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VPH NoE newsletter

VIRTUAL PHYSIOLOGICAL HUMAN NETWORK OF EXCELLENCE

E-Infrastructure for the Virtual Physiological Human

P.16 - 20

VPH I project focus

P.28 - 31

Interview with George Mihalas

P.34

Virtual Physiological Human
network of excellence

CONTENTS

VPH NoE

NoE News 4
- VPH NoE Strategic Consensus Meeting
- VPH2012
- A successful beginning for the VPH Institute!
- 2nd VPH NoE Workshop on Toolkit Hands-on Training
- VPH-FET final Roadmap has now been released
- New paper on the importance of standards in Cardiac Electrophysiology Research
- VPH-NoE and AMEE – Notes on Continuing Cooperation
- The ApiNATOMY toolkit for ontology visualization
- Infrastructure requirements for moving multiscale modeling from research tools to the clinical and regulatory domains?

Workpackage focus 13
- WP4 focus – Integration and Training Activities
- WP2 brief update: Two new Exemplar Projects selected in the Third Call for EPs

Technical focus 15
- VPH-EP10: Modelling Sexually Transmitted Infections

VPH Initiative

E-Infrastructure for the Virtual Physiological Human 16
- Introduction to E-Infrastructure for the Virtual Physiological Human
- European Exascale Research and the VPH
- IT Future of Medicine Flagship
- European Data Infrastructure to Support VPH-I Researchers

New Virtual Physiological Human Projects (ICT-2009.5.3) 21
- INBIOMEDvision – Promoting and Monitoring Biomedical Informatics in Europe
- Synergy-COPD: Modelling and simulation for systems medicine
- AirPROM- Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling

Information and Communication Technologies Call (ICT-2011-7) 27
- DISCIPULUS – A community-led Roadmap for the Digital Patient

VPH I project focus (ICT 2007.5.3) 28
- HAMAM Infrastructure requirements for moving multiscale modeling from research tools to the clinical and regulatory domains?
- VPHOP: The VPH dream is coming to reality

VPH people focus 32
- Interview with George Mihalas

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EDITORIAL

The Virtual Physiological Human Network of Excellence is now entering its final year and we are once again pleased to have been given positive feedback by the European Commission following our third annual review.

There have been lots of interactions between the various Work Packages within the VPH NoE. The aim of WP4 is the development of VPH integration and training activities for both early and in-career VPH researchers. Several successful training events have been organized for the VPH community in the form of Study Groups and Workshops, in collaboration with WP2 (Exemplar Projects) and WP3 (VPH ToolKit). Following the success of previous study groups organised by the VPH NoE Consortium, there will be a third VPH NoE study group (SG3) held in Barcelona in May 2012. The format of SG3 will be similar to that of SG1 and SG2. The organisers have invited three groups of world-recognised experts, including the leaders of large VPH Projects, to submit proposals for a "grand challenge" in the areas of musculoskeletal, cardiovascular, and oncology research. WP4 is working in collaboration with WP2, WP3 and WP5 (Dissemination) to create a VPH Textbook which will be published by Oxford University Press in the first half of 2013. Computational Biomedicine is aimed at integrative life scientists, engineers, computer scientists, medics and clinicians, and computer modellers with an emphasis on the specifics of VPH models and technology. The aim of the textbook is to describe VPH-related material/models (in the first instance from WP2 and the VPH-I projects) in a pedagogical fashion.

Exemplar projects (WP2) are continuing to collaborate with project members working on the ToolKit (WP3). The third and last call for new Exemplar Projects (EPs), in the Spring of 2011, resulted in the selection of the final two EPs. Both projects will work towards building a comprehensive toolkit for the community, which is one of the main objectives for the VPH NoE. The two selected projects address important gaps in the previous coverage of organ systems and pathologies by previous Exemplars, namely, sexually transmitted infections (EP10) and cancer-related angiogenesis (EP11).

Members of different Work Packages within VPH NoE, and the wider VPH community, have continued their collaboration with the journal Philosophical Transactions of the Royal Society A to host an annual two-volume theme issue entirely focused on the Virtual Physiological Human (VPH). This series of issues, which started in 2008, is dedicated to the Virtual Physiological Human project, and provides snapshots of the current state of the art. The latest publication is now available and is entitled "Towards the virtual physiological human: mathematical and computational case studies", compiled and edited by Bindi Brook, Peter Kohl and John King. In this themed issue, a series of case studies have been collated that use mathematical and computational modelling techniques to exemplify the processes underlying complex biological phenomena. For further details, please see **http://bit.ly/pBzdwM.**

We are also pleased to report that WP5 produced a short film in 2011 on the 'Virtual Physiological Human' which is now available on our website and on YouTube. We would like to thank everyone who was involved with the video including Denis Noble, University of Oxford, and Peter Kohl from Imperial College London together with contributions from the VPH Projects preDICT, euHeart, VPHOP, ContraCancrum and PASSPORT. You can see a link to the video, along with links to other useful information, in the "Highlights" column on **www.vph-noe.eu.**

In the VPH Initiative (VPH-I) section of this issue we report on e-infrastructure being deployed to support VPH research. The central objective of the VPH Initiative is to promote the development and use of computer-based models to assist in clinical decision-making. VPH projects have unending requirements for more computing power, and in this issue we highlight two current e-infrastructure projects: EUDAT and CRESTA, and the new FET Flagship project IT Future of Medicine which supports VPH through the development and deployment of ICT resources. We also have profiles of projects from the most recent Virtual Physiological Human funding call, ICT-2009.5.3, which closed on 13 April 2010. We showcase three more profiles of these exciting new projects: AirPROM, INBIOMEDvision and Synergy-COPD. We detail the progress and results of the early FP7 projects HAMAM and VPHOP from Virtual Physiological Human funding call ICT-2007.5.3.

Last but not least please note our call for abstracts for the VPH2012. The second in what we hope will become a series of VPH conferences, VPH 2012 will be held 18 – 20 September 2012, in London. VPH2012 will be an international conference on computational biomedicine, with a focus on the integrative aspects of VPH. We hope to showcase core VPH research, and also to reach outside the VPH community to other relevant communities including those in more conventional forms of systems biology. The vision is to have a conference that truly encompasses all possible scales to model physio/pathology with a clear ICT focus. Similar to the format of the VPH2010 –we also plan to publish the best VPH2012 papers and posters in Interface Focus in a special themed issue on "Integrative Approaches to Computational Biomedicine".

Please keep an eye on our website **(www.vph-noe.eu/vph2012)** for further details!

We would like to close by wishing all of our readers a productive and successful New Year.

VPH NoE News

VPH NoE Strategic Consensus Meeting

The VPH NoE Strategic Consensus meeting took place on Friday 30th September at the Hotel Icaria Barcelona, Spain. This was held in conjunction with the VPH Network of Excellence Annual General Meeting (AGM) on 29th September which took place in the same location. The Strategic Consensus meeting was designed to facilitate discussion on the general strategic directions for the VPH community in the coming years. Peter Coveney chaired the meeting with moderators Peter Hunter and Marco Viceconti. Joel Bacquet, Project officer for VPH NoE and Head of sector, ICT for Health, DG-INFSO, opened the meeting by updating the VPH community on details of the next proposed funding framework from the European Commission - Horizon2020. Marco Viceconti then discussed the role for VPH research in Horizon2020: VPH could be the key which brings together many different common threads in European Healthcare - the Digital Patient, in-silico clinical trials, and personal health forecasting. More specifically, Viceconti proposed that VPH research could fit with the proposed 'ICT for Health in Horizon 2020 ICT for societal challenges: in silico based medicine'. Vanessa Diaz, coordinator of the new Discipulus - roadmap of the Digital Patient support action, which started on 1st October 2011, further elaborated on this. The Digital Patient is the digital representation of the health status/history of patients and can be used for healthcare at all levels for personalized prevention/diagnosis/treatment and research. Vanessa detailed how it was the focus of the project to get VPH research into the clinics and into industry. Alfons Hoekstra discussed in silico clinical trials highlighting how the Pharma, Medical Devices and Biotech Industry were targets for trials and noting early examples of trials by existing VPH projects - VPHOP, PreDiCT and RT3S. Lastly, Marco Viceconti discussed how personal health forecasting was the way forward as demographic changes, cultural change and exploding costs of healthcare increasingly show a need for a role of prevention and early diagnosis. Members of the VPH NoE gave updates on the direction the network itself will be taking in its final year: Peter Coveney, VPH NoE Project Coordinator, gave a talk on how VPH projects need a large-scale distributed European grid infrastructure, able to accommodate their diverse, heterogeneous requirements in terms of storage, computing power and networks. Keith McCormack gave a talk on the VPH NoE ToolKit and ToolKit portal **(http://toolkit.vph-noe.eu/)** and Peter Hunter closed the meeting with a discussion on the VPH NoE 2011 update of the vision and strategy document **(www.vph-noe.eu/vph-repository/)**, coordinated by the VPH NoE to channel the views of the community and to inform European Commission policy for this field. The discussions at the Consensus Meeting have shaped the outline of the next update of the document; more details on this will be available on our website soon. ■

For further details of the Strategic Consensus meeting please see:
http://www.vph-noe.eu/component/content/article/565

VPH 2012

September 18th - 20th 2012
London, UK

Call for abstracts for VPH2012!

The Virtual Physiological Human Network of Excellence (VPH NoE) will hold the second of the series of VPH Conferences (VPH 2012) on **18 – 20 September 2012**.

VPH2012 will be an international conference on computational biomedicine, with a clear focus on the integrative aspects of VPH. Special attention will be given to the 'Digital Patient' as well as 'health forecasts'. VPH2012 aims at reaching outside of the VPH community to other equally important communities: systems biology and genomics. **In this respect, our vision is to have a conference that truly encompasses all possible scales to model physio/pathology with a clear ICT focus.**

The second meeting will take place at the Savoy Place, London. VPH2012 is supported by the European Commission ICT for Health / DG Information Society and Media. The Virtual Physiological Human Network of Excellence is an umbrella project representing the Virtual Physiological Human Initiative set up by the European Commission with a budget of ~ 207 million Euros for the Framework 7 Program.
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. Sessional workshops are those which focus on a particular theme with keynote speakers and will also have an open call for abstracts. Hands-on workshops have invited speakers, their aim is to give attendees a deeper knowledge and familiarity of a specific set of tools or concepts, and will have a more interactive format. Similar to the format of the VPH2010 –we also plan to publish the best VPH2012 papers and posters in Interface Focus in a special themed issue on "Integrative Approaches to Computational Biomedicine".

The deadline for the call for abstracts is 29 February 2012. Submissions should be based on one (or more) of the conference themes (see below).

KEYNOTE SPEAKERS

Professor Raimond Winslow
Director, Centre for Cardiovascular Bioinformatics and Modeling
The Johns Hopkins School of Medicine, USA

Professor Salvador Moncada
Director, Wolfson Institute for Biomedical Research
University College London, UK

Professor Douglas Kell
Chief Executive, Biotechnology and Biological Sciences Research Council (BBSRC), UK

Professor Hiroaki Kitano
President, The Systems Biology Institute, Japan Principal Investigator, Okinawa Institute of Science and Technology, JP

Stephen Friend
President, Sage Bionetworks, USA

CONFERENCE THEME TRACKS:

1. Physiome: multiscale modelling of physiology and pathology
(Track chairs: Peter Hunter and S Randall Thomas)

2. Virtual Physiological Human: infrastructures and technologies for integrative biomedical research
(Track chairs: Rod Hose and Ryutaro Himeno)

3. Digital Patient: ICT for integrating data, information, and knowledge in the clinical practice
(Track Chairs: Dipak Kalra and Marco Viceconti)

4. System Medicine: bridging Physiome / VPH and Systems Biology
(Track chairs: Adriano Henney and Hans Westerhoff)

5. Genomics, proteomics and bioinformatics
(Track chairs: Paul Kellam, Ferran Sanz & Nour Shublaq)

6. Personal Health Forecasting: next-generation technology for Active and Healthy Ageing
(Track chairs: Filippo Castiglione and Emanuela Merelli)

7. In-silico clinical trials: integrative information management and integrative modelling to develop and assess medicines, medical devices, tissue engineering, and biotechnology products
(Track Chairs: Norbert Graf and Peter Kohl)

For further details please see the VPH2012 conference webpage **http://www.vph-noe.eu/vph2012**

Keep an eye on our website for more details of this and other upcoming events!

A successful beginning for the VPH Institute!

Prof. Denis Noble,
current President of the Institute

In only a few months from its incorporation, the VPH Institute has already gained a strong solidity and a large support from the VPH community. Its current membership is composed of 58 organisations worldwide, spanning from European academic and research institutes, to private companies, and National organisations such as the National Library of Medicine, the world's largest medical library.

The first General Assembly of the VPH Institute, which was held in September 2011 in Barcelona, was the official kick off of the VPH Institute's activities. The meeting was very well attended and offered the perfect scenario for opening a two way communication channel with its membership, and the community at large. Many valuable inputs were given by Assembly participants on the role and activities the Institute should carry out in the near future, confirming that the VPH Institute is really responding to a common need to be better represented, to gain more strength in reaching a common goal and to join together the many heterogeneous research interests.
The Institute recently held elections of the Board of Trustees, composed of the President and two financial auditors, who will have the role of supervising the operations of the Board of Directors, ensuring that they do not get into conflict with the interests of the membership at large. It is with great pleasure that we announce that Professor Denis Nobles was unanimously elected President of the Institute: he is currently President of the International Union of Physiological Sciences (IUPS) and is one of the pioneers of Systems Biology, developing the first viable mathematical model of the working heart in 1960.

We also take the opportunity to formally congratulate Professor Randy Thomas (CNRS) and Isabelle Wartelle (Academisch Medisch Centrum bij de Universiteit van Amsterdam AMC) who were elected financial auditors of the Institute.

Since its establishment the VPH Institute has been very active:

- The Board of Directors submitted a Green Paper for the recent EC public consultation "From Challenges to Opportunities: Towards a Common Strategic Framework for EU Research and Innovation funding".
- The Institute contributed to the ARGOS position paper – an initiative whose aim was to foster transatlantic integration of the VPH effort in Europe and the US – and to the VPH Future and Emerging Technologies (FET) Support Action Roadmap.
- From September, the Institute is collaborating with Discipulus, a support action coordinated by Vanessa Diaz, whose aims is to map the territory of the so-called "Digital Patient", a new term that indicates the translation and deployment of VPH technologies into instruments that can be used directly by medical professionals.
- In November the current Executive Director of the Institute, Marco Viceconti (University of Sheffield), was invited to the 4th Global COE Symposium in Osaka –Japan– to represent the Virtual Physiological Human initiative. The Symposium was a great opportunity to establish worldwide contacts for the consolidation of the International Physiome / VPH workgroup chaired by Peter Hunter that the VPH Institute is currently hosting.

A lot is going on, and there is much more in the pipeline. If you wish to get more directly involved with the VPH Institute and its initiatives, the call for members is still ongoing. The ordinary membership does not involve any particular obligations and is open to any organisation that shares the vision of the Institute. ■

For more information, please contact the VPH Institute Manager, Martina Contin **manager@vph-institute.org** or visit: **https://www.biomedtown.org/vphinstitute**

VPH NoE ToolKit Workshop: Hands-on Training

Maxime Sermesant, Inria

The medical imaging "core" of the VPH NoE (Inria, CNRS, UPF) organised the second hands-on workshop on the VPH NoE ToolKit. Medical Imaging Toolkit, Interoperability took place on 21-23 November 2011, hosted by Inria, in Sophia-Antipolis, France. The workshop focused on interoperability between software, algorithms, and research teams working with imaging tools. The goals were to benefit from other participants' expertise through use-case presentations, to have a practical, hands-on workshop to answer image-related problems, and to lead to greater interoperability between tools and algorithms from different research teams.

The audience was a mix: we had researchers and engineers developing imaging algorithms, people looking for algorithms to integrate within their software or workflows, people looking for tools to publish their algorithms and compare them with others, and people who were just happy to share their experience in making their tools interoperable, or adapting existing tools. A particular strength of the meeting was its diversity: we had 22 participants from 11 different institutions, including both academic and industrial research groups.

Perhaps the tool with the broadest appeal was the Inria teams' dedicated reading, processing and visualisation prototype. It was developed in response to a problem at the Academic Medical Center in Amsterdam: they are acquiring cryomicrotome datasets of up to 200 GB, which are far too large to open on their computers. The software enables the Amsterdam team to visualise the image data in 3D, by presenting (see Figure 1) a sub-sampled version of the full image (in blue) and the full-resolution data within a smaller region of interest (in red), which can be interactively moved in the full dataset. Using this system, the full image is never entirely loaded in memory, but researchers can have the necessary detail at their fingertips.

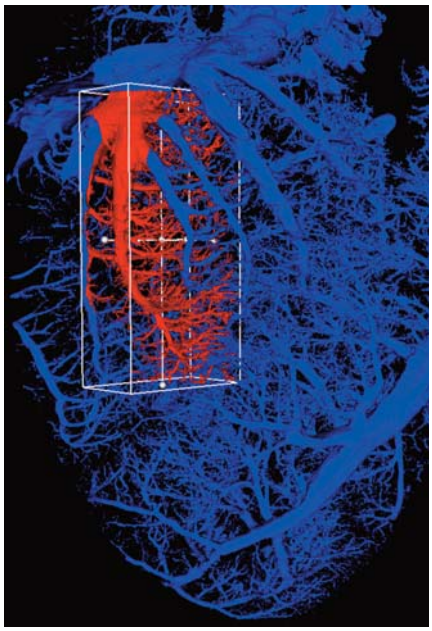

Figure 1. Visualisation of the image data in 3D.

This event took place right after the Common Toolkit Hack-fest (also hosted by Inria in Sophia-Antipolis, 14-18 November 2011). This proximity allowed an exchange between the two communities, extending the reach of the VPH NoE ToolKit to companies and research institutions throughout the world. ■

For further details on the workshop please visit **http://www-sop.inria.fr/asclepios/events/VPHimaging11/**.
For further details on the CTK Hack-fest please visit **http://www.commontk.org/**.

VPH-FET

VPH-FET final Roadmap released

Valeria Codeluppi, Istituto Ortopedico Rizzoli, Italy

The final typeset version of the VPH- Future and Emerging Technologies (FET) Roadmap was released at the end of November 2011. This roadmap is the final consensus document developed by experts during the summer following the discussions that took place in the VPH-FET conference, "Technologies for the Future of the Virtual Physiological Human," which was held in London on 27 June 2011.The scope of the conference was to identify the future and emerging technologies that are most relevant to VPH and to prescribe a framework by which they can be developed further to assist the acceleration of VPH development in the coming years. The resulting Roadmap highlights topics that entail a certain level of risk but which, nevertheless, could provide significant benefits if suitable solutions can be found. It is hoped that the Roadmap will assist the further development of the VPH in new and exciting directions. The VPH-FET project would like to thank all who have shown interest in the project and given support over the past year, in particular those who gave up so much time over the summer to help complete the various Roadmap chapters. ■

For further details visit the VPH FET building on the Biomed Town Portal: **https://www.biomedtown.org/biomed_town/VPHFET**. The full document can be found at **https://www.biomedtown.org/VPHFET/reception/vphfetpublicrep/VPH-FET_final_roadmap.pdf.**

New paper on the importance of standards in Cardiac Electrophysiology Research

A large group of heart specialists and scientists, including many who work with virtual physiological human (VPH) projects from many different domains have come together to state that Cardiac experimental electrophysiology is in need of a well-defined Minimum Information Standard for recording, annotating, and reporting experimental data.

The group, who come from 44 different universities and institutions from all over the world have recently produced a draft standard, called Minimum Information about a Cardiac Electrophysiology Experiment (MICEE). Their ultimate goal is to develop a useful tool for cardiac electrophysiologists which facilitates and improves dissemination of the minimum information necessary for reproduction of cardiac electrophysiology research, allowing for easier comparison and utilisation of findings by others. It is hoped that this will enhance the integration of individual results into experimental, computational, and conceptual models.

This type of initiative is the aim of many in the VPH community. In its present form, the draft is intended for assessment and development by the research community. The authors invite the reader to join this effort, and, if deemed productive, implement the Minimum Information about a Cardiac Electrophysiology Experiment standard in their own work.

To view the paper called 'Minimum Information about a Cardiac Electrophysiology Experiment (MICEE): Standardised reporting for model reproducibility, interoperability, and data sharing' by T. Quinn et al. and published in Progress and Biophysics in Molecular Biology, go to the following link: **doi:10.1016/j.pbiomolbio.2011.07.001** ■

VPH-NoE and AMEE – Notes on Continuing Cooperation

Keith McCormack, VPH NoE WP3 Leader, University of Oxford

In a joint venture arising from a successful collaboration in late 2010, the Association for Medical Education in Europe **(AMEE: http://www.amee.org)** and the VPH NoE have continued to work closely together throughout 2011 on a number of activities designed both to promote awareness and to generate practical outputs in support of increased education in VPH technologies. Spurred on by keen enthusiasm within the NoE and at St George's, University of London, the communities together established a four-stranded development strategy in these key areas:

- **Demonstration**
The creation of tools extending educational opportunities for the explanation of VPH mechanisms and benefits
- **Web**
Collaboration in developing web systems with semantic underpinning
- **Funding**
Joint applications for funding to extend educational developments
- **Dissemination**
Mutual support at key events in both communities' calendars

The Demonstration strand has developed significantly, with close practical collaboration on the design and construction of a new concept in interactive medical education. Several NoE/VPH Initiative partners are working with a group of AMEE experts led by Stockholm's Karolinska Institute to develop an "Education Engine," an automated system allowing students to include the results of complex VPH simulations in the web-based delivery of hands-on "what-if" processes supported by in-depth explanatory materials. To provide a short-cut to results that often take hours to compute the system will allow a potentially limitless library of pre-computed results to be combined with on-the-fly computations, to enable students to explore and appreciate the role that simulation can play in improving diagnostic precision, interventional risk-assessment and treatment selection.

Semantic Web facilities have been investigated in joint activities between the NoE's semantic team at the EBI in Cambridge and the AMEE community's mEducator project led by the Aristotle University of Thessaloniki **(http://www.meducator.net)**. A key focus is the development of a metadata system to describe medical educational content that, when implemented, will enable the automated re-use and sharing of materials to agreed standards, bringing various educational

approaches (conventional teaching, active learning, e-learning, blended learning…), to multiple audiences across language and cultural barriers.

Funding support to encourage further development is actively pursued within several EC funding streams in Health, ICT and Education, and it is expected that the collaborative work begun in the Demonstration strand will be further developed and taken to wider audiences as a result of a collaborative technology project uniting AMEE and VPH-I teams.

Dissemination activities have already seen cross-fertilisation within written materials, and the VPH community united around a well-attended special session at the 3000-strong AMEE 2011 conference in Vienna in August 2011, where seven separate VPH project groups presented the results of their work to an attentive and questioning audience. Several international collaborations have subsequently ensued. The reciprocal process will see a significant presence of AMEE groups at the forthcoming VPH2012 conference in London in September 2012 **(http://www.vph-noe.eu/vph2012).**

Each of these collaborative strands is not only assisting in the process of intertwining the two communities, but is also enabling superior results to be presented within important deliverable materials. The AMEE/VPH partnership seems destined to endure. ■

The ApiNATOMY toolkit for ontology visualization

Bernard de Bono MD PhD, European Bioinformatics Institute & Auckland Bioengineering Institute

As formal activities of the VPH NoE project draw to a close in 2012, it is useful to consider, from a knowledge management perspective, the progress achieved by VPH efforts in enabling the collaborative investigation of the human body as a single complex system, and in so doing reflect on how best to face the interoperability challenges ahead.

This article focuses on the lessons learnt from the collaboration between the RICORDO **(http://vph-ricordo.eu)** VPH-Initiative project and the VPH NoE on the application of knowledge artefacts (known as ontologies) to ensure semantic interoperability between VPH modeling resources. In particular, the key lesson learnt is that the use of ontologies and related technologies must be considerably simplified and rendered more accessible to the community. To this end, visualization techniques that assist with the overview and articulation of ontologies are emerging as significant tools to simplify the management of these knowledge artefacts.

In the discussion below, a brief introductory background to the RICORDO effort is first outlined (A). Section (B) describes the development of the ApiNATOMY toolkit for ontology visualization, driven by lessons learnt in the course of the RICORDO effort.

(A) RICORDO: using ontologies to manage VPH data and models

In order to improve the automated integration of VPH data and model resources (DMRs) in terms of biological meaning, the RICORDO effort has fostered the development of methods for the annotation, sharing and reasoning over 'semantic metadata' of DMRs. 'Metadata' refers to machine-readable documentation material that is linked to a corresponding DMR element indicating how the actual content of that element should be interpreted. 'Semantic metadata' ascribes a DMR element with some meaning. By explicitly representing the meaning of a DMR element, this type of metadata adds semantic features to a resource and provides a machine readable and independent guide as to what a particular DMR element represents. The goal of achieving semantic interoperability for a set of DMRs is motivated by the need to automate the coherent interpretation of DMR content over a large number of diverse DMRs. A key result of attaining this goal is the ability to automatically identify DMRs that are related to each other solely on the basis of their metadata documentation notwithstanding any differences in format, accessibility or ancillary free-text labels the various DMRs may have
The key to relating diverse VPH DMRs in RICORDO is to make use of a small set of knowledge-rich ontologies in the annotation of resource sematic metadata. Specifically, in order to relate VPH DMRs in terms of their biological meaning, a small set of ontologies about biology knowledge are applied in the annotation of multiscale biological structure (from small molecules to gross anatomy), measurable qualities (e.g. mass, temperature), as well as associated units of measurement. A second critical step in automatically relating DMRs in terms of biological meaning is to apply reasoning tools to infer relations between DMR metadata on the basis of how they relate over the ontology (or ontologies) to which they refer.
Although there is evidence for the utility of the above integrative approach, the productive use of ontologies in biology frequently remains the preserve of a comparatively small section of the community. One reason for this is the steep learning curve exacted of those who attempt to work with ontologies of substantial size without appropriate tools to manage such ontologies. This requirement for appropriate tools provided the motivation to develop the ApiNATOMY toolkit **(http://apinatomy.org)**, described below, in support of the visualization of large ontologies.

(B) ApiNATOMY: visualizing ontology schematics and related metadata

The ontology visualization approach central to ApiNATOMY is the depiction of

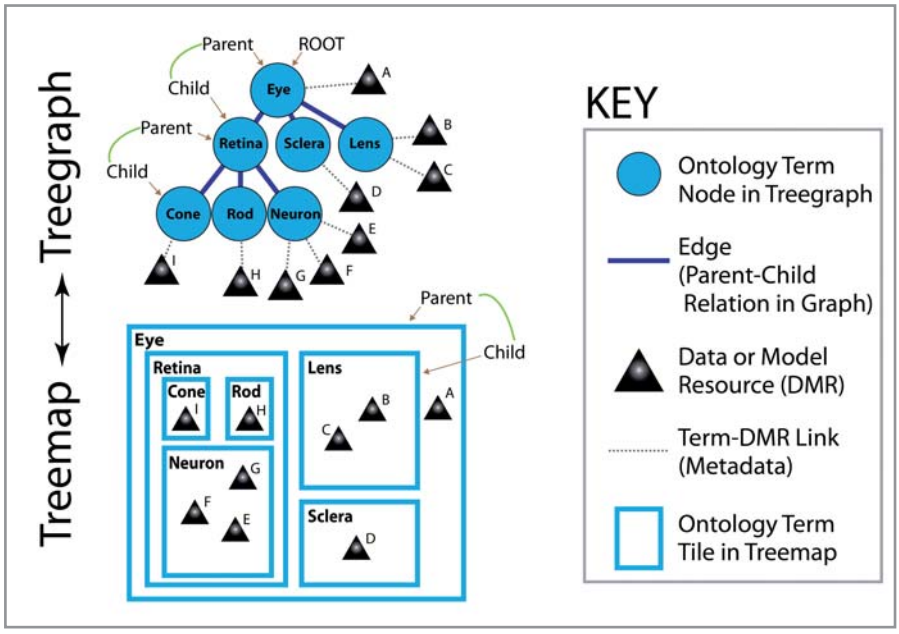

Figure 1. A graph representing a simple ontology of eye anatomy is shown in two configurations – in treegraph (top) and topologically-equivalent treemap form (bottom). Ontology terms are depicted as nodes in the treegraph and as tiles in the treemap. An ontology relation is shown as a graph edge (a blue line) that links two nodes in the treegraph, while the same relation is depicted as the location of one tile within another in the treemap (known as 'nesting') – the type of relation is not specified. Data and model resources linked to ontology terms via metadata are represented in triangular form.

ontology terms as tiles within a treemap (see Figure 1.), where child terms of a parent term as shown as child tiles nested within the corresponding parent tile. A second key feature of ApiNATOMY treemaps is the representation of metadata related to a particular ontology term as a symbolic icon embedded within the boundaries of the corresponding term tile.

Although, as the name suggests, ApiNATOMY treemaps are particularly useful in the graphical depiction of treemap schematics representing anatomical structure, in practice ApiNATOMY can be applied to the consistent layout of any ontology. However, for the purposes of this VPH-related discussion, the use of ApiNATOMY in the automatic generation of anatomy schematics will be described in the context of the visualization of RICORDO metadata.

Ontologies describing biological structure, such as the Foundational Model of Anatomy (FMA), typically consist of a very large set of terms and their relations - the FMA, for example, has over 70 thousand terms. In the case of large anatomy ontologies, the challenge in producing useful treemaps is two-fold:

1) Can the visual depiction of the FMA treemap be laid out such that the 2D map conveys spatial anatomy knowledge? Arranging the relative spatial position of tiles to reflect anatomical location would enhance the VPH user's interaction with the ontology, and convey the biological meaning of related VPH resource metadata with greater immediacy.
2) In practice, the typical visualization use case is for anatomy treemap depiction to be carried out on an arbitrary subset of FMA terms. – dealing with a whole-FMA treemap may be prohibitively and unnecessarily expensive computationally. Can the treemap rendering of FMA subsets still retain the meaningful spatial localization discussed in point 1 above?

While a more detailed treatment of the technical implementation and application of treemap layout is available through the ApiNATOMY website, the overall layout strategy in ApiNATOMY is discussed below.

ApiNATOMY makes use of spatial templates to constrain the layout of child tiles that belong to the same parent term. An example of the application of one such template is illustrated in Fig. 2 and relates to the organization of top-level anatomical regions that are child terms to the parent term 'Body' in the FMA. In general, templates can be associated with any parent term.

The use of a template allows the design of regional anatomy treemaps according to desirable criteria. For instance, in Figure 2 the human body is divided into 24 major regions arrayed over a 6x4 template matrix. In terms of biomedical meaning for this particular scenario, such a template ensures that tiles representing components of body regions that have an epithelial surface is drawn on a peripheral tile of the template and thus convey the meaning associated with their role in interacting with the surrounding environment. Tiles representing vascular or neural body regions are located at the core of the 6x4 template as befits their connectivity role in physiology.

The role of templates becomes even more relevant when subsets of FMA terms are to be laid out. The coherent application of the communal layout constraints ensures that the spatial arrangement of different treemaps derived from the same reference ontology remains consistent. A simple example of the application of one template to constrain the layout of two small treemaps is shown in Figure 3, while a slightly more complex example using two templates is illustrated in Figure 4.

Next steps for VPH Knowledge Management

The development of novel methods that utilize explicit knowledge to display ontology terms and associated semantic metadata in a visually intuitive manner would provide added value to ontology-annotated resources. ApiNATOMY is one such method. ApiNATOMY is being developed to make the annotation of resource metadata more straightforward, and navigation and searching of metadata repositories similarly intuitive.

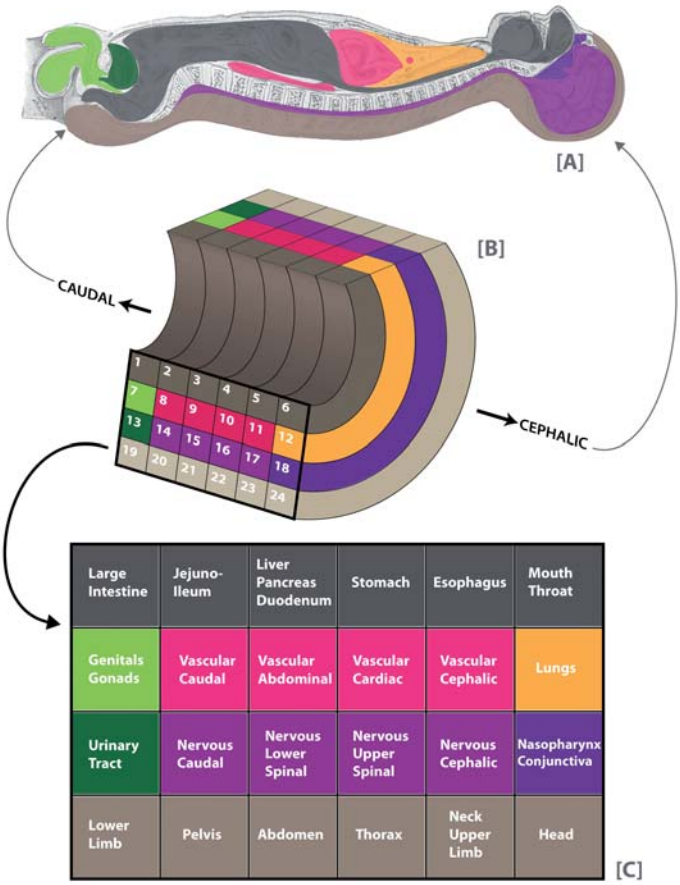

Figure 2. [A] A longitudinal section through the middle of the male human body showing the external and internal surfaces, and organs. The colour coding overlaid onto the picture follows the same colour scheme as [B] and [C] below.
[B] An idealized radially symmetric body plan, apportioned over 24 cylindrical regions. This homunculus has a central longitudinal axis of rotation located in the idealized gut lumen which runs in the cephalocaudal direction. [C] The 24-tile FMA 'Body'template describes regionally co-located tissues. This template is applied by the ApiNATOMY tool to constrain the layout of anatomy term tiles.

Figure 4. Ensuring the consistent layout between two derivative FMA subgraphs [A] and [B]. Both treemaps are colour-coded in the style of Figure 2. Their layout is under the constraining influence of two templates – one for the children of the 'Body' term, and one for the children of the 'Stomach' term (pale grey tiles). The difference between treemap A and B is the removal of term tiles marked with an 'X' from the derivative subgraph for A. The yellow and blue arrows show how, in laying out treemap B, the constraining influence of the two templates ensures that the relative position of the tiles the two treemaps have in common remains consistent.

The overall aim is to support the use of ApiNATOMY schematics as a front-end to metadata frameworks such as RICORDO. For instance, the graphical integration of various types of resource metadata onto schematic 2D depictions of multiscale anatomy would allow epidemiologists, clinicians and biomedical scientists to visually review, and interact with, anatomically aggregated heterogenous data (e.g. anatomical distribution of gene expression, signalling pathways, spread of primary and secondary tumours, etc). To this end, the application of the RICORDO metadata framework in the context of Innovative Medicines Initiative (IMI) projects, such as DDMoRe, is indicative that ApiNATOMY graphical user interfaces (GUIs) may soon have a role to play in drug discovery and development. ■

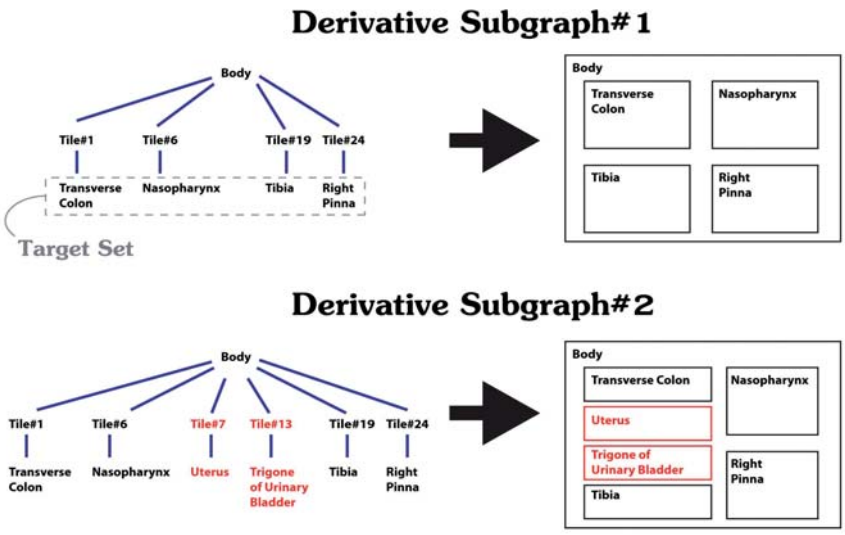

Figure 3. The application of templates to ensure the consistent layout of treemaps derived from the same reference ontology. Note how the relative position of the four tiles (child terms to the parent 'Body' term) in derivative subgraph 1 remains unchanged when two new child tiles (in red) are added to subgraph 2.

For more information please contact Bernard de Bono **bdb@ebi.ac.uk** and visit the RICORDO website: **http://www.ricordo.eu/**

Infrastructure requirements for moving multiscale modeling from research tools to the clinical and regulatory domains

James Sluka, James Glazier and Maciej Swat, Indiana University, USA

If Multiscale biological modeling (MSM) is to move from the basic research domain into the regulatory and medical domains it will become a requirement that models are documented, defensible, transparent, reproducible and archive-able (DDTRA). In a whitepaper published last year for the Multiscale Modeling Consortium there was a discussion on the challenges biological modelers are facing as their work moves from basic research to tools that can be used in the clinical and regulatory domains.

It seems likely that the long term paradigm in MSM will be models that include multiple sub-models, spanning multiple spatial and temporal scales and instantiated in multiple computational modalities. This heterogeneous approach presents unique problems in DDTRA. The authors believe that this transition requires a much more robust and better defined method of describing models. Their view is that a suitable model description should include at least three views of the model. A model description should include (1) a clear biological description of what is being modeled. For each biological component there should be (2) a clear and defensible description of the math and physics used to represent that biology. Finally, there needs to be (3) a description of the computational instantiation of the mathematics that is sufficiently detailed to allow the model to be reproduced in both the original computational framework and also in other frameworks.

Finally, to get users to actually use robust methods of model definition, tools are needed that provide immediate tangible benefit to the user. A suitable "carrot" might be a graphical user interface that allows biologists, both wet-lab and computational, to describe their models. The user would immediately benefit from having a high quality properly annotated description of their model, and would also have a searchable (mineable, sharable…) description of their model(s). The tool could greatly simplify, and hence "enforce", the use of the appropriate reference ontologies at all stages of the model building process. The tool could also greatly simplify the task of provenancing a model and any associated data and results.

Based on feedback from other researchers it is clear that a broadly applicable and robust solution is going to require significant effort. As a starting point, we have begun work on a lightweight annotation scheme and web-based tool that allows a researcher to semantically annotate a broad range of file and data types. Though the lightweight scheme will not fulfill all of our goals it does accomplish several important ones. It will create web-searchable documents, of a broad range of file types (images, data tables, computational code), that are tagged with terms from accepted bio-ontologies. The web based tool will simplify the use of appropriate reference ontologies for entities such as biological processes, cell types, and small molecules.

We believe that in the long term, standardized model description technologies will benefit the general biomodel research community, including the VPH, as well as the medical and regulatory communities in the EU and US. ■

For further information please contact James Sluka **JSluka@Indiana.edu** and consult the white paper at **http://tinyurl.com/MSM-NIH-10-21-10**.

Workpackage focus

WP focus: WP4 – Integration and Training Activities

Michele Spinelli, WP4 Coordinator, Universitat Pompeu Fabra

The aim of Work Package 4 is the development of VPH integration and training activities for both early and in-career VPH researchers. After identification of existing facilities and emerging needs in this last part of the project, the WP4 team is focusing on the outcomes generated from other VPH-related projects (VPH Initiative projects, Exemplar Projects – WP2, Marie Curie Initial Training Network projects) and existing EC-initiatives. The primary goal is to ensure complimentarity with existing activities. The ultimate goal of this work is the design and implementation of actions directed at the development of VPH research education and careers.

Training Activities

The development of Training Activities is intended to strongly promote transversal collaboration within different life science disciplines, also through the use of VPH-related tools. So far, a number of successful training events have been organized for the VPH community in the form of Study Groups and Workshops, in collaboration with WP2-3. The thriving format, promoted by the core expertise of partners from University of Nottingham, allows students to come together to solve real modelling problems by interacting with VPH experts. This facilitates hands-on collaborative work, focused on formulating new models of currently unsolved biological problems. Training is being reinforced with specific hands-on events targeting the VPH community to promote the use of the contents of the VPH ToolKit. The Study Groups series will be completed with 3rd VPH Study Group on the VPH ToolKit that will be held in Barcelona, 7-11 May 2012. Three research areas will be addressed during the study group: musculoskeletal, cardiovascular and oncology. A group of world-class experts, associated to each of the research areas, will submit a proposal for a grand challenge to be discussed and a modeling workflow associated. For each challenge a group formed by the experts, software developers (related to the Toolkit) and young researchers (PhD students and postdocs), will then come up with a workflow to tackle the challenge.

Educational Materials

This area is targeting two individual, but related, components. On one hand the development of the VPH Textbook, and on the other, the provision of educational materials for raising clinical awareness.

The VPH Textbook is intended as a multi-authored community effort on the issue of experimental data-based predictive bio-mathematical modelling, aimed at integrative life scientists, engineers, and computer modellers. The VPH textbook is being compiled under the coordination of the partners from University College London. Their expertise in this area is contributing to produce a textbook different to other books in related areas (for example, Systems Biology or Mathematical Physiology), and with an emphasis on the specifics of VPH models and technology. A printed version with supplementary digital material will be available through Oxford University Press by the first quarter of 2013.

Within this area, partners from the University of Sheffield determined the scope of VPH-related material/models in order to introduce VPH concepts to a wider, essentially non-technical, clinical audience. Materials will come from the VPH Initiative projects, VPH ToolKit **(http:// http://toolkit.vph-noe.eu/)** and the Exemplar Projects **(WP2 - http://www.vph-noe.eu/wp2)** in the first instance.

To get this training to its target audience, the VPH NoE has teamed up with the Association for Medical Education in Europe **(AMEE, http://www.amee.org/)**. Here, the primary aim is to explore opportunities to disseminate the projects and outputs of the VPH within this educational community, giving the VPH an insight into the ways to integrate its outputs into medical education.

Academic Strategy Document

This activity is being developed under the coordination of Universitat Pompeu Fabra and will be delivered at the end of this final year of the NoE. The aim of the VPH Academic Strategy Document is to provide recommendations to the European Academic Area on the design and implementation of a VPH curriculum. The development of an integrated academic/industrial policy in a formal plan for the VPH initiative is the key issue for WP4. This includes engaging both industry representatives and clinicians, fostering mobility among students and producing educational materials. The VPH NoE community is collaborating with the Multi-Institutional Graduate Programme for Virtual Physiological Human Scientist (VPH-MIP) community in order to discuss the potential content of VPH-specific academic curricula. This strategic document will emphasize key-features for the sustainability of VPH-specific training in Europe beyond the life of the NoE. ■

For more information on WP4 please contact **mspinelli@cistib.upf.edu** and visit the work package webpage: **http://www.vph-noe.eu/wp4.**

For more information on the VPH Study Group to be held in Barcelona in May, see **http://www.vph-noe.eu/vph-events/details/188-3rd-vph-study-group-on-vph-toolkit**

Workpackage focus

WP2 Exemplar Projects update: Two new Exemplar Projects selected in the Third Call for EPs

S. Randall Thomas, WP2 Coordinator, CNRS (IR4M UMR8081)

The third and final call for new Exemplar Projects (EPs), in the Spring of 2011, resulted in the selection of two EPs, for a total of eleven projects over the life of the VPH NoE. The two selected projects address important gaps in the previous coverage of organ systems and pathologies by the NoE Exemplars: sexually transmitted infections and cancer-related angiogenesis. Here is a brief overview of these two projects:

EP10: Environment for Sexually Transmitted Infection Modeling

Coordinator: Martin Nelson, University of Nottingham, Centre for Mathematical Medicine & Biology (Partners: Queensland University of Technology, Australia; Norwegian University of Science & Technology, Trondheim, Norway; Chlamydia Research Group, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas, USA)

EP10 is developing an environment for mathematical/computational modeling of sexually transmitted infections (STIs). As a representative case study, the project focuses on mark-up and simulation of three existing "within-host" models of Chlamydia trachomatis infection – the most common sexually transmitted pathogen of humans, with over 90 million new adult cases occurring worldwide each year. These models deploy multiscale approaches to describe the spatial progression of C. trachomatis infection in the female genital tract, coupling a continuum description of extracellular Chlamydial particle motion to cell-scale and tissue-scale models of infection of the genital epithelium. The study will facilitate and demonstrate the interoperability of tools across different spatial scales, and it should be extensible to other STIs, including gonorrhea and syphilis. This STI modeling environment will facilitate comparison of models and results, and will be deployable in identification of suitable vaccines.

EP11: Vascular Tissue Modeling Environment (VTME)

Coordinator: Markus Owen, School of Mathematical Sciences, University of Nottingham (Partners: University of Oxford; Centre de Recerca Matemàtica, Barcelona; Charité - Universtätsmedizin Berlin; Department of Physiology, University of Arizona, Tucson; Textensor Ltd., Edinburgh; Arizona State University, Tempe, Arizona; Department of Neuroscience, Physiology & Pharmacology, University College London)

All tissues require a blood supply to deliver nutrients and remove waste products. Problems with blood vessel development can lead to severe birth defects. Later, vascular growth and remodeling play a key role in pathologies including diabetes, macular degeneration, and rheumatoid arthritis; and since tumor growth is crucially dependent on the host blood supply, the vascular system is a major target for anti-cancer therapies. A multiscale model for vascular tissues has been developed by EP11. The model combines (A) fluid flow in a vessel network; (B) partial differential equations (PDEs) for the transport, release and uptake of diffusible substances such as oxygen; (C) cell division and reinforced random walks of cells on a regular lattice; (D) ordinary differential equations (ODEs) for subcellular networks that regulate the cell cycle and growth factors such as VEGF; and (E) integration of angiogenic and vasculogenic endothelial cells into the vascular network.

EP11 will implement a user-friendly Vascular Tissue Modeling Environment (VTME) within the "Cancer, Heart and Soft Tissue Environment" tool **(Chaste, http://web.comlab.ox.ac.uk/ chaste/)**, already part of the VPH ToolKit. VTME will enable sustainable curation of published vascular tissue simulations within the Chaste environment, adopting existing standards (SBML, CellML, MIRIAM, MIASE) and contributing to the development of new VPH standards (e.g., for vascular networks). ■

For more information on the Exemplar Projects, please contact **stephen-randall.thomas@u-psud.fr** and visit the work package webpage: **http://www.vph-noe.eu/wp2.**

Technical focus

VPH-EP10: Modelling Sexually Transmitted Infections

Martin Nelson, University of Nottingham, UK

September 2011 marked the start of a new VPH Exemplar Project focused upon modelling and simulation of sexually transmitted infections, representing the first application of the VPH Toolkit to the reproductive system. This project is led by the Centre for Mathematical Medicine and Biology at the University of Nottingham, in collaboration with theoretical partners at the Queensland University of Technology, Australia, and the Norwegian University of Science and Technology, Trondheim, together with a clinical partner based in Arkansas, USA.

The project is currently focused upon the representative case study of Chlamydia trachomatis – the most common sexually transmitted pathogen in humans, with over 90 million new adult cases occurring worldwide each year. C. trachomatis infection is a complex, multifaceted system: associated models are necessarily multiphase, incorporating phase-dependent infection and immune responses across the three phases of the menstrual cycle; and multiscale, incorporating extracellular transport of Chlamydia particles, internalisation of particles by epithelial cells, intracellular Chlamydia replication and eventual epithelial cell lysis.

To date, theoretical models of C. trachomatis have been complemented by experimental data upon Chlamydia caviae infection in guinea pigs; a bacterial infection which is highly representative of C. trachomatis infection in humans. Via this exemplar project, we seek to bridge the gap between clinical/experimental and theoretical approaches to studying Chlamydia infection. Using current VPH ToolKit software to simulate both existing and new multiscale models, a graphical software environment will be developed, with which clinicians and experimentalists will be able to easily run their own numerical simulations. This software environment, named STIGMaS (Sexually Transmitted Infections – Graphical Modelling and Simulation) will incorporate both theoretical models and experimental data, packaged behind a user-friendly front end, which allows simulations to be implemented without requiring an in-depth knowledge of programming or multiscale modelling techniques.

A fundamental goal of this project is to explore the interoperability of existing ToolKit software with regard to modelling across multiple spatial scales, bridging disciplines, and integrating theoretical models with experimental data. Recent focus has been upon deterministic tissue-scale models, in which continuum descriptions of the genital epithelium are coupled to equations for diffusion and uptake of Chlamydia particles and immune response components. The resulting systems of ordinary (ODE) or partial differential equations (PDE) have been simulated using Chaste; a tool which rendered itself particularly appealing in its broad range of potential applications. The EP10 team are currently working closely with the Chaste team in Oxford, providing valuable user feedback where possible as both projects continue to evolve.

Current work is examining models which replace the tissue-scale descriptions of the epithelium with a discrete, cell-based approach: each epithelial cell is modelled explicitly and evolves according to a prescribed set of rules. This discrete description of the epithelium is coupled to PDE descriptions of extracellular components as described above, forming what we term 'hybrid PDE – cellular automata' models. Currently, we are working with a relatively simple model in which cell-scale components can be solved analytically. For more complex models, which will become the focus in the immediate future, we plan to mark up cell-scale components using CellML. The resulting hybrid models will be simulated through use of Chaste's inbuilt CellML functionality.

The EP10 team. Top left to bottom right: Martin Nelson, Kelly Heymer, Bindi Brook (University of Nottingham); Dann Mallet (Queensland University of Technology); Daniel Simpson (Norwegian University of Science & Technology); Roger Rank (Arkansas Children's Hospital Research Institute).

An important component of EP10 and the resulting software is to include clinical/experimental data directly alongside theoretical models. The EP10 team is currently working closely with the RICORDO project to define an appropriate semantic vocabulary for annotation of Chlamydia models and data. This project constitutes the first time that RICORDO has been applied to a pathological system. Once constructed, this annotation structure will be representative of a wider range of pathological systems, beyond simply sexually transmitted infections, and will ease future incorporation of research into other similar systems.

Over the forthcoming months, the EP10 focus will be upon further exploiting interoperability between Chaste and CellML, continuing to develop data and model annotation strategies with the RICORDO team, and upon expanding the current model-set to also include stochastic models. ■

For further details please contact
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E-Infrastructure for the Virtual Physiological Human

Introduction to E-Infrastructure for the Virtual Physiological Human

Peter Coveney & Nour Shublaq, UCL Centre for Computational Science & UCL Computational Life & Medical Sciences Network

The VPH-NoE has the responsibility to promote and facilitate access to e-infrastructure for projects within the VPH Initiative as a whole. The central objective of the VPH Initiative is to promote the development and use of computer-based models to assist in clinical decision making. These models are intended to be patient-specific, and therefore depend on access to suitably secured, electronic, digital data pertaining to individuals who are being treated by qualified clinicians within a hospital context. The types of data concerned are typically highly heterogenous and wide-ranging, as they may be comprised of data drawn from the genome, through proteomic, cellular, tissue, organ, and human levels (in some cases even more widely to the population level), including various possible imaging modalities. They also contain standard electronic health records.

It is common for data in VPH projects to be sourced from widely distributed medical centres around Europe, which typically need to be brought together in a unified data warehouse environment, from which various forms of VPH modelling would be conducted. Such modelling needs to be performed as high-fidelity three-dimensional simulations, usually as a function of time; this invariably calls for access to various levels of high performance (parallel) computing on selected supercomputers. Moreover, if the results are going to be relevant to clinical decision-

making, they need to be provided in a timely way, for both the clinicians and the specific patients concerned. This calls for advance reservation and, in some cases, urgent computing access to powerful computing resources which typically today are only available via fare-share batch queues within which one waits one's turn for one's jobs to execute. Moreover, sizeable quantities of data must be shipped both onto and off these supercomputing resources if results are to be furnished to experts in their own research centres and hospitals. That can only be achieved if there is a sufficient high quality network, both in terms of bandwidth and quality of service.

It should be clear from this brief description that delivering the results of patient-specific VPH models at the sharp end of patient treatment makes huge and largely unprecedented demands on e-infrastructure. In one VPH INBIOMED vision Think Tank on "Genotype-Phenotype Resources", convened on 5 October 2011 in Brussels, e-infrastructures that support research are recommended as a continuous area of EU funding. Both national and European e-infrastructures are, in principle, available today to support the work of the VPH. However, what is really required is a robust, usable and persistent set of integrated resources (data, networks and computers) which meets the diverse demands of modern computational biomedicine. The requirements are quite generic, and well within the scope modern e-infrastructure providers to deliver. But the e-infrastructure is, more often than not, controlled, administered and managed by other funded programmes with different aims and objectives. Over the lifetime of the VPH-NoE, we have therefore been obliged to liaise with numerous e-infarstructure providers, all pointing in different directions and not "joined up" in anything like the way VPH researchers would wish. We have enjoyed a number of partial successes, including in particular facilitating access to the EGEE low-end and DEISA high-end EU computing infrastructures for VPH projects. These two infrastructures have now been replaced by EGI and PRACE; and we now have specific projects funded by the European Commissions's INFSO Infrastructure Unit which are developing tighter alignment of VPH requirements with these resources.

One of these projects is called MAPPER **(http://www.mapper-project.eu/)**, which was featured in the sixth version of the VPH-NoE Newsletter. Now, in addition, both the EUDAT **(http://www.eudat.eu/)** and CRESTA **(http://cresta.epcc.ed.ac.uk/)** multi-million euro projects have commenced on 1 October 2011; they aim respectively to support the VPH Initiative projects in their use of a persistent EU-wide data infrastructure, and in developing VPH environments that will perform optimally on the path to exa-scale computers (which will likely feature hundreds of millions to billions of cores on a single heterogeneous platform). These projects are described in more detail below.

Finally, the IT Future of Medicine **(http://www.itfom.eu/)** is one of six short-listed projects bidding for €1 billion in the 2012 call for Future Emerging Technologies. IT Future of Medicine plans to draw heavily on the e-infrastructure that has been established by the VPH initiative; its future success will depend to a considerable degree upon what the VPH Initiative has achieved thus far. ■

European Exascale Research and the VPH

Rupert Nash, Benjamin A. Hall and Peter V. Coveney

Meeting the challenges of computing at 1 exaop (1018 oating-point operations per second) requires research and development on a global scale. Worldwide, a number of exascale research programmes are now being created to tackle these challenges. The European Union announced the start of its exascale research programme in October 2011 with the funding of three complementary Framework 7 research projects (CRESTA, DEEP and Mont-Blanc), with a combined funding of e 25 million. The DEEP and Mont-Blanc projects are concentrating their e_orts on novel hardware architectures that will form the basis of the next generation of Tier-0 supercomputers, while CRESTA focusses on co-design of systemware and applications capable of running e_ciently on leading-edge and future architectures.

CRESTA (Collaborative Research into Exascale Systemware, Tools and Applications) brings together four of Europe's leading HPC centres (project lead EPCC, HLRS, CSC and PDC), a world-leading supplier of HPC systems (Cray), seven application and problem owners from science and industry (DLR, KTH, Abo, JYU, UCL, ECMWF and CRSA), Europe's leading HPC tool company (Allinea) and Europe's leading performance analysis organisation (TUD). The project focuses on the use of six applications with exascale potential and uses them as co-design vehicles to develop systemware and tool, as well as the applications themselves, that are exascale-ready. The VPH's interests will be represented within the project by UCL's HemeLB and by GROMACS, the other projects being: IFS, the Integrated Forecast System for numerical weather prediction and climate simulation; ELMFIRE, a _rst principle plasma turbulence simulation code;

OpenFOAM, an open-source toolbox for computational uid dynamics using the _nite volume method, and Nek5000, a DNS/LES computational uid dynamics solver.

GROMACS is an open-source classical molecular dynamics software package, developed as an international collaboration steered by KTH in Stockholm. A major goal is to extend the length of simulation time which can be explored from microseconds to milliseconds, to allow slower biophysical events such as protein conformational change to be observed. Developers are focussing both on the improvement of the scaling of the code through a combination of re_ning existing approaches and investigating novel, disruptive approaches through Markov State Modelling and kinetic clustering. Such techniques

E-Infrastructure for the Virtual Physiological Human

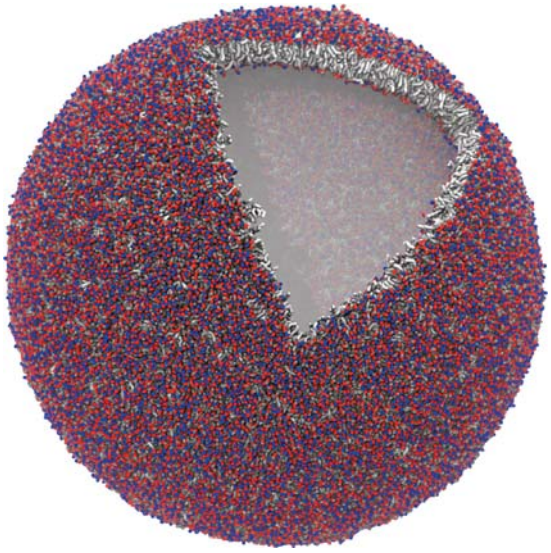

Figure 1. Improvements in scaling will both allow GROMACS simulations to be performed on scales comparable with experiments, such as vesicle systems (shown left), and over time periods which allow biologically important conformational changes to be observed.

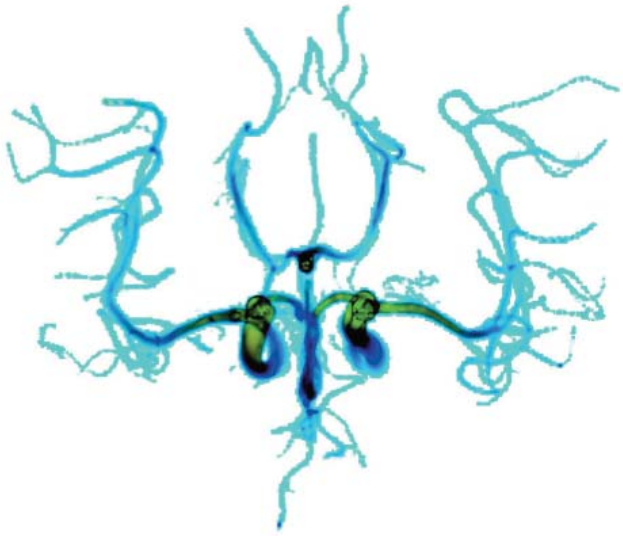

Figure 2. Higher performance systems will allow full-brain, multiscale HemeLB simulations of blood flow, instead of the low-resolution study shown on the right. This will allow clinicians to explore the consequences of virtual interventions for specific patients in detail.

performed using exascale computing resources will allow entirely novel observations, such as multi-millisecond structural transitions in proteins, which are impossible with currently available resources.

HemeLB is a simulation system for blood ow developed at UCL. It can currently perform simulations of the larger intracranial arteries, while creating visualisations in situ on the supercomputer that are sent interactively to the user. Our goal is to perform accurate, patient-speci_c simulations of the haemodynamics around pathologies such as aneurysms and, eventually, perform virtual procedures to choose the optimum course of action. Within CRESTA we will work on hybrid parallelisation strategies and with the developers of advanced visualisation techniques to ensure they will function in real, demanding applications. ■

For more information about CRESTA, see **http://cresta-project.eu/.**

IT Future of Medicine Flagship

Hans Lehrach, Ralf Sudbrak, MPI in Molecular Genetics in Berlin and Peter Bentley, University College London on behalf of the ITFoM consortium

Imagine a future where integrated computational models of individual patients, from molecular scales upwards, are routinely used in health care systems. It is a vision that is shared with the VPH consortium. It is also the ultimate goal of the ten-year IT Future of Medicine (ITFoM) Project, one of six EU Future and Emerging Technology (FET) Flagships competing for a total of 1 billion EUR. The programme follows a visionary, scientific and technology-oriented approach with the aim of enabling a massive roll-out to the public. ITFoM innovates by integrating new and existing models – particularly those generated by VPH researchers – to form one overall

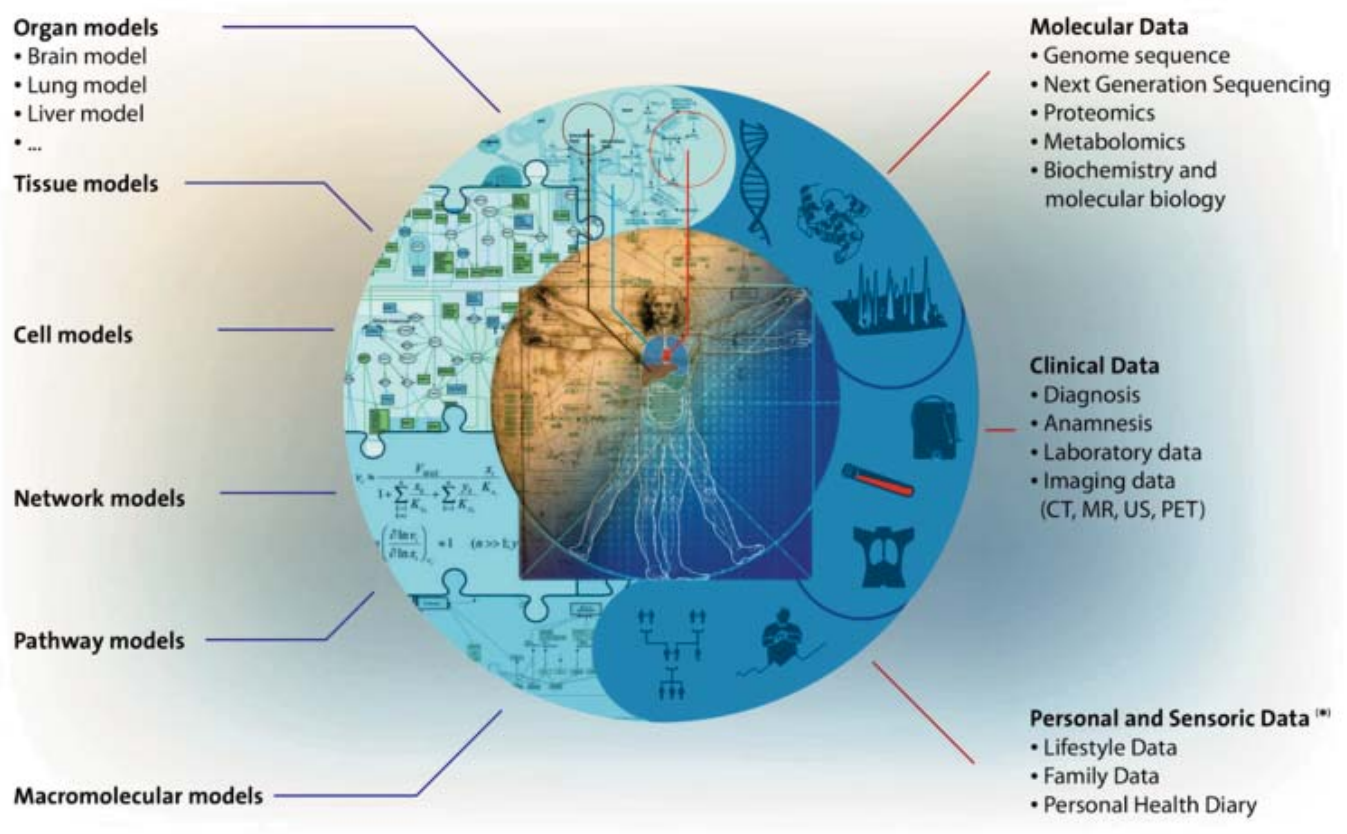

Figure 1. A vision of the silicon human, as foreseen by the IT Future of Medicine project

model: the "Virtual Patient." The clinical application of ITFoM with the Virtual Patient in place for every patient will help launch a paradigm shift in the perception and activity of the way medicine is conducted today.

ITFoM has a core expertise in molecular modelling. The analysis and interpretation of the body on the molecular level has experienced a strong boost thanks to the decreasing costs of sequencing the human genome. New deep-sequencing technologies with the ability to run much faster, yet with an expected price of under $1,000 in the near future, will allow for faster understanding and interpretation of genomic data. These and other innovative approaches will enable the analysis and integration of the genomic information into predictive clinical models, while medical treatments are on-going. On-the-fly provision of interventions could then be applied very quickly, minimising the risks for patients.

Our aim is to exploit a profound understanding of significant processes on the molecular level, integrated with higher-level models, in order to transform today's medicine into a fully personalized procedure with specifically tailored treatments for each patient in the health care system. The project will establish imaging techniques that are easy to use and understandable for the physicians as well as for the patients. Virtual Patient visualisations may be available on mobile computing devices (e.g. a smartphone), allowing the patients to be accompanied by their digital counterpart regardless of their healthcare environment.

The ten-year programme of ITFoM must overcome a host of challenges if it is to accomplish this change in health care. Advances in IT research are needed, as the massive amounts of data and requirements of models at the scale we propose easily exceed our current capacities to store and process this information. Furthermore, these huge amounts of data need to be integrated in one functional system that can be used in every clinical setting: from the general physician treating his patients in the doctor's office to large medical facilities specialising in particular diseases. Even when the technology has arrived, to roll it out will require advances in technical, regulatory, ethical and other areas.

The success of ITFoM also depends on collaboration with the well-established VPH initiative, which has projects investigating many of these technical challenges already. With the exchange of expertise and knowledge from the molecular up to the physiological level of the human, the near future will surely provide some crucial results in the daily application of medicine. ■

For further details visit the project website: **http://www.itfom.eu/**

E-Infrastructure for the Virtual Physiological Human

European Data Infrastructure to Support VPH-I Researchers

Peter Coveney and Stefan Zasada, University College London

European scientific and research communities from a wide range of disciplines are faced with increasingly large amounts of valuable data that stem from new sources, such as powerful new sensors and scientific instruments used in analyses, experiments and observations, as well as growing volumes of data from simulations and the digitization of library resources. In order to make the most of the new opportunities emerging from this explosion of data, a group of European stakeholders has formed a consortium to build a sustainable pan-European infrastructure for scientific data. **http://www.eudat.eu/**

On 1 October 2011, the EUDAT project, co-funded by the European Commission's Framework Programme 7, was launched to produce a pan-European solution to the challenge of data proliferation in Europe's scientific and research communities. The €13.6 million project, co-ordinated by CSC Finland, is working towards the development of a collaborative data infrastructure for Europe, driven by the needs of researchers. It comprises 25 European partners, including many major HPC centres, technology providers, and research communities and funding agencies from 13 countries. VPH is represented in EUDAT via the VPH NoE coordinator, University College London, whose participation is led by Professor Peter Coveney. VPH is also charged with representing the needs of the wider biomedical computing communities, including ECRIN, ELIXIR and EuroBioimaging.

Research communities from different disciplines use different types of data and organise it in different ways, but they also share basic service requirements. There is a strong requirement for long-term data archiving for integrity and authenticity control in many research communities for example, and a shared demand for data federation and services enabling discovery, access, data mining, integration and curation. These common requirements mean that it is desirable to establish generic pan-European services designed to support multiple communities, as part of a collaborative framework. Building this common layer of generic and cross-disciplinary data services is precisely the focus of EUDAT. Research communities such as VPH can then build on these generic data services to provide rich, community specific analysis platforms. The fact that many EUDAT partners are also large HPC centres participating in PRACE should make it easy for VPH researchers to collocate their data with high performance computing.

The benefits associated with creating a Collaborative Data Infrastructure, in which research communities can rely on a set of common data services, will result in better exploitation of synergies. The collaborative data infrastructure put in place by EUDAT will help to support the data infrastructures currently being used and developed by scientific communities by offering them an infrastructure on which they can rely for their more generic data needs. This will allow research communities to focus a greater part of their effort and investment on services that are specific to their discipline. The EUDAT data infrastructure will also provide individual researchers, smaller communities, and projects lacking tailored data management solutions with access to sophisticated shared services, removing the need for large-scale investment in infrastructure development.

One of EUDAT fundamental goals is the facilitation of cross-disciplinary data-intensive science. By providing opportunity for disciplines from across the spectrum to share data and cross-fertilize ideas, the EUDAT data infrastructure will encourage progress towards this vision of open and participatory data-intensive science. Increasing the scale of data federations and improving the interoperability of data objects is central to EUDAT's overall approach to the development, deployment and operation of shared services. EUDAT begins from the principle that individual and community-based data infrastructures should be federated using an architecture that fosters integration without requiring massive changes to existing and proven community-based solutions.

To build a sustainable data infrastructure upon which common services can be deployed for use by diverse communities, a comprehensive approach is required, including several activity strands. EUDAT is currently investigating user requirements including those of VPH. After initial requirements gathering and infrastructure development work has been undertaken, the EUDAT infrastructure will be made more widely available to EU based researchers, with the hope that follow-on funding after the project's initial 3 years will allow it to establish a persistent data infrastructure for Europe. ■

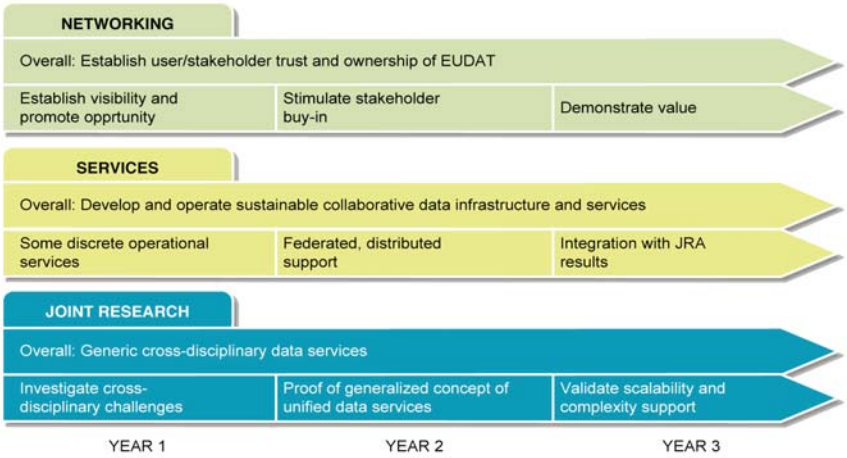

Figure 1. EUDAT is organised into different work streams, each with annual milestones.

New Virtual Physiological Human Projects (ICT-2009.5.3)

INBIOMEDvision – Promoting and Monitoring Biomedical Informatics in Europe

Nour Shublaq, University College London, and Ferran Sanz, Universitat Pompeu Fabra, on behalf of the INBIOMEDvision Consortium

Medicine is undergoing a revolution today. Sixty years ago, we barely understood the genetic basis of heredity. Today, we can sequence an entire human genome in six minutes, at a similar cost to an MRI scan (around $1000). Within a few years, the cost of doing so will be no more than a hundred U.S. dollars. Meanwhile, progress in drug development has significantly slowed down. The time spent today from drug discovery to marketing is around 12-15 years; it was 8 years in 1960. Moreover, conventional approaches to drug design are foundering within the pharmaceutical industry, reflected by a very substantial reduction of new products developed over the past decade. Diseases are diagnosed by general clinical representation, while treatments are based on molecularly targeted drugs. Little wonder a large number of candidate drugs fail at various stages of clinical trials, and drugs are only effective in a fraction of patients. Running clinical trials is becoming more costly, with continually increasing levels of complexity and bureaucracy introduced by regulatory bodies. Furthermore, assuming a given "blanket" therapy, which targets some nominal average person, to be optimal to a population group having the same disease, is no longer satisfactory with today's advanced capabilities in next-generation sequencing and developments in computational biomedicine. All these considerations have paved the way for the emergence of preventive, predictive and personalised medicine, which promises to specifically tailor medication and treatments to a person's specific genome or metabolism, hence improving the quality of outcomes and reducing the chances of relapse.

While some researchers argue that one's genetic blueprint holds the answers to future medical conditions, others consider the nonlinear interactions between genes, and between genes and proteins, as equally important. Beyond that, gene expression is strongly dependent on environmental factors, which determine genetic activity as much as genes directly govern phenotype. Other "levels" of biological activity – sub-cellular, cellular, tissue, organ, and higher functions -- may all be crucial in varying degrees, and cannot be seen as simply controlled by the molecular level DNA "blueprint".

In practice, as a result of tighter funding in the current global economic climate, healthcare priorities are more aligned with delivering frontline patient services that can be quickly and directly mapped into patient outcomes, which are seldom congruent with longer-term requirements supplied by research and its supporting infrastructure in relation to the vision of personalised medicine. The reality is that much of the medical data on patients, held in hospitals is still paper-based. Even when electronic data are available, formats are not standardised, sometimes even within one hospital, let alone between healthcare trusts, districts or countries. The legal ownership of medical data is still an open question, where security, ethical, and privacy concerns are critical as sensitive data on individuals are involved. Various models of data management exist today, centralised, federated and third party provision of compute and storage data cloud services. IT governance remains unclear not only to clinicians but also to researchers who usually pre-suppose that all data will reach them in electronic format.

INBIOMEDvision is a two-year Coordination and Support Action (CSA) project, funded by the European Commission 7th Framework Programme of ICT under the Virtual Physiological Human (VPH) flagship, and aims to address these questions along with various others, through collaborative efforts of a wide range of experts. It was funded as a CSA for VPH because the molecular level is rather largely ignored by much of existing VPH-I activity, which has led to the identification of a gap between basic biomedical research and clinical practice, which INBIOMEDvision aims to bridge and strengthen. We aim to promote Biomedical Informatics (BMI) throughout Europe and beyond, by means of permanent monitoring of the scientific state-of-the-art approaches, methods and existing activities in the area, prospective analysis of the emerging challenges and opportunities, and wide dissemination of knowledge and resources in the field. In INBIOMEDvision, 7 partners from 4 European countries, with complementary expertise in bioinformatics, text and data mining, medical informatics, and computational biomedicine, have dedicated themselves to bridging the gap between the bio- and medical informatics communities. This is being realized by the integrative management and synergic exploitation of wide-ran-

New Virtual Physiological Human Projects (ICT-2009.5.3)

Figure 1. Integration of large-scale heterogeneous clinical information (genomics data, X-ray images etc.) and enabling their re-use in research can elucidate management of diseases such as lung disease. (Courtesy of ISCIII, Spain).

ging and inter-related information generated and required in healthcare settings, as well as in the biomedical research institutions and health-related industry.

Three invitation-only Think Tanks were organised in June and October 2011, on the "Re-use of Clinical Information in Research" (Figure 1), "Translational Systems Biology and Bioinformatics", and "Genotype-Phenotype Resources" (Figure 2). The Think Tanks were followed by the preparation of consensus-view strategic reports aimed at the European Commission as well as the wider scientific community. The first Think Tank report stated that a "digital vision" and agenda are needed within Europe, to cover the next five years and beyond. EU member states are urged to commit significant resources to this effort, and to adopt clear and fully aligned legal positions to allow the optimum re-use of data in research and to support clinical decision-making. This would substantially facilitate the digital revolution in healthcare provision that is urgently required. It is important to involve Internet-savvy "expert patients" and their families not only in their own treatment, but to actively contribute to basic biomedical research into their conditions. Areas covered included data, IT security, information governance, and legal issues with regard to clinical data. The second Think Tank report saw potential in sub-cellular (or molecular) systems biology approaches to biomedicine, as compared to conventional methods of drug design. Despite these approaches being at an infant state, and a vast amount of research remains to be done, they may be able to assist in more personalised approaches to drug treatment, for example in the use of multi-target therapy, for finding genotype association to risk of disease and drug response. For translational systems biology to make a major impact, the whole system of data access (including access to medical records) needs to be transformed into one based on more openness and sharing of information between hospitals, academia and industry. Various societal structures currently impede this development. Regulatory and funding agencies must be involved to overcome these obstacles.

The third Think Tank report addressed prospects for the development and application of genotype-phenotype resources and considered these to be very promising. Establishing clear relationships (correlations) between increasing amounts of genotypic information available from clinical studies (e.g. as provided by genome wide association studies (GWAS)), and similarly of phenotype information at the population level, is still largely impossible today. Also, assuming that the genotype controls the phenotype in all cases is unlikely to be correct. Indeed there are rather general grounds for thinking that, making any trivial correlations will always be fraught with difficulty. This could also assist in "stratification" – instead of rejecting so many drugs, it could be that several existing ones will work well for sets of patients on genetic grounds.

Figure 2. Linking Genotype to Phenotype Resources. (Courtesy of ISCIII, Spain).

Other INBIOMEDvision objectives are to:

- compile the existing knowledge on genotype and phenotype data resources, providing an overview of methods and models that connect biological systems at the molecular level with the clinical physiopathology
- produce periodic state-of-the-art reviews and perform prospective analyses on these themes
- generate a permanently updated and electronically accessible catalogue of initiatives and resources in the field
- consolidate a BMI community of researchers by congregating and promoting the interaction between them (available via our Researcher Directory Tool)
- organise community building activities (Think Tanks, scientific meetings etc.), and (website, newsletter) to widely disseminate knowledge
- develop and carry out activities (INBIOMEDvision Training Challenge) to train new generations of scientists and professionals having a BMI perspective and skills. ■

INBIOMEDvision Project Reference: ICT-270107
Timetable: 02/11 – 01/13
INBIOMEDvision Consortium: University College London (UK), Pompeu Fabra University (Spain), Mar Institute of Medical Research Foundation (Spain), Technical University of Denmark (Denmark), Erasmus University Medical Centre (The Netherlands), Technical University of Madrid (Spain), and Institute of Health Carlos III (Spain).

For further details, please contact Nour Shublaq **n.shublaq@ucl.ac.uk** and visit the INBIOMEDvision project website: **http://www.inbiomedvision.eu**

Synergy-COPD: Modelling and simulation for systems medicine

Luigi Ceccaroni, Felip Miralles and Filip Velickovski, Barcelona Digital Technology Centre, Spain

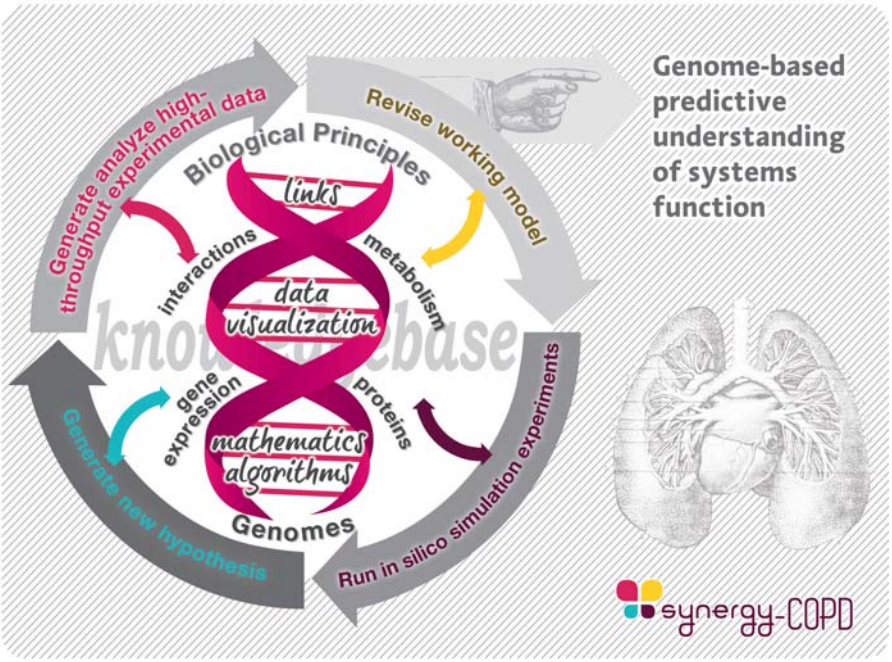

Figure 1. Understanding schema of systems function.

The Synergy-COPD project is developing a clinical decision-support system (CDSS) and a simulation environment aiming at enabling the deployment of systems medicine. The project focuses on patients with chronic obstructive pulmonary disease (COPD), which is a major public health problem and a complex, heterogeneous and multi-component disease.

The Synergy-COPD project began in February 2011 and ends 31 January, 2014. The project consortium is led by Barcelona Digital Technology Centre of Spain, a European leader in health informatics. The consortium includes four universities (Karolinska Institutet, University of Oxford, University of Birmingham, and Technical University of Budapest) and one research institute (Consorci Institut d'Investigacions Biomèdiques August Pi i Sunyer), each with very strong clinical links. As well as these academic partners, the consortium includes three SMEs (Biomax Informatics AG, Linkcare Health Services SL, and Infermed Ltd.), ensuring the necessary clinical inputs and the industrial backing to move the final results forward into prototypes and industrial deployment.

In the current framework, in which a change of focus from acute care to integrated and continuous care is under way, primary-care clinicians (or general practitioners, GPs) take a greater part of the responsibility in treating complex chronic diseases. As new evidence becomes available and new assessment techniques are introduced, best practices are revised, new treatments become available, and the rules for treating a disease are updated. And GPs face a harder time on being up to date with new research developments in many diseases.

Synergy-COPD CDSS assists GPs and non-specialist clinical staff in the diagnosis, assessment and management of COPD, and delivers up to date support. In particular, Synergy-COPD CDSS will have the following features:

New Virtual Physiological Human Projects (ICT-2009.5.3)

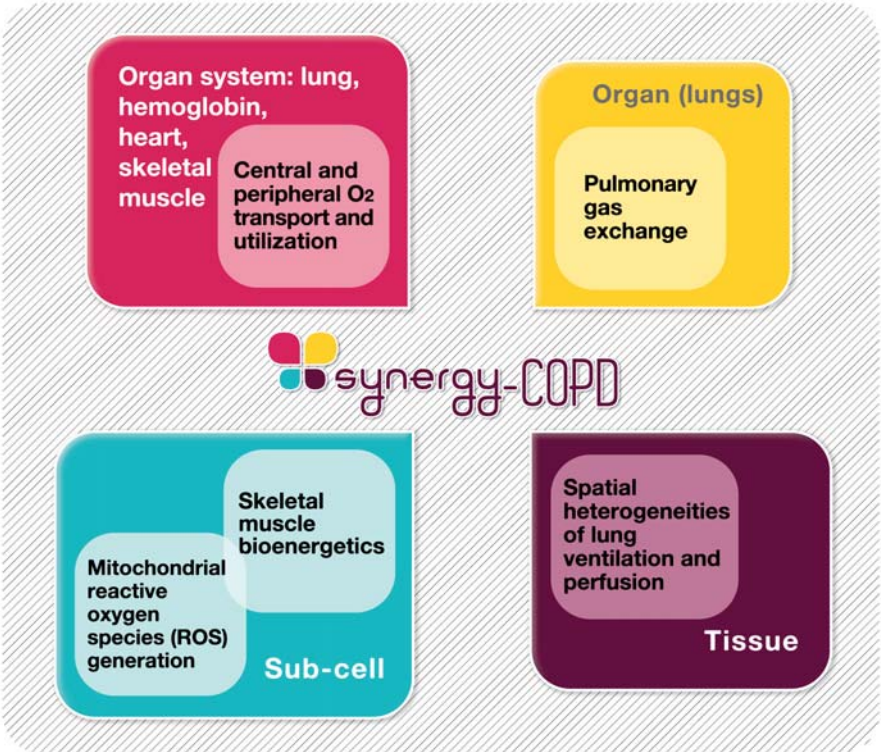

Figure 2. Physiological models included in Synergy-COPD, each of which can be associated to one level of the body: sub-cell, tissue, organ and organ system.

- Flexibility to be updated with information that may affect diagnosis, assessment and management of COPD;
- Combining patient characteristics, family history, symptoms, signs, lung function measurements and co-morbidities to provide a COPD diagnosis, and any other differential diagnosis to be considered;
- Given a COPD diagnosis, being able to guide GPs to investigate initial assessment parameters (examples: exacerbation frequency, status with respect to COPD, symptom level, presence of other co-morbidities);
- Given a COPD diagnosis and assessment parameters, being able (1) to recommend further assessment parameters to check (example: arterial blood measurements), (2) to schedule periodic checkups of these assessment parameters, and (3) to propose initial treatment/therapy/management regime (drugs, exercise, oxygen therapy, etc);
- The ability able to evaluate the response to current management regime;
- Given evaluation and assessment parameters, being able to give advice to alter treatment/therapy/management regime and to suggest patient for specialist referral (e.g. in a critical case, patient not responding, condition is worsening).

The integration of diagnosis, assessment and management with a personalised patient model and into modern COPD-related systems-medicine will allow us to predict the outcome of different treatment options. Since the end-users will be clinicians, we are developing prototypes with GPs and testing them with specialists, to demonstrate their potential for application. The project wants to bring new engineering rationales to the clinical decision process and is directly linked to ICT companies which develop clinical software and hospitals which develop new clinical protocols. This has led us to adopt the following workflow for developing our tools:

- Choose initial decision-support target (diagnosis and initial characterization);
- Define user (GPs);
- Define set of diagnosis rules for COPD;
- Expand diagnosis rules to account for differential diagnosis;
- Define referral trigger-rules (when GPs need to refer to specialists);
- Test system with a small number of users and COPD patients;
- Expand system to take into account assessment and management (including treatment);
- Define set of rules for assessment;
- Expand rules to decide when further assessment is needed;
- Define final set of rules for COPD;
- Test system with a larger number of users and COPD patients.

The project proposes a patient-specific predictive platform that provides clinicians with a rational basis to choose the best treatment, incorporating knowledge of the underlying mechanisms of COPD phenotypes associated with poor prognosis. This is done by simulating different functions of the human body using computer models at different levels (sub-cellular, tissue, organ and organ system). In this way, the behaviour of each physiological network can be observed separately and in an integrated way, and a more complete computer model of the mechanisms of COPD can be produced. ■

Synergy-COPD project reference: FP7-ICT-2009-270086
Timetable: 02/2011 – 01/2014
Synergy-COPD consortium: Barcelona Digital Centre Tecnològic (Spain), Biomax Informatics AG (Germany), Linkcare Health Services, SL (Spain), IDIBAPS, Consorci Institut d'Investigacions Biomèdiques August Pi i Sunyer (Spain), Karolinska Institutet (Sweden), The Chancellor, Masters and Scholars of The University of Oxford (United Kingdom), The University of Birmingham (United Kingdom), Infermed, Ltd. (United Kingdom), Technical University of Budapest (Hungary)

For further details please contact Luigi Ceccaroni **lceccaroni@bdigital.org** and visit the project website: **http://www.synergy-copd.eu/**

AirPROM- Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling

Chris Brightling on behalf of the AirPROM consortium, University of Leicester, UK

Asthma and chronic obstructive pulmonary disease affect over 400 million people world-wide, and airways disease costs the European Union in excess of €56 billion every year. Current therapies are inadequate due to our incomplete understanding of the pathophysiology of these diseases and our lack of recognition of the enormous disease heterogeneity: our current 'one size fits all' approach is inappropriate. We need to fully characterise this heterogeneity in order to identify the 'right target' for the 'right patient' and measure the 'right outcome'. To achieve this goal we need tools that will allow us to predict disease progression or response to current (or future) therapies. Our consortium, **Air**way Disease **PR**edicting **O**utcomes through Patient Specific Computational **M**odelling (AirPROM) aims to address this unmet need. AirPROM brings together the existing clinical consortia (EvA FP7, U-BIOPRED IMI and BTS Severe Asthma), with new expertise in physiology, radiology, image analysis, bioengineering, data harmonization, data security and ethics, computational modelling and systems biology. We have 34 partners across 11 EU countries and comprise 25 academic centres, 3 small-to-medium enterprises, 3 large industry partners, 2 patient organisations (ELF & EFA) and the European Respiratory Society. The AirPROM website has details of the consortium membership, aligned consortia and a video describing the AirPROM concept **(www.airprom.eu)**.

Like many VPH projects, the pedigree of the computational biologists and modellers is excellent, but earlier projects have perhaps struggled to translate their models into the clinic. One of the many strengths of AirPROM is the close interaction between clinicians, patients and pharma so that the project from its outset – and through its development – will be aware of the needs of the patients, as well as the practicality of the application of models in the clinic, drug discovery and development.

AirPROM will develop an integrated multi-scale model building upon existing models. The work flow is as illustrated in Figure 1.

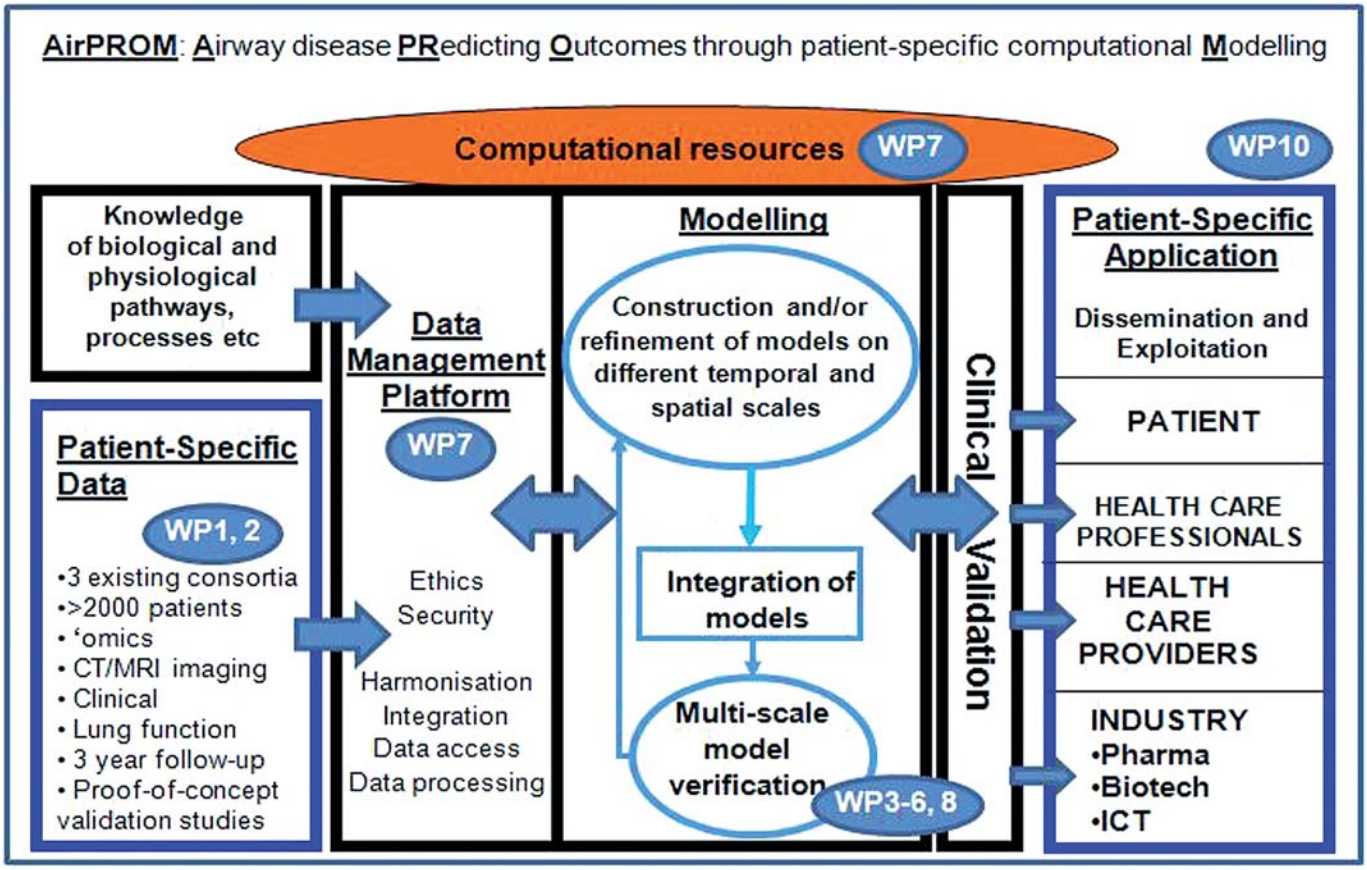

Figure 1. Workflow and work package structure for the AirPROM consortium.

New Virtual Physiological Human Projects (ICT-2009.5.3)

In brief, we will integrate and extend existing patient-specific data from 3 consortia (U-BIOPRED, EvA, and BTS severe asthma) [WP1&2]. These data include extensive genomic, transcriptomic, and proteomic profiles, detailed lung function with novel small airway physiological measures, bronchial challenge studies, computed tomography (CT) imaging and cutting-edge hyperpolarised gas magnetic resonance imaging (MRI), and patient reported outcomes. These measures are available cross-sectionally and in longitudinal follow-up and proof-of-concept clinical trials with standard and novel interventions. These patient-specific data together with known biological pathway data from public databases will be integrated into a 'Data Management' platform supported by 'Cloud' computing and cognisant of ethico-legal, security and harmonisation issues [WP7]. Building upon existing models a 'Micro-scale' [WP3] and integrated large [WP4, 5, 8] and small airway [WP6, 8] 'Macro-scale' model will be developed and validated with ex vivo models, in silico and with in vivo clinical validation. The framework for a multi-scale model has been established at the outset of the project and incorporates models developed at the micro and macro scales as outlined in Figure 2.

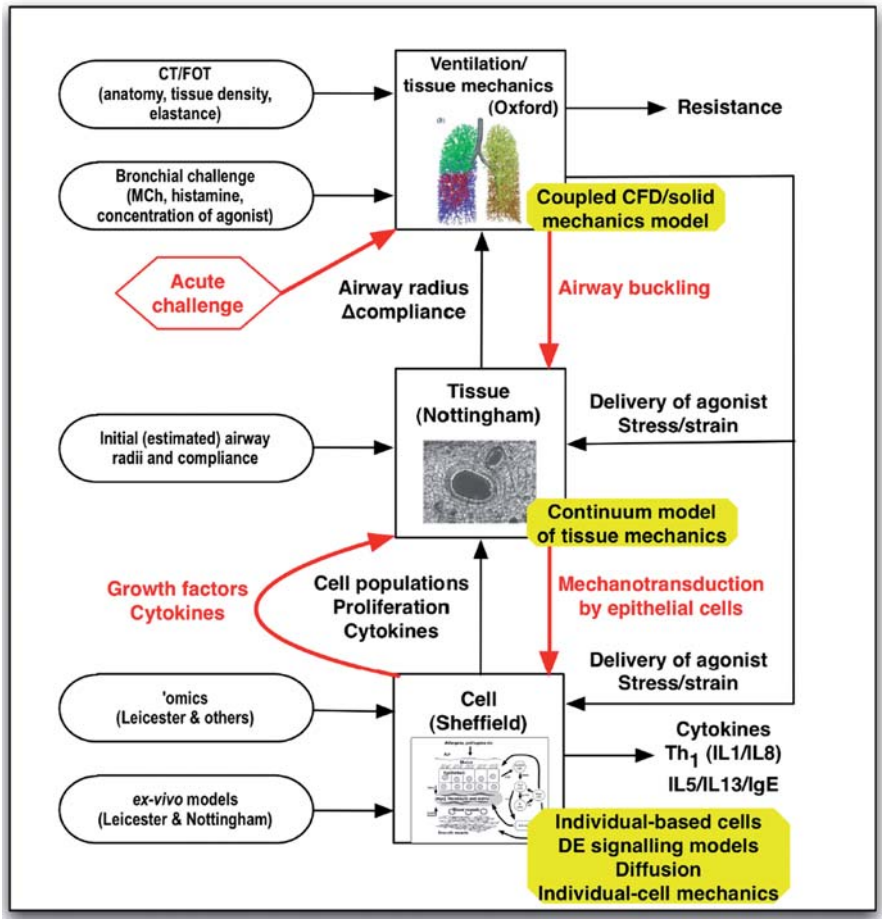

Figure 2. Multi-scale modelling from cell to tissue to organ.

Patient-specific data from WP1 will both inform and validate the models. The model verification, clinical validation and development will occur in 3 iterative cycles each with increasing throughput and automation working towards a 'turn-key' platform. AirPROM will thus develop a validated patient-specific multi-scale predictive computational airway model [WP8] underpinned by our comprehensive scientific coordination and project management [WP10].

Through our exploitation and dissemination plan [WP9] we have already engaged the prospective 'users' and 'providers' and therefore are uniquely positioned to translate the platforms into usable applications. Indeed this has already been realised: collaborations with pharma are already developing into joint projects to help decision making in early-phase clinical trials. This was anticipated for the end of the project, but is likely to become embedded in the project within its first year.

AirPROM therefore will bridge the critical gaps in our clinical management of airways disease, by providing validated models to predict disease progression and response to treatment and the platform to translate these patient-specific tools, so as to pave the way to improved, personalised management of airways disease. ■

AirPROM Project Reference: ICT- 270194
Timetable: 03/2011 – 02/2016
AirPROM Consortium: University of Leicester, Helmholtz Zentrum München German Research Center for Environmental Health, University of Amsterdam, Imperial College London, The Queen's University of Belfast, University of Oxford, University of Nottingham, University of Sheffield, GET/ Institute National des Telecommunications, Department ARTEMIS, University of Arwick, Fundacio Privada Parc Cientific de Barcelona, Materialise N.V.,ANSYS UK, Ltd., Instytut Chemi Bioorganicznej Pan, FluiDA nv, Biomax Informatics AG, European Respiratory Society, BioSci Consulting, Southampton Medical School, University of Catania, Italy, Semmelsweis University, University of Manchester, Universite de la Mediteranee, Marseilles, University Hospital, Umea, Sweden, Karolinska Inst., Objet Geometries, University of Ferrara, European Federation of asthma Associations, National Research Institute of Tuberculosis and Lung Diseases, Queen Silvia Children's Hospital, National oranyi Institute, Centre National de Génotypage, University Hospitals Coventry and Warwickshire, European Lung Foundation.

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and visit the AirPROM project website: **http://www.airprom.eu/**

Information and Communication Technologies Call (ICT-2011-7)

DISCIPULUS – A community-led roadmap for the Digital Patient

Colin Boyle and Vanessa Diaz, University College London, UK

The DISCIPULUS project began in October 2011 and will run for 18 months. It is intended to be a community effort, and we encourage all researchers and interested parties to get involved; now is the time to influence the future direction of the VPH.

Introduction

The DISCIPULUS project will produce a roadmap for the realisation of the Digital Patient. The Digital Patient will build upon the success of the VPH initiative, focusing on the goal of personalised medicine using predictive models. Modelling and simulation are expected to have a significant impact on patient safety through more accurate, "personalised" prediction, diagnosis and treatment. The Digital Patient will be the key to realising this expectation, using a validated and trustworthy predictive framework. It will revolutionise health prediction and disease treatment when the "Digital Me" – the unique environmental and genetic characteristics of a citizen – can make full use of health services. In order to realise the Digital Patient dream, DISCIPULUS will write a roadmap to suggest directions for future research, building on the progress made by the VPH initiative. The roadmap will promote and help reflect the views of the VPH community on the future of predictive medicine to the European Commission. The specific aims of the DISCIPULUS project are:

- To consolidate the existing research and consultation on the roles that predictive models might play in healthcare in the future. In particular we will attempt to quantify the potential of existing research to make an impact in the clinical decision-making process.
- To capture and quantify the needs of relevant stakeholders. We hope to identify the clinical problems that could benefit most from the Digital Patient. What concerns do clinicians have about physiological modelling, and what standards are needed?
- To develop a vision and sound ICT research agenda around the Digital Patient. What needs to be done to bring about the success of the endeavour, and what possible drawbacks can be envisaged?

What will we do?

Firstly, we will conduct an overview of research and innovation in the VPH community. We will describe and consolidate the achievements and capabilities of the different VPH projects, with a particular view to their clinical prediction applications and the potential for patient personalisation.

We will organise consultation exercises with the important stakeholders, including the VPH community and the wider research community. This will include two large consultation meetings and several smaller workshops. The first consultation meeting will bring together leading experts in research and clinical medicine together to highlight key issues and help steer the production of the roadmap. The second will be an open event for all stakeholders to come together in a conference discussion forum to build upon the discussions from the first exercise and form the basis of consensus. Clinical workshops will attempt to clarify key considerations and potential opportunities for use in the clinic. Finally, we will produce a roadmap based on the consultation process for the future direction of the Digital Patient. This will aim to emulate the success of the STEP roadmap which kick-started the VPH project, and will aim to provide a coherent plan for the realisation of the Digital Patient, which must be functional, realistic, and based always on the needs of the end-users and stakeholders.

How will this work in principle?

We must identify and describe clinical and industrial scenarios in which the Digital Patient would be an effective decision-making tool. These exemplar problems would boost the visibility of the VPH endeavours in the clinical arena.

We will describe what could be achieved in the medium-term future (10 years); in particular, the realistic expectation for prediction and use as a decision-making tool. This will involve identifying the "low-hanging fruit" – the clinical needs where integrative, multi-scale modelling can make a difference quickly.

We must elucidate what technological advances are required for the realisation of the Digital Patient. The ICT requirements of the Digital Patient will

be immense, with the processing of large amounts of data, and the usability and speed of simulations being crucial targets. The scientific breakthroughs in knowledge and modelling that are required to realise the Digital Patient must also be described.

We will try to establish what impact the Digital Patient will have on European society, industry and clinical practice. How will individualised data be collected and used? What interactions will patients have with the process? Can the paradigm be extended to citizens, not just disease treatment of patients?

Finally, we must identify the external factors that will impact on the realisation of the Digital Patient.

What will a successful Roadmap bring?

The DISCIPULUS project will provide a roadmap for a sustainable approach to the integration of clinical and biological data of ever-increasing complexity. It will ensure that research and clinical knowledge is used most effectively, and will ensure that technologies supporting the Digital Patient will be intuitive and usable.

Researchers will benefit from the DISCIPULUS project, as the Digital Patient will provide a means to translate physiological modelling to clinical prediction. It will help to focus research and provide a coherent objective for future in silico modelling research.

The DISCIPULUS project aims to directly collaborate with the clinical community. This will ensure that future in silico medicine research is driven by the needs of the clinic.

Join us!

The success of this endeavour and the quality of the roadmap will depend on the support and engagement of the VPH community, and we would like the project to be as inclusive as possible. Please get involved in the discussion to direct the future of the Digital Patient. ■

DISCIPULUS Project Reference: FP7 – ICT - 288143
Timetable: 10/2011 – 03/2013
DISCIPULUS Consortium: University College London (UK), University of Sheffield (UK), Universitat Pompeu Fabra (Spain), Istituto Ortopedico Rizzoli (Italy), Empirica Communication and Technology Research (Germany).

For further details please contact **v.diaz@ucl.ac.uk** and visit the digital patient website: **http://digital-patient.net**

VPH I project focus (ICT 2007.5.3)

HAMAM Project - Rising to the challenge: accomplishing a digital clinical workstation for improved breast cancer diagnosis

by the HAMAM Consortium

In today's digital age there is an array of emerging novel technologies for screening and diagnosing breast malignancy. For an accurate early diagnosis, data from different imaging modalities, such as mammography (MG), 2-D ultrasound, MRI, digital breast tomosynthesis (DBT), positron emission mammography (PEM), and automated 3-D breast ultrasound (ABUS), have to be combined in order to provide a comprehensive, yet clinically robust multimodal breast imaging setup that is both highly sensitive and specific. The HAMAM project has successfully developed a prototypical clinical workstation that incorporates advanced image presentation and analysis methods, allowing physicians to have all the relevant information at their finger tips. This enables them to arrive at reliable treatment decisions and ultimately contributes reduced breast-cancer induced mortality.

Early diagnosis is essential to win the battle against breast cancer and for readers to tailor individual-patient treatment procedures, all the information has to be compiled, presented and available in an efficient and user-friendly interface, supported by automated analysis. The HAMAM project, which started in September 2008, is now drawing to a close and the collaboration between nine international

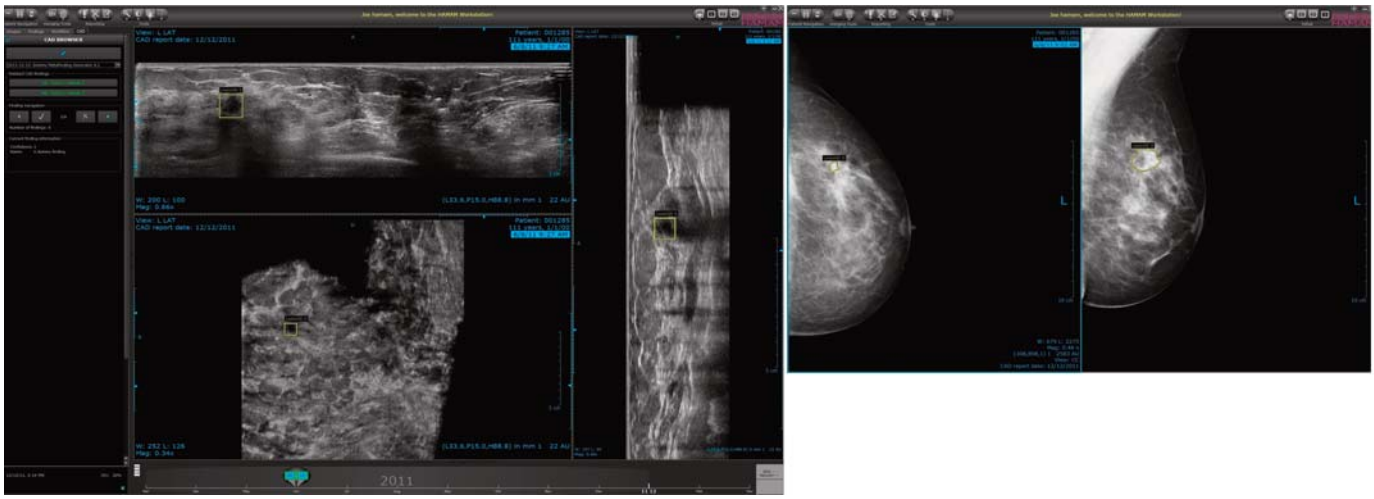

Figure 1. HAMAM workstation with a two-screen multimodal setup for combined assessment of ABUS (left) and mammography images (right). The interactive, multimodal CAD marks (yellow) indicate the location and the estimated malignancy likelihood of a tumour candidate in both modalities. The HAMAM workstation's time-line (left, bottom) allows for flexible selection and combination of patient-related studies.

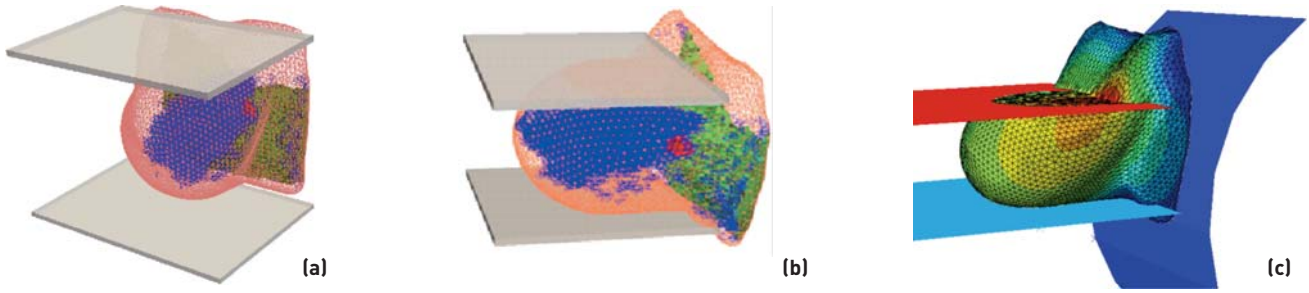

Figure 2. Biomechanical finite element modelling of breast tissue under plate compression to mimic the deformation process during X-ray mammography. (a) Breast model derived from MRI, before compression, with colours indicating tissue types. (b) After compression. (c) Detail view of compressed FE model, with colour map representing the magnitude of the displacement.

scientific and industrial partners from five European countries plus the USA, has realised the vision of a single clinical workstation (cf. Figure 1) that provides accurate assessment of multimodal information to characterise and classify suspicious breast tissue.

Information from different breast imaging modalities is digitally combined using transformation techniques, ranging from linear, geometric transformation models incorporating anatomical landmarks, to more complex patient-specific, biomechanical models (cf. Figure 2). These methods accurately replicate the highly non-linear deformations of real breast deformations in a short computational time and are straight forward to translate into a clinical context. The results are promising [1-5] and show that alignment of MRI with ABUS and MG is capable of locating the mutual spatial correspondences of ambiguous lesions down to a few millimetres on average (cf. Figure 3).

The registered images in the workstation use unique post-processing algorithms to enhance the image contrast for diagnostic presentation and ease the reporting of findings across modalities. The integration of multiple CAD results – both computer-aided detection [6] and diagnosis – is transparent, and the display of information is demand-driven ('interactive CAD'). Additional techniques correct spurious patient motion during MRI acquisitions and temporal comparisons of current and previously acquired breast images can be made. The integrated software allows for efficient reading and enables clinicians to quickly select

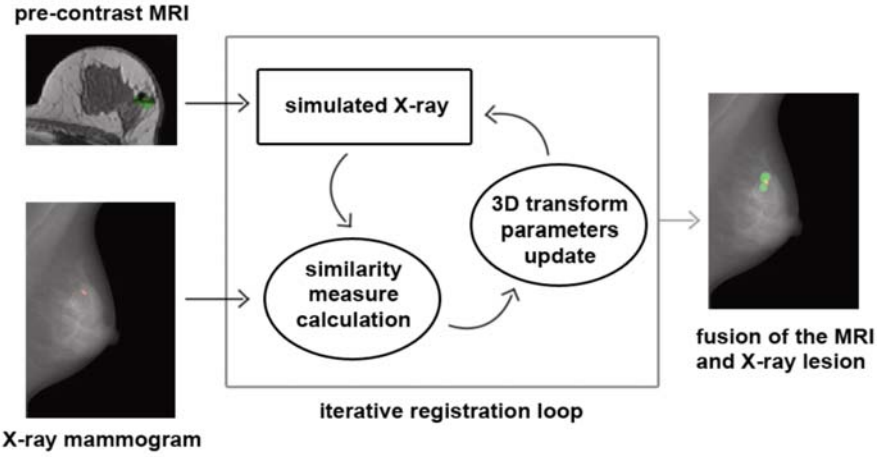

Figure 3. Registration framework for MRI to X-ray mammogram alignment, showing fusion of an annotated MRI lesion (green) with the corresponding lesion identified on the target mammogram (red).

patient-related images from a local workspace or remote PACS archives for combined visualisation with standardized unimodal, multimodal or multi-timepoint protocols. For example, kinetic parameters in DCE-MRI are visualised in meaningful colour maps and in pairs of prior and current mammographs that have been processed differently, which frequently occurs in clinical routine, an automated multi-scale adjustment allows for optimal comparison of contrast characteristics. [7]

The advanced registration techniques developed by HAMAM further support the combined analysis of multiple studies and fusion of the diagnostic information with real-time synchronisation of image cursors in different views, in serial images of the same modality, and across modalities. The display of the image data can be combined with information from novel unimodal and multimodal CAD systems providing a second opinion based on a joint statistical analysis of the multimodal information. The workstation provides conventional modes for sequential as well as a new mode for concurrent, interactive CAD reading that promises to add sensitivity without impairing the reader's specificity. New findings can be reported with the help of consistent digital form sheets and semi-automatic reporting tools. New information can be persistently combined with information from the patient's history on a per-finding basis.

In the hectic clinical environment, the clinical workstation achieves the level of robustness needed for physicians to make accurate decisions. The multimodal data acquired for patients over a period of years is presented in condensed, traceable, and diagnostically relevant criteria and the reporting is consistent for all clinical information and compatible with any clinical PACS. This technique bodes well for the future and the potential clinical impact of the multimodal workplace with its advanced software features for detection and diagnosis of breast cancer is currently being evaluated in a series of reader experiments.

Of particular success is the preliminary study to estimate a woman's risk of developing breast cancer within the next ten years after examination using the patient's genetic profile combined with her family history. The results indicate a decisive influence of genetic information. Also, a comparison of classifiers employed in CAD servers with a focus on reproducibility and robustness was conducted. The baseline performance was systematically assessed and a stable classification strategy with respect to the features selected was identified, which will help to determine the added-value of different modalities in subsequent multi-modal imaging studies. Ultimately, improved kinetic parameters from MRI images, spatially corresponding regions of interest within and between modalities, and genetic risk modelling improves computer aided detection and diagnosis.

Diagnostic breast cancer information originating from various sources and disciplines such as uni- and multimodal imaging, genetic mutation data and risk scores were a focus of joint analysis using the HAMAM data collection. To this end, the breast cancer pathology status of more than 650 patients has been mined using association analysis aimed at identification of correlations between tumour type, grade, receptor status and genetic loci alterations (single nucleotide polymorphisms). Further, whole breast image appearance descriptors and volumetric breast density estimations were correlated against BOADICEA risk scores on a cohort of patients at increased risk. Towards computer aided diagnosis (CADx), a multimodal lesion classification system for the discrimination of benign and malignant findings was developed with the focus on integration of image descriptors from mammography as well as kinetic and morphology descriptors from MRI using support vector machine classification. Not least, a dedicated CAD system has been developed as part of the project with the goal of assisting radiologists in characterizing suspicious lesions in automated 3-D breast ultrasound (ABUS); a promising technology for screening of women with dense breasts. [8] Within a reader performance study, it was shown that the performance of residents significantly increased when working with this new CAD tool compared to conventional ABUS reading. ■

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VPHOP: The VPH dream becoming reality

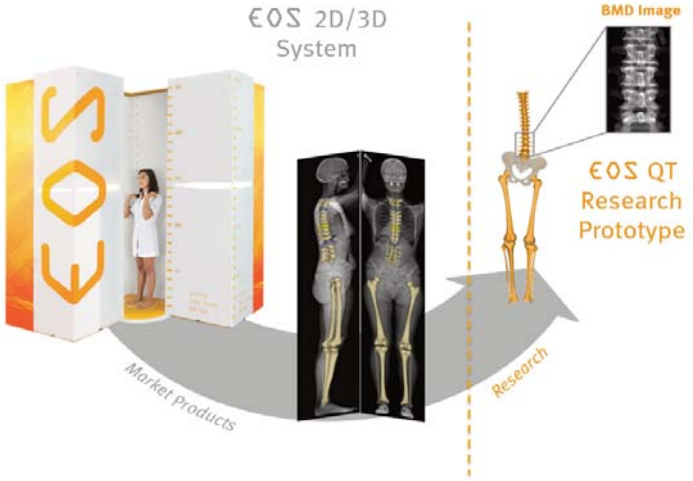
Martina Contin, Istituto Ortopedico Rizzoli on behalf of the VPHOP consortium

In December 2011, the VPHOP (Osteoporotic Virtual Physiological Human) project announced the completion of its clinical recruitment. This is an important reality check for the VPHOP consortium, which has been able to recruit and investigate, with an extensive clinical and instrumental protocol, over 200 patients, whose data will be now analysed with the VPHOP "hypermodel" (a model composed of many sub-models).

The patients were recruited by the four clinical partners of the consortium, **Université de Genève, Istituto Ortopedico Rizzoli, Charitè - Universitätsmedizin Berlin and Institut National de la Santé et de la Recherche Médicale,** under the experienced guidance of the clinical leader Prof René Rizzoli, Head of the Service of Bone Diseases at the Department of Rehabilitation and Geriatrics at the Genève Hospital and former Chairman of the IOF committee of scientific advisors for over 8 years.

"The involvement of real patients early on in the technologies' development cycle is extremely important to ensure that research results do not only provide a research added-value but are also translatable into real clinical practice and clinically sustainable workflows. As leader of the clinical work package, I am proud to announce the completion of the clinical trial: this is a great achievement for the project!" said René Rizzoli. "The VPHOP personalised modelling technology is developing a truly personalized and predictive line of attack against the disease," continued Professor Rizzoli, "which should considerably improve the accuracy with which we estimate the risk of osteoporotic fractures, by accounting for the patient's metabolic, anatomical, biomechanical, and neuromotor determinants in an integrated fashion".

In addition to collecting baseline clinical data, which provided the essential data for the technology assessment, each of the clinical centres also implemented an innovative procedure to explore more specific aspects of the various VPHOP modelling technologies. These procedures involve special technologies provided by the industrial partners, such as Actibelt, a "smart belt" that watches you, or the EOS QT imaging system, the research prototype developed by one of VPHOP industrial partners, EOS Imaging™. Founded by the Physics' Nobel winner Georges Charpak, EOS imaging has implemented a complete orthopaedic imaging solution which enables the simultaneous



acquisition of two full-body X-rays at very low radiation dose and provides a 3D bone-envelope image of the skeleton in the weight-bearing position. It automatically provides over 100 clinical parameters for pre- and post-operative surgical planning.

Based on this commercial product, the research prototype developed in the framework of VPHOP also measures bone mineral density. By combining this information with the personalised 3D envelope of the skeleton, the EOS-QT prototype will ultimately allow 3D densitometry mappings to be used in the VPHOP hypermodel.

A suite of imaging and sensing technologies is required to capture all the necessary information for each patient: high-resolution bone tissue imaging for the axial skeleton (developed by partner Philips Medical System), an advanced model morphing technology (developed by partner Ansys), and the other tools mentioned above. We have worked hard to ensure that these tools will be accepted, and sustained in the future. But the core of the project is the hypermodelling technology developed by partner SCS, and the world-leading predictive models at the body, organ, tissue, and cell level developed throughout the project by the academic partners. The consortium is currently in the process of integrating each of these modelling technologies into the hypermodel framework, and we expect to complete the process by the end of March 2012.

Then, in the last six months of activity of the VPHOP project, the data of these 200+ patients, and of the many others that are part of the retrospective validation studies also part of the project, will be analysed using the VPHOP hypermodelling technology.

"We are convinced that with its probabilistic, personalised multiscale modelling framework, the VPHOP project is setting the scene worldwide in neuromusculoskeletal research and in computational pathophysiology," said Marco Viceconti, coordinator of the VPHOP project.

More information on the VPHOP:

VPHOP is a European osteoporosis research project within the framework of the Virtual Physiological Human initiative. The project is co-funded by the European Union under the 7th Framework Programme of the Directorate General for Research. Ending in August 2012, the VPHOP research project will develop, validate and deploy the next generation of technology to predict the absolute risk of fracture in patients with low bone mass, thereby enabling clinicians to provide better prognoses and implement more effective treatment strategies (both pharmacological and interventional). The aim of VPHOP is to develop a multiscale modelling technology based on conventional diagnostic imaging methods that makes it possible, in a clinical setting, to predict for each patient the strength of his/her bones, how this strength is likely to change over time, and the probability that he/she will overload his/her bones during daily life. With these three predictions, the evaluation of the absolute risk of bone fracture will be much more accurate than any prediction based on the external and indirect determinants used in current clinical practice. ■

For further details please visit the VPHOP website: **http://www.vphop.eu/**

VPH people focus

Interview with George Mihalas

George Mihalas is a Professor of Medical Informatics and Biophysics and head of department at the University of Timisoara. He is also the Romanian representative and previously the President of the European Federation for Medical Informatics (EFMI) . He graduated from the University of Bucharest in 1967 in biophysics, and from the University of Timisoara in 1977 in informatics finally, completing a PhD in physics at the University of Bucharest in 1979. He has been an expert-evaluator for the European Commission DG Information Society and Media in Brussels, since 2002 and has seen the evolution of the Virtual Physiological Human concept from the beginning. His main interests are - mathematical modeling and computer simulation of biological processes (esp. molecular biology), implementation of health information systems and development of e-health strategies.
He won the Gheorghe Marinescu" Prize of the Romanian Academy in 1990 to date has published 12 books and over 250 papers.

Tell me about the EFMI in a few short sentences

The European Federation for Medical Informatics (EFMI), was founded in 1976 as a nonprofit nongovernmental organisation concerned with the theory and practice of Information Science and Technology within Health and Health Science in a European context (The objectives of EFMI are to advance international co-operation and dissemination of information in Medical Informatics on a European basis, to promote high standards in the application of medical informatics, to promote research and development in medical informatics, to encourage high standards in education in medical informatics and to function as the autonomous European Regional Council of IMIA). EFMI is now in 30 countries and members are part of national societies of health/(bio)medical informatics; now 30 countries with 16 working groups (WG) currently running activities. The EFMI organizes 2 conferences per year, the first is a Medical Informatics Europe (MIE) Conference which covers all topics and has an audience from 600 to 900. The second is a Special Topic Conference (STC) which is more specialized with a few WGs and a smaller audience of from 100 to 300.

What is your role in the EFMI?

I am currently the EFMI representative of Romania (Romanian Society of Medical Informatics) and the representative of EFMI to the VPH NoE. I was the President of EFMI from 2006-2008 and the representative of EFMI in the IMIA (International Medical Informatics Association) from 2008-2010

How did you learn about the VPH?

I have acted as an evaluator for the European Commission, DG Infso, ehealth unit, since 2001 and therefore have been informed about the trends in the field and a supporter of the topic from the beginning - also, from the documentation for my personal research (my major topic of research is "modeling and simulation of biological processes")

What was your impression of the VPH meetings in September?

Very good in all aspects: well organized, consistent program, high level audience, a very important "updating" presentation of Joel Bacquet, interesting discussions at the strategic meeting, nice atmosphere, appropriate for "networking" – congratulations to the organizers.

What weaknesses do you see in the VPH initiative – can you recommend any strategic improvements we could make?

I see no weakness in the VPH although I have three points for strategic improvement.

1. A greater emphasis on education would help. For example you could show a "demo" version of some of the new VPH technology, to be added to the current courses of physiology, specifically mentioning that it has been done within the framework of the VPH. At the present time many professors of physiology do not even mention VPH to their students. Students in medicine are also often not aware of modelling. There should be courses available which show the potential and future of the field of VPH. This could be a short seminar or through papers presented at conferences. The first step is to reach the professors and even if they do not attend conferences they often read the listings of conferences. This education should not only target physiology or biophysics professors, but also the clinicians who are supposed to apply these results, in all specialties: cardiology, orthopaedics, gastroenterology, nephrology etc.
2. We can say that formalization is a major theoretical tool in building models and I think that there is still enough room for developing theoretical tools.
3. Another suggestion, without claiming that it would bring strategic improvements, is to extend the methods used for representation of various kinds of information, relying

mainly on visualization. Wecould add, for instance, sonification – a representation by sounds!

Where do you think the VPH approach will have the most impact in the medical profession in these first stages?

If we include "medical research" in the "medical profession", it would, definitely, be there. If we refer mainly to clinical applications, I think, the most developed models now are in orthopaedics, cardiology and oncology. But, for each of them, there are specific applications, like: planning post-traumatic recovery therapy, monitoring of cardiac patients or integration of chemo and radiotherapy in oncology. We also cannot forget the applications in neurology, pneumology, infectious diseases etc.

What are the main barriers to bringing VPH into hospital systems?

Good question. There are so many barriers and it is difficult to select "the main" ones! Let us consider some of them. There are some barriers which are not specific for VPH, but for e-health in general: low user acceptance due to insufficient information (often associated with insufficient desire) about the new methodology and its benefits, absence of a supporting regulatory/legal frame, higher costs (novel equipment) etc. What would be specific for VPH is again insufficient information (there is a need for educational/training modules) on specific applications. Moreover, the validation up to accreditation of any new method in medicine is both lengthy and very expensive. Specific methodology for clinical trials may be necessary (most of the present clinical trials are designed for testing new drugs).

Do you think computational models should start at the molecular level and build up, or zoom in from macro- to micro-?

I do not think these two approaches are exclusive. Integration of a lower level into a higher one is an important consideration, but some specific laws governing the lower level are somehow hidden, or "swallowed"; the laws governing the higher level are qualitatively different from the lower level and not a simple summation, however large the size scale. That is why we can build models at any scale. What is important is to understand the qualitative" jump" and to not neglect the structure of the system nor its integration into a larger entity. This approach is very complex, yielding – naturally – complex models. This is exactly the origin of biological complexity. And the formal representation of such complex systems might need more developed theoretical tools.

How do you think the EFMI could work together with the VPH Initiative to increase awareness of new approaches?

Two scientific communities, with a quite large area of common interests can find several ways to work together. Let me mention just a couple of them. For instance, the EFMI can invite VPH Initiative projects to organize a session in one of our conferences. We can also involve our WG on Education to support VPH actions in this direction. And we can find many other common actions. What is very important now is to have a good start to our cooperation, paving the way for future collaborations.

What impact do you think VPH will have on future healthcare?

I would start my answer here by citing Jean-Claude Healy (head of ehealth unit of the European Commision when the seeds of VPH were included in the strategy for topics to be promoted) in his keynote speech at MIE 2005 in Geneva: "Medicine will change in the next twenty years more than it has changed in the last two centuries!" We can easily imagine that VPH will play a major role in this huge change. A visible and promoted trend in medicine is to move from the present mainly "curative" medicine towards "preventive" medicine, which would be both more effective and cheaper. Why wait to get the disease and then try to cure, when you can prevent it. But prevention needs prediction and risk assessment. What tools can be better than VPH! One day each of us will have his/her "virtual clone" on a computer, able to simulate potential evolutions in various conditions. The term e-patient used by us in 2006 (Integrating Biomedical Information: From eCell to ePatient by Reichert et al.) which is called the "digital patient" in VPH, is the beginning of this gigantic hypercomplex model. But, however complex the model will be, its construction has begun. VPH is building the future of medicine – or the medicine of the future!

The VPH NoE will be participating in the next EFMI conference which is - STC 2012.

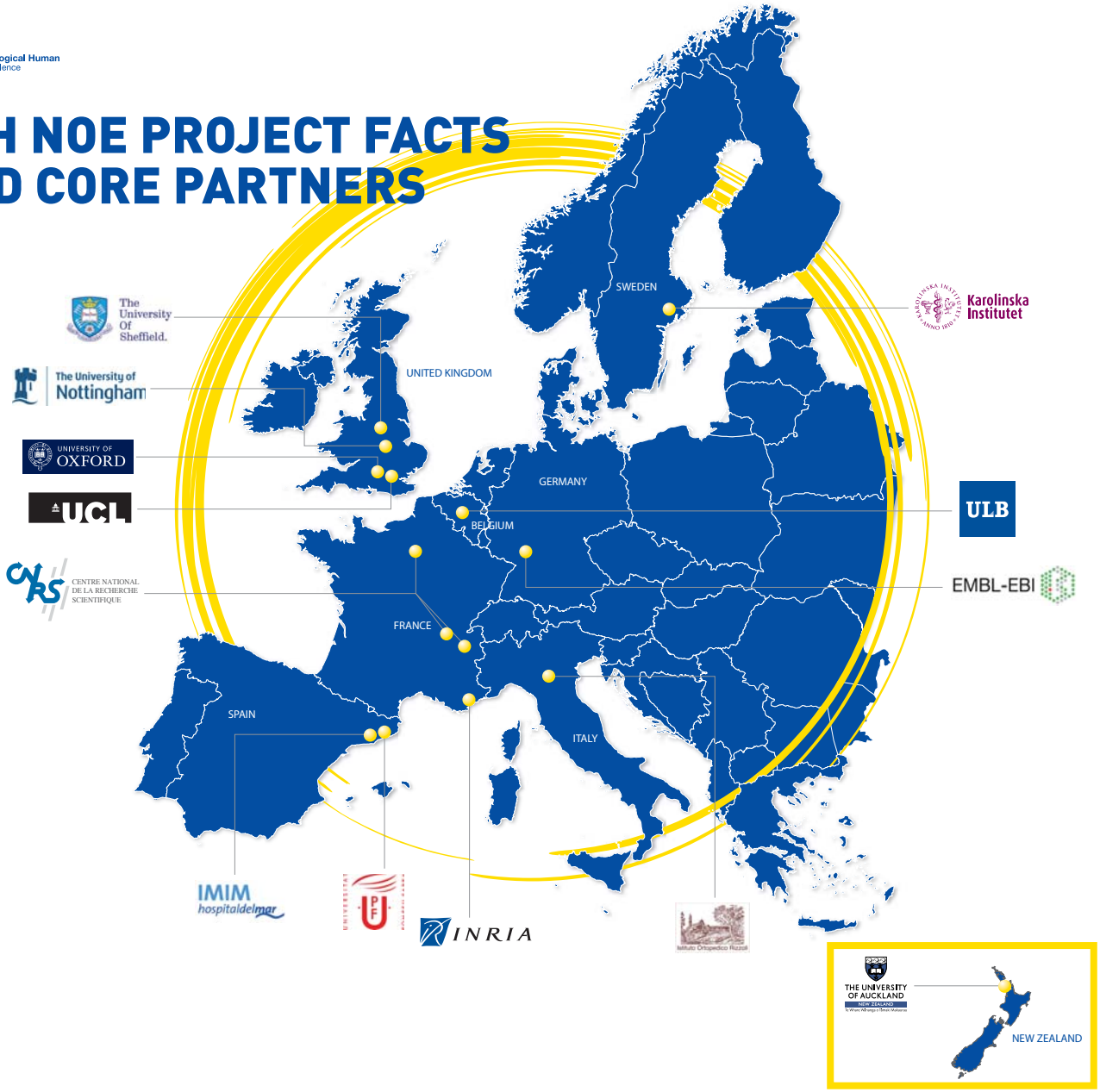
11th International Special Topic Conference of the European Federation for Medical Informatics in Moscow (18-21 April 2012.)
Conference theme - Large Scale Projects in eHealth Partnership for Modernisation.

The aim of the EFMI special topic conferences (STC) is to provide a forum to discuss achievements and actual experiences on specific topics in Medical Informatics in Europe (MIE). Its basis is innovative methods and approaches. STC enhances the communication among the professional communities of health informatics.
STC2012 -carrying on the traditional series of EFMI STC conferences- is one of the most important European events in the common sphere of medicine and informatics. Its major goal is to increase interaction and collaboration among professionals from both health and ICT. The STC conferences are organised in close collaboration with EFMI working groups.
The theme of the STC 2012 is the implementation experience of large scale eHealth projects. These large scale projects can be described by its size, its effects, its complexity, its duration etc. eHealth projects contribute to the success and sustainability of the future health care system. Large scale projects are mostly accompanied by small and dedicated initiatives and solutions. STC2012 will try to bring experience, innovation, new concepts and actual research and development into a discussion resulting in constructive results for a partnership for modernisation.
The objective of the conference is to highlight large scale projects supporting the use of information and communication technology (eHealth) at national, regional, and especially at international level. It will result in requirements for national and regional solutions for medical informatics and health information management.

For further information please go to **http://www.STC2012.eu.**

Virtual Physiological Human
network of excellence

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.

EC Project No: **FP7-2007-IST-223920**
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.

University College London, United Kingdom
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Institut Municipal d'Assistencia Sanitaria, Spain
Istituto Ortopedico Rizzoli, Italy

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