Virtual Physiological Human: From Global Vision to Clinical Practice

Karl A. Stroetmann & Marco Viceconti
empirica, Bonn, Germany & Istituto Ortopedico Rizzoli, Bologna – Italy
with Rainer Thiel, empirica

BiolCT - The Heart in the Computer, Sophia Antipolis, France, April 02-03, 2009
Contents

- The Global Physiome [Project]
- Seeding the EuroPhysiome
- International Cooperation
- Global “Standardisation”
- Towards Clinical Practice: The VPHOP Project - Multiscale Modelling to Fight Osteoporotic Fractures
- Disclaimer
The Global Physiome [Project]
Defining the Physiome

- **Background**: The genome, proteome, and morphome all concern structure, which is necessary but not sufficient for explaining function (the physiome). We need to know about the dynamics, kinetics, and functioning of those structures and how they interact.

- **Rationale**: We need more than statistical descriptions of associations among physiological variables; we need models that include mechanisms and distinguish mere association from cause and effect.

**Defining the Physiome:**

*the quantitative, integrative description of the physiological dynamics and functions of the intact organism*

Response to the macroethical imperative to
• minimize risk
• while advancing medical science and therapy.
• Effort to define the physiome, through databasing and modeling, of individual species, from bacteria to man.

The Physiome Project is not likely to result in a virtual human being as a single computational entity. Instead, small models linked together will form large integrative systems for analyzing data

Seeding the EuroPhysiome
Paradigmatic Shift in Biomedical Research

Complement Reductionism

With Integrationism
Integration across ....

Across sub-systems
Integration across ....

Across Temporal scales

Across dimensional scales
Integration across ....

Across Disciplines

Medicine

BioEngineering

Biology
Integrative Research

- This Integrative Research approach requires a radical transformation on the way biomedical research is conducted.
- It is necessary to create a framework made of technology and methods. We call this framework (in Europe) Virtual Physiological Human (VPH).
Virtual Physiological Human
- The Vision -

The Virtual Physiological Human is a methodological and technological framework that, once established, will enable the investigation of the human body as a single complex system.
The aim behind the VPH is to help achieve the development of:

- Quantitative, integrative and predictive models that describe human life
- From conception to death, and from genes to whole organism.

Motivation is to provide the necessary:

- Infrastructure, including methodologies, databases and tools that will allow scientists working in different fields (at various levels and scales) to communicate and exchange data and technologies in a standardised way.
- Massive computer storage and software tools are necessary which are currently not widely available.
The virtual medical man

Last Updated: 12:01am GMT 31/10/2006

Microprocessors may soon give us an insight into the most advanced entity on Earth, explains Roger Highfield

He can breathe, blister and bleed. He can be damaged, dismantled and dissected. He is a crash test dummy, a military guinea pig and a drug trial volunteer all rolled into one.

Soon it might be possible to do routine experiments on the ultimate living doll without going to jail, without causing a moment’s suffering and without a twinge of conscience, said Dr Marco Viceconti of the Rizzoli Orthopaedic Institute, Bologna, Italy. Current testing methods depend on cadavers, animals and people, all of which raise profound social and ethical issues.

Next week, Dr Viceconti and hundreds of experts from all over the world will meet at the Université Libre de Bruxelles to discuss the virtual physiological human, or VPH, which aims to integrate efforts to model the workings of organs in a computer to create a virtual body. Among the consortium are a handful of British universities –
VPH Research Road Map

Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human

“Anno domini nescio”
“We are not yet at the new potatoes” (Traditional Flemish expression)
“Adparent rari nantes in gurgite vasto”
“Only the few swim in a rough sea” Virgil, Aeneid, 1, 118

http://www.europhysiome.org/roadmap
International Cooperation
The Osaka Accord on Worldwide Integrative Biomedical Research Cooperation signed in Osaka, Japan, on 8 December 2007
World Integrative Research Initiative

The WIRI agenda:

- Common Objectives
- Research Challenges
- Resources Required
- Ethical, Legal and Gender Issues
- Interoperability
- Community Building

The undersigned organisations agree that a paradigm shift is necessary in the way in which biomedical research is carried out. It is necessary that laboratory and clinical observations are accumulated and made accessible to all those who can use them to develop or to validate new hypotheses. It is necessary that we have on a sub-system, a certain dimensional scale, or a certain biophysical aspect can be formalised and interconnected to others that are being developed on contiguous sub-systems, scales, domains. We call this new approach Integrative Biomedical Research.

The undersigned organisations agree to foster all means an international collaboration aimed to promote 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 Integrative Research poses
- Suggest research and technological development objectives considered essential for success of the Integrative Research Initiative

**Resources Required**
- Maintain an Integrative Research Investment Monitor which lists all Integrative Research projects and the relevant resources invested on them
- Develop a lobbying strategy that allow the World Integrative Research Initiative 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 CEL (Gender-Legal-Ethical) observatory to monitor the legal barriers to the development of Integrative Research

**Interoperability**
- Develop standards that ensure the federation of digital libraries and repositories relevant to the Integrative Research Initiative
VPH is a global priority

- €75 millions: FP7-ICT-2007-2: Virtual Physiological Human
- €63 millions: FP7-ICT-2009-6: Virtual Physiological Human
- $100 millions: Predictive Multiscale Models of the Physiome in Health and Disease (R01)
- ¥800 millions: physiome-related global COE programs
FP7 ICT-For-Health R&D Activities
Towards full picture of individual’s health status
Genomics-based personalized medicine

Based on the ideas of the International Physiome project

**Virtual Physiological Human (VPH)**

The aim

**VPH constitutes effort towards**

multi-scale patient-specific models for

- Personalised healthcare solution
- Early diagnostics & Predictive medicine
- Understanding diseases for the first time and across several biological levels

The VPH research roadmap (2007)

[www.europhysiome.org](http://www.europhysiome.org)

developed by the EC project STEP

ICT for Health Unit support for Research & development (FP7)

- **Personalisation of Healthcare**
  - Personal health system
  - € 72 Million (M) in 2007, (€ 63 M in 2009)

- **Patient safety / avoiding medical errors**
  - € 30 M in 2007, (€ 30 M in 2009)

- **Predictive Medicine – Virtual Human**
  - Modelling/simulation of diseases
  - € 72 M in 2007, (€ 68 M in 2009)

Global “Standardisation”
- some examples -
Multimod Application Framework (MAF)

- For the development of computer aided medicine applications
- Strengths are in data fusion (combining into a single information space data from very different sources), data modelling, and interactive multimodal visualisation
- Distributed as open source, developed at CINECA, SCS, Rizzoli Institute (Bologna) and University of Bedfordshire, UK
Graphical Interface for Medical Image Analysis and Simulation (GIMIAS)

- Platform for fast prototyping of medical applications
- Tailored to integrate tools from medical imaging, modelling, computational mechanics and visualisation, by reusing previously defined components
- Aim is to combine tools from different areas of knowledge
- Developed at the University Pompeu Fabra, Barcelona, Spain
Continuum Mechanics, Image analysis, Signal processing and System Identification (CMGUI)

• Includes field storage, 3D visualisation and a mathematical field abstraction layer
• Part of a mathematical modelling environment developed by the University of Auckland Bioengineering Institute, New Zealand
• Developed as a way of visualising and interacting with files for the Physiome Project
• is a National Center for Biomedical Computing, part of the USA’s National Institutes of Health Roadmap for Medical Research
• focus of SIMBIOS is on physics-based simulation of biological structures
• the centre of many of SIMBIOS’ computational tools is SimTK Core, an open-source software simulation toolkit
• strong interest in neuro-musculoskeletal modelling and simulation
• charged with creating “the networked national effort to build the computational infrastructure for biomedical computing for the nation”
CellML (I)

- The CellML language is an open standard based on the XML markup language
- Developed by the Auckland Bioengineering Institute, U of Auckland, New Zealand
- To store and exchange computer-based mathematical models
- CellML allows to share models even if they are using different model-building software.
- Enables to reuse components from one model in another, thus accelerating model building.
CellML (II) - Model Curation

• As part of the process of model curation, it is important to know what tools were used to simulate (run) the model and how well the model runs in a specific simulation environment.

• The four confidence levels are defined as:
  – Level 0: not curated (no stars);
  – Level 1: the model loads and runs in the specified simulation environment (1 star);
  – Level 2: the model produces results that are qualitatively similar to those previously published for the model (2 stars);
  – Level 3: the model has been quantitatively and rigorously verified as producing identical results to the original published model (3 stars).

Source: http://www.cellml.org
Towards a Global Community

- MAF, GIMIAS, CMGUI signed co-operation agreement
- MAF & SIMBIOS plan to co-operate in the context of the recent FP7 4th ICT Call
- Further global projects planned (up to 5 will be funded by the EC)
- Further FP7 calls expected to support further build-up of infrastructure, services and tools
Outlook:
Towards Clinical Practice –
the VPHOP Project
Towards Clinical Practice

VPHOP Project: multiscale modelling to fight osteoporotic fractures
Osteoporosis is a killer

- OP fractures kill as many women as breast cancer.
- 30 to 50% of all women and 15 to 30% of all men will face an osteoporotic fracture in their lifetime.
- 4,000,000 fractures every year cost Europe €30,000,000,000.
- Forecast to double by 2050.
- 250,000 elders will die of related complications within 12 months; all others will remain impaired.
Not enough technology

- The technology in current clinical practice is clearly insufficient.
- The accuracy in predicting fractures is as low as 60%.
- Even if we see the drugs are not working we wait for the fracture, and only then surgically fix it.
Better chances to deliver

- Bone physiology is as complex as any other organ
- But the biomechanics of bone fracture is in itself a purely mechanical event.
- This is one of the few domains where organ-level models already achieve predictive accuracies of over 90%
P2 medicine: the VPHOP project will make possible Predictive and Personalised (P2) medicine for osteoporosis

- **Predictive**: multiscale models representing the skeletal mechanobiology from the whole body down to the molecular constituents, simulate the skeletal loading in various conditions and predict if the bones will fracture in each of them.

- **Personalised**: The multiscale model is personalised using specific patient information. The more available information, the more personalised the model becomes.
Health Technology Impact Assessment: Guiding Towards Clinical Practice

- Move from guidance to guidelines to pathways (within & across HCPs)
- Prepare detailed workflow plans (for osteoporosis)
- Identify clinical entry and end points
- Analyse impacts on all actors & stakeholders
- Develop an economic disease simulation model (e.g. Markov Chain approach)
- Compare present pathway(s) with various options for new workflows and expected clinical outcomes from new eHealth solutions – technology selection guided by socio-economic ex ante assessment
- Undertake initial small trials
- Full-scale clinical trials, including socio-economic assessment
Thank You!

http://www.vphop.eu
Disclaimer

- VPHOP is a project co-funded by the European Commission Seventh FRAMEWORK PROGRAMME
- The research reported upon in this presentation has either directly or indirectly been supported by the European Commission, Directorate General Information Society and Media, Brussels.
- The results, analyses and conclusions derived there from reflect solely the views of its authors and of the presenter.
- The European Community is not liable for any use that may be made of the information contained therein.