT challenges?

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

Model and data encoding standards

Mathematical models are developed by bioengineers, biomathematicians and experimental physiologists to quantitatively describe complex physiological processes. When these models are based on biophysical mechanisms and, where appropriate, incorporate anatomical detail, their predictive capability can provide physical insights into the interpretation of experimental data and can help formulate experimental hypotheses. In fact, the most powerful application of modelling occurs when there is a close interplay between modelling and experiment. With the increasing clinical application of these models in the VPH, a range of new challenges have arisen: In order to be used in clinical decisions, models must be *verified* (e.g., are the units consistent and are physical laws obeyed?), *reproducible* (can someone other than the author generate the model outputs from specified inputs?), *validated* (how accurately and under what conditions does the model match reality) and *available* (is the model encoded in a standard form?). There are other less essential but highly desirable aspects such as *parameter sensitivity* (how sensitive are the model outputs to particular parameter values?), *modularity* (can the model be incorporated as one component of a more comprehensive model?) and *usability* (is there freely available software to run the model, display results and if necessary modify parameters?).

The general strategy for developing the modeling standards is as follows:

1. Develop markup languages (MLs) for encoding models, including metadata, and data.
2. Develop application programming interfaces (APIs) based on the MLs.
3. Develop libraries of open source tools that can read and write the ML encoded files.
4. Develop data and model repositories based on MLs.
5. Develop reference descriptions to demonstrate model reproducibility.
6. Implement web services for a variety of tasks including access to automated scripts to run the models and compare results against experimental data, optimize parameter values for new experimental data and provide sensitivity analyses for changes in model parameters.

A useful way of viewing the development of standards is shown in Table 1, where progress in developing a specification of the minimal requirements for data, models and the simulation experiment are shown, along with the standards for the syntax of the data, models or simulation experiments and the ontologies for annotating the semantic meaning of terms in the data, models or simulation experiments.

	Data	Models	Simulation
Minimal requirements	Not available	MIRIAM [25]	MIASE [26]
Standard formats	PDB [27], DICOM [28] BioSignalML [29]	SBML, CellML FieldML	SED-ML [30]
Ontologies	GO [31], Biopax [32], FMA [33] SBO [34], OPB [35]	GO, Biopax, FMA SBO, OPB	KiSAO [36]

Table 1.The minimum information standards, syntax and semantics being developed for data, models and simulation experiments.

Note that the best example of an eHealth technology that is already in widespread use is the *Picture Archiving Communications Systems* (PACS) , usually based on use of the DICOM image encoding standard. Others close to maturity are *Electronic Transfer of Prescriptions* (ETP), *Computer based Patient Records and Electronic Medical Records* (CPR/EMR) and *Electronic Health Records* (EHR).

Model reproducibility

There must be a concerted effort towards reproducibility, interoperability and the re-use of VPH models, including both future models and legacy, published models. This requires adoption of the above consensus set of standards for the metadata that describe the models and of markup languages for their mathematical description. An integral aspect of interoperability will be the tagging of model variables and parameters with identifiers from reference ontologies such as the Foundational Model of Anatomy (FMA), Gene Ontology (GO), and appropriate ontologies for units, physics-based quantities, physiological processes, etc, as described above. These must be adopted not only by the VPH community but also by the curators of the massive existing gene-, protein- and metabolic-databases in order to enable vertical multi-scale linking of models at the physiological scale (organs, tissues, cells) to the wealth of medically relevant molecular data.

In VPH practice, there are two key types of obstacle to resource sharing and re-use, namely:

1) operational restrictions such as legal, ethical and competitive constraints, and
2) the lack of functional interoperability between data or modelling systems.

A key contributor to the latter is the heterogeneity of formats that data and model resources (DMRs) are encoded in. A second interoperability problem relates to the lack of consistent annotation of DMRs: for example, it may not be possible to discover all datasets in a VPH repository that are relevant to the study of a specific disease (e.g., diabetes) because such DMRs were not annotated using a standardized vocabulary of terms (e.g., instead free-text annotation using phrases like ‘glycaemic response’, FBG, ‘blood glucose’, OGT, *etc.*).

To this end, the VPH-I project RICORDO is developing a toolkit, and an associated set of ontology standards, that allows community users to (i) apply semantic annotation to data and models in a consistent manner, and then to (ii) query and reason logically over distributed repositories that share such annotations. Apart from improving VPH DMR semantic interoperability, RICORDO methodology will also contribute to overcoming other obstacles to resource sharing. For example, as annotations are applied to DMRs in a format-independent manner, the user may choose either to embed annotations directly in the original DMR files or to maintain such associations independently. This separation of annotation from DMR also allows VPH users to serve annotations via a separate repository service that does not require the public availability of the DMR to which these annotations were originally applied. In practice, therefore, this system allows users to make well-defined details of their work known to the community at large, while satisfying the operational constraints and obligations of confidentiality that sensitive clinical/industrial work often entails.

Model curation and annotation is a long-term task that spans a wide spectrum of disciplines and will require a major effort but it is crucial to the success of the VPH vision. Sustainability of model repositories and software (including version control, archiving, technical upgrades, and provision for

updating and expansion) will also be a major expense and limiting factor in the community acceptance of VPH models.

Top down or bottom up?

The VPH needs to encompass ‘top-down’, ‘bottom-up’, and 'middle-out' approaches. A good example of top-down is the Pharmaco-Kinetic-Pharmaco-Dynamic (PKPD) modelling community. PK deals with the advection, distribution, metabolism and excretion of drugs and PD deals with the dynamics of how the drugs affect receptors. PKPD models accommodate human variability in an empirical fashion and treat body compartments with highly lumped approximations. The ‘bottom-up’ approach of modelling molecular mechanisms at the sub-cellular level is the realm of the molecular systems biology community. The 'middle-out' approach is exemplified by simulations of biological behaviour that target those levels at which we have particularly good insight, using lower and higher levels of structural complexity both for the definition of input and boundary parameters, and as a test-bed for the validation of model-based predictions. The anatomically and biophysically based approaches of the VPH project are being designed to link these approaches. The model repositories based on the CellML and SBML standards already contain many models of both types. A particularly relevant challenge will be the nanoscopic representation of intra-cellular structures, that will allow the linking of molecular level pathway models to realistic spatial constraints, thereby providing the currently missing link to project between sub-cellular mechanisms and (patho-) physiological function as it manifests itself at the cellular and supra-cellular levels. Thus, the question is not 'top-down' or 'bottom-up', but how to link the two, in particular from nano to micro (as the micro- to macro-domain already forms an active part of present VPH activities) [36].

The challenges of model reduction and multi-scale model integration

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

Models such as the PKPD one addressed above, combine phenomena featuring very heterogeneous characteristic time scales. From the mathematical point of view, they can be seen as large dynamical systems with multiple time scales. In this case, the model reduction challenge is to automatically identify the most relevant eigenmodes of the system.

A different model reduction strategy can be applied to manage geometrical complexity. This is a fundamental issue in the solution of biomedical problems involving the human body. An example is the development of models for the cardiovascular system or the airways; both systems can be seen as networks of repeating units with decreasing spatial scale. An effective approach to handle this kind of complexity relies on the application of geometrical multi-scale models, where the reference scale is treated with the most accurate model at hand, i.e. Navier-Stokes equations for blood or air flow, while the contribution of smaller scales is described with reduced spatial dimension models, such as one-dimensional models or lumped parameter models. In the framework of VPH, the development of a general formalism to extend such model reduction and integration techniques to different applications (i.e. venous system, lymphatic system, spinal flow…) might be particularly effective.

A distinguishing feature of the multiscale challenge is the property that the reference problem and the underlying physical laws are homogeneous and known with satisfactory exactness, even though the problem is not immediately prone to discretization. In such cases, the role of model reduction and multi-scale integration is to increase the efficacy of computations while maintaining comparable accuracy with respect to the original model. On the other hand, VPH objectives must address biological systems that are characterized by the interaction of many different physical processes at each spatial scale. In these situations, a unifying macroscopic model is seldom available and multi-scale model integration appears to be the fundamental tool for modelling the theoretical input to a

macroscopic/coarse-grained model from a collection of more detailed microscopic models, bypassing the necessity of empirical description, when available. Several examples are possible, each one being a challenge for the VPH Project. For instance, very often the macroscopic properties of a tissue, such as the bone stress-strain curve, or the diffusion coefficient of a drug or chemical in the interstitial space of skeletal muscle, are related to microscopic effects. In these cases, homogenization and volume averaging methods can be used to obtain the strain energy function for bone tissue starting from basic information about a 'representative' microscopic cell. Similarly, mass transfer in biomaterials or within polymeric scaffolds for tissue growth, can be effectively described at the macroscale by using macroscopic parameters that are obtained on the basis of a microscopic 'cell problem' (i.e. on the reference elementary volume describing the scaffold).

A further example at the organ/tissue level is represented by the analysis of the beating heart, where large deformation mechanics of the myocardium are coupled to the reaction-diffusion equations governing the spread of electrical excitation, as well as with the equations of fluid mechanics for blood flow both within the ventricles and within the coronary vasculature. At the sub-cellular level the analysis of cardiac myocyte function requires the coupling of ion channel electro-physiology, calcium transport, myofilament mechanics, pH regulation and complex networks for signal transduction, metabolism and gene regulation. This shows that multi-scale model integration may be a challenging problem where multiple scales are simultaneously interacting, such as a micro-scale (interaction of chemical species, ions and proteins), a meso-scale (cardiac myocytes) and a macro-scale (the cardiac tissue treated as a continuum). Suitable techniques to identify a correct scale separation and to model each of them represent the main objectives of integrative multi-scale modelling.

Dealing with probabilistic and stochastic processes

Another modelling challenge, that has so far received relatively little attention, is that of incorporating stochastic behavior into the multiscale VPH models. At a molecular level stochastic behavior can be a reflection of Brownian (thermal) motion but at higher spatial scales it can be a reflection of unknown mechanisms – i.e. ignorance. It is very important that the consequences of this uncertainty in, for example, parameter values, be quantified.

There are two types of uncertainty:

- Aleatory Uncertainty: This uncertainty arises because of natural, unpredictable variation in the performance of the system under study. In our context, this involves the uncertainty we have on measuring (or more frequently estimating) the input parameters of our model.

- Epistemic Uncertainty: This type of uncertainty is due to a lack of knowledge about the behaviour of the system. In our context this might also represent our inability to measure or even estimate the patient-specific value of an input parameter, which forces us to replace it with a range of possible values observed in a representative population.

Although they are frequently used as synonyms, 'probabilistic' and 'stochastic' have different meanings. Probabilistic models assume that each random quantity can be described with a single distribution, whereas stochastic models accept that such probability can change over time and/or space. For example we can account for the aleatory uncertainty of the average module of elasticity of bone tissue using a probabilistic model where this input is represented with a Gaussian distribution of values. However, if we notice that the variance of the measure increases as the porosity decreases, we should have a different probability distribution in each point of the bone, as the bone tissue porosity changes from point to point, in which case we would need a stochastic model. In the VPH we need both approaches, depending on the particular case.

There are a number of mathematical methods for probabilistic and stochastic modelling, but only a few are adopted in biomedical modelling, and only to a limited extent. However, there are physiological processes that are inherently stochastic, e.g., in neuromotor control. In addition the clinical application of VPH integrative models, where rarely are all the inputs properly identified for each individual patient, requires in many cases that the population-based inputs be modelled as random variables of known frequency distribution. The use of the simpler approaches, such as

Monte Carlo methods, poses primarily a problem of computational weight, since every model must be run hundreds or thousands of times to get a single, probabilistic answer. The use of more complex approaches, for example involving Bayesian modelling, are still largely territory for fundamental mathematical and numerical research.

Aging

Age is still the best predictor for most complex diseases. This implies that if we are to create individualised models describing the development and maintenance of complex disease situations on given genetic backgrounds in a way that is of broad practical utility for medicine, we have to incorporate the effects of aging in multiscale and multiphysics models. The making of multiscale physiological models capturing the aging process defines a very ambitious long-term theoretical-experimental research programme that will be very much dependent on what phenomics can provide. As aging due to its stochastic nature is phenotypically manifested in so many different ways and places, a quantitative understanding of aging physiological systems will demand dramatically more spatiotemporal data than will be needed for understanding the physiology of young and non-diseased individuals.

By offering in silico representations of aging tissues and organs upon which one can systematically study the effects of various chemical treatments, such individualised models would also define the foundation for a new and sorely needed drug targeting paradigm. Even though this is a daunting undertaking, activity in this direction should be invoked in the coming years such that one can get a clearer view of what the major challenges are.

Convergence of image-based integrative prototyping frameworks

Biomedical imaging data, and by extension multidimensional biomedical signals, are key data elements in the construction and personalization of subject-specific models of anatomy and physiology. At the same time, these data sources are both intensive (high-dimensional, large-volume) and extensive (multi-modal, multi-scale, multi-source) resources with associated challenges in their processing, integration, analysis and visualization. Additionally, the requirements associated with the specific application domains where they are utilized (as a research tool, to derive diagnostic biomarkers, to develop interventional plans, or for real-time guidance or navigation in interventional procedures) do impose additional requirements on the underpinning IT systems. It is therefore not surprising that a number of IT toolkits and frameworks have emerged with partially overlapping functionalities but also with complementary focuses and characteristics. Given this context, it is highly unlikely, and possibly undesirable, that a single framework could be conceived that would address all the challenges, satisfy all the requirements, and meet all the needs for every application domain. Based on a number of consultation exercises performed by the VPH NoE, the vision has naturally emerged that the effort during the next period should go to defining a reference architecture that is generic enough to encompass the scope and diversity of current application frameworks to adopt it while, at the same time, is prescriptive enough to ensure the adherence to best practices, the compliance to certain standards, and the access to and/or interoperability between data formats and resources, software components, physiological models and computational resources. Over the last two years and within specific VPH-I projects, several institutions within the VPH-I community developing image-based prototyping frameworks, together with institutions outside the VPH-I promoting similar initiatives, have started efforts to share, identify and adopt best practices and discuss architectural implications of a common toolkit (www.commontk.org), which could become the basis for interoperability. Additionally, a number of other practical experiences have been started, whereby certain application frameworks have shown interoperability and reusability of components from other frameworks. For instance, several communications at the VPH2010 Conference demonstrated the interoperability between GIMIAS, MAF, cmGUI and Slicer3D.

Multiscale simulation and visualization software

Visualisation of the output of complex systems models and the human computer interface issues inherent in user interaction with such models is a new and significant area of research. Complex systems models are likely to have many input and output variables and may produce non-intuitive data representing, for example, emergent behaviours that are not easily represented by classical graphical or text-based methods. This is a rapidly moving area of cross-disciplinary research that may need specific funding under future calls for VPH project proposals.

The above challenges provide worthwhile and challenging problems for the mathematics and computational science communities and some VPH funding should be directly targeted to attract their expertise.

Data security

One of the main challenges for VPH-I researchers is to provide seamless and secure access to shared patient data for the benefit of clinicians, and academics for the purposes of patient care, as well as for scientific and translational research. As high profile security breaches and data losses are frequent headline news, the protection of medical patient data is of critical importance for VPH. The EU Data Protection Directive makes it a legal requirement for VPH-I projects to collect, hold and process patient data in a secure way. Hence, there is a need for VPH security solutions not only to protect the data itself, but also to protect VPH-I researchers from the consequences of unauthorised disclosure of medical information including negative publicity, legal liabilities and fines; and from unauthorised modification of patient data, which may lead to incorrect patient treatment and results in a loss of life, or identity theft that is currently creating a considerable concern.

There are many security issues that can arise when sharing data within VPH-I projects, including:

(i) How to give information owners assurance that their data are adequately protected when it is transferred to VPH research groups?
(ii) How to give data owners and VPH scientists assurances that patient records used in the research are protected in the right way?
(iii) How to give data owners assurances that the process of sharing data does not increase the risk of compromising their own resources? (i.e. opening firewall ports to access data)
(iv) How does a VPH scientist get access to shared data?
(v) How does one determine whether a VPH researcher is allowed to perform a task on shared patient data?
(vi) Who decides what the access rights of VPH researchers are?
(vii) How much change to the data providers' IT infrastructure is required to provide secure access to patient data? What are the hardware, software and support costs?

Some of these issues will be addressed by the p-Medicine and VPH-Share projects as well as a new VPH-NoE Exemplar Project ('The NoE, Infrastructure and the Challenge of Call 6'), which in turn should lead to a set of open source tools and best practice guidelines that can be applied throughout the VPH-I community.

Workflows and driving clinical problems

Routine clinical diagnosis or treatment follows well-defined care pathways, in the form of data workflows or operational or decision-making processes. Most VPH-I projects have developed, or are developing, IT-intensive clinical applications which deliver IT suites supporting model-based disease understanding, diagnostic decision-making or therapeutic plans or guidance. Such suites are usually composed of a workflow of complex information processing modules some of which can involve advance interactivity and visualization, data management, computational modelling or computationally intensive tasks. In many cases, such workflows involve a sequence of operations that start, for example, with clinical data (complying with standards relevant for privacy, security and ethics) and, by using the tools and models, end up with a clinically useful diagnostic index or treatment strategy. Therefore, the need has emerged for process modelling in addition to data and physiological modelling, and to envision application frameworks that enable such process modelling by its very IT architecture. Over the next period, the NoE will work closely with the VPH-I projects

and other related communities to analyse how the models, data and tools are used in biomedical and clinical workflows and to what extent they improve our understanding and modelling of diagnostic and therapeutic processes. This understanding should provide a solid basis for defining the requirements for the development or extension of future IT application frameworks that should be architecturally aligned both with healthcare processes and with the underlying business models and quality assurance mechanisms. Current efforts in the community, including software platforms like MAF or GIMIAS, which are part of the VPH Toolkit, have a workflow-oriented architecture inspired and particularly suited to this end.

7. A strategy for the VPH

Timelines

A timeline for the STEP project (an FP6 initiative), the NoE, and other VPH projects funded under the first Call 2 of FP7 and the recently funded international Call 4 projects, is shown in Figure 1 together with the anticipated future calls. The establishment of a VPH Institute is also indicated. The anticipated impact that the VPH activities will have is also illustrated, first on biomedical research, then on industry and finally on the general public.

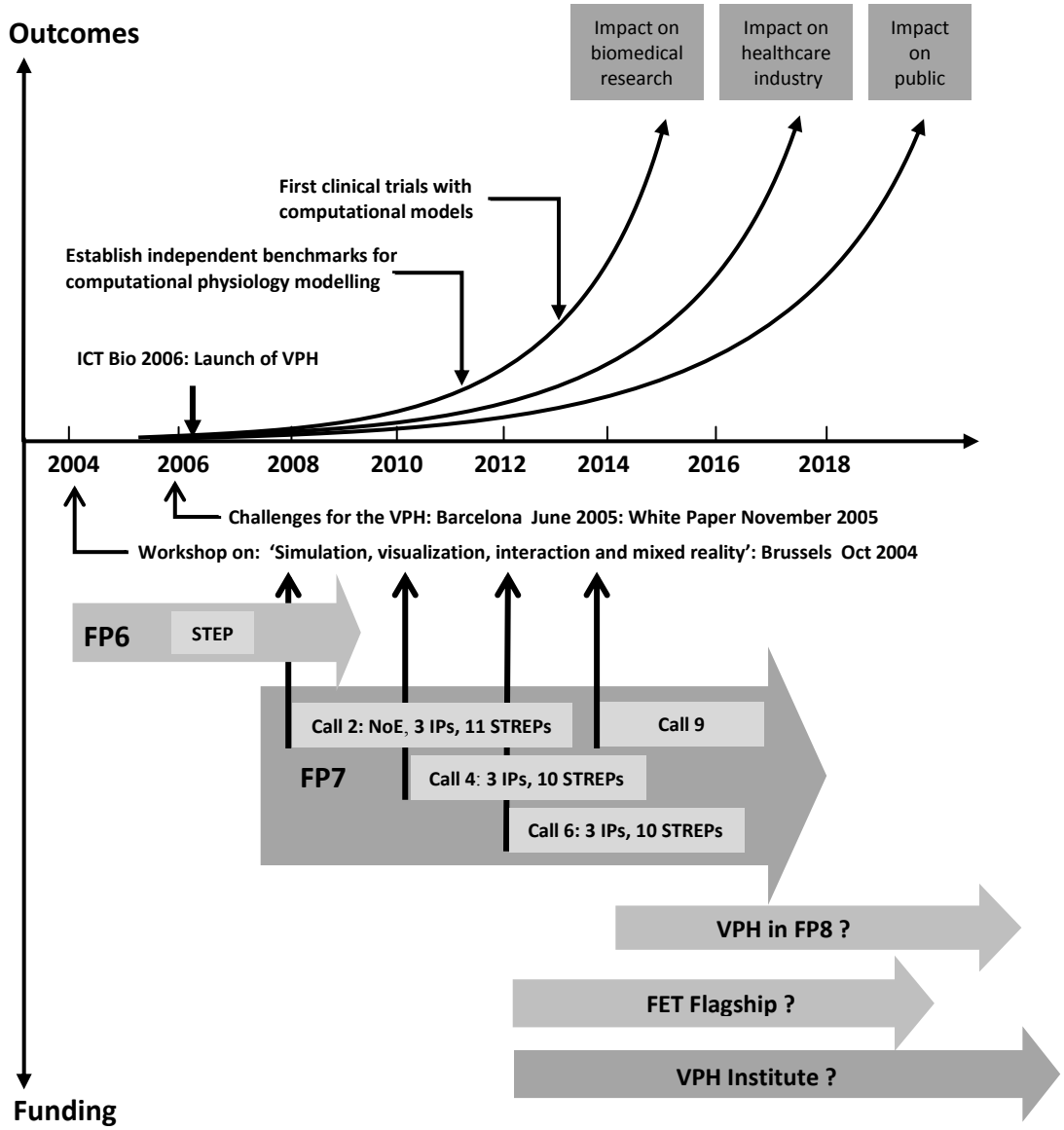

Figure 1. Timelines for VPH funding calls, the VPH projects and their impact on various communities. Sustainability of the NoE, and hence ongoing support for the VPH and the healthcare industries that depend on it, will be achieved through a VPH Institute.

The next steps

The VPH is a grand challenge. We propose the following specific actions.

2009-2011: Establish a collective identity

It is important that the multitude of players involved be able to speak with a single voice in a few strategic situations. This requires the creation of a collective identity around the VPH brand name. The VPH community is already working in this direction and will have a VPH Institute fully operational in early 2011.

2010-2012: definition and quantification of needs

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

- Road-mapping CSA[4] on VPH FET ('Future and Emerging Technologies')
- Road-mapping CSA in integrative health research
- Road-mapping CSA in health e-infrastructures

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

The figure below shows how the VPH initiative is positioned in this regard to date.

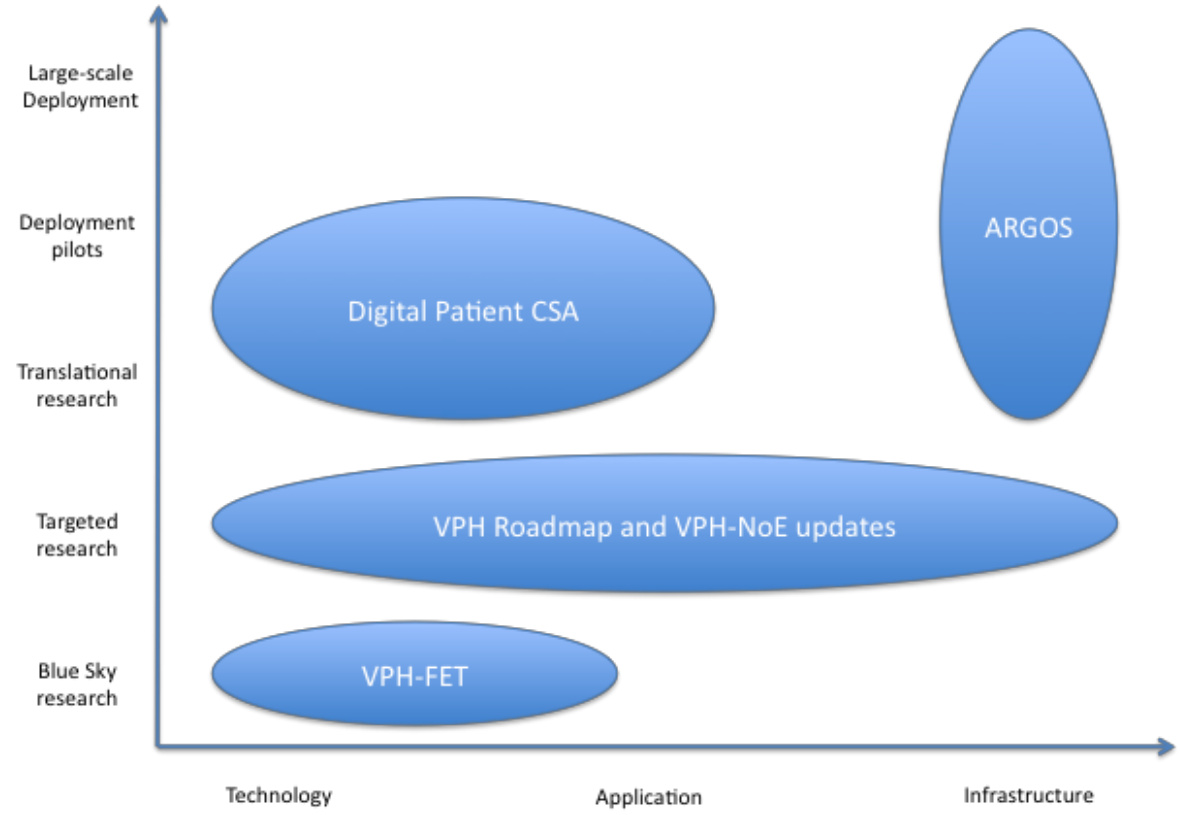

Figure 2. The VPH in relation to other related initiatives

[4] 'Coordinated support action'

The VPH Research roadmap produced by the STEP Action, and the annual update elaborated by the VPH NoE remains the primary source of strategic vision for the entire VPH initiative. In terms of recommendations, this roadmap focuses on targeted research, which is where most VPH funding has been targeted so far.

The FET Proactive unit funded a VPH-FET support action that is expected to produce a roadmap targeting 'blue sky' technological research by the end of 2011. In this action we are reaching out to the neighbourhood communities that work on fundamental technological research in computer science, applied mathematics, complexity theory, etc.

No calls for VPH e-infrastructure roadmapping were made, but the ARGOS observatory [6] is elaborating a policy brief for transatlantic cooperation on VPH Research. Such a recommendation will focus on the need to establish coordinated policies between Europe and the USA in order to ensure the interoperability and integrability of VPH infrastructures, as well as the long-term sustainability, in the current perspective of a research infrastructure, as well as in the future perspective of clinical and industrial infrastructure. As part of this action the VPH community is reaching out to those neighbourhood communities that operate large biomedicine-related cyberinfrastructures, i.e. molecular biology, biomedical imaging, cancer research, neuroscience, etc. There is still a hole in the area of blue-sky research for VPH infrastructures; the VPH community should consider positioning this specific challenge in the context of future ESFRI Roadmaps, possibly in concertation with these neighbourhood communities.

The current call for a support action on the 'Digital Patient', based on the necessarily short text provided in the work programme and in the call, will probably be positioned across both technology and its clinical applications, but with a more translational perspective. Once the proposal is selected, it will be possible to be more specific.

In all these actions, the general strategy the VPH community should adopt toward these neighbourhood communities should be inclusive, not invasive. We need to make clear that as VPH researchers we do not want to start designing e-infrastructures, running wet-bench biology experiments, or developing fundamental research in computer science, mathematics, or physics. We recognise that there are neighbourhood communities that can do this much better than we can. What we offer is a common goal toward which all these skills and those we represent as a VPH community can join forces. In the continuum of skills and interests, we need to find among VPH researchers those who are working closer to the fence with each of these communities, and support them as ambassadors toward the formation of mixed consortia that can run these road-mapping exercises in a qualified and representative way. It is equally clear that in each of these neighbourhood communities we need to find the experts who are fascinated by the challenge we pose, and who are not afraid of the change that this would necessarily require to their research practice.

2011-2014: Disseminate and structure

As the results from these road-mapping exercises emerge, it will be necessary to coordinate and organise them into an operational plan to tackle this European Large Scale Action. This action will have to find substantial dedicated funding at the European level, but at the same time will be sustained and nurtured by a number of funding actions in the various neighbourhood domains that will take place as part of FP8. Another important dimension will be played by member state funding agencies that case by case will support horizontal or vertical initiatives. Preparing such composite and structured action requires in our opinion a specific coordination action, which will play a preparatory role in this direction.

2014-2019: European Large Scale Action on personalised, predictive, and integrative healthcare

These five years will make it possible to face this grand challenge at all levels (research, technological development, implementation, assessment, deployment) only if the necessary critical mass is reached in terms of skills, resources, and commitment of all stakeholders. We hope this document will serve as the first step toward the creation of such a critical mass. We recently took the first

steps to position the VPH as a candidate technology for the future in the *European Innovation Partnership* on Active and Healthy Aging.

Toward a European VPH meta-infrastructure

We conclude this review with a brief description of other European Research Infrastructures (or e-infrastructures) that are currently being established or considered:

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

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

The VPH Community could consider an exploratory action for the creation of a European Biomedical Engineering meta-infrastructure specifically aimed at generating new knowledge by processing, modelling, and integrating all data and information stored in the above infrastructures, possibly using the available computing infrastructures.

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