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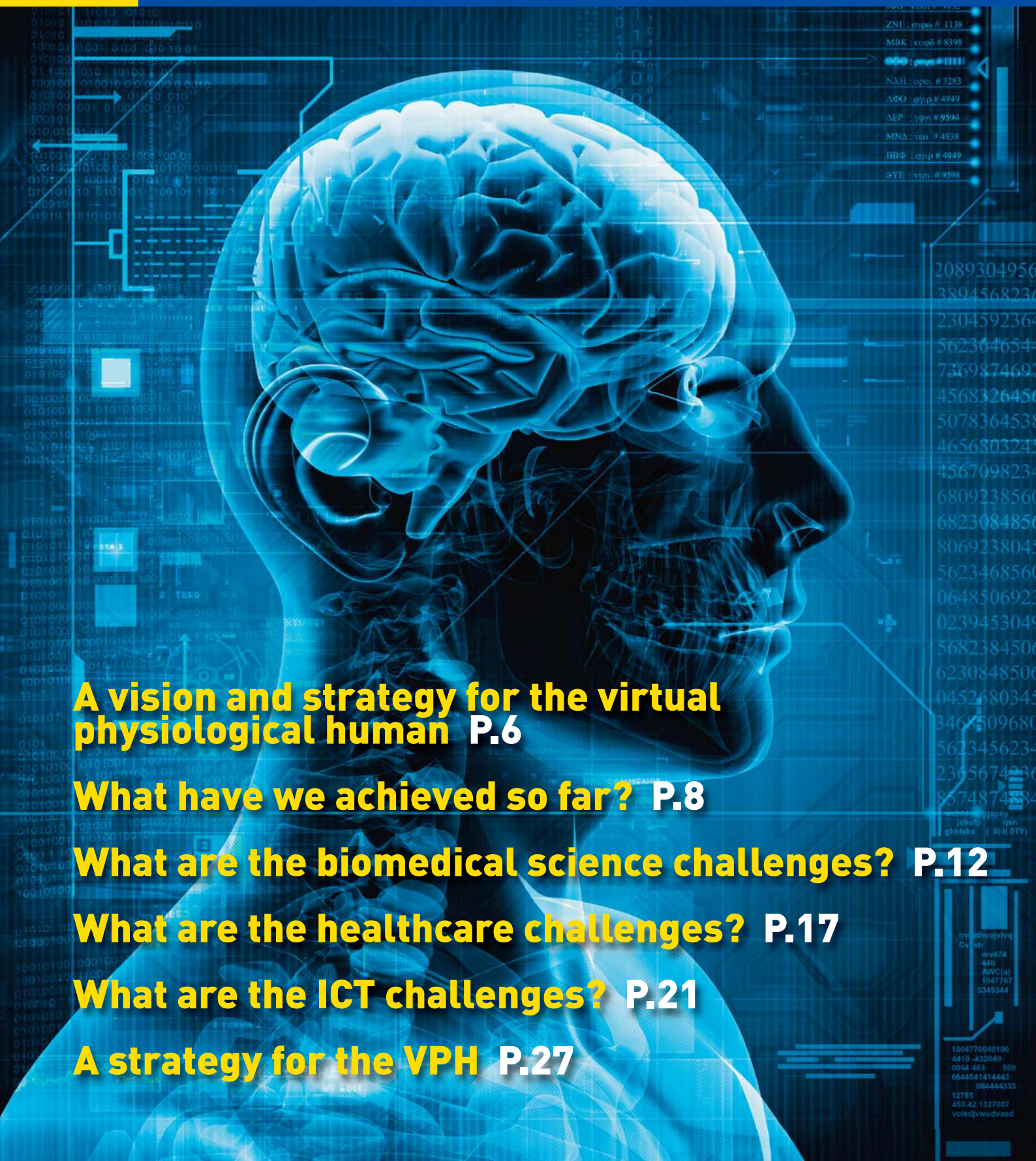
VPH NoE newsletter

VIRTUAL PHYSIOLOGICAL HUMAN NETWORK OF EXCELLENCE



Virtual Physiological Human
network of excellence

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EDITORIAL

The VPH Network of Excellence is close to completing four successful years of achievements and I am delighted to announce that the VPH NoE has been granted a six-month extension until March 2013. The VPH NoE was set up with 'service to the community of VPH researchers' as its primary purpose: we believe that our efforts in the creation of the VPH NoE ToolKit, the implementation of VPH study groups, educational meetings and training events, clinic- and industry-orientated events and the creation of the VPH conference series has come some way to achieving this service.

I would like to thank Tara Chapman for her exceptional work as Editor in Chief of the newsletter over the VPH NoE years. The VPH NoE newsletter has been an important way in which the VPH NoE has connected with the VPH community. We have given updates on news within the VPH NoE, highlighted events and provided updates on developments both within and outside the NoE relevant to the VPH initiative. We featured interviews with leading international experts, clinicians, researchers and industry personnel in VPH related fields. Each issue of the newsletter also featured an update on Exemplar projects in the form of a 'Technical report' discussing their progress.

To look back at the history of the VPH NoE newsletter: the first issue highlighted the VPH NoE project and introduced some of the new VPH Initiative (VPH-I) projects from the FP7 Virtual Physiological Human Call (ICT-2007.5.3.) Issue 2 introduced the VPH NoE Exemplar projects and gave an update on SuperComputing, whilst issue 3 continued to update on the progress of the VPH-I projects. Issue 4 focused on clinical trials with VPH-I projects and demonstrated some of the new and exciting developments in the VPH field. Issue 5 was dedicated to the 50th anniversary of cardiac modelling and saw contributions from some of the most promising groups in cardiac modelling. Issue 6 focused on the new and exciting virtual physiological human projects (Call ICT-2009.5.3) and issue 7 focused on the E-infrastructure for the Virtual Physiological Human whilst continuing to highlight new projects.

In this eighth and final issue of the VPH NoE newsletter we'd like to look at some of the achievements of the project. The project and its partners have been involved in a total of eight hundred and fifty-three events over the last four years promoting the concept of the VPH. VPH2012 is the second in the series of international VPH conferences organized by the VPH NoE, and is supported by the European Commission ICT for Health / DG Information Society and Media. We are pleased to have four keynote speakers who are internationally acclaimed leading experts in their respective fields: Professor Raimond Winslow, Professor Salvador Moncada, Professor Douglas Kell and Professor Hiroaki Kitano. This year there will be an overall theme of integration of the VPH projects with subthemes on: (1) Physiome: multiscale modelling of physiology and pathology; (2) Virtual Physiological Human: infrastructures and technologies for integrative biomedical research; (3) Systems Medicine/-omics and (4) VPH in Translation. We hope to see as many of you as possible there!

We have been extensively involved in education and training. Alongside the study groups, 2013 will see the release of the 'VPH Textbook' which represents a major effort from a large number of contributors. In the final year, the VPH NoE will continue to work with AMEE in a major collaborative effort to deliver effective Virtual Patient teaching materials. We have also produced a short video of the VPH and edited five special VPH dedicated issues in Phil. Trans. R. Soc. A., and also several articles in newspapers, professional association newsletters and others.

The VPH NoE newsletter and outreach activities have been fundamental in fostering the development of a VPH community, but what is the VPH without the necessary tools to enable different software, built by different laboratories in different universities, towns and countries all over the world, to speak to each other? To achieve the aim of a truly 'digital patient' an infrastructure needed to be put in place. The VPH NoE has worked hard throughout its lifetime to create such an infrastructure. The VPH Toolkit is a shared and mutually accessible source of tools, research equip-

ment, managerial and research infrastructures, facilities and services. A great deal of effort has made throughout the VPH NoE on building internal – and capturing external – ToolKit materials to maximise the availability of software resources to the VPH community. There were eleven Exemplar projects set up with the VPH NoE to work closely with the VPH ToolKit. These individual projects have met with considerable success during the lifetime of the project and presentations from nine of these projects will take place at the forthcoming VPH2012 (**www.vph-noe.eu/vph2012**).

We recognise that there needs to be a continuation of the knowledge and resources built up after the lifetime of the project. To this end we have been working hard to create a VPH Portal. The portal will house the ToolKit and aims to be the future source of all VPH resources. This portal will be run by the VPH NoE during its lifetime and will then transfer to the VPH Institute. The Virtual Physiological Human (VPH) Institute for Integrative Biomedical Research (or VPH Institute) is an international non-profit organisation, whose mission is to ensure that the Virtual Physiological Human is fully realised, universally adopted, and effectively used both in research and in clinic. The VPH institute will take over from the VPH NoE in many respects, including the running of the VPH conference series and the management of the VPH Portal after the VPH NoE has finished.

The VPH Network of Excellence as a project will end, but its legacy will certainly remain. This legacy includes a roadmap for the future of the field. The 'VPH Vision and Strategy Paper' has been coordinated by Prof Peter Hunter and is the combined result of continued input from consultation with VPH projects, experts in relevant fields and yearly strategic consultation public meetings. A previous version of the VPH NoE Roadmap/Vision and & Strategy Paper was edited and published in May 2010 in Phil. Trans. R. Soc., 'A vision and strategy for the virtual physiological human in 2010 and beyond' by Hunter et al. Most notably, it was one of the most cited papers of the journal in 2010*. For this final issue it is therefore fitting and appropriate that this document should be published in the last VPH NoE newsletter.

I would like to thank all the partners of the VPH NoE for their dedication throughout the lifetime of the project. I would like to thank Joel Bacquet , former VPH NoE project officer, for his hard work and enthusiasm that was fundamental to the success of the project and to our current project officer, Amalia Vlad for her continuing support. I would also like to thank Miriam Mendes (project co-ordinator) and Vanessa Diaz (technical co-ordinator) who have brilliantly succeeded in steering the network of excellence. I would also like to thank you, the VPH community for your continued support and wish you good luck in all your future endeavours.

By Peter Coveney,
VPH NoE Project Coordinator

*http://rsta.royalsocietypublishing.org/site/misc/top_ten.xhtml.

A VISION AND STRATEGY FOR THE VIRTUAL PHYSIOLOGICAL HUMAN

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SUMMARY

European funding under Framework 7 (FP7) for the Virtual Physiological Human (VPH) project has been in place now for five years. The VPH Network of Excellence (NoE) has been set up to help develop common standards, open source software, freely accessible data and model repositories, and various training and dissemination activities for the project. It is also working to coordinate the many clinically targeted projects that have been funded under the FP7 calls. An initial vision for the VPH was defined by the FP6 STEP project in 2006 [6]. In 2010 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 [9]. We proposed that a not-for-profit professional umbrella organisation, the VPH Institute, should be established 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 [9]: (i) a vision for the VPH updated in the light of progress made so far, (ii) biomedical science and healthcare challenges that the VPH initiative can address while also providing innovation opportunities for European industry, and (iii) external changes needed in regulatory policy and business models to realise the full potential that the VPH has to offer to industry, clinics and society generally.

KEYWORDS

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

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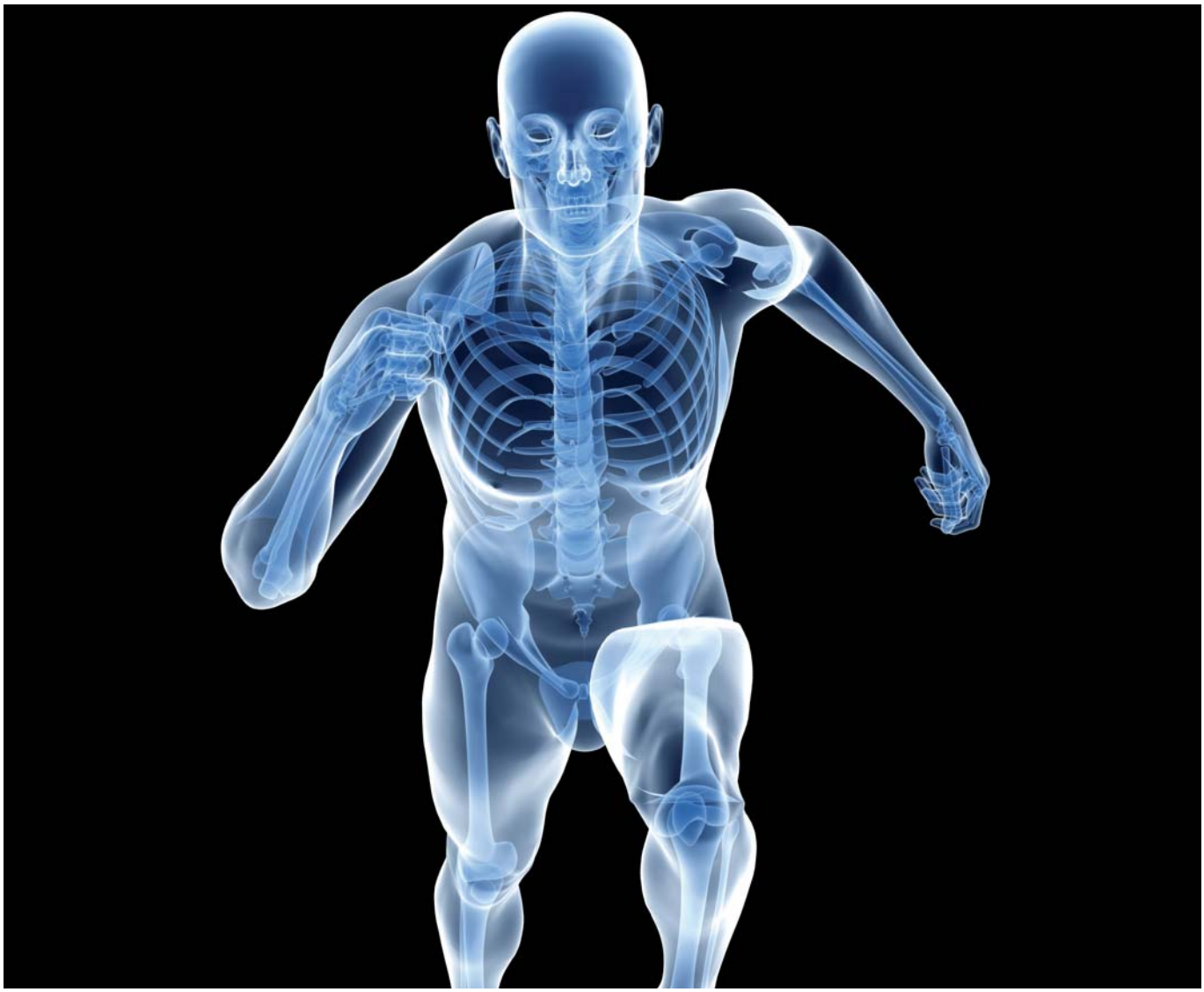


1.A VISION AND STRATEGY FOR THE VIRTUAL PHYSIOLOGICAL HUMAN

Specialisation, in both clinical and scientific practice, has supported the most rapid growth in medical knowledge ever known. Yet drug discoveries are faltering, healthcare budgets are unsustainable and patients are sometimes falling between the cracks of medical specialists who cannot treat the patient holistically. Meanwhile, biophysically-based computational modelling of the human body and physiology is poised to revolutionise 21st century bioscience by fundamentally shifting the basis for the diagnosis and treatment of disease. Medical innovation should therefore now be directed towards optimising treatments using integrated functional simulation in silico, assembling a customised computer model of the patient's condition across multiple organ systems and length scales, and across time and environment. This is the vision for future patient care that drives the personalised Virtual Physiological Human (VPH) project.

The Physiome, Systems Biology, the Virtual Physiological Human, Personal Health Systems, Biomedical Informa-

tics, Life Science e-Infrastructures, Systems Pharmacology; these domains share one issue: the need for integration. To implement the outputs of biomedical research in clinical practice and within the healthcare industry, we need to integrate data, information, knowledge and wisdom. As in [21] we need to integrate

- Data for the same patient stored across different systems, across different hospitals, across different member states and in clinical research databases [19];
- Patient-specific knowledge with domain-specific knowledge;
- Information related to various parts and processes of the human body into a systemic understanding of pathophysiology;
- Knowledge digitally captured via metadata, ontologies and models in order to respond to the combinatorial explosion of complexity that integrative research is producing; and
- 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 initiative is therefore:

- **To establish an ICT[1] and computational science framework for digital, personalised, predictive medicine.**
- **To link discoveries in molecular biology with clinical imaging and other technologies using computational physiology, based on the mathematical and engineering sciences.**
- **To link genotype to phenotype for humans and other animals through anatomical and biophysical multiscale models of physiological structure and function, at the levels of proteins, cells, tissues, organs and systems.**

The concept of a fully-informed 'Digital Patient', maintained with each person's current healthcare data, is powerful and compelling, and in meeting the challenge of its design we will make a significant impact on the lives of our citizens and on the economy. Yet the range of application means the complexities are significant, not least in areas of privacy and security; a few examples of the consequences of building the Digital Patient expose the complexities:

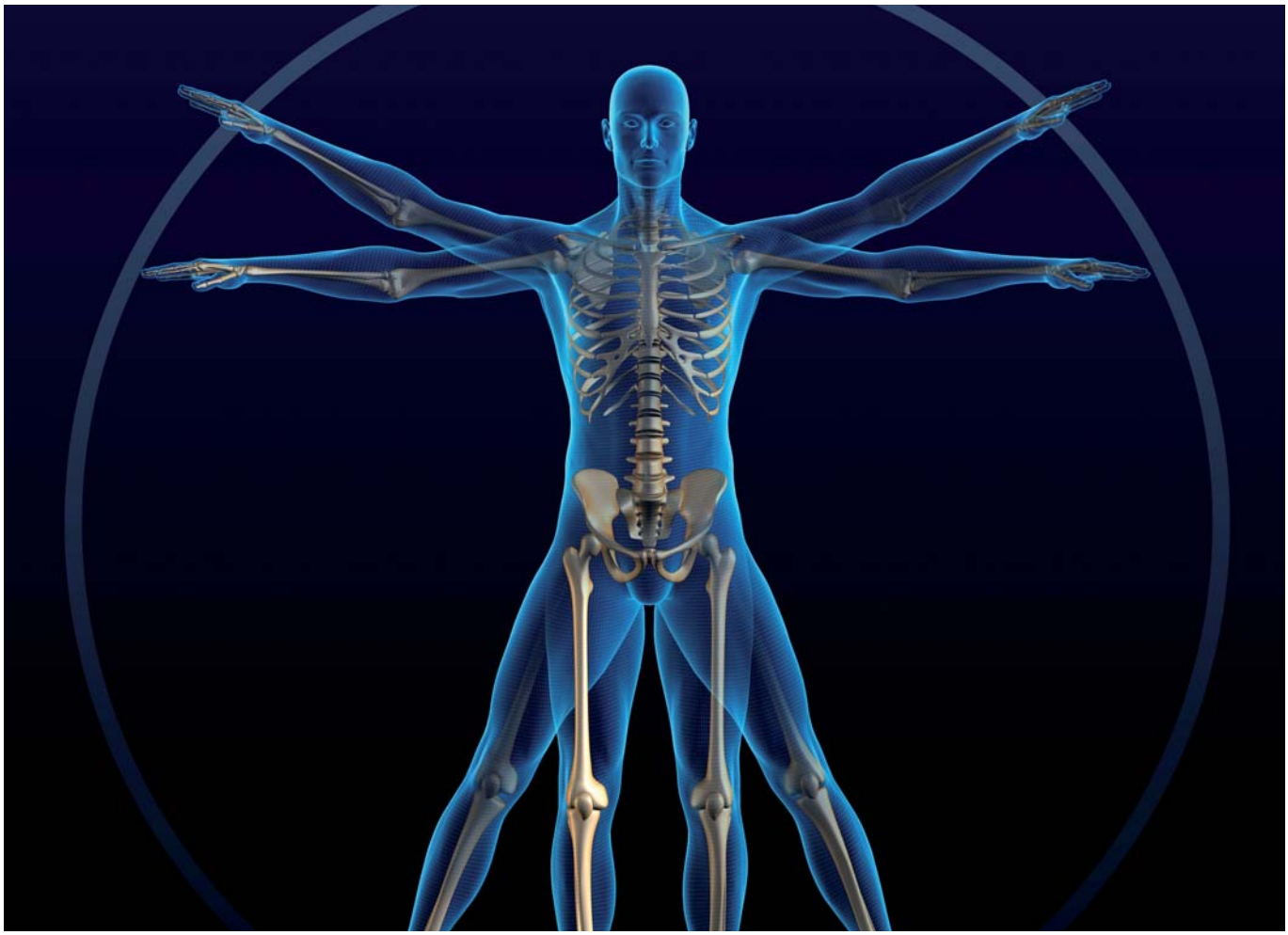
- Biomedical professionals require approved secure access to my personal data, routinely and in emergencies;
- My wearable and implanted technology must update my Digital Patient routinely with status data;
- An alarming event, detected by device or Digital Patient computation, must inform me, my family and friends, and my trusted healthcare providers of the need for an intervention;
- The infrastructure must support the collaboration of trusted specialists around my complex systemic diseases;
- Models must be able to employ the totality of my data to predict the future development of my health;
- Models must be able to access a wealth of anonymised reference data, routinely amassed from patients;
- My goals are fully self-aware lifestyle and health management, disease prevention, and optimised intervention at any time.

The FP7 VPH Network of Excellence is addressing these challenges by promoting and facilitating the use of computational models, software tools and web services, and this work is being extended and exemplified by the FP7 Call 6 Infrastructure projects P-MEDICINE[2] and VPH-Share[3], which are developing frameworks under which the VPH community can streamline developments. Stability and overarching authority has been added to the initiative with the establishment of the VPH Institute, an international non-profit body whose mission is to ensure that the Virtual Physiological Human is fully realised, universally adopted, and effectively used both in research and clinical practice. In another significant move the biomedical community has now adopted a new model for data standards and a common set of reference ontologies with which to understand genotype-phenotype relationships by linking databases of genetic and proteomic data to anatomy and function at the cell, tissue and organ levels.

The success of this opportunity is highly dependent on the development, adoption and integration of ICT and eHealth infrastructures throughout Europe [21], and on the coordination of this effort with other related international initiatives such as the IUPS[4] Physiome Project. The NoE is concerned primarily with ICT infrastructure, coordination and training, and the VPH-I projects themselves are primarily focused on developing and implementing biophysically-based computational models into clinical environments via industrial partners. The success of these endeavours is significantly dependent on the continued progress of biomedical science in revealing the biophysical mechanisms underlying structure and function at all spatial scales, and the continued development of the integrated structures established by the VPH Initiative.

A Roadmap[5] for the VPH project was laid out in 2006 by the STEP coordinated action [6]. The outcome of the first FP7 VPH funding round in 2007 (Call 2) was the VPH Network of Excellence, three Integrated Projects (IPs), nine Specific Targeted Research Projects (STREPs) and two Cooperative Actions (CAs), all of which formed the initial core of the European VPH Initiative (VPH-I). The second and third funding rounds (Calls 4 & 6) added four more IPs and six more STREPs, and Call 9 is about to introduce a further series of projects. With nearly six years of experience behind us, and with Horizon 2020 taking shape, it is time to assess our achievements and plan for the short, medium and long term future of the VPH. ■

[1] Information & Communications Technology
[2] http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/502-p-medicine
[3] http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/506-vph-share
[4] International Union of Physiological Sciences.
[5] http://www.europhysiome.org/roadmap



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, 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 now become the top priority targets. These goals are discussed below, along with proposals for the identification and use of additional resources and engagement needed to establish digital, personalised, and predictive medicine in Europe.

2.1 Standards, tools and services

The first stage of the NoE project was largely concerned with recognising the need and establishing standards for models and data, as well as building model and data repositories for published models, and assembling a toolbox of existing software programmes that are relevant to the VPH (known as the VPH-NoE ToolKit [7,15]). Most content of the NoE ToolKit is open source. More recently, the NoE's preoccupation with standards has precipitated support for high quality ToolKit submissions. This has involved the development of formalised, 'best practise' guidelines. These outline the nature of 'desirable' ToolKit content, encouraging submissions that offer maximum utility to the end user. Currently, eight guidelines have been released and demonstrate the breadth of interests pursued within the NoE. Their titles are:

- Tool Characterisation
- Model Characterisation

- Data Characterisation
- Ontological Annotation
- Interoperability
- Ethico-Legal and Provenance Issues
- Licensing
- Usability and Training

A high priority for the NoE is that all efforts must be considered in the light of sustainability. The latter refers to mechanisms and strategies that enable the VPH to continue to profit from the legacy of the NoE, even beyond the official lifetime of the project. This influences every corner of its activities. The production of the guideline documents is one example and the sustainability of the NoE model/data repositories is another. This denotes transitional mechanisms that have been negotiated and are currently being put in place, to secure the longevity of the model/data repositories that have been nurtured within the NoE. Links with FP7 Call6 infrastructure projects have proven particularly productive in this regard. Population of these repositories continues to be an explicit outreach function of the NoE, overseen by working groups from partners responsible for the ToolKit. This is an inclusive exercise that forages beyond the badged VPH projects to include globally sourced biomedical tools and data (eg. BIRN, JSim etc). This expands the ToolKit, and also helps to forge wider VPH/Physiome collaborations. Complementary to this effort, is development and support for workflows. Links between the NoE and the FP7 Call6 infrastructure projects are key to the success of these activities.

Finally, a specific strand of effort addresses training and dissemination, which is particularly important if the reach of the ToolKit and its contents is to be maximised. Here a fresh cooperation with the education community is proving valuable, and details of this area are presented more fully below.

2.2 Dissemination, training and outreach

Many communities will benefit from 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 is being tailored separately for these various audiences. The initial focus for the NoE was the website containing descriptions of the various VPH-I projects and giving access to the VPH modelling and data resources and training programs, suitable for the first target community. The NoE website receives 13,000 visits per month and the newsletters, which mainly focus on the progress of VPH projects, are published at six monthly intervals, and continue to be well received by the VPH community. The average number of downloads for each electronic version is 2500. Interest in the VPH continues to grow as evidenced by the successful VPH-Industry Day hosted in Barcelona in September 2010, and the VPH2010 conference in Brussels also in September 2010, The conference was the first of a series of scientific meetings intended to be held every two years to showcase the best of VPH research with a clear remit to reach junior VPH-related researchers and those from neighbouring knowledge fields. There are 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 healthcare workforce. The important contribution that education and training can make in the context of the long-term sustainability of the VPH 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 secured external funding, under the ERASMUS life-long learning programme (LLP), 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. Modules under development for on-line access focus on core VPH topics including; multiscale and multiphysics modelling, data fusion/workflows, the role of experimental work in the VPH and ethical and privacy considerations.

An essential and urgent step identified in the last Vision Document was the implementation of workshops and summer schools to train researchers 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. This initiative is well in line with the EU agenda for research and growth. The European level document[6] Europe 2020 "A strategy for smart, sustainable and inclusive growth" indicates the need to generate not just excellent convergent scientists but scientists who are flexible, who can work on different problems at different stages in their careers and who can move easily between sectors. Also, according to the document[7] 'An Agenda for new skills and jobs: A European contribution towards full employment', serious deficits in qualified professionals, in management and technical, job-specific skills are hampering Europe's sustainable growth objectives with shortages in areas critical for innovation, in particular Science, Technology, Engineering and Mathematics. An additional 1 million researchers are needed to meet the EU ambition to establish an Innovation Union. Many of these scientists will be engaging with biological and medical research. Two study groups and one workshop have been successfully convened and a third study group is planned for mid-2012. 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 strategies for combining models developed by different groups.

Aside from training initiatives many other efforts are contributing to the formation of the VPH community: the BiomedTown on-line community, which

[6] http://ec.europa.eu/europe2020/index_en.htm
[7] http://ec.europa.eu/education/news/news2675_en.htm

hosted the consensus process of the STEP action, now has 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 preDICT, VPHOP or euHEART are - or have been during their tenure - publishing periodic newsletters that reach thousands of stakeholders worldwide.

Industry outreach has been facilitated by the joint activities of the VPH community with the Pistoia Alliance, a 45-member organisation conceived by informatics experts at AstraZeneca, GSK, Novartis, and Pfizer to lower barriers to innovation by improving the interoperability of R&D business processes through precompetitive collaboration. The VPH NoE co-organised a very well attended workshop on biomedical data and model interoperability at the Sanger Centre in Hinxton on the 28-29 March 2011 with the Pistoia Alliance in collaboration with the Innovative Medicines Initiative[8] (IMI), and Computational Modeling in Biology Network[9] (COMBINE) communities.

2.3 International connections

Internationally, the WIRI agreement[10] and the Osaka Accord[11] have established a worldwide agenda for physiome research under the patronage of the European VPH initiative and the IUPS Physiome Project [10,11,14,30]. Other important recent events have been the participation of a European delegation at the IMAG[12] symposium in Washington in 2010; the annual CellML meetings[13] (2007-2012), and 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[14], is another opportunity to encourage US input to the VPH as well as VPH input to IMAG [28].

2.4 VPH-I projects

The goals of the current 30 VPH projects (not including the VPH Network of Excellence) are summarised briefly below. There are major technological achievements in various areas, including: data collection, management and integration; processing and curation of data; 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 VPH consortia, both at the level of 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. Clinical partners are providing a vital contribution to many of the VPH projects, participating enthusiastically and with considerable commitment. Note that the NoE advisory board is now playing a more active role and provides a mechanism for generalising the lessons learned from 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 VPH community. Even at this embryonic stage of the Toolkit, it is clear that the community is nurturing a wealth of potentially powerful and relevant tools (e.g. [26,29]). 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 still not widely adopted, but at least 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, there appears to be active uptake of underpinning technology frameworks like MAF[15], GIMIAS[16], ITK[17], VTK[18], CMGUI[19] and OpenCMISS[20]. 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 prag-

[8] http://www.imi.europa.eu/
[9] http://sbml.org/Events/Forums/COMBINE_2010
[10] http://www.biomedtown.org/biomed_town/LHDL/Reception/lhpnews/wiri
[11] http://www.biomedtown.org/biomed_town/VPH/wiri/OsakaAccord
[12] 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.
[13] http://www.cellml.org/community/events/workshop
[14] http://argos.eurorec.org/
[15] http://www.biomedtown.org/biomed_town/MAF/Reception
[16] http://www.gimias.org
[17] http://www.itk.org
[18] http://www.vtk.org
[19] http://www.cmiss.org/cmgui
[20] http://www.opencmiss.org

matic 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[21] (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
AirPROM (IP) is building an airway model validated by omic data and ex vivo models at the nome-transcriptome-cell-tissue scale and by CT and functional MRI imaging
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), now completed, used 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
FUSIMO (STREP) is developing patient specific modelling and simulation of focused ultrasound in moving organs
GRANATUM (CA) is a social working space semantically interlinking biomedical researchers, knowledge and data for the design and execution of in-silico models and experiments in cancer chemoprevention
HAMAM (STREP) is establishing a database of curated and annotated imaging data and software tools for breast cancer diagnosis
INBIOMEDVision (CA) 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
IMPPACT (STREP) is developing minimally invasive, patient-specific treatment strategies for liver cancer based on bioengineering multiscale modelling principles
INTEGRATE (STREP) is developing flexible infrastructure components and tools for data and knowledge sharing and large-scale collaboration in biomedical research
MSV (STREP) is developing visualization of multiscale data through open-source extension to the visualization toolkit (vtk)
MySPINE (STREP) is establishing a prototype computing platform with a graphical user interface for clinical settings and a patient-specific database of the lumbar spine
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
p-Medicine (IP) is creating 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, Wilm's tumour)
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
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
TBIcare (CA) is creating an objective and evidence-based solution for management of TBI by improving diagnostics and treatment decisions for an individual patient by matching a patient's individual data with the injury's characteristics
THROMBUS (CA) is developing a quantitative model of thrombosis in intracranial aneurisms
TUMOR (STREP) is an interoperable, clinically oriented, semantic-layered cancer digital model repository
VIGOR++ (STREP) is about research and development of ICT tools for the analysis, modelling and simulation of human physiology and disease processes of the GI tract
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
Several other FP7 projects funded outside the VPH Call are very relevant to the VPH Initiative and involve close collaborations with VPH researchers:
EUDAT – is working to develop a persistent data storage infrastructure for European researchers
CRESTA – brings together supercomputing centres, vendors, software providers and researchers to address the challenges on the path to exascale computing
ITFoM – is a proposed FET (Future and Emerging Technologies) initiative to develop a new ICT infrastructure to link bioinformatics at the genomic and proteomic scale to improved health care

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 user-friendly in general) and an appreciation of community. Previously identified limitations in ontology annotation and inadequate infrastructure for the secure and wider sharing of models and data (authentication, authorisation etc) are being addressed, for example 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 legal uncertainty (e.g. lack of harmonization of EU law across member states), evolving quality standards and inadequate provenance. ■

[21] http://www.vph-noe.eu/vph-projects

3. WHAT ARE THE BIOMEDICAL SCIENCE CHALLENGES?

The VPH project is achieving 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, orthopaedic and respiratory diseases), but the real impact in the long term will be to transform 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.

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, related epigenetic information on the DNA, RNA and protein level, and the environment. 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 personalized clinical treatments based on simulation studies that take into account the genetic profile of the individual patient are to become a reality [22]. 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.

To facilitate the construction of such models 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 that underpin a mechanistic explanation of physiological function at the molecular level. 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 networks within multiscale VPH models is vital. To this end there are a number of active communities outside the VPH community that possess experimental and theoretical competences of vital importance, and it is important for scientific advancement of the VPH vision to facilitate better communication with communities dealing with different types of data, from the molecular level and up to the clinical level [10].

It should be acknowledged that 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 [8]. Only large-scale systematic and concerted efforts by a wide range of scientific communities are capable of realizing this vision.

One major challenge is to account for the fact that age is the dominant risk factor for most complex diseases. The making of multiscale physiological models capturing the ageing process defines a very ambitious long-term theoretical-experimental research programme of vital importance to the VPH vision.

Further development and use of multiscale and multiphysics modelling as envisioned above will be very much dependent on the development of new high-throughput phenotyping technologies (phenomics). This provides a tremendous opportunity window for new innovations and subsequent European industrial developments with a worldwide market potential. On the other hand, without guidance from multiscale models such technology development and subsequent large-scale phenotyping programmes will risk to become highly unfocused and unnecessarily costly. This synergistic relation between the VPH initiative and a new innovation arena for European high-tech industry should be given attention within Horizon 2020.

Below we discuss in more detail the challenges outlined above requiring specific attention in the years to come.

3.1 Further inclusion of molecular systems biology

The last 50 years have seen a revolution in our understanding of the molecular basis of life, much of it driven by the development of new imaging and measurement technologies. As molecular data were accumulated in web-accessible databases, the new discipline of molecular systems biology emerged to make sense of the enormously complex interactions underpinning life [13,16]. These developments have been accompanied by an equally important revolution in our ability to image and measure physiological-scale structure and function with confocal microscopy, MRI, CT, PET and other such clinical imaging technologies, and also by the rapid improvement in computing hardware performance that has enabled the new discipline of computational physiology to emerge. This discipline invokes the mathematical equations representing the conservation laws of physics, themselves the great achievement of 19th century science and on which, along with the law of evolution, all life is based. Mathematics is the language of quantitative science and predictive models based on biophysical principles are essential for understanding complex phenomena. The equations, incorporating multiple coupled physical processes, are solved numerically on anatomically realistic geometries with models that include both tissue structure and the link to cellular function. As elsewhere, the key to progress in the biomedical field is the right combination of data-driven, physics-driven and computationally-driven science. The "bottom up" molecular systems biology approach has been largely data-driven, while the "top down" computational physiology has been largely physics-driven. These are complementary approaches and it is time they were more integrated.

Most of the models being developed by the VPH-I projects deal with structure/function relations at the tissue, organ or organ system level, with applications primarily to clinical diagnosis, surgical planning and the development of medical devices. Some link to proteins - for example, preDICT[22] examines the influence of cardiac drugs on ion channel models, and euHeart[23] includes a number of cellular protein mechanisms in whole heart models, but there is very little linkage to molecular systems biology in many of the VPH projects. The systems biology projects in Europe, on the other hand, are providing a comprehensive data-driven framework for understanding cellular physiology in terms of signalling pathways, metabolic networks and gene regulatory networks that are linked to molecular mechanisms. They seldom, however, interpret these molecular pathways in the context of structure-function relations at the cell, tissue or organ level. The first project that is attempting to bridge this gap comprehensively is the Virtual Liver Network[24], funded by the

[22] http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/47-predict-strep
[23] http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/44-euheart-ip

German Federal Ministry for Education and Research (BFBM), which is in the first year of a five year programme.

Integrating molecular systems biology into the higher scale modelling has always been the goal of the VPH/Physiome project but it is an enormously challenging task and establishing the link to clinical outcomes was the higher priority. However, achieving this integration is clearly essential if we are to understand and diagnose human disease, exploit personalised pharmaceutical interventions, and improve many other aspects of 21st century healthcare. A white paper published in January 2012 [22], addresses the opportunities and obstacles that confront us as Europe explores the translational role of bioinformatics and systems biology in drug discovery and clinical medicine.

3.2 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 genetic variants (SNPs and CNVs[25]). A major effort within the biomedical community during the last 5 years has been the use of genome wide association study (GWAS) designs to identify a select set of putative SNPs. The requirements for standards and databases are active research areas in bioinformatics that, within Europe, are exemplified by efforts such as ELIXIR[26] (a European effort to develop an infrastructure for the life sciences), and recommendations that make full use of the integration of genome-based data resources with resources detailing disease-based and other human phenotypes [23].

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 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, and 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. 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.

3.3 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 link extracellular stimuli such as hormones to adaptive responses of the cell. Intracellular signalling networks and metabolism are not separated but interact strongly, regulating each other. Modelling human physiology requires not only consideration of the large 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). Transport processes of metabolites between organs in the body including transport in the blood, across blood vessel walls and cell membranes must be included in physiological models.

A large body of biochemical literature on human metabolism is available, and metabolic genes in the human genome have been partially characterized. There are several sources available for reconstruction of metabolic networks including KEGG[27] and BioCyc[28]. A consortium of almost fifty scientists from about twenty academic departments worldwide, including members of the VPH, has produced a reconstruction of the human metabolic system which integrates data from several prominent, already existing databases. This reconstruction is captured in a database containing more than six thousand biochemical reactions forming a descriptive model of metabolism in the human body.

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 is substantial. The metabolites in this database are linked to (bio)chemical databases such as CheBI[29] and HMDB[30]. The reactions are linked to the Enzyme Commission nomenclature and to databases with corresponding genes and genomic loci. This effort, which has adopted an open source approach and is supported by an informal consortium consisting of most of the leading scientific groups in this field, will require ongoing cycles of updating and improvement in the future. This may therefore constitute a de facto standard for metabolic reconstruction of human metabolism. This recent development forms an excellent basis for physiological modelling in the

[24] http://www.virtual-liver.de
[25] Single Nucelotide Polymorphism and Copy Number Variation
[26] http://www.elixir-europe.org
[27] http://www.genome.jp/kegg
[28] http://biocyc.org
[29] http://www.ebi.ac.uk/chebi/
[30] http://www.hmdb.ca/

VPH. 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 useful for physiological modelling should be undertaken. An example to be included is the COBRA 2 package for constrained-based metabolic model analysis. In addition a completely open source package with some similar functionalities, using approaches more common in genomics and ecology, was developed by a VPH-linked group. The 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. The recent efforts to develop metabolic models mostly aimed for a general database covering all of human metabolism. For the VPH effort, models specific for cell type and tissue must be developed.

3.4 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 [20,24]. 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[31] 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) 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 5.1).

Note also that an important, yet generally overlooked, aspect of cell modelling is the fact that cells represent 'crowded environments'. Not only does this affect the way in which proteins form and interact, but the pronounced compartmentalisation, common in particular to mammalian cells, both enables and restricts the extent of network interactions that are possible within a cell. Therefore, nano-resolution three-dimensional (3D) reconstruction of individual cells is likely to be as important for linking the challenges described above as it has been for organ-level multiscale models to incorporate micro-resolution 3D information.

Techniques are emerging to provide connected 3D volume data of membrane and filament compartments in the entire cell, including electron-microscopic (EM) tomography or focussed ion beam approaches that are combined with EM observation of progressively shaved cell surfaces. These approaches are, by and large, still relatively time-consuming, and the associated image analysis and mesh-generation techniques still require significant amounts of user-interaction.

Computational integration of nano-to-micro structure-function relations will benefit from multi-scale tools and approaches developed for the micro-to-macro ranges. In fact, the computational challenge of reconstructing one cell with a 1nm voxel resolution is no different from reconstructing the heart with para-cellular detail. At the same time, many aspects of biological and biophysical behaviour undergo step-changes as you approach the single molecule level, and new modelling techniques will be required to build bridges across molecular dynamics, coarse-grained protein, and reaction-diffusion modelling approaches.

3.5 Incorporation of ageing in multiscale and multiphysics models

The somatic damage that accumulates as we age (i.e. senescence of tissues and organs) makes us more frail and thus more prone to develop pathophysiological conditions. Frailty is generally viewed as the accumulation of deficits affecting various organ systems that renders the individual vulnerable to functional decline. There currently exists no mathematical-physical conception of frailty for any organ system, and proper handling of this key biogerontological phenomenon brings a new layer of complexity to the field of multiscale modeling of physiological systems. There is no better framework than what is offered by the VPH to pursue this integration.

We foresee that the development of drugs that make us less prone to complex diseases (see below) by reducing frailty will in mathematical terms have to focus on how to impose controls that expand the operational regimes of particular mathematical behaviours (i.e. physiological functions) of dynamic systems, where age-dependent underlying changes in the control structure might otherwise cause radical changes in robustness and resilience features.

As ageing due to its stochastic nature is phenotypically manifested in so many different ways and places, a quantitative understanding of ageing physiological systems will demand dramatically more spatiotemporal data than will be needed for understanding the physiology of young and non-diseased individuals, and thus become a major driver behind the development of advanced phenotyping technologies (see below).

In summary, if we are to create individualised models describing the development and maintenance of complex diseases on given genetic backgrounds in a way that is of broad practical utility for medicine, we have to incorporate the effects of ageing in multiscale and multiphysics models.

3.6 The VPH as a potential platform for a new drug targeting paradigm

Even though model-based drug development is gaining acceptance as a vital approach in understanding patient risk/benefit and attrition, current drug targeting research typically aims to identify a key molecule involved in a particular metabolic or signaling pathway that

[31] http://www.c3d.org

is specific to a disease condition or pathology. Treatment then focuses on inhibiting or enhancing particular pathways or processes. This paradigm has been one of the major drivers behind the development of genomics and other –omics platforms. In particular, it was thought that large genome-wide association studies would provide a plethora of putative drug targets for complex diseases. However, despite huge investments almost all such studies to date show that the number of determinants (genes and non-coding DNA sites) can be very high, such that each determinant does not account for more than a small fraction of the total phenotypic variation, and that the total variation explained by the cumulative effects of the identified determinants is much less than would be expected from the estimated heritabilities of the actual diseases. This strongly suggests that the relationship between genetic variation and complex diseases is such that genomics alone is not likely to provide the sorely needed rejuvenation of pharmaceutical R&D, and calls for radically new drug targeting approaches.

It may be argued that if we do not take the full consequence of the fact that complex diseases are characteristics of complex dynamic systems and thus being phenomena that in principle are amenable for mathematical description, analysis and control, drug-targeting R&D will not make much headway.
Multiscale mathematical representations of what causes and maintains complex disease may thus become a very important tool for rejuvenating drug-targeting research. In a multiscale model capable of describing a pathophysiological phenotype, the major determinants of this phenotype will manifest in the model parameters. A particular value of a given parameter may be due to numerous low-level processes, but in terms of control, the parameter is key. This means that instead of a head-on single-molecule drug targeting approach, one may step back and focus on the relationship between parameter variation and phenotypic variation predicted by multiscale models. As parameters are lower-level phenotypes themselves, we can focus on exploiting a causally cohesive mapping between low-level phenotypes and high-level ones for which we have a mathematical representation. By identifying parameter changes that can cause a phenotypic change from the disease regime to the normal regime, conditional on the values of other "background" parameters, one may be able to identify multiple putative drug targets in terms of different parameters to manipulate as well as numerous ways of manipulating a particular parameter. Furthermore, if a drug perturbs a biological process that cascades into a stable change of the value of a focal parameter, it is evident that the parameter itself can be considered a state variable in a lower-level dynamic system richer in biological detail. One may thus foresee layers of models that finally bring us to a resolution level allowing us to glean molecular clues about how to manipulate a given parameter. If this scenario turns out to be feasible, we will be in a unique position to link this drug targeting approach to drug design, i.e. the inventive process of finding appropriate medications based on the knowledge of the biological target. This in turn allows for more rapid drug discovery, cycling between model refinements and experimental testing of drug candidates.

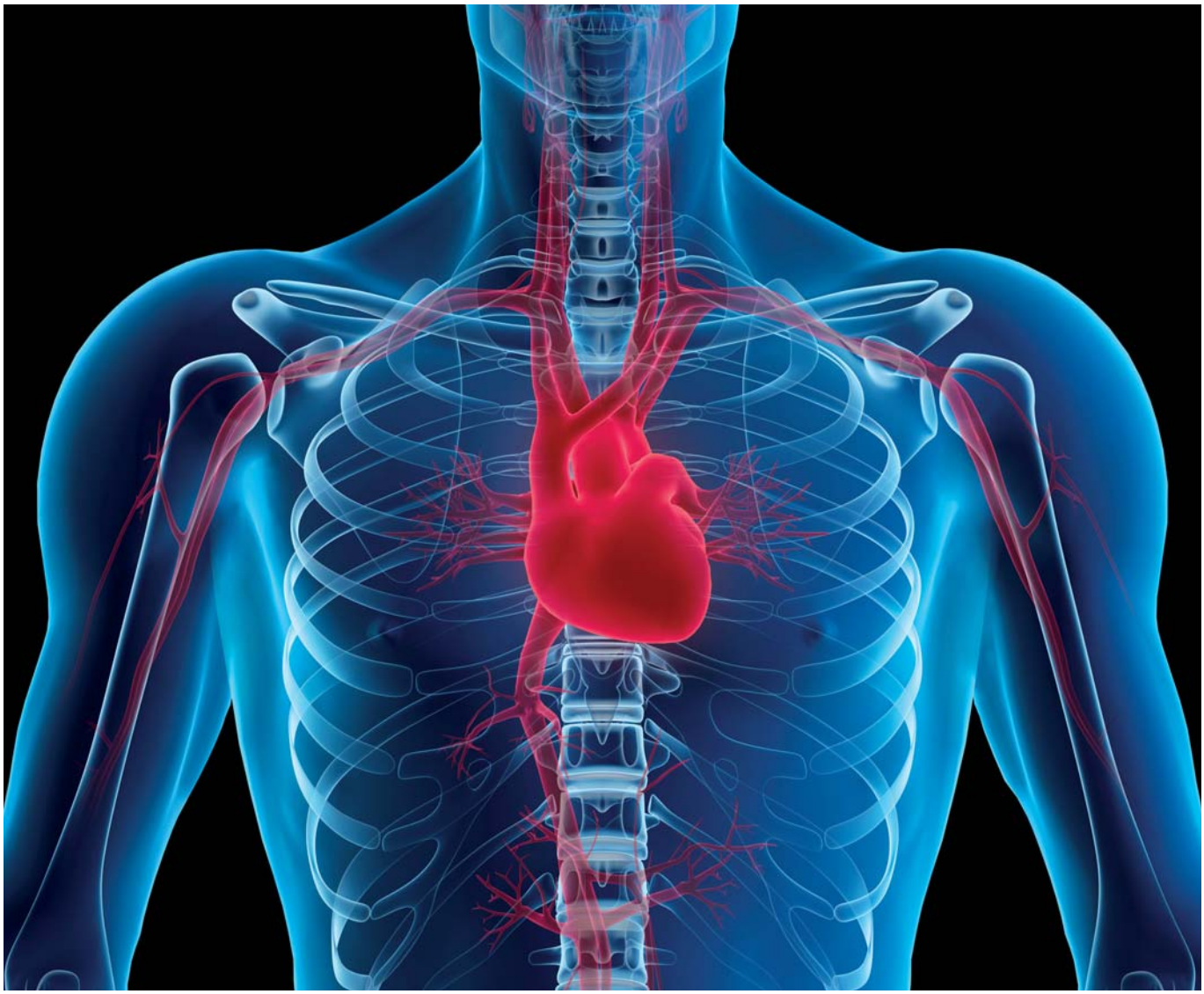
In summary, this suggested ICT-intensive and VPH-based approach has the potential to transform drug-targeting R&D into a highly structured enterprise capable of making the best of genomic and phenomic information and targeted experimental research. Even though this is a daunting undertaking, the potential gains in terms of innovation and better healthcare are so high that feasibility studies ought to be supported in coming years.

3.7 Phenomics technology – a new innovation arena for European industry?

Even though very advanced models of e.g. human physiology are now emerging, for this modelling work to really become transformative, it is mission critical that it becomes nourished and confronted by massive amounts of data that only a mature phenomics technology can provide. The modelling of human heart function may be used to illustrate two major ways a mature phenomics may support the development of a comprehensive causal and quantitative understanding of phenotypic variation.

First, phenomics may quantitatively and qualitatively enrich the intimate relationship that exists between experimental measurement and quantitative model construction and validation. In the case of the heart, much of the experimental data needed requires time-consuming, expensive efforts by highly trained personnel. This laborious "business-as-usual" phenotyping provides a very modest amount of information compared to the high-dimensional spatiotemporal phenotypic data from several individuals that is really needed for making fast progress. Second, because model parameters are really phenotypes, phenomics may open up completely new ways of using multiscale models for uncovering functional genetic and environmental variation across the whole phenotypic hierarchy. In a well-validated model describing one or more phenotypic features and capable of accounting for observed variation in a population, the genetic and environmental variation influencing these features have to be manifested in the parametric variation of the model. Genetic mapping to such parameters are likely to provide much stronger genotype-phenotype signals and make us able to identify more causative variation. If we could rapidly obtain reliable measurements of parameters across a wide range of resolution levels, this would have a dramatic impact on our understanding of the GP map.

The engineers have a major responsibility for the very fast improvements in genome sequencing technology we are now witnessing. Considering the diversity of technologies needed, the development of a mature phenomics technology will have to engage much broader parts of the engineering community in academia as well as in industry than what has been the case for genomics. Phenotype space is a vast place, however, and the development of a mature phenomics will always demand prioritizing what to measure. If we want to avoid misspending enormous human and financial resources, the major guide for this prioritization will have to be mathematically formulated conceptions (or models) of how phenotypes are created and maintained in causal terms. Thus the VPH is ideally suited to provide mission critical guidance for the development of a European phenomics technology development. ■



4. WHAT ARE THE HEALTHCARE CHALLENGES?

Major diseases like cancer, neurological and cardiovascular diseases are complex in nature involving environmental, life style, ageing 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.

4.1 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, common requirements are emerging in a number of analysis documents produced by very diffe-

rent sources[32,33,34,35,36,37]. 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 member states dealing with a constantly ageing population.

More specific 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 different medical specialities, 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.

4.2 Personalised, predictive and integrative healthcare and the 'Digital Patient'

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, as well as 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.

The Digital Patient is a vision of a coherent digital representation of each patient that is used to provide an integrative framework for Personalised, Predictive, and Integrative Medicine. This vision and the currently open call for a support action targeting the so-called 'Digital Patient', include three major challenges:

a) To provide medical professionals and biomedical researchers with advanced user interfaces based on the digital patient metaphor, that make it easier to cope with large amounts of information related to different organ systems, different space-time scales, and different diagnostic imaging modalities.
b) To provide healthcare providers with an ICT layer capable of recovering and integrating all 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 generating new insight.

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.

4.3 Access to clinical data

The re-use of clinical data remains a key challenge, and [21] is an important precursor for an EU digital vision and agenda for the next 5-10 years. The community has long championed this message, and as identified even in the original 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[38], Deloitte writes:

"Most Life Sciences (LS) Research and 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 and Development 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".

There is clearly agreement that significant value would attach to the federation of these databases. Yet it is important to recognize that from an ICT perspective there are multiple shortcomings to be overcome:

- The majority of the 'clinical databases' behind the firewalls are poorly structured and inconsistently annotated. This remains a serious hurdle for medical informatics in realising 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,

[32] Dobrev, A., Jones, T., Stroetmann, V.N., Stroetmann, K.A. Interoperable eHealth is Worth it - Securing Benefits from Electronic Health Records and ePrescribing. Luxembourg: Office for Official Publications of the European Communities, 2010
[33] Apoteket and Stockholm County Council, Sweden, "eRecept, an ePrescribing application", ec.europa.eu/information_society/activities/health/docs/events/opendays2006/ehealth-impact-7-2.pdf
[34] "The benefits from translating biomedical research into the health care system" Report to Bio21 Australia 2007
[35] "Personalized health care: opportunities, pathways, resources" US DHHS 2007
[36] "Pharma 2020: Virtual R&D", PWC 2008
[37] http://www.inbiomedvision.eu/PDF/D4.1_INBIOMEDvision_First%20think-tank%20report_v5_Final.pdf [21]
[38] "Secondary uses of Electronic Health Record (EHR) data in Life Sciences", Deloitte Development LLC, 2009

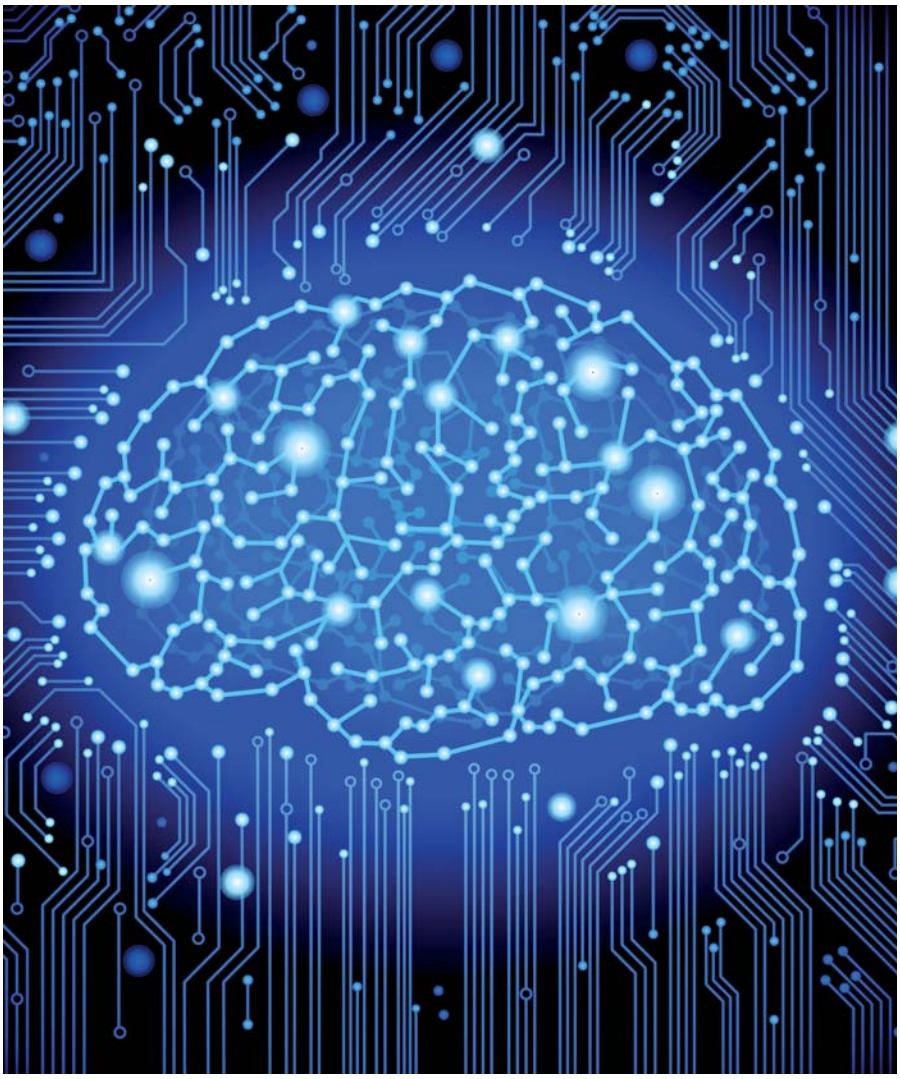
exchange and interoperability need to be explored and evaluated. A viable data infrastructure must support many activities (curation etc) giving data prospectors the freedom to revolutionise clinical procedures from the data they obtain, and yet issuing data providers with necessary assurances that their 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.
- There are important legal issues to be addressed. By its very nature, the VPH crosses scientific and national boundaries. Differing interpretations of data protection law (e.g. 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 require management if they are not to become a stumbling block to the progress of the VPH.

Note that the following three initiatives are relevant:

The FP7 Call 6 Infrastructure projects, though not specifically aimed at tackling these issues, are nonetheless addressing their impact as part of their remit to provide community-wide facilities for the construction, development and testing of simulation-based methods. In particular they are examining the changing ethical and legal landscape as it affects potential users of their infrastructures, and in doing so will not only expose the issues in a consistent, structured way, but will identify and liaise with experts across Europe with both insight and influence.

Call 7 project DISCIPULUS is a Support Action bringing together community and public representatives to identify and optimise the strategy for the introduction of the Digital Patient, the healthcare avatar that will accompany all citizens in their journey through healthcare, indeed through life. In consulting widely, and informing significantly, the project will come into contact with a large diaspora of relevant opinion-holders,



and will provide an important platform for the dissemination and acquisition of intelligence relating to clinical data-sharing.

Call 7 project INBIOMEDvision is a Coordination Support Action bringing together the scientific community, healthcare and industry representatives to discuss challenges and opportunities in the area of biomedical informatics, and come up with various strategies and recommendations to better integrate clinical data, exploit this data in research, translate innovation in research to improved clinical outcomes, and achieve a better mapping of genotype-phenotype resources. In addition, the project promotes the dissemination of knowledge, training of new generation of scientists and medical practitioners in new ways of thinking, and the consolidation of a community of experts with this unified approach to personalised medicine.

The VPH Institute is well-placed to offer a mechanism by which formal authorisation procedures can be managed and policed, whilst also providing guidance on recommended procedures (e.g. anonymisation) that are important to the clinic. The Institute is also well-suited to advise on standardisation, since it is well-informed on community needs and able to identify strategies maximising data interoperability; indeed it is already concerned with other fundamental efforts including the harmonisation of nomenclature through ontologies, recommendations for data formats and data interchange, and representation on international standards committees. Standards activities are necessarily multifaceted, with the need to recognise the competing demands of research, industry and the clinic and to avoid the dangers of over-regulation.

In summary, increasing and consistent interaction between projects, regulators

and users is required to further the cause of increased access to clinical data, and each project has a responsibility to participate in the collective endeavour to improve the data landscape on behalf of all stakeholders.

4.4 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, necessarily, tight regulation. Few basic researchers have the knowledge and experience required to undertake this final step. The VPH should plan the development of an environment to foster translation. Industry will be a critical partner in the translation process but, whilst industry is used to accessing regulatory guidance in support of the introduction of a new pharmaceuticals or medical devices to market in the EU, this is not necessarily 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. In addition to the changes already implemented, a re-cast of the Medical Devices Directives is currently underway with a draft expected to be released by the Commission in Spring/Summer 2012. As yet the potential impact of the re-cast remains unclear.

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 is 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.

4.5 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, multifaceted health technology innovations already during their early phases of development requires innovations also in clinical and socio-economic impact assessment [25]. A new, multilevel generic methodological framework should 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 [12,18,19]. ■

5. 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[39] and SBML[40] - and the spatially varying fields used with systems of partial differential equations - FieldML[41]. 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[42] now includes models for a wide variety of subcellular processes.

[39] http://www.cellml.org
[40] http://www.sbml.org
[41] http://www.fieldml.org
[42] http://www.cellml.org/models

We have recently seen the first public sharing of models expressed in the FieldML standard, under the auspices of the euHeart project. As well as a range of anatomies, these include descriptions of functional benchmarks. One criticism of many of the models exposed by the community is that they do not adequately represent physiological variations and uncertainties. A first step is to ensure that variation and uncertainty can be represented in the modelling languages. We need to learn how to represent the physiological envelope of the individual in our simulations, and how to inform the parameters in this envelope from the rich information in the electronic health record of the patient.

5.1 Model and data encoding standards: model reproducibility

Mathematical models for the VPH-I are developed by bioengineers, biomathematicians and experimental physiologists to quantitatively describe complex biological 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 interest in clinical application of these VPH models, a range of new challenges have arisen [21]: 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? Is it available as open source?). The functional benchmarks mentioned in the previous section are an important component of verification and validation strategies for sophisticated numerical codes developed by the VPH community. 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? does it have a good user interface?). The understanding of parameter sensitivities is also important in the context of the interpretation of the physiological envelope of the individual.

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 [2,3,4,7].

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).

The VPH Initiative is also represented in the EUDAT project via partner UCL. EUDAT is an FP7 project launched to target a pan-European solution to the challenge of data proliferation in Europe's scientific and research communities. The project, coordinated by CSC Finland, aims to work towards the development of a collaborative data infrastructure for Europe, driven by the needs of researchers. VPH is a core research community in the project, and a major activity within the project is to examine how to store VPH data on the generic data infrastructure being developed, and link that underlying infrastructure with specific VPH data storage systems, such as those being developed by VPH-Share and p-medicine.

	Data	Models	Simulation
Minimal requirements	MIAME[43], MICEE[44], etc	MIRIAM[45]	MIASE[46]
Standard formats	PDB[47], DICOM[48] BioSignalML[49]	SBML, CellML FieldML	SED-ML[50]
Ontologies	GO[51], Biopax[52], FMA[53] SBO[54], OPB[55]	GO, Biopax, FMA SBO, OPB	KiSAO[56]

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

[43] http://www.mged.org/Workgroups/MIAME/miame.html
[44] http://www.micee.org [17]
[45] http://www.ebi.ac.uk/miriam
[46] http://www.ebi.ac.uk/compneur-srv/miase
[47] http://www.rcsb.org/pdb/home/home.do
[48] http://medical.nema.org
[49] http://www.embs.org/techcomm/tc-cbap/biosignal
[50] http://www.ebi.ac.uk/compneur-srv/sed-ml
[51] http://www.geneontology.org
[52] http://www.biopax.org
[53] http://sig.biostr.washington.edu/projects/fm/AboutFM.html
[54] http://www.ebi.ac.uk/sbo
[55] http://bioportal.bioontology.org/ontologies/46667
[56] http://www.ebi.ac.uk/compneur-srv/kisao

A concerted effort will move us closer 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 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.

5.2 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 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…) would 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 multiscale integration is to increase the efficacy of computations while maintaining comparable accuracy with respect to the original model. On the other hand, VPH objectives address biological systems that are characterized by the interaction of many different physical processes at each spatial scale. In this situation, 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. One example is the fact that 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. Here, 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).

Another example at the organ/tissue level is 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 simulation 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 is a challenging problem where multiple scales are simultaneously interacting, such as the nano-scale (interaction of chemical species, ions and proteins), the micro-scale (cardiac myocytes) and the macro-scale (the cardiac tissue, usually treated as a continuum).

More generally, when addressing biomedical phenomena featuring multiple time and/or space scales, suitable mathematical techniques need to be developed to identify a correct scale separation, to model each of them and to express the interactive/coupling mechanism among them. This development, accompanied by the necessity to set up efficient multiscale numerical algorithms, represents a major challenge for integrative multi-scale modeling [1].

Note that 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).

5.3 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 extreme sensitivity to initial conditions (usually called chaotic behavior) or simply unknown mechanisms – i.e. ignorance. It is very important that the consequences of this uncertainty, for example in parameter value estimation, are quantified.

There are two types of uncertainty:

Aleatory 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: 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 biological property or behavior in question.

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 are modelled as random variables of known frequency distribution. The use of simpler approaches, such as Monte Carlo methods, primarily poses 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.

The identification and quantification of uncertainties is crucial in order to obtain more realistic results from biomedical numerical models. Many strategies to describe uncertainties, based for example on fuzzy set theory, worst scenario analysis, and probability representation, have been experimented with. Among those, characterization of uncertainty by probability distribution function including random variables, random processes, and random fields are applied in combination with deterministic models and is considerably stimulating

the activity on uncertainty quantification by stochastic models.
In forward problems, uncertain inputs are explicitly represented as probability distribution functions. The goals is to compute the probability distributions (or statistical quantities) of the output of the biomedical system in order to assess the way uncertainties propagate into the system, as well the output sensitivity to uncertainties.

In backward problems, the probability distribution functions for the uncertain input are to be determined in order to fulfill specific requirements on the observed output, yielding optimal control problems, inverse problems, or data assimilation problems, all of them featuring a high level of complexity (see also [27]).

5.4 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 partners 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[57], 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.

The integrated project VPH-Share is constructing an 'infostructure' to facilitate sharing of tools, models and data across the community. One of its targets is to promote the idea of 'virtual collaborations', so that, for example, a research group with expertise in computational fluid dynamics can test their algorithms and code in a fully developed workflow that includes those processes (such as image segmentation) that they might not be expert in. To support this effort some of the complex workflows developed in earlier projects are being decomposed into a series of atomic services that can be re-assembled, with new components, into new workflows. A concomitant issue is that of access to these services through a community computational infrastructure. There are many interesting questions, some associated with data protection, data security and ethical issues, some associated with the volumes of data, some associated with IPR and service models, around the issues of transfer of the data to the service or the service to the data.

5.5 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.

VPH is also working with the FP7 MAPPER project[58], which seeks to develop a persistent, generic infrastructure for multiscale modelling, on top of the lower level infrastructures provided by PRACE, EGI and other National Grid Initiatives (NGIs). VPH is a constituent user community of MAPPER, and work is already underway to port VPH application scenarios to run on the initial MAPPER infrastructure.

5.6 Supercomputing challenges

A major challenge for VPH-I researchers remains the need to secure access to computing resources of a sufficient scale to support their simulation work. The VPH-NoE has built a relationship between the NoE and the VPH-I research projects through the development of a DEISA[59] 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. The Virtual Community was renewed by DEISA on

[57] http://www.commontk.org
[58] http://www.mapper-project.eu
[59] http://www.deisa.eu

a year by year basis, until the end of DEISA in late 2011. During that time, over 50% of VPH-I projects were supported, as well as additional EU funded projects working in e-Health related domains are also being supported

The end of DEISA has created a vacuum in terms of available compute support for VPH-I researchers. DEISA has been replaced by PRACE Tiers 1 and 2, which do not currently support community based allocations similar to the DEISA Virtual Community programme. However, PRACE have issued a call for expressions of interest in whether such an allocations programme is required, to which the VPH NoE responded. We hope that such a community based allocation mechanism will become available in the near future and allow us to provide further support to VPH-I researchers.

Through the MAPPER project, VPH researchers also have access to select EGI resources. MAPPER has signed a memorandum of understanding with EGI to deploy software components onto EGI resources. VPH can use its relationship with MAPPER to help deploy multiscale VPH simulations on EGI nodes.

5.7 Informatics and "big-data"

Health research and health services provision faces many of the challenges already evident in "big-science" such as astro-physics and particle physics and in a wide variety of data-rich domains such as global economics, meteorology and environmental monitoring. Rapid sequencing technologies and the widespread use of diagnostic imaging are examples of "big-data" generation in research and hospital settings, but when considered as an integrated international process it is already clear that new approaches will be needed to allow effective storage, discovery, analysis and application of the knowledge being accumulated across Europe and by its international partners.

The extent of the challenge is clear when we consider that there are already over 20 million published papers in the National Library of Medicine PubMed database and many more in digital libraries collected in other relevant domains such as scientific, medical, engineering, social and legal studies. In the proposed integrated, predictive models of the VPH initiatives it will be necessary to track relevant developments and to determine the most useful information for any specific application. The extent, location and linkages of research, publication and health service activities will form very substantial metadata sets and allow monitoring of the effectiveness of investments in health-related programs.

In addition to published information there will be extraordinary accumulation of primary data for individuals and populations. It has been estimated that for one individual the combined output from the common imaging, biochemical and genetic modes of analysis will generate approximately one terabyte of information. When multiplied by the total population of Europe the challenge of "big-data" in health science is abundantly clear.

The VPH is well placed to address the challenges and opportunities posed by 'big data' including the use of appropriate information visualization tools. These will offer researchers and health professionals a technology platform with capabilities to rapidly discover and gain insights from the copious amounts of information being made available from the wide variety of publication sources. The VPH community needs to recognise the 'connections' linking bio-medical and life sciences research and researchers around the world, and to visualise those linkages through interactive 'information communities' for exploration, analysis, and education.

It is envisioned that through the VPH Institute and its European and international partners the VPH teams will describe and specify the range of ICT infrastructures required to match the generation of health data with the needs and capacity of the social environments. Development of appropriate tools will build upon the standards already encompassed by previous VPH initiatives under the structure of the next health program frameworks"

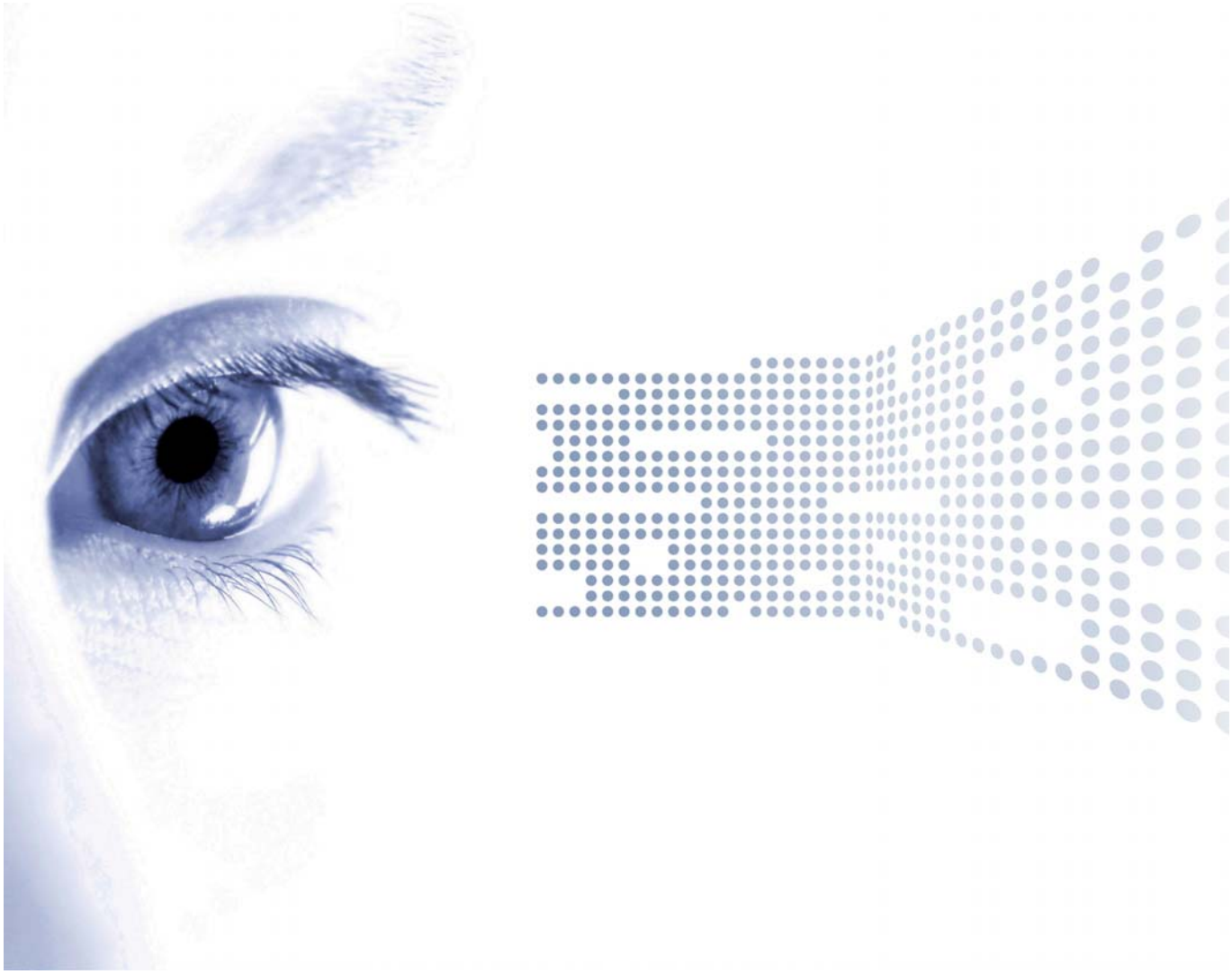
5.8 Data security

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 [21]. 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 appropriately protected?
(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? How do we assess the security requirements for derivative data that arises from privileged access of a VPH researcher?
(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, 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. ■



6. A STRATEGY FOR THE VPH

Currently, coordination of the VPH-I projects is via the VPH NoE, which is also pursuing additional specific goals such as the VPH toolkit. In order to transform the VPH vision into a reality for European stakeholders, 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;
- further the 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 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. We have therefore established 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.

6.1 The VPH Institute

The need for a non-profit organisation capable of representing the whole VPH research community, in itself highly heterogeneous and spread over a large number of traditional academic domains, was first mentioned in the 2009 update of this document. The 2010 update described the constitutive process that has now been completed. On

March 2011 the "Virtual Physiological Human (VPH) Institute for Integrative Biomedical Research" was incorporated as an international non-profit organisation according to Belgian law. Ten institutions, including one from the USA and one from New Zealand, formed the founding supporting membership. Representatives from these ten founding members formed the Board of Directors to manage all institute operations. Marco Viceconti was appointed as first Executive Director of the VPH Institute during the first Board meeting.

On September 2011, following the annual VPH NoE meeting, the VPH Institute held its first general assembly. During that meeting 42 applications for membership were ratified. Thus, including the founding members, 52 organisations joined the VPH Institute in its first year of activity.

Soon after the General Assembly the membership elected the first President of the VPH Institute (Denis Noble from the University of Oxford) and two financial auditors (Randy Thomas, University of Evry and Isabelle Wartelle, University of Amsterdam). The President and the financial auditors together form the Board of Trustees of the VPH Institute.

The VPH Institute has since produced a position paper on the European Commission's Green Paper on Horizon 2020, the next framework programme. In this document an "in silico medicine" follow-up project to the FP7 VPH is proposed and three new research priorities named Digital Patient, In silico clinical Trials, and Personalized Health Forecasting are advocated.

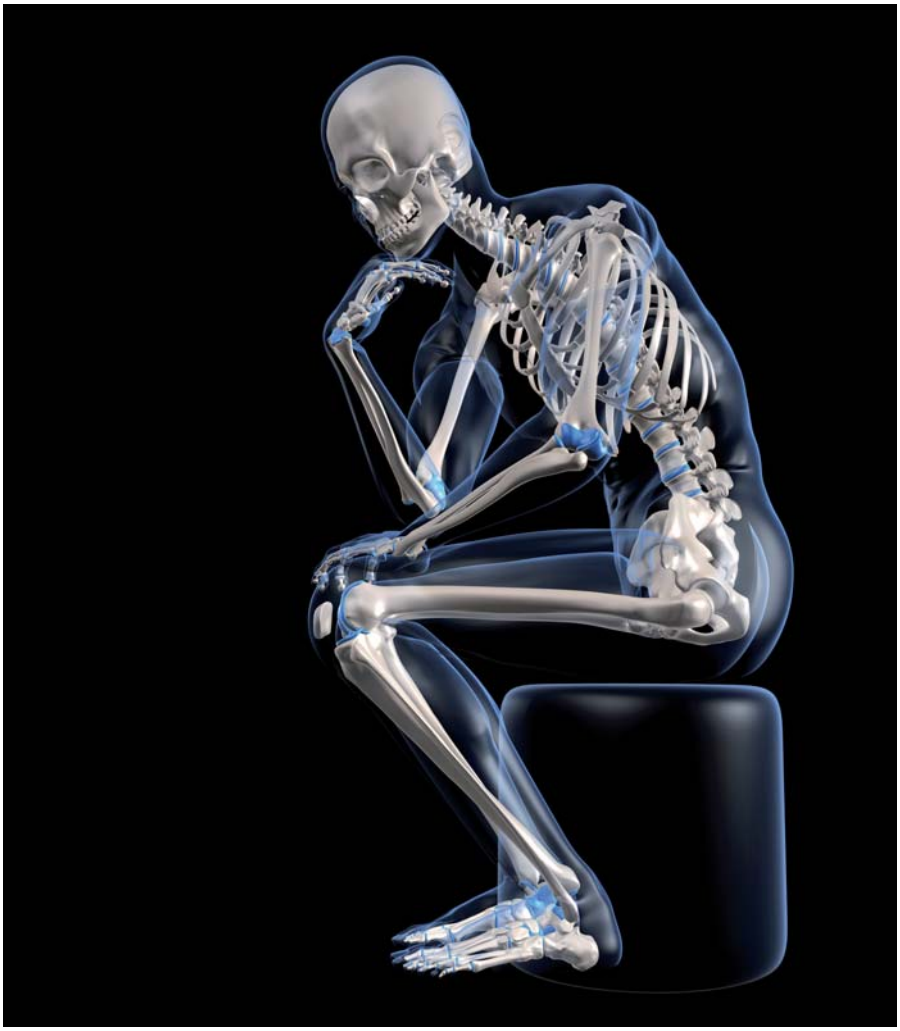
6.2 VPH conference series

The ICT-Bio meeting[60] held in Brussels in October 2008 was the kick-off meeting for the VPH. The ICCB2009 meeting[61] held in Bologna in September 2009 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 stated that they came to VPH2010 because of networking opportunities, which demonstrates a real need to continue with dissemination activities. The VPH NoE will continue to host VPH events until the end of the project in November 2012.

Work is currently in progress for the second conference of the series 'VPH2012: Integrative approaches to computational biomedicine' which will be held in London in September 2012. VPH2012 will have a focus on the integrative aspects of VPH and aims at reaching outside of the VPH community to other relevant communities including systems biology. The vision is to have a conference that truly encompasses all possible scales to model physio/pathology with a clear ICT focus.

Four parallel sessions will be held on all days with talks and dedicated poster sessions. Additionally, there will be parallel workshops in relevant areas not addressed in the main scientific tracks. There are two types of workshops which will be held in VPH2012. Hands-on workshops have invited speakers, their aim is to give attendees a deeper



[60] http://ec.europa.eu/information_society/newsroom/cf/itemdetail.cfm?item_id=3956
[61] http://www.iccb2009.org

knowledge and familiarity of a specific set of tools or concepts, and will have an interactive format. Sessional workshops are those which focus on a particular theme with keynote speakers and will also have an open call for abstracts. Similar to the format of VPH2010, the best VPH2012 papers will be published in Interface Focus in a special themed issue on Integrative Approaches to Computational Biomedicine.

6.3 Training and dissemination

Training will continue to be an important VPH activity. The results of a survey carried out amongst Industrial, Clinical and Academic partners emphasised the importance of a qualified VPH-formed workforce to provide future professionals for highly-skilled jobs in the pharma and medical devices industry as well as in regulatory bodies.

It thus follows that the development of educational systems within the VPH community is an essential part of enlarging the skilled workforce available to develop clinical care through simulation and, as described, the NoE has made significant efforts to extend the scope and quantity of appropriate facilities. It is now the case that, as VPH technology begins to have an increasing impact on patients, clinicians and medical institutions, internal community activities have become insufficient, and engagement beyond the VPH, with the wider, established world of medical education becomes a requirement.

The VPH community has now forged a successful relationship with the EU's largest community of medical educators, the Association of Medical Educators in Europe (AMEE), which boasts a membership in excess of 30,000 practising educators and an annual conference attended by over 3,000 members. The collaboration has so far seen the engagement of all NoE partners and many of AMEE's leading institutions in collaborative planning, grant applications, projects and publications and, at the AMEE 2011 conference in Vienna, an entire session was devoted to showcasing VPH concepts, projects, plans and collaborative opportunities, at which seven VPH-I and NoE project teams presented their outputs and engaged with the audience in discussion and debate. Importantly, a new sophisticated approach to the generation of interactive project-related educational materials aimed at medical trainees was announced, and joint work on this concept is well underway.

Consideration should also 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.

6.4 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 international Call 4 projects, is shown in Figure 1 together with the anticipated future calls. The establishment of the 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.

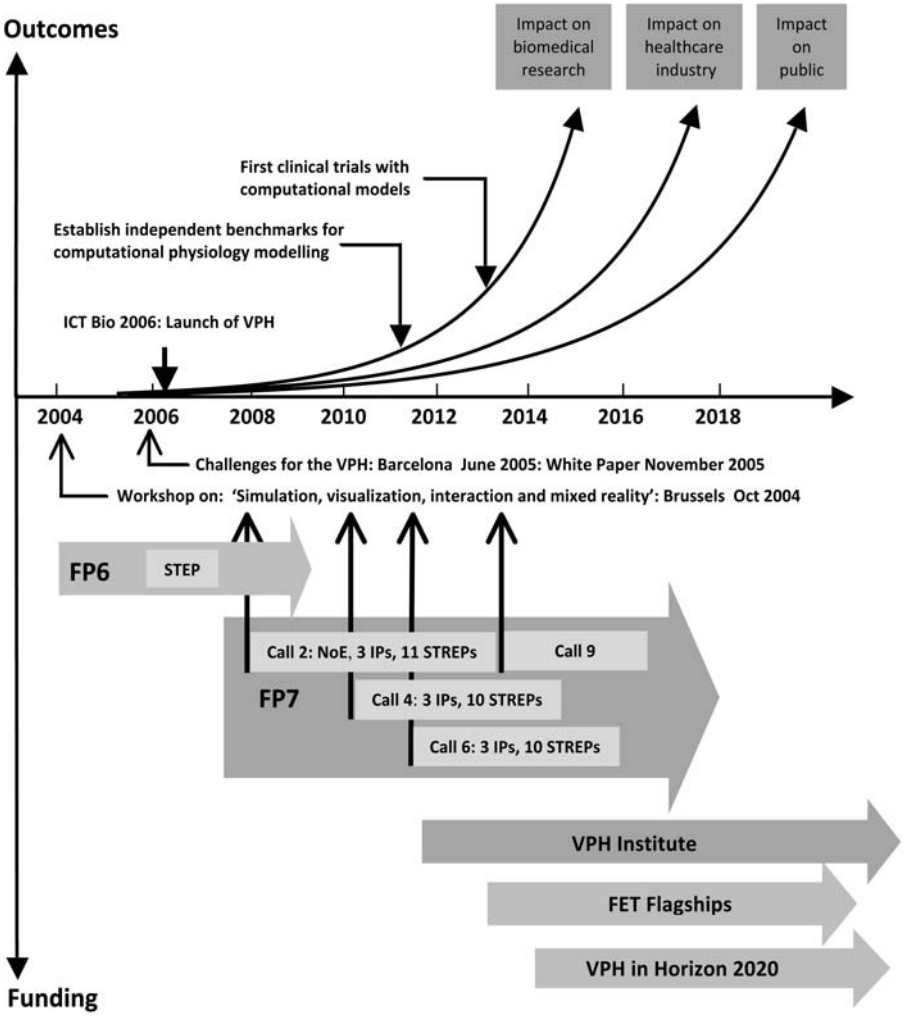


Figure 1. Timelines for VPH funding calls, the VPH projects and their impact on various communities. Sustainability of the NoE, and hence ongoing support for the VPH and the healthcare industries that depend on it, will be achieved through the VPH Institute.

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

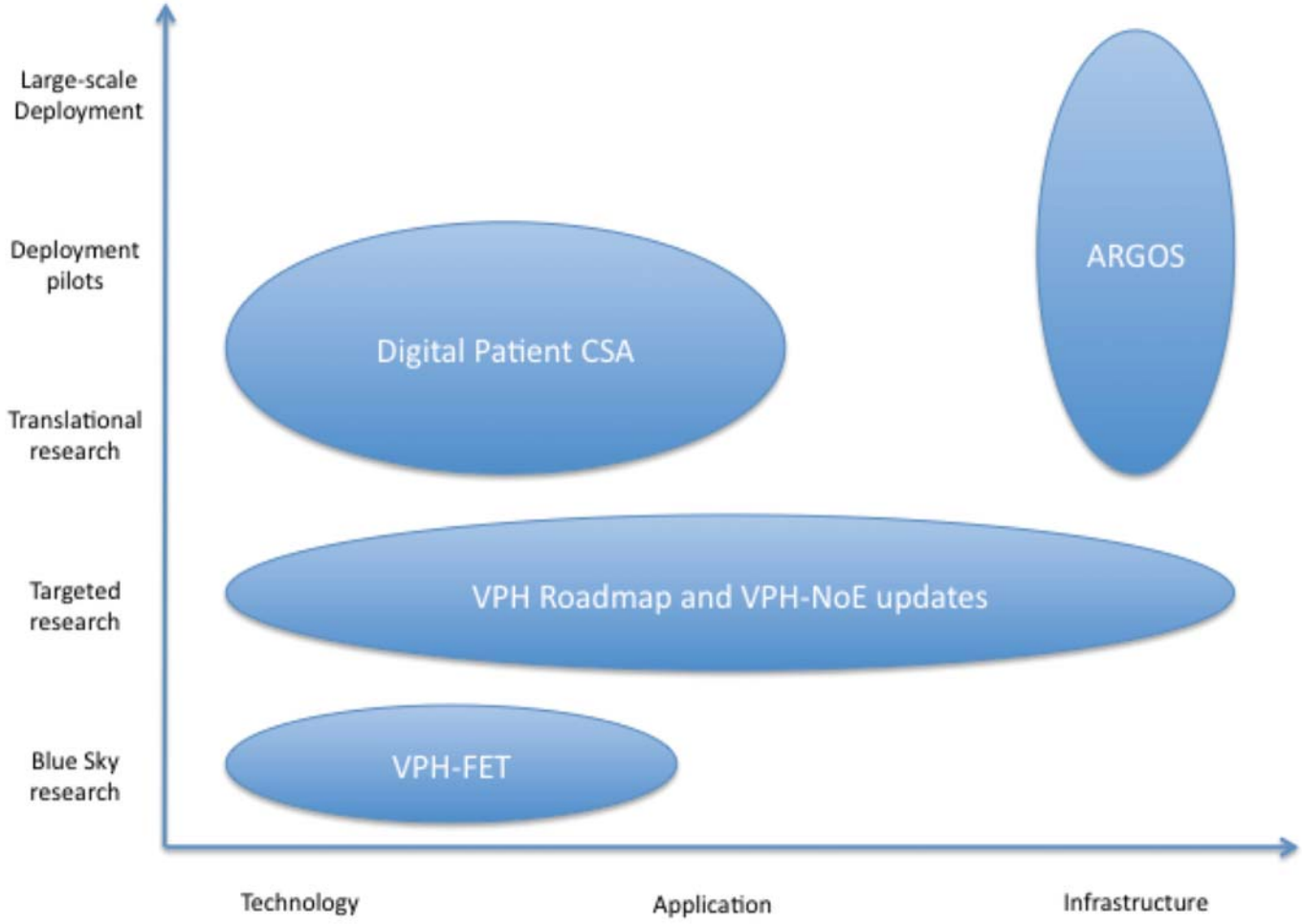


Figure 2. The VPH in relation to other related initiatives.

6.5 The next steps

The VPH is a grand challenge. Here we identify some current and future 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. This process was completed in late 2011 with the full activation of the VPH Institute. From now on the VPH community will have a collective identity represented by this democratic and participative non-profit organisation.

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[62] 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.

[62] 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 directed so far.

The VPH-FET support action, funded by the FET Proactive unit, has produced an extensive research roadmap targeting the 'blue sky' technological research needs of the VPH community. Three strategic reports with specific recommendations relevant to the EU and beyond, are: "Re-use of Clinical Information in Research" [21], "Genotype-Phenotype Resources" [22], and "Translational Systems Biology and Bioinformatics" [23].

No calls for VPH e-infrastructure roadmapping were made, but the ARGOS observatory[63] has elaborated a policy brief for transatlantic cooperation on VPH Research. The recommendations 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 consultation with these neighbourhood communities.

In October 2011 a support action called Discipulus began, aimed at developing a research roadmap for the first of the new strategic objectives identified in the VPH Institute position paper: the digital patient. The action expected to complete in March 2013, will provide a first important piece in the definition of the VPH research agenda in Horizon 2020. In all these actions, the general strategy the VPH community should adopt toward these neighbourhood communities should be inclusive, not invasive or elitist. 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 our neighbourhood communities 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 intersection of 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 challenges, and who are not afraid of the change that this would necessarily require to their research practice.

2013-2020: the VPH in Horizon 2020

The structure of Horizon 2020 is currently being defined. In the first document elaborated by the European Commission for the Europarliament to describe Horizon 2020, under societal challenges is identified a priority named in silico medicine.

Following the recommendation of the VPH Institute, discussed and approved during the last VPH NoE Annual meeting, this general priority should be divided into three streams of research funding targeting:

Digital Patient: the use of VPH modelling to provide personalised, predictive, and integrative technologies to the medical professionals. The Digital Patient is intended to be a framework of information technologies that enable a more integrative, predictive, personalised, and patient-centric medicine, following the indications that will emerge from the specific research roadmap the Discipulus support action is expected to produce. By its nature the Digital Patient program should begin from targeted research, followed by innovation and deployment pilots as the framework develops.

In silico Clinical Trials: the use of VPH modelling to provide the biomedical industry an personalised, predictive, and integrative approach to the assessment of medical devices and pharmacological products. In silico clinical trials research targets the use of ICT to simulate how large cohorts would react to new drugs, medical devices, biotech and tissue engineered products. If proved effective these new technologies could be positioned before real animal and clinical trials, in order to increase the efficacy of their design, reduce the size of the cohorts, the risks for the patients (or the invasiveness for the animals), and the costs for the biomedical industry (which could turn into a reduction of costs for these products). It could also open an entirely new market, for In Silico Clinical Research Organisations, a new type of CRO that would conduct these simulated clinical trials on the next-generation computing cloud.

Personal Health Forecasting: the use of VPH modelling to provide personalised, predictive, and integrative services to the patients/citizens. What we propose is to develop personalised VPH models (integrative predictive models) that constantly elaborate all the data transmitted by personal health systems, wearable sensors, ambient assisted living technologies, mobility monitors, etc, and predict how specific aspects of our health will evolve in a near or not-so-near future. Such models should account for chronic diseases, recurrent prescriptions, or specific disabilities and could be further personalised with clinical data such as medical imaging, biomedical instrumentation, biomarkers, etc.

6.6 Towards 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:

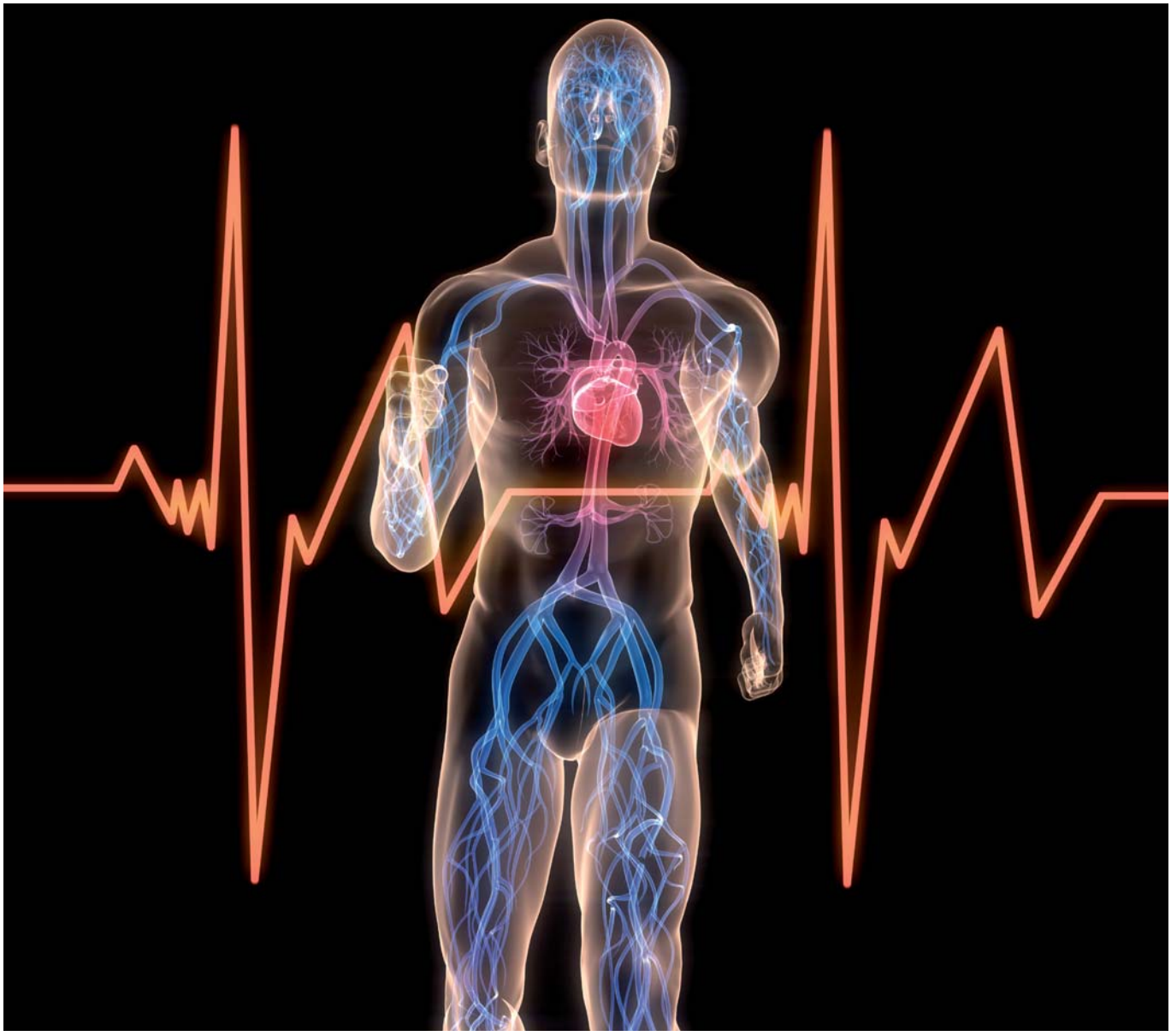
- Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)

[63] http://argos.eurorec.org/

- 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.

We are in the midst of an explosion of online biological and medical data. Moreover, the European Strategy Forum on Research Infrastructure[64] (ESFRI) will be providing new data production services (sequencing, imaging, etc) across many fields of biological science. The rationale for many of these initiatives is to understand high level phenotypes from genomic, metabolomic, proteomic, imaging and other types of data. But establishing high level phenotypes from lower level data requires multiscale models. The multiscale modelling framework being developed by the VPH project is an ideal environment for guiding this endeavour because, as in all other fields of science, mathematical models based on physical principles provide the only method for guiding experimental measurement and integrating and interpreting large amounts of heterogeneous data. ■



[64] http://www.ugent.be/nl/onderzoek/financiering/int/ESFRI.htm#biological-and-medical-sciences

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Virtual Physiological Human
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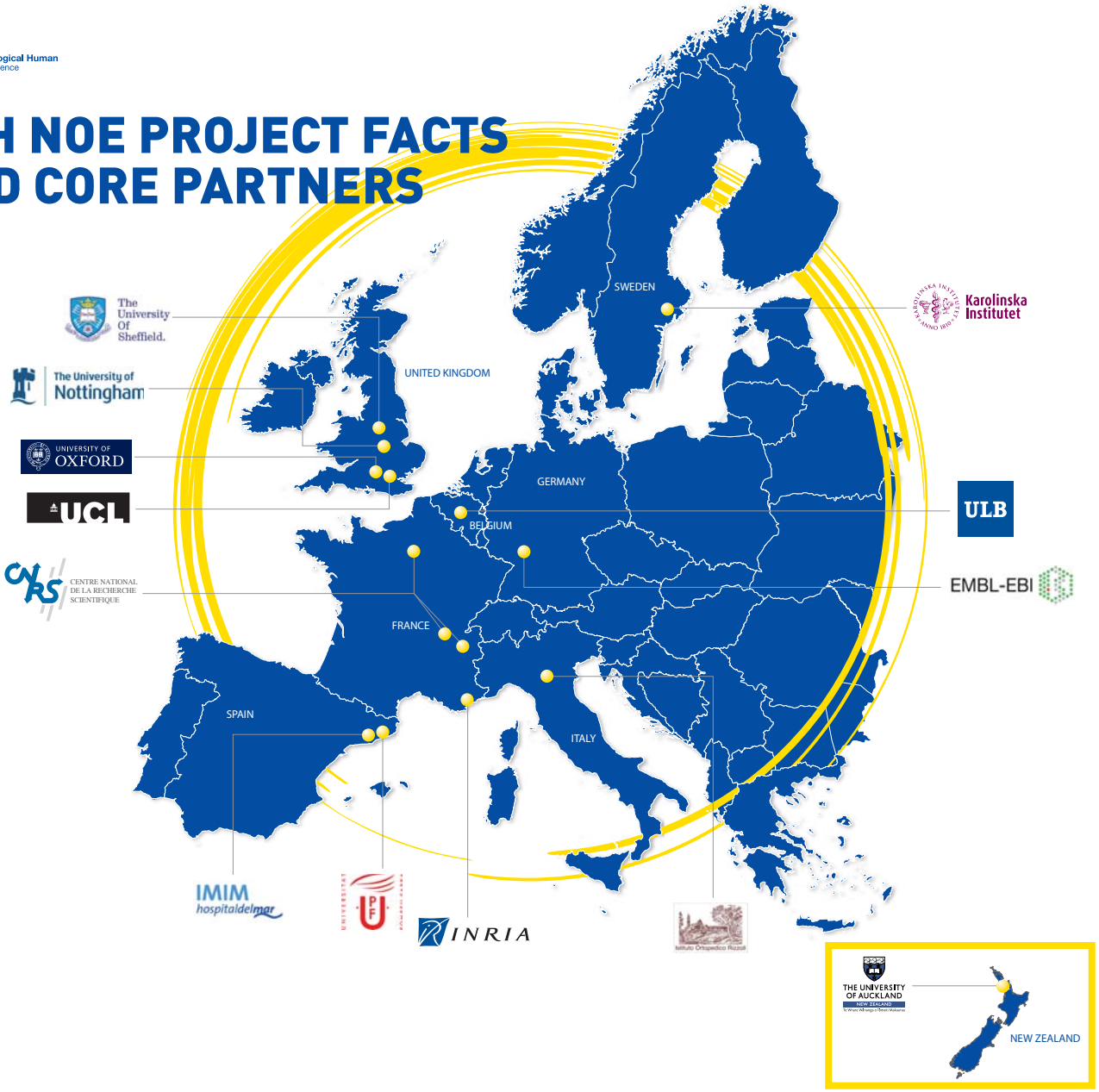
VPH NOE PROJECT FACTS AND CORE PARTNERS



VPH NoE project facts and core partners
VPH NoE is a network of excellence funded by the European Commission's Seventh Framework Programme. It contributes to the Virtual Physiological Human initiative.

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Instrument: **Network of Excellence**
Start Date: **June 1st, 2008**
Duration: **4.5 years**
Project Management: **UCL/UOXF**
Workpackage Leaders : **UCL, CNRS, UOXF, UPF**
Core Project Members: **EMBL, KI, IMIM, ULB, UNOTT, UOA, USFD, INRIA, IOR**
Total Project Cost: **9.65 million euros**
EC Funding: **8 million euros**
Further Information: **www.vph-noe.eu**

Core Partners:

The VPH NoE is comprised of 13 Core Project Partners and an extended Associate (for industrial bodies and organisations) and General (for academic institutions) Membership.

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For additional information and to take and active part in the VPH NoE activities, please visit:
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