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Policy needs and options for a common approach towards modelling and simulation of human physiology and diseases with a focus on the Virtual Physiological Human

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1. Executive Summary

“One Life, One Knowledge: Technology To Integrate”

In spite of the human need to reduce to parts in order to understand, life is the result of an intricate systemic interaction between very many processes occurring at radically different spatial and temporal scales. Every day worldwide biomedical research and clinical practice produce a huge amount of information on such processes. But this information is highly fragmented, and its integration is largely left to the human actors, who find this more and more difficult as the breadth and depth of information available increases exponentially. We need to develop a new approach, which makes possible the integration of information, and simplifies its transformation into integrated knowledge.

The European Union and the United States of America are investing substantial research funding in the development of frameworks of computational methods and technologies that make possible an integrative approach to biomedical research and clinical practice.

This approach that in Europe is called “Virtual Physiological Human” (or VPH for short), involves laboratory and clinical data collections, information databases, models repositories, as well as simulation, information and communication technologies that make it possible to overcome the “reductionist chaos” produced by the fragmentation and the dispersion of scientific and clinical data, information, and knowledge that together compose what we humans know and understand about the biological mechanisms of life and disease.

These investments in VPH research are largely motivated by the need for improved healthcare delivery: as all health information becomes digital, the complexity

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of care increases, and pressure imposed by growing demand and shrinking budgets. The way to achieve the dream of a personalized, preventive, and participative medicine at sustainable costs is the systematic integration of all available data, information and knowledge.

Some results of these research projects are finding their way to clinical deployment and industrial exploitation; in Europe some of the early VPH projects funded by the DGINFSO “ICT for Health” unit have already entered initial phases of clinical trials, with promising results suggesting that VPH technology can be used to address particular clinical problems.

The time is ripe to go to the next level: to coordinate research efforts toward the complete integration of all data, information, and knowledge about human physiology and pathology into a global “VPH cyberinfrastructure” that will produce socioeconomic benefits by:

- Enhancing the understanding of diseases, promoting prevention and early diagnosis;
- Accelerating the development pipeline and the assessment of safety and efficacy for innovative drugs and medical devices;
- Assisting the medical professional in coping with “information overload”;
- Fostering the development of new healthcare policies that promote a more integrative approach to complex diseases and to the promotion of an active and healthy aging.

But this will be successful only if Europe and United States elaborate a joint policy. This document aims to illustrate the reasons why we, the academic, industrial and clinical stakeholders of the VPH initiative recommend the European and United States governments:

- Work together on a common policy to harness outcomes of all VPH-type research efforts toward the creation of a global VPH Cyberinfrastructure, by ensuring that all repositories of data and models, as well as all the methods and technologies developed during these research projects funded by governmental agencies are mutually interoperable.
- Support the establishment and the operations of an International Multistakeholder Advisory Group responsible of elaborating a collective vision, as well as the minimum set of standards and the technical guidelines that ensure the interoperability and the integrability of all VPH resources into the global VPH Cyberinfrastructure, to achieve the vision of the Virtual Physiological Human.

2. Preface

2.1. Purpose of this paper

The European Union, through the European Commission Directorate General for External Relations, is supporting the ARGOS eHealth Pilot Project. The overall goal of the ARGOS eHealth Pilot Project is to contribute to establishing a “Transatlantic Observatory for Meeting Global Health Policy Challenges through ICT-enabled Solutions” in order to develop and promote “Common Methods for Responding to Global eHealth Challenges in the EU and the US”.

The EU and the US care about these global challenges because (a) citizens travel and migrate globally and there is a wish to foster good healthcare everywhere (b) the EU and US wish to refine their products to better penetrate global markets (c) experiences and lessons learned globally are useful in Europe and the United States.

The Observatory promotes mutual understanding and learning among EU and US policy researchers and policy makers on the following general challenges with global dimension:

1. Improving health and well-being of citizens through accelerating eHealth strategy development and through supporting large scale eHealth infrastructure implementations;
2. Supporting R&D in eHealth to promote the benefits from the pursuit of consistent strategies.

A key output of ARGOS will be three Policy Briefs. They will concisely analyze and summarize project results on the three topics of the project on policy needs and options regarding

- Interoperability in eHealth and Certification of Electronic Health Record systems (EHRs);
- Measuring adoption, usage and benefits of eHealth solutions;
- Modelling and simulation of human physiology and diseases - Virtual Physiological Human (VPH)

and provide recommendations for developing together and aligning trans-Atlantic eHealth policy & RTD strategies and cooperation in these three topical fields, including setting concrete goals, proposing adoption measures and processes to be followed.

The **Virtual Physiological Human** (VPH) is a framework of methods and technologies that, once fully established, will make possible the investigation of the human body as a whole. Started in Europe in 2005, it has rapidly grown to become one of the research priorities of the Information and Communication Technologies Programme of the EU Seventh Framework Programme for Research and Technological Development. In the US, VPH-type research is funded by all the federal agencies that participate in the Interagency and Analysis Group (IMAG), whose grantees are coordinated in the Modelling Multi Scale Modelling consortium.

On the Virtual Physiological Human, the ARGOS Proposal formulated these objectives: “Its potential from clinical and industrial perspectives as well as from the perspective of treating citizens with rare diseases will be at the focus of the ARGOS policy analyses and recommendations”.

2.2. Genesis

The elaboration of this policy brief was coordinated by a small group of experts led by Marco Viceconti, responsible of the VPH NoE outreach program, coordinator of the VPHOP Integrated project. The prime advisor for the USA side was Andrew McCulloch, Chair of the IUPS Physiome and Systems Biology Committee and a member of the Multi Scale Modeling (MSM) consortium of the US Interagency Modeling and Analysis Group (IMAG).

To support them a small editorial team of experts from EU and US was formed, which drafted a first version of technical document aimed to the research community itself, the “ARGOS VPH Position paper”. This document was open to the public discussion on an Internet forum called Biomed Town, which has hosted all relevant community activities related to the VPH since its inception in 2005, and disseminated with the VPH News mailing list. On the basis of the comments received a second revision was made, and presented at the VPH Strategic Consensus Meeting organized by the VPH Network of Excellence in Brussels that saw nearly 300 registered delegates, and at the Annual meeting of the Multiscale Modeling Consortium promoted by the USA Interagency Modeling and Analysis Group.

The final revision that emerged from these public discussions was used as a basis to elaborate this policy brief, which was first drafted during the ARGOS Stakeholders meeting in Washington DC, and then opened to public discussion through Biomed Town. Overall, the policy brief was exposed to over 10,000 individuals involved with the VPH initiative worldwide; we estimate that more than 700 experts and stakeholders participated to the elaboration of the position paper of our policy brief.

2.3. Key Policy Messages

We recommend that the European Union, its member states, and the United States governments:

- **Agree on a common policy to harness the outcomes of all VPH-type research efforts toward the creation of a global *VPH Cyberinfrastructure***, by ensuring that all repositories of data and models, as well as all the methods and technologies developed during these research projects funded by governmental agencies are mutually interoperable;
- **Support the establishment and the operations of an International Multi-stakeholder Advisory Group** responsible of elaborating a collective vision as well as the minimum set of standards and the technical guidelines that ensure the interoperability and the integrability of all VPH resources into the global *VPH Cyberinfrastructure*, according to the vision of the Virtual Physiological Human.

3. Terminology

3.1. Choice of the core terms

The focus of this document is upon a global resource that will play an infrastructural role. However, this resource is not a distinct physical entity, but an organised cloud of databases, services, collections, portals, simulation engines, etc. accessible via the Internet.

Currently we are referring to this as the term *VPH Infostructure* in Europe, and *Multi-Scale Modeling Cyberinfrastructure* in the USA.

The term Virtual Physiological Human (VPH) was first proposed by a group of European researchers in a white paper published in 2005, and substantiated by the European STEP action, which published in 2007 a full research roadmap for its realisation. In this roadmap the VPH is defined as a “framework of methods and technologies that once established will make possible to investigate the human body as whole”. The VPH intends to be the technological materialisation of notions and objectives that had commonly been described as the Physiome, a term coined and adopted jointly by Jim Bassingthwaight at the University of Washington and Denis Noble at the University of Oxford. The International Union of Physiological Sciences organized and promoted the international Physiome Project, under the leadership of Peter Hunter at the University of Auckland. Although the term VPH is used primarily in Europe, it has a very strong ethos, a clear definition, and a large number of documents and papers that materialise it. In the US, Systems Biology captured many of the key concepts of model-based integration but without a specific emphasis on the integrative physiological function of the whole human. Thus IMAG settled on Multi-Scale Modeling (IMAG) to describe the ideal of Physiome research.

In computer science, the term cyberinfrastructure popularized by the NSF is now mature a clearly defined, for example in the Wikipedia entry: “*The term cyberinfrastructure describes the new research environments that support advanced data acquisition, data storage, data management, data integration, data mining, data visualization and other computing and information processing services over the Internet. In scientific usage, cyberinfrastructure is a technological solution to the problem of efficiently connecting data, computers, and people with the goal of enabling derivation of novel scientific theories and knowledge*”. NSF has an Office of Cyber Infrastructure (OCI), and there is a 2007 NSF roadmap entitled “Cyberinfrastructure Vision for 21st Century Discovery”, which describes a general vision for all sciences, that fit closely to the idea we have in Europe of the VPH Infostructure. The term returns 283,000 entries in Google (on 22-11-2010).

In contrast, the term Infostructure has a much less clear pedigree. Apparently, it first appeared in 1994, in an informal document in which the following definition is provided: “*An infostructure is the layout of information in a manner such that it can be navigated -- it's what's created any time an amount of information is organized in a useful fashion. A table of contents is an infostructure, as is a bibliography, or an index. GopherSpace is an infostructure. The World Wide Web is an infostructure*”. The term returns 105,000 entries in Google (on 22-11-2010) but most of them are not relevant here. For example the same is used for some companies in the area of Information Technology (IT) services, telecommunications, etc. The term has been adopted by the

Canadian healthcare services to indicate the new healthcare IT structure: “Health infostructure is the development and adaptation of modern systems of information and communications technologies in the health sector in order to improve access, efficiency, effectiveness and the quality of clinical or health services processes”.

After some discussion, it was agreed to use in this document the term “VPH Cyberinfrastructure” combination of the term *VPH* mostly used in Europe and that *Cyberinfrastructure* mostly used in USA.

Another similar dichotomy between European and American terminology is that used to define the general application of information technology to the healthcare. This in USA is mostly indicated with the term Health Information Technology (HIT), whereas in Europe the term eHealth (electronic health) is more used. Both will be used interchangeably throughout the text.

3.2. List of acronyms used in the document

FP6	EU Sixth Framework Program for Research and Technological Development
FP7	EU Seventh Framework Program for Research and Technological Development
ICT	Information and Communication Technology
IMAG	USA and Canadian Interagency Modeling and Analysis Group
IT	Information Technology
MSM	Multi-Scale Modeling
NIH	National Institutes of Health — USA federal agency
NSF	National Science Foundation — USA federal agency
VPH	Virtual Physiological Human

4. Analysis framework

- The strategic importance of VPH research both in terms of basic knowledge and of socioeconomic impact was analyzed in depth in the VPH Research Roadmap by over 600 experts in 2006 under the coordination of the STEP consortium.
- Such importance was reflected in Europe in the Seventh Framework Program, the most important community research action, which indicated the VPH as one of its priorities in the Information and Communication Technologies Programme [1].
- In the United States, Botstein and Smarr’s BISTI (Biomedical Information Science and Technology Initiative) report (1999) to the NIH director made key recommendations emphasizing the importance of information technology in post-genomic medicine and health research and led to the creation of the National Centers for Biomedical Computing. This was followed by other influential reports, notably the National Academy of Sciences report in 2005 by Wooley and Lin on “Catalyzing Inquiry at the Interface of Computing and Biology”.

- The specific need for the development of *ad hoc* Information and Communication Technologies (ICT) infrastructural components emerged in the 2009 update to the VPH Roadmap [2].
- This recommendation was again reflected in the seventh framework program, which funded in the most recent VPH call for proposals two large integrated projects aimed to develop essential elements of such infrastructures, VPH-Share, and P-Medicine.
- At the NIH, the BISTI consortium of representatives from each of the NIH institutes and centers was established in May 2000 to serve as the focus of biomedical computing issues at the NIH. Major related NIH initiatives include the Cancer Biomedical Informatics Grid (CaBIG), the Genome Informatics and Computational Biology Program and the Neuroscience Information Framework (NIF).
- Beyond the NIH there are also important inter-agency initiatives, principal among them the Interagency Modeling and Analysis Group's (IMAG) Multi-Scale Modeling (MSM) initiative established in 2004, which brought together over 80 investigators funded by ten federal agencies. This call was followed by the NIH call in 2008 for research proposals on "Predictive Multi-Scale Models of the Physiome". In 2011, the IMAG MSM request for proposals was reinstated through 2014.
- With respect to the integration of these new ICT research infrastructures with those resources already available and largely in use, such as the bioinformatics resources managed by the European bioinformatics Institute and the US National Center for Biotechnology Information, the Biomodels and CellML models repositories, the PhysiomeSpace data sharing service, PhysioNet, NIF and the Neuroimaging Informatics Technology Initiative (NifTI), the need to integrate all these resources into a coherent framework is becoming evident.
- Similarly, it is now recognised that locked up in our hospitals is a wealth of data and information that in principle could be integrated with data collections produced by research activities and clinical trials, in order to maximise their usage and potential benefits.
- All these roadmaps, position papers, research funding allocations, in-depth analyses point in the same direction: in spite of the great difficulties involved, all biomedical data, information, and knowledge should be captured digitally, and should be integrated into a coherent framework worldwide.
- A Memorandum of Understanding was recently signed between the European Commission and the United States Department of Health and Human Services on Cooperation Surrounding Health Related Information and Communication Technologies, where are laid down the foundations for a global conceptual framework that articulates how health-related information and communication technologies support improved health [3].

In this policy brief we analyse how research activity can be aligned and deployed so as to establish a global VPH cyberinfrastructure that can make significant impact first onto biomedical research and then onto the clinical practice and the biomedical industry, as long as it is properly developed, operated, serviced, and maintained.

The analysis framework was organised around six aspects:

- Needs and challenges that could be addressed by the Virtual Physiological Human;
- Policy and strategic approaches being used to tackle these challenges;
- Results these strategies have produced so far, and their limitations;
- Methodological challenges to be faced;
- Lessons learned so far, and need for future actions;
- Recommendation for the development of a trans-Atlantic joint policy.

5. What are the issues?

5.1. *Let's go digital*

By 2020 we can expect the digitalization of virtually all healthcare information, at least in the developed world. Despite the costs involved, the lack of a digital information workflow within a healthcare organization will eventually incur a higher cost in the effectiveness of healthcare delivery, which could threaten to create a digital divide between fully digital healthcare providers that will benefit from this integration trend, and those that are not.

This issue will be amplified by increasing demand from patients for secure online access to personal health records. By 2020, the elderly population will comprise citizens who retired in the '90s or later, the vast majority of whom will expect to have the same degree of digital access to all their health information as they do for all their other personal information.

Investments in healthcare Information Technology (IT) in the next few years must account for the trend toward integration of all available data, and they should emphasize solutions that facilitate integration; the idea that the information systems of our hospitals are islands, isolated from the rest of the digital world, is rapidly becoming obsolescent.

5.2. *Let's get personal*

Modern medical science is all about the “average person”. The signs of a disease, the efficacy of a drug, or the appropriateness of a therapy, are always observed on many patients, and from them an “average response” is derived, which is then considered valid for any other patient.

But as our therapies become more and more complex, the best option for an individual patient is frequently a balance between opposing factors; the option considered the best based on the “average responses” might not be actually the best for each individual.

The solution is personalization of therapy. Some experts suggest that personalization is only related to the genes. The way our genes are, as we received them from our parents, surely have an influence of how we shall react to a medicine.

But we are lot more than our genes. If we have been smoking all our life, if we drink a lot, if we run 20 miles per day, this can make a lot of difference. So personalization involves the integration of all details on the patient, not only the genetic ones.

5.3. *Explanation-based medicine*

A term that is quite popular nowadays is “evidence-based medicine”. This means that every doctor should base his/her medical decisions on solid evidences that such decision is the correct one. By observing a reporting the health condition of million of individuals over the centuries we now know that there are some solid evidences. For example, if you get a cold, an aspirin can relieve you of some symptoms. It might not be true for all or under all conditions, but it has found true for millions of peoples in millions of conditions: this is evidence. So when a doctor prescribes a drug to a patient, we expect he/she takes this decision not because he personally thinks is a good idea, but because there is *evidence* based on clinical trials to support the decision.

However, the fact that we know for sure that aspirin takes away cold symptoms does not necessarily means that we know *why* this happens. Do we care? Well, in many cases probably not. But in some cases, having an *explanation* of why something happens is critical. For example a certain drug worked well for a lot of people with a certain disease; this is evidence. But it does not work for me, even if I am supposed to have the same disease. Population-based evidence cannot help in solving this problem. But if we can provide an explanation of how the drug works, we can search for a specific condition that I have but that others tested did not have, for example another disease, a certain genetic predisposition. So evidence-based medicine is important, but to go further we need to add *explanation-based medicine*.

But how can we produce such explanations? When available they come from scientific studies. But in many other cases what we observe is the result of very many complicated processes happening all together. In many other domains of science, when we must deal with problems that are too complicated for our brains, we resort to mathematical models. Take weather forecasting: to predict tomorrow’s weather, we need to take into account so many factors, and so many calculations, that it could take months, if not years to come up with an answer, which of course by that time would be useless. But if we write all we know about weather in a mathematical model, a computer can do those calculations fast enough predict the weather for tomorrow in a few hours.

Can we use the same approach to provide explanations in medicine? Yes, now we can. The problem is that even the simplest medical problem is much more complicated than what any traditional computer model can deal with. But recently we started to develop a whole new generation of biomedical simulation models that can predict accurately what happen in the human bodies under many different conditions, and many more are developed every day. In a near future we can imagine personalized computer models that provide the most plausible explanation for each patient, making the dream of explanation-based medicine closer to reality.

5.4. *Integration will rule them all*

Another problem that we have is fragmentation. Take for example health data. Most of the information that describes our health over the years is probably stored in digital format, but it is spread over several hospitals, clinics, points of care, family doctors, pharmacies, etc. No one can really see my health history as a whole, including myself. We need to make biomedical information accessible by anyone from everywhere and through whatever type of computer, mobile devices, etc. And we need to do this without compromising the security, confidentiality, and integrity of personal health information, among the most sensitive information computer systems can store.

A second dimension of the problem of fragmentation is that of the *integration of knowledge*. We know so much about the human body nowadays, that no one can know it all. So every medical professional, every biomedical researcher becomes a specialist of something, and they try to know as much as possible about a very specific topic. This has been happening for some time, but now we start to realize that in the long run this is not such a good idea. Indeed, while we can attempt to separate knowledge about the human body into parts, the reality is that the human body is one, and works as a whole.

A third dimension, less obvious for non-experts, is the fragmentation, or better separation, between biological research and medical practice. In spite of all claims, going “from the bench to the bed” remains largely an unresolved issue. The problem again is fragmentation, but this time in the *production* of knowledge: reducing what we are studying to its smallest part make it easier to understand, but frequently prevent us to understand that such small part is indeed a part, the part of a bigger and more complex system.

5.5. *Faster, cheaper, safer innovation in healthcare*

The relationship between biomedical research and clinical medicine has also another dimension: that of the development of new methodologies, technologies, and pharmacological products. The more we advance the more this process become difficult, expensive, and slow. Again, the fragmentation of knowledge and of its production processes is the main culprit.

5.6. *And the patient? In the centre!*

A key concept that is recurring in debates on the future of healthcare delivery is the need to keep the patient at the centre of the information cloud. In reality, the human relationship between the patient and the doctor remains the core of medicine, which will never be reducible or simplifiable. In relation to age, culture, social status, and geographical location, some patients will always expect to transfer the major part of their health responsibility to their doctor, whereas others will fight to retain total control, even when this is ill advised. This issue ultimately must balance the needs of the individual with those of society and of the other stakeholders, which often becomes a complex philosophical and political issue.

6. Policies, strategies, approaches presently pursued

6.1. European Commission: the Virtual Physiological Human

In Europe the need for integration in biomedical research and clinical practice was approached with a pragmatic perspective. Having recognized the need for such integration, the European Commission started to support the development of the *Virtual Physiological Human* (VPH), intended as a framework of methods and technologies that once established will make possible the investigation of the human body and of its diseases in an integrated way. So the accent was placed on the development of the tools, primarily information technology tools that can make possible such integration.

The VPH started in Europe primarily as a research initiative; however, the fact that it was initially funded by the *ICT for Health* unit imposed from the beginning a stronger translational and industrial perspective. Toward the end of the Sixth Framework Programme (FP6) a support action called STEP steered the development of a research roadmap for VPH research. Even if STEP was a European action the scientific advisory board that was formed to supervise the consensus process that led to the roadmap included experts from Japan, New Zealand, and of course the USA.

STEP was a great success mostly thanks to the enthusiastic participation of over 600 experts in the elaboration of the roadmap. This happened primarily because the times were ripe: in many areas of biomedical research spontaneous exploration were started on the use of predictive computer models in an integrative way so as to properly represent processes happening at radically different space-time scales. This approach was already quite advanced in cardiac modeling, but some researchers were starting to apply it to other biomedical problems.

The VPH research roadmap, which thanks to the annual updates is still the primary reference document for the European VPH initiative, identified as the primary challenge in integrative research the development of an exhaustive framework of methods and technologies that once fully established would have made possible the investigation of the human body as a whole.

Today we recognize the VPH is not only methods and technologies, but also a global cyberinfrastructure that unifies all data, information, and knowledge on the human body we are accumulating worldwide.

As part of the Seventh Framework Program (FP7) the EC selected in a first funding round a network of excellence, two large integrated projects, and 12 medium-sized projects. A second funding round closed recently, and a number of new projects will soon kick-off; meanwhile a third funding round is already planned for early 2012.

Meanwhile also national agencies of European member states started to invest resources in VPH research. Two examples are the Epitheliome project funded by UK EPSRC, or the €40m virtual liver project funded in Germany.

This first batch of grants was followed the year after by five internationalization projects, aimed to reconnect these research experiences.

6.2. US National Institute of Health Grants on Physiome Models

In USA the development of the integrative research vision was a bit different, with more focus on basic science research (especially at the molecular and cellular scales)

and developing computer science infrastructure for biomedical research, producing a stronger academic development. One outgrowth of the MSM initiative that specifically encouraged the extension of multi-scale modeling to “higher scales” of biological organization and applications to clinical translation was the NIH program first announced in 2008 on “Predictive Multiscale Models of the Physiome in Health and Disease”. This program announcement continues to be reissued and currently ten NIH institutes and centers including the National Institute of Biomedical Imaging and Bioengineering, the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Deafness and Other Communication Disorders, the National Institute on Drug Abuse, the National Institute of Environmental Health Sciences, the National Institute of General Medical Sciences, the National Institute of Neurological Disorders and Stroke and the National Library of Medicine. The goal of this solicitation is to move the field of biomedical computational modeling forward through the development of more realistic and predictive models of health and disease. NIH recognizes the need for sophisticated, predictive, computational models of development and disease that encompass multiple biological scales. In 2011, the IMAG MSM call for proposals was renewed through 2014.

6.3. NSF Cyberinfrastructure policy

The National Science Foundation in the US has long been the focal point for research on cyberinfrastructure. Its 2007 report “Cyberinfrastructure Vision for 21st Century Discovery” [4] summarizes the NSF vision for the use of computing systems, data, information resources, networking, digitally enabled-sensors and instruments, virtual organizations and observatories, interoperable software services and tools, together with interdisciplinary teams of professionals in enabling new advances in scientific research and education. At the NIH, the National Center for Research Resources has supported research resources and centers over the past 15-20 years that aim make the NSF sponsored progress in IT research and cyberinfrastructure development accessible and useful to the biomedical research community. Wooley’s 2004 report at NSF entitled Building a Cyberinfrastructure for the Biological Sciences [5] outlines the needs to the biological science community in this regard.

6.4. Memorandum of Understanding

The 2010 “Memorandum of Understanding Between The United States Department of Health and Human Services and the European Commission on Cooperation Surrounding Health Related Information and Communication Technologies” is a remarkable signal and encouragement to all stakeholders that common standards and interoperability in eHealth will bring opportunities for a global approach for the benefit of patients, health systems and the market. The memorandum encourages more effective use of health related information and communication technologies in healthcare delivery including disease prevention and health promotion services. Of relevance to the VPH initiative is the encouragement to develop a global conceptual framework “that articulates how health-related information and communication technologies support improved health” and also “the promotion of

continuous innovation". An approach on a global scale with the focus on boosting innovation through international cooperation lies at the heart of VPH cyberinfrastructure.

6.5. VPH infrastructure projects: VPH-Share and P-Medicine

Also the European Commission recognized the need for a global cyberinfrastructure that unifies all data, information, and knowledge on the human body, by funding two large-scale research projects aimed to develop core information technologies for the creation of such infrastructure.

VPH-Share will develop the organisational fabric (the infostructure) and integrate the optimised services to (1) expose and share data and knowledge, (2) jointly develop multiscale models for the composition of new VPH workflows, (3) facilitate collaborations within the VPH community. Four flagship workflows (from @neurIST, euHeart, VPHOP, Virolab) provide existing data, tools and models, engage with the services developed by VPH-Share to drive the development of the infostructure, and pilot its applications. Data sources are usually clinical data from individual patients - medical images and/or biomedical signals - sometimes with population information. The operations range from secure access and storage through annotation, data inference and assimilation, to complex image processing and physics-based mathematical modelling, to data reduction and representation. The project focuses on a key bottleneck – the interface with the wealth of data from medical research infrastructures and from clinical processes. VPH-Share will provide the essential services, as well as the computational infrastructure, for the sharing of clinical and research data and tools, facilitating the construction and operation of new VPH workflows, and collaborations between the members of the VPH community. Evaluating the effectiveness and fitness-for-purpose of the infostructure and developing a thorough exploitation strategy are key activities, creating confidence in the communities. The consortium, through its optimal mix of medical, mathematical, engineering, software & hardware and industrial knowledge and expertise from the EU and internationally, will make this effort a success, delivering to European citizens clinically useful outcomes that will benefit society. The duration of the project is 4 years, its budget is € 15.5m, and the requested EC contribution is € 11.3m.

P-medicine aims to create an infrastructure that will facilitate the development from current medical practices to personalized medicine. The main drivers will be clinicians. The project is scenario based. Two categories of scenarios will be addressed:

- The composition of large, pseudo-anonymized datasets from multiple sources, used for the development of VPH tools;
- The use of data obtained from a single patient to run a simulation workflow in support of an individual clinical decision making process;

The infrastructure of *p-medicine* will consist of an IT and a clinical research infrastructure that are smoothly interconnected and guarded by a legal and ethical framework. Previous R&D work done in European funded projects like ACGT (Advancing clinicogenomic trials in cancer), ContraCancrum and ECRIN (European Clinical Research Infrastructures Network) fits perfectly into this approach and will be

interlinked. The system architecture will be modular, such that switching to the *p-medicine* system is not an all-or-nothing decision.

In *p-medicine* anonymized data and tools will be stored in repositories potentially as private cloud services and will be open source. The data warehouse serves as a data collection for running VPH simulations and testing developed tools, for which standardization and semantic interoperability is a major issue to be solved. Most of the data come from clinical trials. Data from clinical information systems will be made available by a 'push' model, where data owners initiate data transfers. Access to biobanks will help to answer research questions without running new trials. Allowing patients to decide at any time what kind of research can be done with their data and their biomaterial supports patient empowerment. This will be specifically addressed by the legal and ethical work package. *P-medicine* will develop eLearning tools to train and educate end-users. Three areas of clinical trials will focus on three different aspects of the developed framework:

- The Wilms tumour trial will be used to employ the newly developed and validated tools of *p-medicine*. The trial also provides data for the OncoSimulator testing a specific Wilms Tumour scenario (continuation of ACGT)
- The breast cancer trials will be used for the validation of decision making tools and data acquisition, sharing, joining and analyzing and the breast cancer neoadjuvant pharmacodynamic phase II trial will be used to extend the VPH tools.
- The leukaemia trial and the breast cancer neoadjuvant pharmacodynamic phase II trial will be used to run system biology and postgenomic dynamic scenarios to find, also by using simulations based on systems biomedicine modelling approach, individual risk factors for decision making and to validate the proposed models

To sustain a self-supporting infrastructure realistic use cases will be build that can be run easily and show tangible results for end-users in their daily practice.

6.6. EU policy on biomedical e-infrastructures

The European Commission is establishing a number of European ICT research infrastructures (e-infrastructures) targeting biomedical research. Among the others:

- Generic infrastructure for connectivity in Europe with links world-wide: GEANT (<http://www.geant2.net/>)
- Generic infrastructure for distributed computing in Europe with site world-wide: EGI (<http://www.egi.eu/>)
- Generic infrastructure for supercomputing in Europe: PRACE (<http://www.prace-project.eu/>)
- Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)
- European Life Sciences Infrastructure for biological information (ELIXIR)

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

There are also complementary e-infrastructures that are aimed at managing very large databases, networking services, and high-performance computing systems. As an example we provide here some details on one of them, the ELIXIR bioinformatics infrastructure.

ELIXIR (www.elixir-europe.org) is a European Infrastructure that unites Europe's leading research organisations in managing the staggering volume of biological data being generated every day in publicly funded research. This large-scale initiative will provide the facilities necessary for life science researchers to share, analyse and protect our rapidly growing store of information about living systems.

In recent years, many European countries have been investing heavily in biological research. As a result, life scientists are finding out more every day about genes, proteins and the complex networks at play in living things. The results of these experiments are a goldmine for life scientists, both in academia and industry. This information provides valuable insights into how we and other life forms (like plants and bacteria) grow and change, and how diseases progress. It helps us to understand a patient's family history better, and to discover molecules that can be used to make new drugs to treat disease. It can also inform the way we plant crops, or how we might use them differently.

Advances in DNA sequencing and in other areas have led to massive growth in the amount of new knowledge being generated in biological experiments - in fact, the volume of new data is doubling every five months or so. This growth in data generation far surpasses the growth in storage capacity. Yet all of this information must be stored, managed and quality controlled by experts in biology, chemistry and bioinformatics. In addition, new types of data - for example, images acquired using microscopes, physiological datasets, mathematical models - will need to be integrated with the old. This requires innovative tools as well as vast computational and storage resources. The collection, curation, storage, archiving and integration of these data present an immense challenge that cannot be handled by a single organisation or country alone. It requires international coordination. ELIXIR brings together Europe's leading bioscience facilities to manage biological data in a sustainable way. This pan-European initiative aims to enable all facets of the life science community - from health to agriculture - to extract optimum value from work that has already been done, and whose nature we can now only imagine.

ELIXIR is entering its construction phase, and many leading researchers and institutions throughout Europe are working together to ensure that it is robust, forward-looking and sustainable. Coordinated by the European Molecular Biology Laboratory's European Bioinformatics Institute (EMBL-EBI), ELIXIR already has significant

financial backing from Denmark, Finland, Spain, Sweden and the United Kingdom. In total, 53 European institutes in 23 countries have put forward proposals to participate.

6.7. Europe 2020 Innovation Union

The Council of the European Union recently concluded on the European Commission communication [6] "**Europe 2020 Flagship Initiative: 'Innovation Union'**: Accelerating the transformation of Europe through innovation in a fast changing world" [7] as well as the flagship initiative "Digital Agenda", in the context of the Europe 2020 strategy. In this document the European Commission seizes 34 commitments with respect to innovation from now to 2020. Two of them are of particular relevance here:

- *Innovation Union commitment #31.* The European Union and its Member States should treat scientific cooperation with third countries as an issue of common concern and develop common approaches. This should contribute to global approaches and solutions to societal challenges and to the establishment of a level-playing field (removing barriers to market access, facilitating standardisation, IPR protection, access to procurement etc.). In 2012 together with the ERA Framework, the Commission will propose common EU / Member States priorities in S&T as a basis for coordinated positions or joint initiatives vis-à-vis third countries, building on the work of the Strategic Forum for International Cooperation. In the meantime, the EU and Member States should act in a concerted manner when engaging in S&T agreements and activities with third countries. **The potential scope for "umbrella" agreements between the EU and Member States with third countries will be explored.**
- *Innovation Union commitment #32.* **The European Union should step up its cooperation on the rollout of the global research infrastructures. By 2012, agreement should be reached with international partners on the development of research infrastructures, including ICT infrastructures, which owing to cost, complexity and/or interoperability.**

In the same document, the Council endorses also the ongoing work by the European Commission in bringing forward the pilot **European Innovation Partnership (EIP) on Active and Healthy Ageing**, the overarching goal of which is to increase on average, by 2020, the healthy lives of Europeans by two years. The pilot European Innovation Partnership on Active and Healthy Ageing will pursue three goals:

- enabling EU citizens to lead healthy, active and independent lives while ageing;
- improving the sustainability and efficiency of social and health care systems;

- and improving the competitiveness of the markets for innovative products and services, responding to the ageing challenge at both EU and global level, thus creating new opportunities for businesses.

The approach to integrate all available data, information and knowledge in order to form a personalized, preventive, and participative medicine at sustainable costs, and to foster the development of new and healthcare policies through break-through innovative business and technology models, makes the VPH initiative in itself a flagship candidate community for innovations in active and healthy ageing. VPH endorses the proposal that “the pilot partnership provides [...] actors with a forum in which they can, united around the common goal, identify and overcome potential innovations barriers”.

7. Past and present achievements

7.1. VPH: early results

The VPH is a broad initiative, which targets virtually all aspects of biomedical research and clinical practice. Currently, we estimate that over 100 research projects developing and applying VPH-related technology are active worldwide, with clinical targets that go from the early diagnosis of the Alzheimer’s disease to the prevention of osteoporotic fractures in the elders. To provide an exhaustive coverage of the early results produced by all these research activities is clearly impossible. Here we mention a few examples, which can provide the impression of what VPH research can achieve. For a more detailed overview, the reader can refer to the recent article on Physiome/VPH research on Biomedical Computation Review [8].

- The Living Human Digital Library Project has created the first multiscale data collection on the skeletal system in the world, and made it available to the research community through the Physiome Space data sharing service [9].
- The AneurIST project developed an integrative approach that for the first time was able to consider all factors that concur to the rupture of a cerebral aneurysm [10].
- Sim-e-Child’s project developed a combination of medical imaging and personalized modelling that makes possible to visualise the blood flow inside the heart over the entire cardiac cycle [11].
- The VPHOP model was able to accurately predict the incidence in the Italian general population of osteoporotic fractures [12].
- A combination of imaging and computer models was also used by the PredictAD researchers to identify and quantify changes in brain that could be used to make early and more accurate diagnosis of the Alzheimer’s disease [13].
- Biologically detailed models of the heart function now promise to provide insights into rare life-threatening disorders. For example, a recent model made predictions of the clinical effects of a rare gene mutation [14]. Some

of the alterations in the electrocardiogram predicted by this computational model of life-threatening genetic *Long-QT Syndrome* were actually first reported in human subject [15] the year *after* the model was published. This is one of the first examples of a computer model predicting the clinical effect of a rare genetic disease before it had been recognized clinically.

7.2. Existing VPH-related cyberinfrastructure

Being the VPH a relatively young initiative, only small number of dedicated cyberinfrastructures existing to date, mostly devoted to the sharing of data, models, or tools.

- Created as an output of the LHDH project, the PhysiomeSpace digital library service provides a free-for-no-profit service for the sharing of large volumes of biomedical research data of all kinds [16]. Currently running as a beta service, it already hosts over dozen of precious data collections for researchers and clinical experts [17].
- The PhysioNet repository makes freely available a large collection of data on physiological signals, such as electrocardiograms, for research purposes [18].
- The CellML repository hosts nearly 500 models of physiological and pathological processes at the cellular or metabolic level, that researchers worldwide can freely download and reuse in their studies [19].
- The Biomodels databases hosts over 600 models of biochemical reactions and other processes relevant for biological research [20].
- The VPH Toolkit hosts a directory of all software tools available for VPH research [21].
- SimTk.org hosts modelling tools and models developed by Simbios, the United States National NIH Center for Biomedical Computing focusing on Physics-based Simulation of Biological Structures [22].
- The National Biomedical Computation Resource [23] develops multi-scale modelling tools and cyberinfrastructure for the biomedical research community with applications to drug development, infectious disease, neuroscience and cardiovascular diseases.
- The e-Infrastructure neuGRID is a virtual imaging laboratory where neuroscientists can carry out computationally intensive experiments on large image datasets of functional and structural scans of brains of patients with Alzheimer's and other neurodegenerative diseases [24]. The international cooperation chapter (outGRID) aims to kick-start interoperability of neuGRID with related infrastructures in North America (LONI in the US and CBRAIN in Canada) [25].

7.3. Early success stories in US-EU cooperation on VPH research

Musculoskeletal diseases

The musculoskeletal apparatus is perhaps the organ system where the need for the integrative approach advocated by the Virtual Physiological Human (VPH) initiative is most pronounced. Neuromotor control involves the entire body, whereas the processes involved in muscle excitation, bone and muscle adaptation, musculoskeletal ageing, and most musculoskeletal diseases take place at the molecular level. What we observe clinically is the emergence of complex bidirectional interactions between these two extreme dimensional scales, and of everything (cells, tissues, organs) in between them. The traditional reductionist approach is reaching dead ends in several important areas of musculoskeletal research, such as those related to osteoporotic fractures, the pathophysiology of growth in cerebral palsy children, the pathogenesis of rheumatoid arthritis and osteoarthritis, etc. It is becoming evident that the path forward is the development of new Information and Communication Technology (ICT) that makes personalised, predictive, and integrative (PPI) musculoskeletal medicine possible.

Worldwide, the two largest research projects that are developing technology for PPI musculoskeletal medicine are the Osteoporotic Virtual Physiological Human (VPHOP) integrated project funded by the European Commission, and the Center for Physics-based Simulation of Biological Structures (SIMBIOS), one of the National Centers for Biomedical Computing (NCBCs) funded by the United States National Institutes of Health. These two projects are targeting the same strategic objective and developing highly complementary technologies. This unique condition creates an compelling opportunity for international collaboration, one which would dramatically increase the international impact of the work being done by the VPHOP project, and foster global cooperation on one of the grand challenges of biomedical research.

With the Neuro Musculo Skeletal Physiome (NMS-Physiome) project, funded by the European Commission as part of the internationalization initiative for VPH Projects, the SIMBIOS and VPHOP consortia intended to establish a more organic and synergistic cooperation. Already in the first year of activity, this collaboration produced already some important results:

- *Integrate the projects' research communities:* each consortium has its own on-line portal, to provide the research community they serve with dissemination, community building, and data management services. SIMBIOS's is called *SimTk.org*, VPHOP's is called *BiomedTown.org*. Thanks to NMS-Physiome the two communities are now interconnected, through mutual membership, cross-dissemination, global search services, etc. Together these two on-line services are supporting the work of over 8000 researchers worldwide.
- *Integrate the projects' tools:* SIMBIOS's OpenSIM is probably the best software for musculoskeletal modeling; VPHOP's NMS-Builder software is capable to elaborate the patients' data into such models. The two tools, both free available for research purposes, are now being fully integrated, so as to provide to laboratory and clinical researchers worldwide a complete workflow for the creation of personalized models of the patient's musculoskeletal system.
- *Integrate the projects' knowledge:* researchers at Stanford University in California and at the Rizzoli Institute in Italy are working together on a new modeling approach that could dramatically improve the way we cope with

patients affected by a number of musculoskeletal diseases and also with various degree of neuromotor disability, which is typical scenario for elder patients.

Cancer-related diseases

Predictive and personalized cancer treatment seems to be the next big opportunity in the fight against cancer, especially since traditional clinical frameworks seems to be reaching their limits. The EU Virtual Physiological Human (VPH) initiative has invested on improving cancer treatment by administering therapy that most closely matches the precise individual circumstances of each individual patient taking also into consideration prediction models. The Interagency Modeling and Analysis Group (IMAG) held an IMAG Futures Meeting [26] on December 15-16, 2009 on the National Institutes of Health (NIH) Campus, discussing the impact of computational modeling. Success cancer multiscale modeling stories includes the BRCAPro and CISNET (cisnet.cancer.gov) models that have made an impact in breast cancer management. Initial evidence both in the EU² and US front, suggest that by changing the manner in which we treat cancer patients, we can maximize the efficiency and efficacy of the therapy and, thereby, reduce both the pain and inconvenience to the patient and the overall cost to the health service.

To achieve this sooner rather than later EU-US collaboration *is mandatory*. A successful collaboration between the Complex Biosystems Modeling Laboratory of the Massachusetts General Hospital (MGH) in the US, and the In Silico Oncology Group (ICCS-NTUA) in the EU, led to the *First Transatlantic Workshop on Multiscale Cancer Modeling* within ICT BIO 2008, co-sponsored by the European Commission and the US National Cancer Institute. The above collaboration has also critically contributed to the formation of the transatlantic TUMOR project funded by the European Commission, linking together EU models (from VPH projects) and US cancer models from the Center for the Development of a Virtual Tumor (CViT)³, in order to better simulate and predict cancer treatment outcome. Also, the HAMAM project (with US partner the Boca Raton Community Hospital), is joining transatlantic forces for more accurate breast cancer diagnosis through integration of biological knowledge, novel imaging modalities, and modeling.

The availability of a plethora of EU-US models and their complementarity in modeling the various scales of cancer phenomena (from molecular to tissue level), allowed the TUMOR partners to develop more complex, and biologically accurate, predictive oncology clinical scenarios which are currently being validated. This successful collaboration strongly indicates that EU-US synergies can drive much faster the developmental milestones needed for clinically translating models and transforming them into powerful treatment optimization technology on the clinical setting.

Another successful dimension that emanated from TUMOR is that the EU-US patient data sharing has been addressed. For the time being, due to the harsh legislation

² ContraCancrum has developed models that integrate a broad range of data to define the most appropriate treatment, and to predict the patient's likely response to it, in the context of dedicated clinical studies related to brain and lung cancer patients at the University of Saarland Hospital. Similarly, the IMPACT project is developing a multiscale infrastructure for predicting the Radiofrequency Ablation (RFA) incurred lesion for treating cancer in minimally invasive fashion and increasing the survival of patients. The NeoMARK projects deals with ICT enabled prediction of cancer reoccurrence.

³ <https://www.cvit.org> (is administratively located at Massachusetts General Hospital supported by the NIH-National Cancer Institute.

in both sides of the Atlantic data need to be stored locally in the EU or US hospital, while tools and models will be exchanged and shared instead, in order to run the joint workflows and avoid legal and ethical complications. This solution has however significant implications for the infrastructure that has to be developed and TUMOR has initiated work on analyzing the EU-US legal and ethical regulations and identifying possible ways to overcome the many difficulties in harmonizing such regulations. This effort will be even more pronounced in a new EC project called p-medicine.

Cardiovascular diseases

Biophysically and anatomically based cell-organ level modelling has recently shown to have a great impact in cardiovascular applications.

An example of an EU FP6 funded project which worked in this direction is Health-e-Child (HeC, www.health-e-child.org). HeC delivered a platform for paediatrics, leveraging distributed computing resources federated in a so-called “grid”. Using this platform, clinicians are able to run computing intensive tools such as the CaseReasoner, a flexible and interactive decision support system, allowing to simultaneously filter data and look for similarities across populations of patients, and CardioViz which enables the rapid personalisation of the patient’s heart specificities, allowing doctors to simulate the effects of heart surgery and overall cardiovascular function over time.

Worth noting as well, the EU FP7 euHeart project (www.euheart.eu) has been developing patient-specific cardiac models combined with anatomical and functional pre-operative data to assess the negative or non-response to the implantation of a pacemaker as part of Cardiac Resynchronisation Therapy. From the clinical point of view, euHeart’s mechanical and electrophysiological cellular models, coupled with tissue activation and finite deformation mechanics allow for in-silico tests of different device settings (e.g. number and position of leads, chamber delays).

In the US, in parallel to these EU VPH initiatives, the Johns Hopkins University’s Centre for Cardiovascular Bioinformatics and Modelling (www.ccbm.jhu.edu) has been developing new methods for the representation, storage, analysis and modelling of biological data, and to use such quantitative approaches to better understand healthy and diseased cardiovascular function. The National Biomedical Computation Resource (www.nbcn.net), the National Center for Biomedical Computation at Stanford (simbios.stanford.edu), and the Center for Integrative Biomedical Computing (<http://www.sci.utah.edu/cibc>) all have major software development, modelling and data dissemination activities in cardiac and vascular physiome research that involve numerous international partners including investigators in the UK, Norway, Germany, Italy, France, Belgium and the Netherlands, most of who also participate in the VPH project. At the time of writing, FDA’s Division of Cardiovascular Devices is leading four projects leveraging on simulation-based engineering and medical imaging technologies, using computer modelling and image processing techniques to enhance the regulatory review process of cardiovascular devices and to shed light on the biomechanical environment of the heart.

Funded through an EU FP7 call specifically designed to internationalise European VPH research, Sim-e-Child (SeC) is developing the first grid-enabled trans-Atlantic platform for large-scale simulations in paediatric cardiology, offering an online collaborative environment for the construction and validation of multi-scale personalised simulations of a growing heart and vessels. Thanks to this EU-US collaboration, SeC is bringing forward HeC’s promising anatomical and physiological models. Three of SeC’s most advanced research areas are:

- SeC/HeC heart modelling capabilities being validated on an FDA clinical trial database (i.e. the Coarctation Of the Aorta Stent Trial [COAST] by the Johns Hopkins University hospital, in collaboration with the American College of Cardiology, and on newly collected independent MR data at Johns Hopkins and Bambino Gesù hospital in Rome,
- Based on high-quality models of patient-specific geometry and dynamics, SeC's "Cardiac Hemodynamics Computation" tool being developed to simulate and analyze the blood hemodynamics within a child's heart and the ascending aorta and aortic arch,
- SciPort, an online facility for sharing scientific experiments, providing users with a multi-site, Web-accessible database of SeC's paediatric cardiology data, information and knowledge for translational research and to support the definition, execution and sharing of scientific cardiac modelling and simulations.

Thanks to its enabling trans-Atlantic cooperation, SeC's goal is to ultimately provide clinicians with a model-driven decision support system capable of better personalising congenital aortic disease treatment and assessing when to intervene on patients.

8. Lessons learned and needs for future actions

We have learned a number of lessons from these early experiences. In the following they are briefly summarised.

Simple and easy-to-adopt standards: each part of the VPH cyberinfrastructure currently stores and communicates data, information, and models with different computer formats, many of which are used only in that single service. To create a global VPH cyberinfrastructure we need to establish a set of standardised formats to store and communicate data, information, and models. The problem is only partially in the definition of such standards, which for good part already exist, but rather in their widespread adoption, which involves simple standards, with adequate support to make their adoption easy. The process must be both bottom-up and top-down, with *de facto* standards being progressively experimented in single services and then adopted over the whole cyberinfrastructure once they are proved effective, but also with minimal set of globally adopted standards defined centrally, and adopted by all services.

Quality Assurance and Validation: as emphasized in the accompanying report on Semantic Interoperability, well-structured and consensus-based ontologies, minimal information standards and validation protocols are critical pre-requisites for quality assurance in complex integrative computer modelling applications, where the model assumptions, theoretical formulations, data sources, and numerical methods all affect the validity and reliability of the model outcomes and in a manner that is usually specific to the context and application of the particular analysis.

Outreach and community building as the base for the success of a global endeavour: the human factor is of vital importance in fostering any large scale collective initiative, and the development of a world-wide VPH cyberinfrastructure is not an exception. Community building, social networking, mechanisms for peer recognition and career development, are all necessary elements of such endeavour.

Opportunistic governance, excellence in technology: the development and the deployment of the VPH cyberinfrastructure must be driven by an opportunistic governance, that foster the development in those directions that are most rewarding for our community of users, and that produce the biggest impact in research and clinical practice. It must also consider the development of the commercial and industrial dimensions, essential to the long-term sustainability. On the other hand, this should not impair the pursuing of technological excellence. The VPH cyberinfrastructure is and will be one of the most advanced research infrastructures available, from a technological point of view. This will drive the excellence also on the application side, and will create interesting fall-down onto industrial segments other than healthcare.

Maintenance, transform research prototypes into consolidated resources: the majority of the components available are currently at the stage of research prototypes. To transform them into consolidated resources that compose the VPH cyberinfrastructure will require a considerable amount of work for curation, deployment, standardisation and interoperability, etc. And of course, once established these services must be operated indefinitely, until such service is found useful and valuable by the community.

Outreach: promote and monitor adoption, provide training and support: the effective use of a global VPH infrastructure pass also by an aggressive outreach activity, which promotes the effective use of the available resources and services, and where necessary provides also training and user-support. In parallel we also need to monitor the adoption, understand the “customer satisfaction”, the new needs, etc.

A global VPH cyberinfrastructure policy: the VPH cyberinfrastructure will express its full potential only if we design it as a global, worldwide cyberinfrastructure, to which every country can access and contribute. This requires a clever governance model, which favour de-centralisation of resources and activities, and requires only a minimal centrally coordinated effort. Particularly important here is the integration into the VPH cyberinfrastructure of the clinical data, an aspect that poses some problems, but also opens up very interesting scenarios.

9. Recommendations

9.1. Cyberinfrastructure for VPH Research

This vision of a personalized, predictive, and holistic medicine will become a reality only when a comprehensive framework of methods and technologies for analyzing organisms as integrated systems has been developed. In the EU, this

framework has been sponsored by the European Commission's Seventh Framework Programme and named the *Virtual Physiological Human*. In the USA and Canada, there is no similar coordinated large-scale effort, but similar goals have been articulated in a variety of publications and venues, notably the Multi-Scale Modeling (MSM) consortium of investigators supported by the 12 participating agencies of the Interagency Modeling and Analysis Group (IMAG).

The investments that many European and United States funding agencies are making in this direction are transforming what was formerly the dream of a handful of visionaries into a reality, which is starting to bear fruit. But as the vision of a whole new generation of methods and technologies that enable integrative biomedical research becomes more concrete, concern is also rising in the research community worldwide for the long-term support and viability of a cyberinfrastructure consisting of new tools, services, and data collections that will be needed for the widespread adoption of integrative approaches within the existing research infrastructure.

While the mechanisms exist to maintain the infrastructures already available for biomedical research worldwide, the concern is that the revolutionary nature of the **VPH cyberinfrastructure** will require special policies to its long-term sustainability.

In particular three aspects appear of fundamental relevance: *maintenance*, *service*, and *outreach*.

- **Maintenance**: we need to transform the research prototypes developed in the various research projects into consolidated resources, through a process of re-engineering, consolidation, standardization, and maintenance. Such activities cannot be supported with the funding mechanisms available from most funding agencies, though there are isolated programs supported by NIH and other agencies for maintaining specific software and data resources. And recently the United States NSF has recognized this problem through its establishment of the Scientific Software Innovation Institutes [27]. By their nature, in order to be effective there should also be strong international collaboration in these projects; and similar initiatives should be created also in Europe.
- **Service**: we need to deploy these consolidated technologies into services that are operated and curated in ways that ensure their persistence, reliability, security, etc. This is an essential requirement if we want the vision of integrative biomedical research, with all its advantages, to percolate deeply into the worldwide practice of research, and into its most relevant clinical applications.
- **Outreach**: motivated organizations must be established and supported not only to operate these services, but also to promote an outreach campaign that: a) ensures the widest possible adoption and utilization of the computational model based research technologies; b) provides training and re-training to researchers and medical professionals in these technologies and methodologies, to ensure their most effective and appropriate usage; and c) monitors the development and the adoption of information and computational modelling technologies in research and healthcare, providing decision-makers with factual and up-to-date evidence on which to base policy decisions and to communicate the impact of investments made in this domain.

9.2. The role of the VPH Cyberinfrastructure in biomedical research

The contribution that such a cyberinfrastructure can make for research is already quite clear. Biomedical research in most of its branches and articulations is progressing towards comprehensive digitization of experimental observations and the associated information; this will make it possible to share with our peers not only the conclusions we draw from such observations, but also the raw data themselves. By speeding up the circulation of data, we can expect a better peer-reviewing process, and the reuse of experimental data in new contexts and applications, reducing the costs of research. This process is already under way.

But the VPH vision goes much beyond this. With predictive models it is possible to capture in a digital and reusable form the knowledge we produce as scientists. A global cyberinfrastructure where such models can be accessed, used to elaborate other data, and combined to form a holistic understanding of complex processes could be a real breakthrough for biomedical research.

Once available through the VPH cyberinfrastructure, reusable models can be combined to describe processes that involve more than one function of the body, at different scales from the whole body down to the atoms. Owing to the specialization of biomedical research, it is a rare expert in cardiovascular biology that is also well versed in neuroscience or orthopaedics for example, despite the critical interactions between these systems. So it should not be a surprise to find out that the vascularisation of the bones tissue, in spite of being a vital process both in physiological and pathological conditions, has been poorly investigated to date.

But it is probably the last point that is the most exciting of all. There is increasingly strong evidence that biological processes are characterized by unexpectedly complex upward and downward causations that link processes and events that occur at radically different space-times scales, across sub-systems, and involving different bodies of knowledge. In some cases, it is now clear that what we observe is the emergence of the systemic interaction of a complex system; this means that studying any part of the process will never fully explain the observations we make. This realization is also driving the “omic” approach to personalized medicine. Only by studying the system, made of all its parts, will we be able to obtain good explanations of what we observe.

But how can this vision of an integrative biomedical research be done in practice? The VPH cyberinfrastructure will help make it possible to curate accurate models of each part of the system, store it in a digital artefact, share it electronically, so as to allow the combination of these parts into *integrative models* capable of explaining complex systemic interactions, which might be otherwise defy intuitive explanation.

9.3. The role of the VPH Cyberinfrastructure in clinical practice

The VPH cyberinfrastructure will impact clinical practice in two ways. The first is *clinical decision support*, where Internet-based services based on fully validated integrative models will be used by properly trained clinical users to integrate the data and information available on the patient with the existing knowledge relevant to the clinical problem. Such knowledge is captured in the integrative model, so as to provide support and assistance during prevention, diagnosis, prognosis, treatment planning and execution, monitoring, and rehabilitation. Already today, VPH models are being used

to help identify responders to cardiac resynchronization therapy and make it a more cost-effective repeatable and reliable treatment for patients with dyssynchronous heart failure. Similar results are being reported in pre-clinical or early clinical trials in other domains such as treatment planning in acute myocardial infarction, diagnosis of the risk of fracture in osteoporosis, model-guided ablation of liver tumours, etc.

A second way through which the VPH cyberinfrastructure promises to impact clinical practice is *via* the biomedical therapeutics industries. The large-scale availability of data and models about human physiology and pathology will make it easier to conduct preliminary investigations on the safety and the efficacy of new medical devices with computers, in order to reduce risks and costs associated with clinical trials. VPH models will also make it easier to test whether modifications to existing therapies might produce unintended consequences, thus improving patient's safety. In pharmacology, molecular and cellular modelling are transforming drug discovery. For example, one of the EU VPH projects, PreDICT, is developing computer simulations to assess the risk of cardio-toxicity for new compounds. As the VPH cyberinfrastructure develops, it will become easier and more effective for regulatory authorities to verify that the pre-requisite conditions exist to start new clinical trials, through the availability of standard simulation benchmarks that all products of a given category must pass. Scenarios are also emerging where medical technologies for diagnosis, planning, or treatment are augmented with VPH models that can transform patient data into predictions of the natural history of disease, treatment outcomes, and prognosis. There is now also considerable penetration of population-based modelling in developing clinical guidelines, healthcare policies and designing clinical trials [28].

9.4. Impact of the VPH cyberinfrastructure on eHealth at large

Interoperability, standardisation, and certification

The VPH cyberinfrastructure will have to enable the integration of disparate biomedical data, information, and knowledge, including those contained in current hospital information systems. This is why the VPH initiative aims to follow closely the efforts at standardization and interoperability of the information contained in electronic health records (EHR). Furthermore, given the VPH initiative's definition of health to encompass environmental and lifestyle factors, interoperability efforts must be extended to also include data from personal health systems (PHS), personal health records (PHR), and, eventually, from databases mapping environmental/ecological variables with health variables.

Semantic interoperability requires the use of standards that will enable the clinical content of the EHR to be interpreted consistently across different EHR regimes. Accurate and complete clinical documentation and interoperability between systems require widespread and dependable access to published and maintained collections of coherent and quality-assured semantic resources, including for example models such as archetypes and templates that provide clinical context, mapped to interoperability standards for EHR and PHR and biomedical data, linked to well specified terminology value sets, derived from high quality ontologies.

The VPH is already now discussing the technical and semantic interoperability of types of data and information that may soon become part of mainstream healthcare, and thus part of EHRs; the work VPH delivers should provide a useful starting point for

any extension effort by the electronic health record standardization bodies and organisations, and other eHealth stakeholders.

Promotion of continuous innovation through impact assessment

The EU-US MoU on Health Related Information and Communication Technologies calls for a framework that articulates how health-related ICT support does and can potentially improve health, i.e. the assessment of the economic benefits of eHealth. In the same way, the VPH cyberinfrastructure will employ means and expertise to guide the promotion of continuous innovation through impact assessment and the measuring of its adoption, usage, and benefits. To monitor and guide the development, implementation, and success of the VPH cyberinfrastructure, it is necessary to measure the diffusion and usage of its services and applications across health service actors and across the research communities. At the level of any member state or regional health system, this necessitates a clear understanding of the role of measurements, indicators and benchmarking in policy and their appraisal for policy making – for research, innovation, health, and social care policy planning.

Measuring and assessing benefits for policy making

In many contexts, health technology assessment (HTA) has become the preferred approach for policymakers to base decisions on health technology investments and reimbursement policies on factual evidence, gained as independently as possible from the many biases that tend to revolve around the introduction of a new health technology.

On the problem of measuring the adoption, usage, and benefits of eHealth technologies, the contribution of the VPH initiative will be primarily related to the development of new HTA approaches, with the VPH cyberinfrastructure contributing to benchmarking performances. Both do not have to begin only after the technology will have been fully deployed, but before, when the technology is in the research and development phase. This will help steering public and private research investments towards those approaches that show the highest potential for efficacy and other benefits. This implies new challenges for benefits assessment and requires new approaches and methods to be defined and identified. There is a need for a more dynamic approach to impact assessment of medical technologies, and in particular of VPH-based technology and cyberinfrastructure.

The assessment of benefits arises directly from the effective use of ICT (“meaningful use”). Such socio-economic evaluations of the impact VPH technologies and the cyberinfrastructure will have on research, clinical, and industrial domains can offer significant advice and support to health policy decision-makers. A major reason for the relatively slow progress in eHealth deployment is the lack of awareness of robust empirical evidence on benefits, which in turn could feed into sustainable business cases, driving economic activity and boosting the diffusion of innovation. VPH fully understands that there is a need to disseminate existing best practices and the associated benefits as well as to examine existing methodologies of economic assessment. There is a need to propose common approaches to proving benefits of interoperable solutions and infrastructures using coherent and quantitative (scientific) methods.

Benchmarking adoption and usage for the monitoring of policy impact

For the VPH cyberinfrastructure to deliver the expected benefits, from a regulatory aspect, two policies are required: policies to foster actual deployment (including

investments, improvement of interoperability, reducing legal and other barriers) and policies to monitor policy impact itself. For this monitoring, measures of deployment, diffusion, usage and the effectiveness of current and future take-up are needed, typically realised through benchmarking.

The evaluation of the VPH cyberinfrastructure developments and outputs through benchmarking can take place along dimensions like:

- accessibility and usability for simulation and modelling efforts;
- accessibility and ability to interface with other infrastructures (resources, tools and methods);
- potential interfaces to and integration with EHR and PHR systems;
- perceived and experienced benefits by type of user;
- facilitation of virtual collaborations between members with different expertise;
- uptake and acceleration of model development and integration.

In more concrete terms, the particular success of the VPH cyberinfrastructure can be directly benchmarked by monitoring these levels of supply and demand:

- The number of sites, portals, and services that share as digital artefacts data, information, and knowledge captured into models, concurring the global VPH cyberinfrastructure, as well the number of artefacts that the cyberinfrastructure deploys;
- The number of users of the artefacts the VPH cyberinfrastructure distributes, and their number of accesses, clustered by research, clinical and industrial applications.

Indirectly, the VPH Cyberinfrastructure can be benchmarked by measuring the impact the VPH initiative will have on research, clinical, and industrial domains through the following indicators:

- The number of international peer-reviewed publications targeting biomedical researches where VPH-related technologies were used to unravel relevant research questions. This indicator quantifies the impact of the VPH vision onto biomedical research at large.
- The number and size of clinical trials that aim to evaluate the clinical accuracy, clinical efficacy, and clinical impact of VPH-related technologies and services. This indicator quantifies the rate of translation of VPH-derived technologies to clinical practice.
- The number and size of VPH-based medical technology products and services that enter the market. This indicator quantifies the level of adoption of VPH-based technologies in clinical practice.

9.5. The role of the VPH Cyberinfrastructure in Pharmaceutical Discovery and Medical Device Development

There is near-term potential for integrative physiological modeling to accelerate device and drug development and facilitate regulatory approvals. In the US and Europe,

companies such as Entelos are already proving integrative modeling tools and services to these industries. The US FDA has shown interest in the role of computational modeling for improving the development and regulatory assessment of implanted devices and organizes an annual meeting on the topic of modeling cardiovascular devices and their interaction with the circulatory system *in vivo*. Models have significant potential to support filings for regulatory approvals by permitting a larger range of conditions to be investigated than can be studied experimentally and by facilitating the integration of reconciliation of diverse data from pre-clinical bench and animal testing and clinical trials. The challenge for regulatory agencies will be to find ways to encourage the adoption of integrative modeling by the device and pharmaceutical industries without compromising competitiveness with mandates that single corporations will not have the in-house infrastructure to meet. The proposed VPH Cyberinfrastructure could help regulators to address this challenge.

In drug development, the pharmaceutical industry has long recognized the role of pharmacokinetic (PK) modeling (“simulating what the body does to the drug”) and pharmacodynamics (PD) modeling (“simulating what the drug does to the body”). Consider, for example, the kinetic distribution of a drug or toxic compound throughout the body. Understanding and predicting drug distribution is a critical part of the decision making process in therapeutics. The pharmacokinetics observed in a rat, for example, will not exactly mimic that observed in a human. Nor will the kinetics observed on one human necessarily parallel that in another. However, if the underlying processes governing the pharmacokinetics in a mammalian system can be captured in a physiologically-based model, then that model can be readily scaled accounting for differences in organ and tissue masses, relative proportions of fat, and relative blood flows, to make predictions for one specific species (or individual) based on measurements in another.

Pharmacokinetics represents one of many potential applications using computational simulation as a tool for translation. A common infrastructure (of ontologies, data standards, model standards) is needed to facilitate this translational potential. Such an infrastructure will open the door to: sharing data and applications between clinical and basic research domains, to multiple parallel approaches to integrating and probing patient data, and to making connections between basic research and clinical applications.

9.6. The role of the VPH Cyberinfrastructure in environmental regulation

There is a pressing need for reliable biological models to assist in the regulation of industrial chemicals. Both the EU and the US have large ongoing efforts in developing computational models to assist non-medical regulatory decision making processes. As these aspects do not directly relate to a specific disease, or a specific medical treatment, the community of practice behind environmental research and regulatory affairs is largely distinct from that involved with eHealth. However, both contexts require a VPH Cyberinfrastructure; it would be unfortunate if two incompatible infrastructures were developed for these two related domains, missing the considerable synergies that the application of VPH technologies could provide in common areas such as research or regulatory affairs.

9.7. The role of the VPH Cyberinfrastructure in personal health services

On the horizon of health policies is appearing, in relation to multiple socio-economic challenges such as prevention, chronic diseases, or active and health ageing, a completely new scenario where the citizen/patient becomes a prime actor in the collection and management of information about his/her health. This involves the collection of personal health data (personal health systems) and the management of health information (personal health record). In this context the global VPH Cyberinfrastructure could provide two essential services:

- Integration and dynamic exchange of key information between the personal health record and the clinical health information systems, both electronic health record and clinical research databases;
- Provision of *Personal Health Forecasters* [29], services that constantly process personal health data to predict health risks, the appearance of specific conditions, or simply advise the patient on specific lifestyle aspects.

9.8. Benchmarking

The success of the VPH cyberinfrastructure can be directly benchmarked by monitoring the levels of offer and demand:

- The number of sites, portals, and services that share as digital artefacts data, information, and knowledge captured into models, concurring the global VPH cyberinfrastructure, as well the number of artefacts that the cyberinfrastructure deploys;
- The number of users of the artefacts the VPH cyberinfrastructure distributes, and their number of accesses, clustered by research, clinical and industrial applications.

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9.9. Governance model

The distributed, international, loosely coupled nature of the VPH Cyberinfrastructure recalls a famous sibling: the Internet. The network of the networks has a governance model that has been revised and adjusted over the years, while enabling the Internet to grow rapidly and flourish beyond all expectation. With this inspiration, we propose the following governance steps:

1) Establish a permanent Observatory on eHealth:

A first step toward the creation of a worldwide VPH Cyberinfrastructure could be the transformation of the ARGOS Transatlantic Observatory for Meeting Global Health Policy Challenges through ICT-Enabled Solutions into a permanent body. For what matters the VPH part of ARGOS this is already happening. The recently established VPH Institute has already announced that within 2011 will be established a permanent international observatory on the VPH initiative, hosted by the VPH Institute, and formed by representatives of relevant worldwide scientific societies, of public agencies funding VPH-related research, and of clinical, industrial, and societal stakeholders.

2) Establish a Multistakeholder Advisory Group (VPH/MAG) to:

- Constantly review the goals of the Cyberinfrastructure;
- Promote the development of standards for interoperability and integrability;
- Maintain a worldwide research roadmap;
- Develop regulatory guidelines and processes in cooperation with regulatory bodies.

Such an advisory group could be established at the very beginning of the initiative. Its structure would include a master board where all stakeholders are properly represented, and a series of work groups, much like the Internet Engineering Task Force, that would produce technical recommendations and specifications related to the operations of the VPH Cyberinfrastructure.

3) Establish a globally distributed cyberinfrastructure:

- Whose backbone is operated by a private not-for-profit organization;
- Whose leafs are voluntarily interconnected cyberinfrastructures operated at regional, state, and/or federal levels.

Essentially, we propose to minimize the role of the centralized authority, delegating this role to a private non-profit organization, designed on the model of the Internet Corporation for Assigned Names and Numbers (ICANN), that would be responsible to ensure through training, certification, and auditing services that all peripheral nodes of the VPH Cyberinfrastructure correctly comply with the agreed interoperability standards, and provide the global integration level services such as management of the VPH cyberinfrastructure main portal, and global services such as ID management, directory, namespaces resolution, etc. Most of the work would be

done by the peripheral nodes, which would be operated, governed and funded autonomously by the various local authorities.

4) Commit the financial support

We expect that government agencies may initially need to provide financial support for the Cyberinfrastructure, though much of this support might be provided in kind by allocating existing staff and infrastructures, where reorganization plans de-allocate some of them from other mission (i.e. the re-organization of HPC centers that is happening in many countries in relation to the changes in the demand of high-performance computing). However, we also feel that because of the research efficiencies and high translational potential for this research, the Cyberinfrastructure should eventually derive most of its financing from the pharmaceutical, medical device and healthcare industries that benefit from its deployment.

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