The Virtual Physiological Human — A European Initiative for in silico Human Modelling —

Marco VICECONTI1, Gordon CLAPWORTHY2, and Serge VAN SINT JAN3
1Laboratorio di Tecnologia Medica, Istituto Ortopedico Rizzoli, Italy; 2Centre for Computer Graphics & Visualisation, University of Bedfordshire, UK; and 3Laboratory of Anatomy, Biomechanics and Organogenesis, Université Libre de Bruxelles, Belgium

Abstract: The Virtual Physiological Human (VPH) is an initiative, strongly supported by the European Commission (EC), that seeks to develop an integrated model of human physiology at multiple scales from the whole body through the organ, tissue, cell and molecular levels to the genomic level. VPH had its beginnings in 2005 with informal discussions amongst like-minded scientists, which led to the STEP project, a Coordination Action funded by the EC that began in early 2006. The STEP project greatly accelerated the progress of the VPH and proved to be a catalyst for wide-ranging discussions within Europe and for outreach activities designed to develop a broad international approach to the huge scientific and technological challenges involved in this area. This paper provides an overview of the VPH and the developments it has engendered in the rapidly expanding worldwide activities associated with the physiome. It then uses one particular project, the Living Human Project, to illustrate the type of advances that are taking place to further the aims of the VPH and similar initiatives worldwide.

Key words: Virtual Physiological Human, physiome, Integrative Research, musculoskeletal system, multiscale modelling.

1. The genesis of the VPH concept
In June 2005, a group of European researchers met in Barcelona to discuss a broad European approach to the development of physiome research. As a result, the concept of the Virtual Physiological Human (VPH) [1] was created. This was projected to be “a methodological and technological framework that, once established, will enable the investigation of the human body as a single complex system.” The workshop participants also agreed on the necessity for the associated activities to be coordinated at a European level.

In parallel, and independently, a consortium composed of the leaders of the most relevant physiome-related research projects in Europe had developed a proposal for a Coordination Action, strongly aligned with the ideas supporting the VPH. This consortium consisted of the following members:
• Renal Physiome Project — Centre National de la Recherche Scientifique (CNRS), France
• Giome Project — University of Aalborg, Denmark
• Epitheliome Project — University of Sheffield, UK
• Living Human Project (LHP) — Istituto Ortopedico Rizzoli (IOR), Italy; Université Libre de Bruxelles (ULB), Belgium; University of Bedfordshire, UK
• Cardiome Project — University of Oxford, UK
• Physiological Flow Network (PFN) — University of Nottingham and University of Sheffield, UK

The proposal was submitted in March 2005, and the resulting project, “STEP: a Strategy for The EuroPhysiome,” began in January 2006, funded by the European Commission (EC). Thus, the EuroPhysiome initiative was born.

STEP was coordinated by the two authors of this paper. In addition to the institutions listed above, it also included University College London (UCL), which, with the University of Bedfordshire, provided expertise in Information and Communication Technologies (ICT) for physiome research.

STEP was an incredible success [2–4]. In less than two years, the action catalysed the active participation of more than 300 experts from around the world — from academia, industry, clinical practice, and society at large — who worked within a complex consensus process towards the development of the VPH Research Roadmap [5]. The Biomed Town [6] Internet community that was created to provide support for these activities has a membership that recently passed 1,000 members. STEP also initiated an international collaboration programme, which recently culminated in the World Integrative Research Initiative (WIRI) [7].

2. The VPH Research Roadmap
The objective of STEP was to consider and recommend effective strategies to promote the VPH and to
provide a blueprint for its future development. Its deliberations were published in spring 2007 in the advisory document “Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human” [5], mentioned above. This was designed to advise the EC with respect to future VPH development and was to have particular relevance to the provision of funding to support ongoing research activities. The underlying emphasis that emerged was that the VPH is a technological framework that aims to be descriptive, integrative and predictive:

— Descriptive: the framework should allow observations made in laboratories, in hospitals and in the field — at a variety of locations situated anywhere in the world — to be collected, catalogued, organised, shared and combined in any possible way

— Integrative: the framework should enable experts to analyse these observations collaboratively, and to develop systemic hypotheses that incorporate the knowledge of multiple scientific disciplines

— Predictive: the framework should facilitate the interconnection of predictive models defined at different scales, with different methods, and with different levels of detail, producing systemic networks that breathe life into systemic hypotheses; simultaneously, the framework should enable their validity to be verified by comparison with other clinical or laboratory observations.

The VPH roadmap opens by suggesting an appropriate scope for the VPH and providing justification and motivation for its existence, based on foreseen needs (research, clinical and industrial). An international perspective provides the context to this, supported by a series of case studies.

The importance of a suitable structure for the proposed VPH is underlined by an identification of the challenges associated with its implementation, which are broadly categorised as challenges in science, in description, in integration and in IT, and ultimately in the solution of these challenges. The IT challenges are formidable, bearing in mind the volume of the data flows involved (petabytes), but carefully evaluated case studies focusing on research, clinical, industrial and societal impacts clearly demonstrate the benefits to be gained by providing suitable infrastructure support for EuroPhysiome activity [3]. Other sections in the roadmap are concerned with exploitation, dissemination and sustainability, and include a consideration of the many political aspects associated with ethical, legal and gender issues. The final chapter recommends actions necessary to secure the future of the VPH.

More than 1,500 copies of the roadmap were printed and they were distributed in June 2007 to a long list of academic, industrial, clinical, and societal stakeholders, including all key political figures in Europe both at the national and supranational levels. Another print run was completed later in 2008 to meet further demand.

Despite the short time since publication, some of the concepts voiced in the VPH roadmap are already emerging in the funding strategy of various agencies. In particular, in late 2007, the ICT for Health Unit of the EC launched a call for proposals worth 76 million euros for research projects aimed at developing the ICT required to support VPH development. The first projects to emerge from this call commenced in late 2008.

3. The WIRI agreement

STEP was also seminal in instigating a more structured and coherent international vision for physiome work. Early agreements were established with LHDL (Living Human Digital Library), the Chinese Virtual Mechanical Human project (VMHC), the Physiome project of the International Union of Physiological Sciences (IUPS), which is coordinated from New Zealand, the Japanese Centre of Excellence (COE) of in silico medicine, the American NSR (National Simulation Resource) Physiome and SIMBIO5 projects, and others.

These projects have agreed that a paradigm shift is necessary in the way in which biomedical research is carried out. The scale of the problems to be tackled implies that rapid progress can be made only if we work at a truly international level. Laboratory and clinical observations should be accumulated systematically and made accessible to all who can use them to develop, or to validate, new hypotheses. Knowledge that we have on a subsystem or a certain biophysical aspect at a particular dimensional scale should be formalised in a way that makes it possible to interconnect it with results from other researchers who are working on contiguous subsystems, scales and domains, and such interconnection should be actively pursued. This group has adopted the term “Integrative Biomedical Research” to describe the new approach.

These organisations have also agreed to foster, by all available means, international collaboration aimed at promoting the development of Integrative Research in biomedicine by pursuing collectively, or independently, the following common goals:

— Common Objectives
  • call the same things by the same name: consensus on definitions
  • define and constantly revise the goals of the Integrative Research Initiative
  • develop descriptions of the expected results, and of their impact on the life of humanity

— Research Challenges
  • promote consensus over the grand challenges posed by Integrative Research
  • suggest research and technological development objectives considered essential for success of the Integrative Research Initiative

— Resources Required
  • maintain an Integrative Research Investment Moni-
tor that lists all Integrative Research projects and the relevant resources invested in them
- develop a lobbying strategy that will allow the WIRI to support Integrative Research within public and private grant agencies
- start a collective open source software project for supporting this Integrative Research Initiative
- promote studies on long-term sustainability and related business models
- Ethical, Legal and Gender Issues
- maintain the GLE (Gender-Legal-Ethical) observatory to monitor legal barriers to the development of Integrative Research
- Interoperability
- develop standards that encourage the federation of digital libraries and repositories relevant to the Integrative Research Initiative
- create a central repository of software tools to document all software that might be useful for an Integrative Research project
- develop, maintain and harmonise semantic representations of the Integrative Research knowledge space
- Community Building
- create a single web site or a federated portal that can provide a single entry point for the whole Integrative Research community
- promote Integrative Research with a top-down approach by ensuring that each major scientific society has an Integrative Research panel (this includes IEEE, IUPS, ASME, IFMBE, EAMBES and others)
- promote Integrative Research with a bottom-up approach by encouraging initiatives aimed at fostering the creation of new Integrative Research projects and the idea of team science in biomedical research
- publish Integrative Research News, a monthly electronic newsletter
- promote initiatives that will establish a sense of community, such as logos and T-shirts
- run the World Integrative Research Conference and other similar events.

To date, the WIRI Agreement has been signed by STEP, LHDL, @neurIST, SIMBIOS, NSR Physiome, IUPS Physiome and VMHC, and the approval of the recently established Japanese COE is in progress. The initiative is open to all projects willing to support these objectives and scopes.

4. VPH: Early developments

Several VPH projects are now running in Europe. Among them, we can mention some organised by the original partners of the STEP action, such as SAPHIR [8], which is aimed at the integration of renal, cardiac and respiratory functions; GIOME [9], which is undertaking integrative modelling of physiological and pathophysiological processes in the gastrointestinal tract; and PFN [10], which is promoting interactions between experts in the field of physiological flow modelling.

Two important projects funded by the EC in the Framework 6 Programme are @neurIST [11] and LHDL [12]. @neurIST will provide the clinicians with an integrated decision-support system to assess the risk of aneurysm rupture in patients and to optimise their subsequent treatment [13]. LHDL is a collection of Internet services and software applications that should make it possible for the research community involved with the biomechanical modelling of the musculoskeletal system to work collaboratively by sharing data sets, models and any other digital artefact that may be useful in the process. As illustration, we provide below further details of LHDL and the broader context within which it resides, because the authors are heavily involved in it.

5. The Living Human Project

As mentioned in Section 1, LHP was one of the original projects from which STEP was formed. It is developing a worldwide distributed repository of anatomo-functional data and of simulation algorithms, fully integrated into a seamless simulation environment and directly accessible by any researcher in the world. It should be emphasised that LHP has a highly inclusive philosophy, and it is not necessary to be a formal member of an LHP-related project to become involved with, or contribute to, the LHP.

At present, the LHP infrastructure is being used to begin to create the physiome of the human musculoskeletal system, though it could also be used more widely.

Current LHP activities are mostly concentrated within the LHDL project, which commenced in February 2006 and will run until January 2009. LHDL is developing two supportive technologies (LhpBuilder and LhpRepository) and conducting a large-scale data collection and modelling exercise. Now that this technology is becoming available for broader use, however, it will be adopted also in several other projects that are about to begin.

5.1. LhpBuilder. The LhpBuilder (Fig. 1) is a software tool to import, fuse, and store within the digital library almost any type of biomedical data, including medical images in DICOM format, gait analysis data and finite element analysis results. It was developed using the Multimod Application Framework [14].

LhpBuilder exposes all of the capabilities previously found in the Multimod Data Manager [15, 16], but it has been further extended and empowered. By using it, any researcher contributing to the LHP (not necessarily a member of the LHDL consortium) can import the data he/she has collected, can register and synchronise them, can process them to extract relevant features and parameters, and can use the resulting data to generate predictive models whose results can be also integrated into the same collection of data resources. Once the work is completed, the researcher will be able to use the LhpRepository to share all these data and models with any other LHP researcher.
without the need for any additional software or hardware. In this way, it is possible to aggregate large data collections (preexisting or newly captured) and provide a uniform way of accessing them.

5.2. LhpRepository. The LhpRepository service (Fig. 2) will be made accessible via Biomed Town. The user will be able to upload any data resource directly from inside LhpBuilder to a sandbox, in which the resources can be stored and managed. Each resource will also be annotated with a comprehensive set of metadata organised according to the LHP Resources Ontology. The use of these metadata will make it possible to search the digital library for resources created at a certain time, or of a certain digital type, or that provide certain anatomical or biomechanical information, and so on; as such they form a critical feature of the data. Once a resource is fully annotated, the owner will be able to publish it, and also to define the access rights — who can download that resource and under what conditions.

Users will be able to search all of the published resources via their metadata and to download those for which they have access. This will allow the same infrastructure to be used for both public sharing and consortium-reserved sharing.

5.3. Large-scale data collection and modelling. At partner institution ULB, two cadavers (one male, one female) are being processed as follows. The body is first scanned along its entire length using both Computed Tomography (CT) imaging [17] and Magnetic Resonance Imaging (MRI) to provide a full picture of both hard and soft tissues (Fig. 3). Skeletal markers are attached to the cadaver to ensure a global registration framework between the

Fig. 1. Snapshot of LhpBuilder v3, in which a CT data set, a surface model of the lower body skeleton, and motion-capture data have been imported and fused in time and space. (©LHDL Consortium, reproduced with permission)

Fig. 2. Snapshot of the home page of LhpRepository v3, from which users can access all services and the complete documentation. (©LHDL Consortium, reproduced with permission)

Fig. 3. Left: Whole body CT scan of the female cadaver, and surface model of the skeleton extracted from it. Middle: Dissection field, showing the stereophotogrammetric reference systems, attached to the underlying skeleton, and the coloured pins used to mark the pennation of the muscle fibres. Right: Anatomical realism of the muscle model obtained by registration of medical imaging with dissection data; here a right semimembranosus muscle model including 4 fibres (each including tendon length, muscle length, pennation, and wrapping). (©LHDL Consortium, reproduced with permission).
images and the other data. The cadaver is then dissected by an expert anatomist, who collects the 3D coordinates of all anatomical features relevant to the modelling of the musculoskeletal system, including the origin and insertion areas of muscles and the direction of pennation of the muscle fibres.

In parallel, gait analysis data from volunteers who match the anthropometry of the dissected cadavers is being collected at the Movement Analysis Lab at IOR.

LhpBuilder is used to process and fuse these data; an advanced registration algorithm allows fusion of the motion data taken from volunteers with the detailed anatomical data obtained from the cadavers [15, 18–21]. The same protocol can be used on patients, using a special set of skin landmarks (Fig. 4).

The bones of each cadaver undergo a long list of biomechanical and morphometry examinations at the Medical Technology Lab of IOR. Long bones are tested nondestructively in bending and torsion to measure their stiffness and deformation and they are then loaded until failure [22]. Bone tissue biopsies are taken at various skeletal sites and examined with micro-CT imaging before being subjected to tissue biomechanical tests, including compression tests, microhardness, and histological analysis [23–25]. The bones are also scanned again using high-resolution CT imaging to provide data for the creation of finite element models of each major bone [26–28]. Again, the same procedure can be performed on living patients, and the biomechanical strain predictions can be used in clinical practice (Fig. 5) [29, 30].

New numerical methods are currently being developed to run similar models at the tissue level, using micro-CT data as input.

All of these data, obtained from data collection, processing, and modelling, are being imported into Lhp-Builder and stored in the LhpRepository. From January 2008, this collection has been made freely accessible to other selected projects that are willing to share similarly valuable collections, or who are ready to contribute with significant processing and modelling efforts. Anyone interested is asked to contact the authors.

6. Conclusion

In this brief overview, we have described the European VPH initiative and provided some concrete examples of an early implementation of the aspects that are most rel-
evant to the musculoskeletal system. Progress in this area continues to be rapid.

The authors would like to thank Luigi Lena for the illustrations and Mauro Ansaloni and Paolo Erani for their support during the experiments. The STEP (contract #IST-2004-027642) and LHDL (contract #IST-2004-026932) projects were partially supported by the European Commission as part of the Framework 6 Programme.

REFERENCES

10. http://www2.imperial.ac.uk/ssherw/physflow/pfn/
11. http://www.aneurist.org/