

# ICT-BIO 2008

Brussels  
23-24 October



## **Conference Report – December 2008**

[http://ec.europa.eu/information\\_society/events/ict\\_bio/2008](http://ec.europa.eu/information_society/events/ict_bio/2008)

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# Report of the ICT-BIO 2008

## 1. The report and its aim

This is the report of the ICT-BIO conference held in Brussels on 23 and 24 October 2008, entitled “Computer Modelling and Simulation for Improving Human Health”. The conference was organised jointly by two Directorates-General of the European Commission – DG Information Society and Media (DG INFSO) and DG Research (DG RTD) – with the first transatlantic cancer modelling workshop which was co-organized by NCI’s [Center for the Development of a Virtual Tumor, CViT](#), and EU’s [Advancing Clinico Genomics Trials Program, ACGT](#).

Alongside the plenary talks and discussions, 12 specialised break-out sessions analysed the state of play in a wide range of applications of modelling and informatics to a variety of aspects of human health, each with its own rapporteur. Their accounts of these sessions are contained in this overall report.

The two days of the conference sessions were paralleled by a Transatlantic Workshop of Multiscale Cancer Modelling, with twin European and American chairs and rapporteurs; a report of the workshop will appear separately on the conference webpage dedicated to the workshop<sup>1</sup>.

This report aims to give an overview of the conference and present its key conclusions.

## 2. Introduction

In response to the seemingly intractable challenges posed by diseases such as cancer, neurological conditions and cardiovascular illness, researchers have developed a new approach. Called “systems biology”, this approach aims to integrate information and communication technologies with biomedical research to deliver improved health. But as systems biology has progressed, researchers have come up against the challenges inherent in the sheer quantity of data being generated – and

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<sup>1</sup> [http://ec.europa.eu/information\\_society/events/ict\\_bio/2008/ta-cancer-wkshp](http://ec.europa.eu/information_society/events/ict_bio/2008/ta-cancer-wkshp)

to be generated – as well as in the complexity involved in analysing it. It is clear that no one laboratory, or country, or even continent can solve them all on its own. It is, indeed, a global challenge that requires a coordinated response.

For an idea of the scale of the ambition of this new paradigm, consider the idea of the Virtual Physiological Human. As Rudolf Strohmeier, Head of Cabinet, Information Society and Media, said in opening the conference, this initiative aims “to translate all functions of the human body into computer models at different scales, ranging from the whole body down to the smallest scale, the cells and molecules”. Armed with these models, we will be able take an integrated approach to predicting the risk of developing a disease, its prevention, diagnosis and treatment.

Three introductions set the tone for the meeting.

First, Research Commissioner Janez Potočnik highlighted the scale of complexity. Many of the diseases affecting us – such as Alzheimer’s – are multifactorial, caused by combinations of genetics and the environment, he said. Pancreatic cancer alone, fatal in more than 90 per cent of cases, involves 60 genetic mutations, 12 different pathways and hundreds of genes. The situation demands a holistic response, he said, across the divide between computing and biomedical sciences. New scientific tools will have to be developed, as well as new computing tools to store and order the vast amounts of data.

In Europe, said the Commissioner Potočnik, we can tackle this better if member states team up and coordinate policies – especially when it comes to making databases interoperable: “In this research field Europe could look at mechanisms of joint programming – the term given to a process whereby member states can choose to work together more closely in certain areas of resource, with the European Commission facilitating.” And he warned that if we miss the opportunity, Europe’s patients will lose out, and Europe’s pharma industry will decrease and move to parts of the world where it will get the necessary support.

Commissioner Potočnik ended with a plea for continued financial support. “One thought about the financial crisis: none of the challenges we are facing ... none has changed, none has become less important than before. Education, science, research

and innovation are in these uncertain times probably more important than ever. Not understanding this will turn a financial problem into a long-term structural one.”

Second, Viviane Reding, Information Society and Media Commissioner, said that biomedical research and healthcare is now “inconceivable” without the contribution of information and communication technologies (ICT). ICT has revolutionised our understanding of human physiology and disease, and the way medicine is practised. But it is not just one-way traffic: the challenges posed by biomedicine “also drive the development of basic information technologies such as software systems for modelling biological processes, new-generation supercomputers, grid technologies and privacy-enhancing technologies.”

The need for synergy and a cross-disciplinary approach in solving real-life problems is not new, said Commissioner Reding, adding: “Real-life problems cut through not only established research disciplines, but also through administrative layers and geographical boundaries.” She welcomed the close cooperation between her services and those of Commissioner Potočnik, as well as the international delegations present at the conference – in particular those from the United States and Japan. Global cooperation, she said, is “our only chance” to find effective solutions for the health needs of our ageing society.

Commissioner Reding referred to the Virtual Physiological Human as an area where progress has been made since the previous (and first) ICT-BIO conference in 2006<sup>2</sup>. The strategic importance of this and related research is reflected in a doubling of the research budget in ICT for Health. A call for proposals last year, she said, resulted in several exciting projects. Further calls – including a specific call for international cooperation – are planned for this year and next. The overall aim: a global “scaffold” of medical knowledge and a “toolbox” for researchers and health providers.

The third introduction came from Mary Baker, President of the European Federation of Neurological Associations. During our lifetime, she said, we may have witnessed one of mankind’s greatest achievements: the almost doubling of life expectancy in the past century. But like most achievements, it brings its own challenges. With an

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<sup>2</sup> [http://ec.europa.eu/information\\_society/events/ict\\_bio\\_2006/index\\_en.htm](http://ec.europa.eu/information_society/events/ict_bio_2006/index_en.htm)

ageing population, we can expect more brain disease, more cancer, more respiratory illness, and more bone and joint disease.

At the same time, she said, there will be fewer people to care for the old. A couple in their seventies in the 1920s would have had 44 female relatives alive, 14 of them without work outside the home. Last year a couple in their eighties would have had only 13 female relatives, and only 3 of them would have been without work.

The threats bring opportunities, however, including “an incredible opportunity to be able to harness the ICT and take it to that great crossroads where it meets medicine”. Imagine, said Baker, a world where we could prevent some of these terrible illnesses. Imagine better detection, treatment and management. Imagine personalised medicine. To reach those goals, she said, we have to reach across disciplines. It is challenging, but she pointed out that the model is not new: in hospital you get multidisciplinary teams all the time. But it requires inspirational leadership and shared values.

Above all, said Baker, don't forget the patients – and, sooner or later, we will all be patients. Reach out to the media, she said, to keep patients informed: “It is much better to debate with a well informed society than one that gets misinformation and myths.”

### **3. Key messages**

The conference extended over two days, and was marked by a wealth of ideas and suggestions, and a number of broadly shared key conclusions emerged. Briefly summarised, they are these:

- Models of complex biology such as metabolic pathways, cells, and organs are a scientifically valid way of addressing human disease and hold exceptional promise for human health;
- That promise cannot be delivered without both interdisciplinary and international cooperation at all levels – which is indeed taking place;

- Given human similarities and the scarcity of research funding, it makes little sense to develop separate disease models and generate separate data in each scientific nation. In any case, no one country or continent can solve the problems on its own;
- Focus is essential. Priorities in research programmes – which pathway, which disease, which cell, which organ – are best established by the research community in dialogue with research funders;
- There is a need for infrastructure that enables collaboration between researchers; exchange of data, protocols, biomaterials; and a common basis for analysis;
- A major effort is required to ensure the standardisation of data and consistent data curation;
- Open access to data, models and programs is essential;
- Patients will need to be persuaded to allow researchers access to their data.

#### **4. Keynote presentation, Iain Mattaj, Director General, EMBL/EBI**

The traditional recent strength of biology has been mainly in the area of reductionisms, said Iain Mattaj in his whistle-stop tour of the relations between biomedical research and ICT – studying the properties of objects by taking things down to their constituent parts. This, he said, is a very useful approach, and there is no reason to “insult the methodology”, but it has severe limitations.

Complexity was Mattaj’s overall theme. Almost nothing acts alone – things act in complexes. “If you make a complex that has various components they don’t behave as if they were on their own.” His prime example: “Imagine the gas hydrogen and the gas oxygen, and then think of what happens when they combine to form water.” Such a combination, he said, is impossible to predict by studying their properties individually.

And that is just a combination of two components. In biology, even simple functions have interactions of hundreds or thousands of components.

In the human body there are vast numbers of potential combinations between 23,000 coding genes, which give an inconceivably large number of functions. It is, said Mattaj, inconceivable that we can determine all these experimentally: “It can only be done by combining experiment with computational methods.”

Mattaj talked about two “tricks” that researchers can use to get round the problems. The first is to make use of evolution. Because of the way organisms evolved, all living organisms are related to a greater or lesser extent. So we can study complex things in simpler organisms, and there are mouse models for many illnesses. “But as we move forwards we go to much more complicated models,” he said.

The second “trick” is to use systems approaches. These start with finding out what we need to know about a part of a living system before we model it reliably: “It is not enough to simply generate lots of data about what’s in a cell or a patient. One has to have a hypothesis. What are the important variables?”

Mattaj used the example of the mitochondria, the “power stations” of the cell, which produce the energy that enables cells to function. They have their own genome. But almost all their components are encoded in the host genome and made into the human cell cytoplasm. Many human diseases are caused by variations in mitochondrial proteins – differences, he said, that are statistically important but incompletely understood.

At the EMBL, researchers in the laboratory of Lars Steinmetz have been looking to model the mitochondrion in yeast, starting with collecting an enormous amount of data on biochemistry, genetics, and bioinformatics analysis of the entire literature on mitochondrial genes. One of Steinmetz’s most surprising conclusions is that there are about 80 genes in mitochondria that cause human disease. Moreover, by eliminating yeast genes without obvious human counterparts, the researchers were able to prioritised candidate genes for putative human mitochondrial disorders; and at least three new disease genes have so far been identified. Mattaj warned that since there is a great deal of human variation this approach is not a universal way to analyse proteins, but when it works “it predicts very easily”.

Likewise with model organisms. Studying them can provide exact analogies, and it may be possible in certain cases to model organisms to identify patients at risk of genetic disease. But again, Mattaj warned, “It is very important for all of us as scientists to avoid generalisation and oversimplification. Model organism studies are not always useful, because evolution is continuous, so even closely related species have differences that can have important medical consequences.”

We are at a very early stage in the process of understanding human variation, Mattaj said. But already, with fewer than 10 complete human genomes, there is a surprise: the major source of differences is not, as originally thought, single nucleotide polymorphisms (or SNPs). Instead, it comes from insertions, deletions and duplications. “This tells us that we need to understand where human variation comes from before you start applying these technologies to patients with disease,” he said.

The 1000 Genomes Project<sup>3</sup> has been set up to provide this background. In this ambitious exercise, a thousand different people will have their complete genomes sequenced. On average 8.2 billion base pairs being sequenced every day, delivering in two weeks more sequence data than has been produced since the technology of DNA sequencing developed. The project is also delivering an enormous ICT challenge: to analyse, store and distribute this data.

Modern bioinformatics and ICT tools can also help to explore many issues of drug development *in silico*. One example, funded in part by the European Commission, has been the attempt to quickly identify lead compounds for drugs against avian flu in the event that it is transmitted to human beings: 300,000 chemicals were computationally tested for likely interaction with neuraminidase structures. This resulted in a “very considerable” enrichment in the number of lead compounds when the best compounds were taken and put into experimental testing for binding and inhibition.

There are many examples of drugs developed for one disease being useful in other contexts – a topical example being Alemtuzumab, developed to fight leukaemia, but

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<sup>3</sup> [www.1000genomes.org](http://www.1000genomes.org)

discovered serendipitously to work in multiple sclerosis. But do we have to rely on serendipity? What about doing it informatically? The problem, said Mattaj, is that there is no data resource that allows you to do this efficiently. There are, he said, “no publicly accessible good databases in chemistry and medicine”. It took one group of researchers three years to do a series of tests on 745 marketed drugs to see whether similar side effects were caused by chemical similarities. (The answer is yes.)

Mattaj drew several major conclusions.

First, Europe must invest in biomedical modelling and simulation data. There are still no adequate sustainable mechanisms to support even the core biomolecular databases in Europe, even though they are used by a million different resources every year, downloading three million pages a day. We lack generally accessible, clinically useful databases holding molecular information.

Second, interdisciplinarity is essential, particularly in the life sciences, because life scientists are not trained in computer modelling, simulation and engineering. “So we need to be able to get people from these areas to get together to work with life scientists.”

How to foster interdisciplinarity? Mattaj said that Europe must continue to fund multidisciplinary projects as an incentive to bring different scientific communities together. It should also develop infrastructure with a long-term perspective and openness to new user groups – “I am enormously impressed with open access,” he said.

Europe must continue technology development in biology and ICT and at the interface, Mattaj said. It will not be enough to rely on existing technologies. “The Grid is a fantastic resource, particularly for physicists,” he said. “Grid takes huge amounts of data and does complex but essentially standard calculations.” It is clear that the Grid technology must be better adapted to the specific needs of the biomedical field.

All this, he added, will require common visions and strategies if we are to address the major health issues we face.

And finally Mattaj raised a point that was to be echoed by speakers later in conference: the need to overcome the technical and privacy hurdles to access to

medical data. “We need to find ways in which patient data can be anonymised, secure, but accessible to the huge number of smart people who if they did have access to it might be able to bring more understanding of human disease,” he said.

## **5. Plenary session 1: Future perspectives for computer modelling and simulation in health research**

The session began with a look at Clinical Decision Support by Henk van Houten, Senior Vice President and Program Manager Healthcare, Philips Research. Medicine may be transforming from an art into a science, he said, but the real point is not science: it is to transform outcomes by translating science into clinical decision support tools to help clinicians make the best decisions for the patient.

The high-level goals are simple: to improve outcomes for a particular class of complaints, diagnoses or procedures; to improve patient safety; to foster evidence-based clinical practice; to enhance patient education and empowerment; to improve quality of care; to foster compliance with clinical guidelines; to address clinicians’ recognised and unrecognised information needs; and to meet reporting, regulatory and accreditation requirements. But how to get there?

It all starts, said van Houten, with getting to grips with the medical knowledge we have, either in textbooks or in great minds. Knowledge has to be acquired, and translated into guidelines, something currently done by what he called knowledge engineers, and applied through software. “Some people say you’re taking decisions instead of the physician,” he said. “We believe the physician will always be in charge. What we will replace is the knowledge engineer: the system will take over that role.”

Giving examples from already-implemented solutions for Intensive Care Units, van Houten explained how a system can give early warning of sepsis, or monitor a patient’s condition generally. Another example showed computer-aided detection of mammography or chest X-rays. In the future we will go further, he said, providing clinical guidance from multiple data sources – not just detection, image recognition and interpretation, but “really going a step further to diagnostic assistance, therapy planning and outcome planning”.

Take lung cancer, said van Houten. With 235,000 new cases a year, it is the number one cancer killer in the world. Only 15 per cent of those affected survive for 5 years, a figure that has hardly changed in the past 20 years (unlike the figures for breast cancer). One would like to screen everybody, but no one wants large numbers of healthy patients doing tests. So you start with those with risk factors and screen them for lung nodules. But 60 per cent of lung nodules are not harmful, which is where computer-aided diagnosis comes in, ensuring – as far as possible – that only cancerous nodules are sent for biopsy. The results of an initial test looking at retrospective data show that Philips’ system and its associated algorithm can detect cancerous nodules with a sensitivity of 87 per cent and specificity of 81 per cent. “In other words, the system consistently estimated high probabilities of malignancy for the truly malignant nodules, and likewise low probabilities for truly benign nodules,” he said.

And that is just the start. Disease-specific *in vitro* testing at the molecular or cellular level will be able to identify patients at risk. Individual characterisation of tumours will lead to the possibility of personalised treatment, since no two tumours are exactly the same. PET and CT scanning can illuminate how a tumour is behaving, shedding light on tumour metabolism.

Finally – though still in the future – it will be possible to simulate the effect that particular therapies will have on individual patients. This is the object of ContraCancrum<sup>4</sup>, a consortium including Philips that is part of the Virtual Physiological Human initiative<sup>5</sup>. At the moment we are restricted to what van Houten called “single modality solutions”, taking and analysing data from a single kind of source. For the dream of personalised medicine to become a reality, he said, we will have to move to multimodality solutions, knowledge-based disease models and computer-interpretable guidelines linking diagnosis and treatment.

Martin Hofmann-Apitius from the Fraunhofer Institute for Algorithms and Scientific Computing, Germany, outlined the challenges for IT environments in supporting multiscale modelling and simulation. The problem across all scales – from molecules

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<sup>4</sup> [www.contracancrum.eu](http://www.contracancrum.eu)

<sup>5</sup> <http://www.vph-noe.eu/vph-initiative-forum>

up to whole populations – is the lack of real data to a large extent, he said. “We need statistically sound high-quality real world data. We’re dealing with real patients!”

One of the problems is open access – it needs to be more open, he said. Science should drive the availability of data, he said, not the way around. Gene and protein data, as well as microarray and SNP data, are readily available through the US National Center for Biotechnology Information and the European Bioinformatics Institute. The literature is publicly available as abstracts through PubMed. But there are restrictions on automated text mining, which is what is required. We need, said Hofmann-Apitius, access that is more open.

The potential of text mining is shown by @neuLink, a knowledge discovery suite developed in the EU Framework-funded project @neurIST<sup>6</sup>. When the system was asked for the genes and proteins associated with intracranial aneurysm it came back with large list. Significantly, out of the system’s first 17 hits, 14 were mentioned in a recent landmark review by Krischek and Inoue of the Institute of Medical Science at the University of Tokyo.

How does this help to find new applications? Hofmann-Apitius was careful not to say that the machine approach is more valid but, he said, it “comes up with more focuses for hypothesis”.

Yet the lack of high-quality, comparable data is a severe problem. Take cranial aneurysms. About 4 per cent of the population have a cranial aneurysm, but only one in 10,000 will rupture, and a group within @neurIST is developing a descriptor for use in predicting those that will. But, said Hofmann-Apitius, the group needs more than the 65 cases it has before it can develop a clinical guideline. There is no NCBI or EBI database hosting tissue data, no way of comparing imaging data from different databases – and little chance of extracting comparable data from PubMed abstracts.

Lack of data is also holding back the use of electronic health records, though Hofmann-Apitius cautioned that examination of these records might never be a substitute for a nicely designed clinical study. In addition, the legal situation

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<sup>6</sup> [www.aneurist.org](http://www.aneurist.org)

regarding the use of patient data (much of it typically held on paper and requiring manual parsing) is not clear. And comparability is a constant issue: we don't know whether different simulations of blood flow, for example, are different because data were taken while one patient was standing up, one sitting down, or another had just had a cup of coffee.

His conclusion: multimodal modelling and simulation need representative high-quality data. Access to that data is limited not by technological but by organisational, legal, ethical and sociological factors. This, said Hofmann-Apitius, is where the Virtual Patient Metaphor will come in: a curated database of medically relevant information – but it will require standardised input.

“We could continue playing with models and simulations endlessly and never know whether they are valid or not,” he said. “The reason why clinical data are not being made available in sufficient amounts has a lot of reasons. There are also medical practitioners who see no reason to go through the hassle because they don't get any direct benefit. We'd love to learn from large amounts of data showing shapes of tumours, but that has to be given to the world so that many people can create their own algorithms.”

Finally, Denis Noble, from the University of Oxford and one of the founders of systems biology, developed the first mathematical model of the human heart as far back as 1960. He began his talk with the scale of the problem: there are 23,000 human genes, meaning that the total number of protein-protein interactions could be  $10^{300}$ , a number vastly greater than the estimated number of atoms in the Universe ...so there could never be enough material in the Universe to store the data. “We simply have to focus,” he said.

The heart, said Noble, is controlled by electrical excitation, although its main function is mechanical. But “evolution has not covered all the things that come along, hence cardiac arrhythmias”, he said. To understand these, we have to integrate activity at all levels: genes, proteins, whole cells, whole body.

There is a lot of money at stake. The price tag when a promising drug fails late in development can be \$1 billion. But although there are various ways of assessing cardiotoxicity, none of them predicts the potential for arrhythmia. That, he said, is

why the EU-backed preDICT consortium is using multiscale models of the heart to understand the mechanisms of drug-induced effects on electrical activity.

The scales range from ion channels to simulations of interactions in ventricular cells and simulations at the level of the whole ventricle. Does it work? “We already have a track record in helping to produce drugs in pharma,” said Noble.

Noble also showed a simulation of the spread of electrical excitation moving up through the structure of a ventricle, showing the detail through which the waves of excitation move through the structure and interact with each other. This model can be used to transfer patient-specific data and study the arrhythmic heart.

There are technological limitations, though. To compute tens of milliseconds of activity took 13 hours of computer time, said Noble. The consortium is working with Fujitsu, Japan, and a petaflop computer to be able to compute in faster than real time. “This work is driving the development both of the machine and the software that is going to be running it,” he said.

The end result of the project would be an openly available virtual research environment. Indeed, it is already available in its core. At lower scales – an ion channel, or a cell – it would run on desktop computers, although at tissue and whole-organ level it would need high-performance computing.

A second project, euHeart, involves 17 industrial, clinical and academic partners and aims to develop individualised human heart models. It uses comprehensive patient-specific data and will be applied to heart failure, arrhythmias, coronary artery disease and disease of the aorta.

Noble also referred to the VPH-NoE project itself, which he described as interacting with preDICT<sup>7</sup>, euHeart<sup>8</sup> and the other VPH projects<sup>9</sup> but going way beyond to apply the principles to modelling other organs and systems of the body. It’s being progressed in a highly focused way – although, he said, you are not going to get a Virtual Physiological Human that can come down a staircase and start giving my lecture within any reasonable length of time!

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<sup>7</sup> [www.predict.org](http://www.predict.org)

<sup>8</sup> [www.euheart.eu](http://www.euheart.eu)

<sup>9</sup> [http://ec.europa.eu/information\\_society/activities/health/research/fp7vph](http://ec.europa.eu/information_society/activities/health/research/fp7vph)

## 6. Plenary session 2: Opportunities and challenges for international cooperation.

**Chair: John Hodgson, Director, Critical I Ltd**

From the start, session chair John Hodgson set out four assumptions, asking delegates whether they agreed. These were:

- Models of complex biology such as metabolic pathways, cells, and organs are a scientifically valid way of addressing human disease;
- Given human similarities and the scarcity of research funding – it makes little sense to develop separate disease models and generate separate data in each scientific nation;
- Priorities in research programmes – which pathway, which disease, which cell, which organ – are best established by the research community in dialogue with research funders;
- There is a need for infrastructure that enables collaboration between researchers; exchange of data, protocols, biomaterials; and a common basis for analysis.

There was no dissent, and yet as the later panel discussion showed (and as might be expected) not everyone gives the same weight to all the priorities.

First, though, came presentations giving snapshots of the approach to international cooperation from Europe, the US and Japan, beginning with Manuel Hallen from the Health Directorate of DG Research.

For DG Research as well as for national governments, systems biology is a field of increasing importance. It is a priority under the Framework 7<sup>10</sup>, and already the Commission has invested €90 million in the first two calls under the programme – several of which were presented in the conference's specialist sessions. But why is

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<sup>10</sup> <http://ec.europa.eu/research/fp7>

international cooperation so important? The overall answer is clear: because the challenges are so great. But there are specific policy reasons as well: to set international standards for data quality; to ensure interoperability between databases; to ensure open access to data, software and computational tools; and to establish a critical mass of resources and multidisciplinary expertise.

There are good examples already, such as the Knockout Mouse Consortium. The examples Hallen gave were mainly related to the US and Canada but, he said, were “not meant to be limited to transatlantic cooperations”.

How to promote the field better? The Commission is active in bringing funders together, but also researchers via workshops and funding. Hallen stressed that scientists from outside Europe are eligible to receive funding from the Framework programmes, which is not restricted to researchers from the almost 150 International Cooperation Partner Countries. Crucially, the Commission has recognised the opening of National Institutes of Health programmes to researchers outside the US by making researchers established in the US eligible for funding in the context of the current Health theme within Framework Programme 7.

From the Health Unit of DG Information Society, Gérard Comyn outlined the short- (5 year), medium- (10 year) and long-term focuses in ICT for health. Central to the long-term focus is the Virtual Physiological Human initiative, first established under Framework Programme 6 and described as a methodological and technological framework that once established will enable the investigation of the human body as a single complex system.

Comyn said that international cooperation was vital to the success of the initiative, referring to a “clear need” to exchange experience and expertise. “No one country can tackle the challenges alone,” he said, pointing out that the issues of managing huge volumes of data, multiple data formats, interoperability and standardisation were not limited to Europe.

International cooperation is in fact the subject of a specific research call opening in mid-November 2008, aimed at linking Europe’s work on the Virtual Physiological Human with similar projects abroad, Comyn said. It will specifically target

interoperability, tools and services for global cooperation (in particular modelling simulation) and helping to set up an international validation framework.

Next delegates heard from Roderic Pettigrew, Director of the NIH's youngest constituent, the National Institute of Biomedical Imaging and Bioengineering. With a mission to lead the development and application of biomedical technologies, he said, "It's no surprise we're particularly interested in ICT." ICT, he said, was central to the move to a more predictive and pre-emptive paradigm of medicine.

The major challenge, said Pettigrew, was to understand the molecular events that precede the clinical manifestation of disease. "Addressing that challenge should let us move from a reactive to a proactive paradigm," he said. But the challenge is "indeed daunting".

The NIH<sup>11</sup> has funded European scientists to the tune of some \$300 million in the past seven years, with a growth rate outstripping overall NIH funding. Now, as part of the US-EU agreement on funding that has opened up Commission funding to US-based researchers, the US itself has updated its own policy, said Pettigrew, underscoring that researchers outside the US can get support and also adding funding for minor alterations and renovation costs. He noted awards for modelling to European-based researchers of \$2.8 million in the current fiscal year – much of it to the United Kingdom.

Pettigrew drew attention to the role of IMAG, the Interagency Modeling and Analysis Group, which covers 17 of the 27 NIH institutes, 7 US federal agencies and the Canadian agency MITACS (Math of Information Technology and Complex Systems). IMAG has formed a consortium of multiscale modellers and issued calls for research into Predictive Multiscale Models of the Physiome in Health and Disease. Applications – granted purely on scientific merit – are welcome from foreign institutions, he said.

Among other international collaborative activities, Pettigrew highlighted the IMAG Wiki<sup>12</sup> site, created to provide a forum that would help modellers from around the

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<sup>11</sup> [www.nih.gov](http://www.nih.gov)

<sup>12</sup> [www.imagwiki.org](http://www.imagwiki.org)

world to work together and to facilitate information exchange and the establishment of best practices. The site, he said, encourages collaborators from around the world to populate it with models and progress.

Japan, too, is looking internationally as it deals with the challenge of ICT and systems biology. In the final presentation before the panel discussion, Professor Yoichiro Matsumoto from the Department of Mechanical Engineering at the University of Tokyo talked about the Peta-scale Supercomputer Project. The project is being handled by the RIKEN research institute<sup>13</sup>, with three industrial partners – Fujitsu, Hitachi and NEC. The target is a 10.2 petaflop machine in 2012. The hardware will consist of scalar and vector components, with tens of thousands of processors.

The field of life sciences has been designated as one of the Grand Challenges for the supercomputer, with four target areas: molecular simulations on complexes of proteins and ligands; cell simulations for systems biology; organ/whole body simulation; and data analysis research. Matsumoto explained that Japanese researchers are now separating the body into small boxes, or “cells”. He said that at the moment these cells could be no smaller than 1 millimetre – but that, in the future, “maybe we can reach down to 0.1 millimetre”.

A tentative name has been picked for the centre to house the new supercomputer: CACST, the Center for Advanced Computational Science and Technology. Its policy is being decided, but Matsumoto said that users would be chosen by an independent committee, and urged international researchers to apply to use it.

The panel discussion on international cooperation that followed featured Matsumoto, as well as Grace Peng from the US NIBIB; Patrick Kolar (Head of Unit, DG RTD); Ilias Iakovidis (Deputy Head of Unit, DG INFSO); Patrick Chaussepied (Responsable Département Biologie Santé, ANR, France); and Frank Laplace (head of the unit of molecular sciences in Germany’s Federal Ministry for Education, Science and Research). Both Patrick Chaussepied and Frank Laplace explained how France and Germany aimed to spend up to 20 per cent of their research budgets on transnational projects, though this year the French spend would be around 12 per cent.

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<sup>13</sup> [www.riken.jp/engn](http://www.riken.jp/engn)

Session chair John Hodgson wanted to know where we are now with data: “Have we got a little bit of data that is growing gradually but that will take off? Or do we have quite a lot of data and in a few years’ time a bit more? Or have we got a little bit of data and complexity, but this is going to explode?” What, he speculated, would be the cost of retrofitting 1,000 times as much data as we have now? The answers he received tended towards the explosive end.

Grace Peng said that in 1972 the US NIH funded around 700 computational modelling projects. Now the figure is 5,000 – and around 2,000 applications were submitted last year alone. Janet Thornton from the EBI had even more encouraging – or depending on your point of view, alarming – news. Changes in sequencing technologies used to sequence entire genomes at a very high speed will lead to a mass of new data. As an example, she said, when the pilot phase of the 1000 Genome project began three months ago, the EBI received more data in one day than it previously had in total. “The flood of data will go through the sky. In preparing, we clearly need the models to make sense of the data, and we also need to get the standards and image data under control. The core procedures for handling the data and describing the experiments must be sorted out, and it must be done internationally.”

All agreed that the time to standardise is now. Andrew McCulloch from the University of California San Diego went further, arguing it was 10 years ago. “We’re looking at a five-order magnitude increase in data in [the next] five years,” he said.

For many, infrastructure is a key concern. Traditionally people using the biomedical databases have downloaded data, but that will not be possible with huge data sets, said Janet Thornton. As Peter Kohl, from Oxford University, put it, “Terabytes don’t travel easily across the internet.” Kohl also called for executable code to be added to open source models.

“It is very difficult, even within Europe, to get transnational agreements [on infrastructure],” said Thornton. “... all of Europe needs to sign up to the concept that we develop a strategy for the data infrastructure in Europe ... That infrastructure is not properly funded. We need a solution for this.” One country cannot do this alone, she said, calling for transnational centres for data curation, before returning to funding: “We share our data nightly and weekly with resources in Japan and the US.

But we cannot jointly apply with other institutes from Europe for infrastructure funding.”

Frank Laplace agreed: “We believe in Germany that we should improve the infrastructure needed for systems biology. This is a clear promise. We also need to set up more systems bio centres in Europe, and we are doing so in Germany.” He added, “Transnational cooperation is essential to solve all these problems.”

A second main topic was access to data collected from patients. “The clinical data are the priority,” said Yoichiro Matsumoto, warning that until we had that kind of data – “with standard ontologies and databases” – much money would be lost. Rodney Hose from the University of Sheffield, UK, noted that the “formidable funding” for computational biology was dwarfed by the actual amount spent by health services in collecting clinical data, and he wondered whether researchers should start to lobby for a data donor card, like the kidney donor cards. What is needed, said Ilias Iakovidis, is a legal framework on re-using clinical and behavioural data for research. Industry, he said, agrees, but it will require a political statement from research organisations and patients.

John Hodgson, though, sounded a note of caution: “If we are going to sell this whole exercise as something that will benefit health, we have to connect to the healthcare system. What can’t we do without these data?” Grace Peng was equally wary: “Models [are] frankly a very hard sell to the general public, [the idea] that maths can affect their lives.” Clearly, patient confidentiality is an important issue, but as Peter Harris from the University of Melbourne, Australia, said, “ It is difficult enough to keep data private in a hospital, left alone internationally.” The solution, he said, would be a standardised international project on de-identifying patient data.

For others, such as Iakovidis, the first concern is standardisation of data. “My priority is access to patient and clinical data in a standardised form that can be used,” he said, referring to a workshop with the US on the subject the previous week. He was supported by Marco Viceconti of the Istituto Ortopedico Rizzoli, Italy, who along with others wanted international action on curation to ensure that all the data are there with the information that matters.

Gaby Lenhart from ETSI, France, said no one disagreed that standardisation is a

priority, but looked for a willingness to put resources into it: “Without resources we can’t do anything,” she said. Peter Hunter from the University of Auckland, New Zealand, pointed out that there are only four people curating the two standards we have (SBML and CellML) – not enough for the models being produced already.

Concluding, John Hodgson noted that the role of the general public had not been discussed in depth. But he ended on a positive note: funding programmes are now opening out, he said, such that it is now possible to design from scratch international programmes that have a good chance of being funded.

## **7. Conclusion: José Manuel Silva Rodriguez, Director-General, DG Research.**

As often observed in many areas of science, said Silva Rodriguez, progress in this emerging field of research will come from crossing the borders between different disciplines. “There is no doubt that new information and communication tools and technologies will drive progress in health research,” he said.

The opposite is also true. Computer hardware developments are also triggered by the need of medical sciences. One example is from IBM, which is developing the Blue Gene supercomputer to explore the frontiers in computer architecture and in the software required to program and control massively parallel systems such as important biological processes.

The FP7 Cooperation programme can play an important role in Europe in this field of research. The transnational collaborative projects it encourages are well suited to create the multidisciplinary networks that are essential for these integrative approaches, said Silva Rodriguez.

He pledged that the EU’s health and research directorates-general will work together to create in Europe the necessary means to generate the biological and medical knowledge and the computational tools and data resources that are essential for developing reliable models of human diseases. Special attention will also be given to the building up, through the FP7 Capacities programme, the database infrastructure without which this new field will not progress.

This emerging field of research is also resource-demanding. If we want to tackle ambitious research objectives in Europe and discover new therapies for major diseases, he said, member states will also have to coordinate their research policies and investment.

The field has also a strong international component. Robust models of human diseases cannot be developed without open access to high-quality and standardised data. International cooperation will be essential to establish these quality standards and to generate databases and mining tools that are freely accessible to all researchers.

Industry has a strong interest in the success of the field. Over the past 10 years several promising drugs have failed to reach the market because of severe side effects. One reason for these repetitive failures is that many of these drugs were targeted to a single gene or pathway but did not take into account the complex network of genes behind multifactorial disease. Silva Rodriguez indicated potential synergies with the Innovative Medicines Initiative in the future.

“I am convinced that this ICT-BIO conference has taken place at a crucial moment for this emerging field,” he said in conclusion. “The European Commission understands the importance of creating the necessary synergies to face the challenges in the field. I am sure that when we see each other in future events, major progress will already have been achieved.”

This report was prepared by Peter Wrobel, Editorial Director of Science Business Publishing Ltd.

# **Annexes**

# Session 1.1: The Virtual Physiological Human: Connecting Basic Science to Healthcare via Multiscale Modelling and Simulation

**Chair: Peter Kohl** (Dept Physiology, Anatomy and Genetics, Oxford University)

**Rapporteur: Joël Bacquet** (European Commission, DG INFSO/H1)

## **1. Summary of the session**

This session was dedicated to the Virtual Physiological Human (VPH) initiative, which aims at developing data-based predictive computer models of structure and function of the human body for applications in healthcare. The temporal parameters range from nanosecond behaviour (e.g. in protein dynamics) to decades (chronic disease development), requiring a  $10^{18}$  resolution range. Spatial parameters go from angstrom (the dimensions of ion channel pore) to metres (intact organisms), a range of ten orders of magnitude. This poses hitherto unexplored dimensionality challenges. As an illustration, Google Earth's scope, from the 40,000 km diameter of the Earth to tens of metres detail – covering “only” eight orders of magnitude.

This session included presentations about the European STEP process, which led the way towards the VPH initiative; the VPH Network of Excellence and its role in building communities and integrating related FP7 research efforts; the IUPS Physiome project, which pioneered and championed this direction worldwide; and a snapshot of US Physiome activities. The session concluded with a visionary talk illustrating the clinical potential and relevance of this endeavour.

## 2. Quick summary of the different presentations

Marco Viceconti from the Istituto Ortopedico Rizzoli, Italy, gave a short introduction to the STEP coordination action, which was seminal in the development of the concept of the Virtual Physiological Human, and in the definition of the VPH research roadmap. His presentation summarised the consensus process that STEP steered, and the primary results that it achieved. This coordination action gathered the VPH community through daily interaction on their dedicated website (BioMedTown) and at two conference events. The main achievement of this project is the “roadmap to the VPH”.

Peter Coveney, from University College London, UK, presented the aims and objectives of the VPH NoE. As an outward-facing, inclusive entity, it aims to foster the development and integration of all EU FP7-funded projects within the VPH initiative. The NoE is expected to serve as a beacon for all VPH-style research activities, whether funded by this initiative or not, on both national and international levels. The prospect of horizontally and vertically linked physiological models progressively moving to the whole human level is conceivable only if common specifications and standards are adhered to by modellers working at all functional levels and in the organisational hierarchy. One of the core aims of the NoE, accordingly, is to develop and promote adherence to common standards wherever possible. Another responsibility is to facilitate access to the IT infrastructure and interoperability of the resources necessary to deliver the central objectives of the VPH initiative, concerned with enabling patient-specific healthcare.

Peter Hunter, from the University of Auckland, New Zealand, presented an overview of the IUPS Physiome Project. This project involves international collaborations on most of the body’s 12 organ systems but is particularly focused on the heart, lungs, musculo-skeletal system, digestive system and skin. Jointly with the VPH NoE, the Physiome Project is continuing the development of the Physiome markup languages (CellML and FieldML), model repositories and open source software tools that facilitate multi-scale modelling. CellML, together with SBML, provides a robust framework for encoding lumped parameter (differential-algebraic) models of cellular function and FieldML, currently under development, will encode the

spatially varying fields required for representing anatomical structure and the solution of the partial differential equations governing function at the cell, tissue and organ level scales.

Andrew McCulloch, from the University of California San Diego, United States, summarised major multicentre research activities relevant to the physiome in the US, including the National Biomedical Computation Resource, the Biomedical Informatics Research Network, the CardioVascular Research Grid and Simbios. Areas include cardiovascular, neuroscience, and musculoskeletal physiology and diseases. The term “Physiome” shares its origins in Oxford and at Washington University in Seattle. Other related activities include the Multi-Scale Modeling Consortium of 24 grantees funded for the past three years by the Interagency Modeling and Analysis Group (IMAG) coordinated by the National Institute for Biomedical Imaging and Biomedical Engineering (NIBIB).

Alejandro Frangi, from the Universitat Pompeu Fabra, Spain, provided an overview on the vision of future application of the VPH concept. VPH will have to be aligned with, and benefit from, the broader perspective of future healthcare and hospital trends: patient-centric design; individualised risk assessment; clinical workflows; treatment strategies; converging medical technologies; federated information systems. The availability of more sophisticated real-time information processing techniques will ultimately leverage the most out of the current information sources and measurement systems. The VPH supports the modelling, interpretation and integration of multi-source patient information which otherwise would be inefficiently exploited, thus leading to a more solid understanding of disease. Finally, as one of the potential barriers to these concepts, it is essential that all applications of the VPH concept devote a substantial effort to clinical evaluation and dissemination in the clinical community.

### **3. Discussion & conclusions**

The VPH research initiative, which started in June 2005 with a white paper, has grown exponentially. It is now a priority in the EU FP7 research programme with a significant funding volume of €140 million. But there are many other international collaborations around the world, such as the IUPS Physiome project ,which is at the

origin of the integrative physiology, and many other US and Japanese multi-centre research activities relevant to the physiome.

The session concluded that the VPH approach will become a reality in clinical practice through a convergence of various technologies (medical imaging, medical devices, signal/image processing, computational modeling, etc...) if the VPH community can to address clinically relevant scenarios, in collaboration with the clinical community, which will ultimately be evaluated by demonstrating value added for clinicians and patients.

## **Session 1.2: Biomedical Informatics : information processing in human biology and disease**

**Chair: Fernando Martín-Sanchez** (Institute of Health Carlos III - Spain)

**Rapporteur: Alessandra Martini** (European Commission, DG INFSO/RTD)

### **1. Summary of the session**

The session was devoted to reviewing the current research challenges in the field of biomedical informatics. These challenges include the design of new clinical decision support systems for the effective use of organ and disease models developed under the Virtual Physiological Human (VPH) initiative, and the integration of specific “omic” and clinical patient data to illuminate the mechanisms of disease and discover and validate biomarkers in the framework of personalised medicine. The speakers described some examples of relevant ongoing projects and research activities that aim to overcome existing barriers in translational biomedical research through novel phenotype models and representations, integration of individual molecular information into the electronic health record, and semantic organisation, retrieval and interoperability of biomedical information.

### **2. Quick summary of the different presentations**

Fernando Martín-Sanchez from the National Institute of Health “Carols III”, Spain, introduced the session by providing an overview of the biomedical informatics (BMI) discipline, which works like a glue to connect together different types of research domains. The goal of BMI is to facilitate the integration and combined analysis of all the data relevant for the study, prevention, diagnosis and treatment of complex diseases, thus providing tools to enable individualised medicine. First, he gave an overview of the EC-supported activities in BMI (such as first workshop on BMI held in 2001, two roadmaps (Bioinfomed in 2002 and Symbiomatics in 2005)

analysing the synergy between medical and bioinformatics, and the ICT-LIFE meeting in 2004, where the VPH was identified at the top of the pyramid of BMI activities). Second, he gave an overview of activities in the US, where BMI is highly funded and many training programmes already exist.

Amnon Shabo, from IBM Haifa Research Lab, Israel, focused on the challenges involved in integrating molecular patient data into the Electronic Health Record, and described the EU-funded FP7 project Hypergenes. The project seeks to define a comprehensive disease model of essential hypertension (EH) by integrating new technologies of high-throughput genotyping with sophisticated statistical-mathematical modelling and genetic epidemiology. To address this challenge a Biomedical Information Infrastructure will be developed. The goal is to have a single information infrastructure providing both research and healthcare environments as well as all types of data (environmental, clinical and genomic) and finally serving the distributive nature of data in research and healthcare. Shabo emphasised the need for semantic interoperability and the use of internationally recognised health information standards to reach the project's objective. He presented the two main methods used for this purpose: the fusion of major standards (from HL7, IHE and CEN) into the Biomedical Information Infrastructure; and the constraint of generic standards such as the HL7 v3 Clinical Genomics, Clinical Document Architecture and CEN EHR 13606 to accommodate the unique semantics of the EH data in the Hypergenes cohorts. The EH-associated DNA variants will be placed on a lab-on-chip that will facilitate the personalised healthcare provided at the point of care.

Norbert Graf, from the University of Saarland, Germany, spoke from the clinical point of view on the challenges and needs in moving towards translational medicine. The completion of the Human Genome Project<sup>14</sup> sparked the development of many new tools for biomedical researcher looking for the mechanisms behind diseases. He described ACGT (Advancing Clinico Genomic Trials, an IP of FP6) as an example of why translational research in cancer needs informatics. The bottom-line: only with informatics as an integrated clinico-genomic environment can be delivered to the cancer research community. In achieving this objective ACGT has formulated a

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<sup>14</sup> [www.ornl.gov/TechResources/Human\\_Genome/home.html](http://www.ornl.gov/TechResources/Human_Genome/home.html)

coherent, integrated workplan for the design, development, integration and validation of all technologically challenging areas of work: delivery of a European Biomedical GRID infrastructure offering seamless mediation services for sharing data and data-processing methods and tools, and advanced security; semantic, ontology-based integration of clinical and genomic/proteomic data – taking into account standard clinical and genomic ontologies and metadata; knowledge discovery – the delivery of data-mining GRID services in order to support and improve complex knowledge discovery processes. Finally, Graf explained how the technological platform will be validated concretely in advanced clinical trials on cancer. The pilot trials selected are based on clear research objectives, raising the need to integrate data at all levels of the human being. Graf stressed that multidisciplinary teams working together are the key to success in translational medicine.

BMI was presented by Victor Maojo, from the Polytechnic University of Madrid, Spain, as a discipline that has changed clinical practice and expanded its scope. He began by with the history of BMI and the approach of integrating bioinformatics with medical informatics. He also explained, in the context of the Virtual Physiological Human, how BMI still has an enormous potential for facilitating research in all biomedical areas and for developing numerous applications with a great impact on healthcare. He described the recently funded coordinating action Action-Grid, which has two main objectives: to foster exchanges of BMI and Grid methods and tools among the EU, Latin America, North Africa and the Western Balkans; and to develop a white paper for the European Commission on challenges and demands in the BMI and Grid areas. The new Grid area of nanoinformatics was introduced as the new exciting frontier of biomedicine.

### **3. Discussion & conclusions**

The audience of the session considered the presentations to be very interesting. During their talks the invited speakers provided their visions of the future for the field of BMI, which could expand its scope beyond genomic medicine. Martín-Sanchez highlighted and discussed some of these new research topics in his conclusion remarks that are listed below:

- An integrated approach could provide a unified vision and help to overcome the existing gaps.
- Data on molecular basis of disease and on the patterns of individual genetic variation and environmental exposure should be incorporated into the new generation of models of human pathophysiology.
- Association studies can facilitate the identification of relevant pathophysiological processes that only then could be deciphered applying the approaches arising from systems biology and implemented through VPH models.
- Clinicians will need support systems for decision making, coupled with models that incorporate personal data.
- Preventive approaches require risk profiling based on Electronic Health Record and biomedical knowledge.

New trends (regenerative medicine, nanomedicine) pose new challenges for BMI.

## **Session 1.3: Computer-aided approaches to understanding ageing and its effects on health**

**Chair : Olivier Toussaint**, Université de Namur, Belgium

**Rapporteur : Beatrice Lucaroni**, European Commission, DG RTD, F4

### **1. Summary of the session**

To fully understand the ageing process and the causes of individual variation in ageing, we need a detailed knowledge of the underlying mechanisms. A better knowledge of the interplay of genes, nutrition, lifestyle and environment is crucial if Europe is to maximise the benefits of increased longevity. A key challenge is to bridge biology, medicine and computer science research, which traditionally have been separated by their conceptual approaches. One important need is to develop and apply a multidisciplinary approach to unravel the ageing process.

The session highlighted a series of EU-Framework Programmes funded projects that are furthering our understanding of human longevity and have shown how the systems biology approach developed within the projects can contribute to fast scientific progress. The modest number of delegates attending the session implied that much remains to be done in terms of promoting multidisciplinary.

### **2. Quick summary of the different presentations**

Tom Kirkwood, Newcastle University, United Kingdom, focused his presentation on how computer modelling can address the challenge of population ageing.

In showing us two pictures of the same person, taken at an interval of 50 years, Professor Kirkwood asked two simple questions: "What happened and why?" Ageing is a complex phenomenon, so we should follow the adage of the Nobel laureate Lord

Rayleigh in 1904:“Neither seek nor avoid complexity in finding the appropriate solution to a problem.”

Since we study multiple mechanisms, with multiple experimental models and human studies, we clearly need systems integration. Indeed, big questions cannot be answered by disconnected and separate studies, and the added value of data coordination justifies the effort required to integrate and share.

But without standardisation, experimental data are not comparable and much of the value of an experiment is wasted. With standardisation, each experiment contributes additively to previous data. So how can we introduce effective standards? What will be the impact on experimental design?

Key themes in ageing research are the investigation of the molecular consequences of telomere uncapping, DNA damage pathways affecting cellular ageing, the mitochondrial function and dynamics in cellular ageing, high-throughput robotic screening, functional network inference and analysis, biomathematical and statistical modelling, and systems biology data capture, management and integration.

CISBAN<sup>15</sup> (Centre for Integrated Systems Biology of Ageing and Nutrition) was created with these goals in mind. The CISBAN data portal is called SyMBA. A generic data capture system, it archives “raw” data, with high-throughput “omics”, images etc., captures and integrates a high level set of common metadata, and tags data with lifelong unique identifiers. Based on the Functional Genomics Experiment Object Model/Markup Language (FuGE-OM, FuGE-ML)<sup>16</sup>, it creates a systems biology data portal, archive, and data integration tool with a simple front-end web view for experimentalists.

Olivier Toussaint, Université de Namur, Belgium, introduced some of the complexities of ageing research, such as the study of stress, damage and biochemical activity. We still do not know whether these are the consequences or the causes of ageing but we believe that such factors could regulate lifespan. Obviously,

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<sup>15</sup> [www.cisban.ac.uk](http://www.cisban.ac.uk)

<sup>16</sup> <http://fuge.sourceforge.net>

understanding the molecular basis of ageing is a prerequisite prevention and intervention, early detection, diagnosis and therapy. The study of the stochastic accumulation of damage is key to ageing research. It is important to determine the extent and biological relevance of molecular damage as well as the efficiency and effectiveness of specific maintenance and repair pathways of cells, organelles (mitochondria, nucleus, etc.) and molecules (DNA, protein).

For many important diseases, ageing is the largest single “risk factor”. Understanding why aged cells and organs are more vulnerable to illness will open new paths to prevention and cure.

There is an urgent need for more powerful model systems (preferentially short-term models, new or improved models). These models should include cell systems (cellular senescence, reconstructed tissues, etc.) and model organisms (both “classical” and new ones) and allow translation and extrapolation to the human population. Models complement studies in humans. Long-term longitudinal studies on specific human populations (very old, young, centenarians, etc), as in the GEHA<sup>17</sup> FP6 contract, also need to be performed.

Dr. André Schrattenholz, ProteoSys AG, Mainz, Germany, explained how systems biology provides novel concepts to tackle ageing research.

Protein biomarker signatures, against a background of fast cellular signal transduction and post-translational modifications, are becoming more and more of a core occupation in systems biology. Relatively small genomes, like the roughly 20,000 genes in humans, are translated to an unknown number of highly dynamic protein molecules, ranging in the millions. This imposes strategic challenges on the analytical side, due to the huge dynamic range of protein concentrations and the sometimes very rapid kinetics of post-translational modifications.

The major disadvantage of current nucleic acid-based high-throughput technologies is that they cannot detect redundant post-translational protein isoforms. Nor can they match the dynamic range or the kinetic timescales of protein changes. The

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<sup>17</sup> [www.geha.unibo.it](http://www.geha.unibo.it)

changes in oxidation, phosphorylation or proteolytic cleavage that typically occurring during age-related events can take place in seconds.

Recent results from the work performed by André Schrattenholz's group in the MIMAGE<sup>18</sup> FP6 project have been used to illustrate the related oxidative changes in a few key proteins and the network implications for the pathways where these biomarkers integrate normal cellular function and certain age-related oxidative damage.

Annexin A3<sup>19</sup>, a novel biomarker for prostate cancer, is an example of what is needed to move from purely descriptive phenomena to validated surrogate biomarkers in a clinical/biological setting, using large numbers of samples. The presentation ended showing how quantitative protein biomarker information is used in drug development (essentially generating series of modified protein-reactive drug-derivatives which are used for affinity-based capture of interacting proteins).

### 3. Discussion & conclusions

Ageing research has become established in Europe only over the past two decades. EU support to R&D has been an important stimulus but much still needs to be done. At the national level, several European countries have seen the establishment of the first research centres on ageing. Critical mass should be promoted through the integration of theoretical modelling of ageing, mechanistic research and systems biology.

Challenging issues ahead of us will be to routinely integrate biology and bioinformatics to identify, define and compare the mechanisms of ageing which are conserved, from simple systems to humans. Following this road will allow the translation of knowledge from one system to others and strongly contribute to the identification and understanding of the interactions governing ageing in humans.

Although the genomes of [organisms](#) are relatively small and quite similar across nearly all species, their biological reality is complex. This is primarily due to the

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<sup>18</sup> [www.mimage.org](http://www.mimage.org)

<sup>19</sup> [http://en.wikipedia.org/wiki/Annexin\\_A3](http://en.wikipedia.org/wiki/Annexin_A3)

proteins and their changes over time, implying that systems biology will be largely a proteomic exercise with a huge analytical challenge. Applying this concept to ageing research requires first of all a correct understanding of the key ageing mechanisms and of age-dependent post-translational modifications; then the development and study of robust models of ageing; the handling of large data sets relevant for systemic investigations of age-dependent molecular and functional events; and the use of advanced approaches, including novel mathematical concepts, to analyse data.

This is why there is an ever-growing number of experimental strategies aiming to exploit the emerging potential of “systems biology” concepts in drug development and biomarker discovery. Many novel treatments for human diseases will be proteins themselves, hence “biologicals”.

# Session 1-4: Systems Biology and Modelling of Diseases Relevant Pathways

**Chair: Olaf Wolkenhauer**, University of Rostock

**Rapporteur: Jacques Remacle** (European Commission, Unit F4, DG RTD)

## 1. Summary of the session

This session was dedicated to mathematical and computational modelling approaches to important biological pathways relevant to health and diseases and how these models could foster the prediction of strategies for effective intervention and thereby facilitate the design of novel therapeutic strategies. Three EU projects were presented: COSBICS, CANCERSYS and APOSYS. These projects involve strong collaborations between biologists, mathematicians and computational scientists, to develop predictive dynamic modelling approaches of important signalling pathways commonly subverted in cancer. These presentations demonstrated how computational modelling can make progress in understanding these complex biological pathways and their role in disease.

Following the presentations, a fruitful discussion with the participants took place. Following this discussion, the chair wrapped up some conclusions.

## 2. Quick summary of the different presentations

Olaf Wolkenhauer, from the University of Rostock, Germany gave a short introduction of the session topics. He presented the SysBioMed survey, which explored the potential of systems biology for medical research, therapy and drug development and aimed at establishing a strategic vision for the future of the field. Wolkenhauer also presented COSBICS<sup>20</sup>, a project that is establishing and applying a

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<sup>20</sup> <http://www.sbi.uni-rostock.de/cosbics/index.html>

novel computational framework to the investigation of dynamic interactions of molecules within cells. Instead of simply mapping proteins in a pathway, COSBICS is concerned with “dynamic pathway modelling”. Dynamic pathway modelling establishes mathematical models to quantitatively predict the spatial-temporal response of signalling pathways and subsequent target gene expression.

Boris Zhivotovsky, from the Karolinska Institute, Sweden, presented the APOSYS<sup>21</sup> project. Experimental biologists, biomathematicians, biostatisticians and clinical scientists are teaming up in APOSYS to approach cell death signalling in health and disease, placing particular emphasis on cancer and AIDS. He clearly indicated that the knowledge of complex diseases like cancer will strongly benefit from systems biology approaches since these diseases involve complex interactions between many genetic and environmental factors.

Jan G. Hengstler (IfADo, Germany) and Dirk Drasdo (French National Institute for Research in Computer Sciences and Control) presented the CancerSys project. CancerSys investigates molecular and cell-biological processes in the formation of tumours in the liver. The researchers will create mathematical models on the basis of quantitative molecular and cell-biological tests and then build a bridge from this set of formulas to the visible changes caused by the cancerous process in the liver. CancerSys also signifies an expansion and better visibility for German systems biology research, especially for HepatoSys, on an international level.

### **3. Discussion & conclusions**

Several points were raised during discussion:

- Modeling should help scientists to develop their experimental procedures and strategies for optimal experimental design
- Systems biology is not feasible without mathematics. Systems theory is a field of mathematics applied to dynamic systems. A distinction should be made between statistical modelling and systems modelling.

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<sup>21</sup> <http://www.apo-sys.eu/>

- Medical sciences and pharmaceutical industry make insufficient use of modelling
- Existing funding mechanisms are not suited to the comprehensive systems biology approach, which requires large collaborative networks
- Medical and biomedical training should include more and more quantitative rather than qualitative approaches for experimentation.
- Success will come once enough high-quality quantitative data becomes available.
- When we talk about the approach, we should say “integrative” rather than “holistic”
- We should also say “mathematical modelling and computer simulation” rather than “computer modelling”.

## **Conclusions**

Systems biology will help understanding complex biological systems by implementing a shift from a reductionist to an integrative approach and the use of quantitative data. Today, we are still in an intermediate situation. Most researchers are still using reductionist approaches as they have over the past 50 years. Even now the move towards integrative approaches is ongoing, further progress will be catalysed by better training of the researchers in mathematics by adapting funding instruments to allow comprehensive systems biology approaches.

# Session 1-5: Medical imaging and ICT for clinical applications

**Chair: Markus Schwaiger** (Technical University Munich)

**Rapporteur: Philippe Jehenson** (European Commission, Unit F5, DG RTD)

## **1. Summary of the session**

About 60 people attended this session on new multimodal medical imaging techniques being developed that need ICT (software, image processing, modelling, simulation, and so on.) for their development and use. The final aim is new or improved applications in the clinics, for the direct benefit of patients. The focus was on simultaneous multimodal imaging, that is, on the combination of different imaging techniques, such as PET (positron emission tomography), CT (X-ray computerised tomography), or MRI (magnetic resonance imaging) to provide more and better information than the techniques separately.

After a general introduction by the session chair, Markus Schwaiger from the Technical University Munich, Germany, on translational aspects of molecular imaging, three EU FP 7 projects that started recently were presented. These projects involve strong multidisciplinary collaborations and their ICT aspects were emphasised. These presentations demonstrated the current and potential importance of imaging for medicine and of multimodal imaging in particular, and how ICTs are important in the difficult development of these techniques and in their normal functioning in the clinics. Speakers also gave some ideas on future research challenges.

## 2. Quick summary of the different presentations

Steffen Rennisch from Philips Research, Germany, looked at the ICT challenges posed by the concurrent combination of PET and MRI, and the HYPERImage<sup>22</sup> project. When the diagnostic modalities of MR (or MRI) and PET are combined, he said, this opens up a wide range of new clinical applications, especially in oncology, cardiology and neurology. The HYPERImage project aims at building a prototype system of a fully integrated PET/MR-scanner that is capable of concurrent acquisition and in addition features a time-of-flight-capable PET detector – thus improving PET image quality beyond the current clinical standard. But many challenges remain to be overcome before the capabilities of this system can be exploited fully. Rennisch emphasised two of the ICT-related challenges in his talk. One challenge is MR-based attenuation correction for PET, where two approaches are pursued, the first one using a model-driven segmentation of the MR-image with attenuation values assigned to the segments subsequently, with the second using several MR-sequences with complementary contrast. The second challenge highlighted in the talk is the motion correction of the PET acquisition, which could be based on MR-navigator sequences together again with a model of the respective motion of the patient (for example, breathing motion or heartbeat). On the other hand, a fully integrated PET/MR-system will be a superb tool for verifying and validating many functional aspects of models of human biology, an example being much more robust and reliable pharmacokinetic modelling.

Daniel Razansky from the Technical University and Helmholtz Center Munich, Germany, discussed whole-body optical imaging using multi-modality approaches and the FMTXCT project. Optical imaging of tissues has recently opened new pathways to study many pathological processes *in vivo*. This results from the great variety of probing mechanisms that can be used for tissue interrogation by light, from intrinsic functional information on blood oxygenation to molecular sensing. Over the past decade, progress in optical technologies and in the modelling of light-tissue interactions has also enabled whole-body tomography of numerous tissue biomarkers in living organisms. The use of fluorescent proteins and other exogenous

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<sup>22</sup> <http://p101002.typo3server.info/?id=>

optical agents has further advanced noninvasive photonic imaging by allowing the visualisation of otherwise invisible molecular processes associated with diseases such as inflammation and tumour progression. His talk focused on multi-modality and hybrid approaches that will lead to the next generation of high-performance imaging systems utilising the optical spectrum, such as the combination of fluorescence molecular tomography (FMT) with X-ray CT and multi-spectral opto-acoustic tomography (MSOT).

Finally, Risto Ilmoniemi from Helsinki University of Technology, Finland, described a hybrid MEG-MRI device: the MEGMRI project. MEGMRI will combine magnetoencephalography (MEG) and MRI by building a sensor array capable of simultaneous MEG and low-field MRI. These two techniques are of great interest for the study of the brain, and in particular its function, both in health and disease. The hybrid instrument will lead to highly accurate and reliable alignment of the MEG and MRI coordinate systems, because both recordings are taken with same detectors at the same time. The combination of the two techniques may also save significant amounts of time where high-field, high-resolution MRI is not needed. In other cases, the distortion-free low-field MRI can be used to correct geometrical distortions of high-field MRI. Furthermore, low-field MRI is safe (no projectile danger, less effect on cardiac pacemakers or other implants) and acoustically quiet. It will have a good signal-to-noise ratio and superior T1 contrast. Much of the development work will aim at reducing the long measurement times that are needed with present methods. New sensor technology suitable for this application is being developed within the project.

### **3. Discussion & conclusions**

A number of participants, including the speakers and chair, said they liked the session – for example, describing it as a “very interesting session on hybrid imaging”. It was clear that all techniques presented have an interest for both research and clinical applications.

The questions raised by the audience mainly concerned the MEG/MRI combination. The interest of having a simultaneous acquisition, for instance in MEG/MRI, was clearly explained as strongly limiting the possible positioning errors that could

otherwise occur when trying to superpose the signals. For instance, an error of more than 5 mm can easily occur in the brain localisation, which can be highly important, for instance for brain surgery. Spatial resolution of MEG was also discussed.

All speakers also shortly highlighted the main challenges that they saw in the specific projects or in the field. A number of the discussions on future challenges will be further developed in a 1.5 day workshop in November 2008 in Brussels (focused on imaging and *in vitro* molecular testing only).

# Session 1-6: Multi-scale Cardiovascular Modelling

**Chairs: Dr. Olivier Ecabert** (Philips Research Europe – Aachen)

**Dr. Nicolas Smith** (University of Oxford)

**Rapporteur: Karin Johansson** (European Commission, DG INFSO/RTD)

## 1. Summary of the session

The session sought to outline the state-of-the-art and current research challenges in the mathematical and computational modelling of the heart for improved clinical outcome. An additional aim of the session was to foster the interactions between the scientific, clinician and industrial communities needed to achieved the ambitious goals of the Virtual Physiological Human(VPH).

## 2. Quick summary of the different presentations

Nicolas Smith from University of Oxford, United Kingdom, opened the session with a presentation entitled “Introduction: Current State and Future Challenges for Cardiovascular Modelling”. The presentation outlined the session’s aims, and gave a brief overview of the current state of cardiovascular modelling and the future challenges faced by the modelling community, such as: coupling of data to models; non invasive personalisation; clinical translation; and multi-physics integration.

Andrew McCulloch from University of California San Diego, United States, talked about “Systems Biology and Multi-Scale Modelling of the Heart”, where he provided an overview of the different levels of modelling required as well as detailed examples of on-going research activities in the field.

Working on a model organism (*Drosophila melanogaster*), hypoxia response and its regulatory control was studied and modelled using constraint-based models, where constraints of various natures were imposed on a function describing all possible

variations, after which an optimal solution was found by solving the function within the constraints. Subsequent genetic perturbation analysis led to the identification of new candidate genes involved in hypoxia response.

Other areas studied included  $\beta$ -adrenergic regulation of excitation–contraction coupling and Long QT syndrome, and in several examples showed that the models constructed could accurately predict the physiological behaviour seen in patients. The presentation also highlighted the need to couple models on different levels (here: from cell to system level) and it was suggested that the addition of a baroreflex model would provide feedback on a cellular level, thus closing the loop.

Yiannis Ventikos from the University of Oxford, United Kingdom then looked at the topic of simulation techniques for personalised medicine, in particular multiphysics and multiscale modelling for vascular disease. Ventikos pointed out that the use of computational models is a very promising method to meet the increasing demands for better and more cost-effective disease diagnosis that are being placed on healthcare systems, and he highlighted three points of particular importance when creating clinically relevant models: the compromise between being comprehensive and practical; the case for validation; and the logistics connected with uptake

Ventikos proceeded to show examples of areas where computational models have been developed for specific cardiovascular conditions, such as aortic dissection, and cerebral aneurysms that cause thrombosis. For aortic dissection, he showed how intelligent remeshing techniques can be used to model this condition, and how a coupling of four modelling techniques (computational haemodynamics, thrombosis modelling, deformable domains remeshing and 1D modelling to account for small spinal feeders) leads to a clinically relevant model. For cerebral aneurysms, he showed how growth and rupture modelling leads to better understanding of the behaviour of an aneurysm and consequently of its risk of rupturing. Ventikos also showed how the result of a treatment (the insertion of a platinum coil to minimise blood flow in aneurysm) could be simulated and evaluated on a patient-specific basis to determine the effect of the planned treatment.

Reza Razavi from King's College London, United Kingdom continued the clinical theme in his presentation on cardiovascular modelling from a clinical application

perspective, arguing that recent advances in medical imaging have enabled dramatic improvements in the diagnosis, surgery planning and therapy of cardiovascular disease. These developments, together with improvements in computing and numerical techniques, now enable the use of multi-scale and multi-physics computational models to simulate the cardiovascular system.

Razavi illustrated his point with the example of cardiac resynchronisation therapy (CRT), which only has a 60% success rate in spite of very stringent patient inclusion criteria. The use of patient-specific cardiac models increases the success rate of the procedure; – partly by providing a better basis for patient inclusion, and partly by allowing for simulations of the placement of the implanted device to maximise its use for each individual patient.

His conclusion: a new era in management of cardiovascular disease has begun where computational models of the cardiovascular system will play a large role. In order for them to be more widely accepted in the diagnosis and treatment of patients, it is also important to do the following: show first-in-man clinical translation in different cardiovascular diseases; educate the clinical cardiology community about the potential of these advances; do rigorous trials to show the clinical and health economic benefits of these technologies

Next, Peter Hunter from University of Auckland, New Zealand, and the University of Oxford, United Kingdom presented on “Physiome<sup>23</sup> Project contributions to multi-scale modelling in the heart. Current developments and future directions”. He provided an overview of the different levels and scales involved in cardiac modelling before going into details about some recent developments in cardiac modelling within the areas of geometry and fibrous-sheet structures, ventricular mechanics, myocardial activation, coupled electro-mechanics, and the modelling of cell processes.

Hunter also listed the topics that he predicted would become focus areas over the next few years of cardiac modelling, such as models coupling the electro-mechanics of the heart with computational fluid dynamics, further integration of cellular

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<sup>23</sup> [www.europhysiome.org](http://www.europhysiome.org)

processes, 3D cell modelling and coarse-grained molecular modelling. From a more general modelling point of view, he also saw a need for open source software; markup language standards for encoding models; web-accessible model databases; and high performance computing and grid-enabled tools for collaboration

Olivier Ecabert of Philips Research, Germany, concluded the session by providing an overview of the cardiovascular modelling projects currently funded under the VPH theme and of their application areas.

### **3. Discussion & conclusions**

One question for Andrew McCulloch related to the status of modelling of hypertension, and the response indicated that in order to be able to model hypertension successfully one must first learn more about the signals which drive the remodelling of myocardium at pressure overload. Another question concerned the level of detail needed for a model to be clinically useful. The answer was that this very much depends on the clinical question, and that while simplified models may work well for a well defined clinical issue it is difficult to add new information (such as drug interactions) to them in a meaningful way. This view was supported by Yiannis Ventikos, who offered a similar analysis in his presentation.

Reza Razavi was asked what he sees as the big next challenge in cardiovascular modelling from a clinical perspective, and his response was that it will be the modelling of chronic heart effects (as opposed to acute ones which is the current state-of-the-art). To a follow-up question about the extent to which such effects can be covered using existing models, he replied that the current models can probably cover some of the effects but that further research and modelling efforts certainly would be needed in order to be able to predict the effects correctly.

Interest in the topic was evident in the questions posed to the speakers as well as in the number of separate discussions that took place between members of the audience and the speakers immediately after the end of the session.

# **Session 2-1: Multiscale modelling of the muscular-skeletal system**

**Chair: Marco Viceconti** (Istituto Ortopedico Rizzoli)

**Rapporteur: Alessandra Martini** (European Commission, Unit H1, DG INFSO)

## **1. Summary of the session**

The session provided an overview of some of the most exciting research developments in musculoskeletal multiscale modelling, the musculoskeletal system being one of the most promising targets for the application of simulation methods in clinical practice. A summary of the current state of the art in this field at European and international level was presented. In addition, speakers defined the research challenges and set out a vision of the future in this area

## **2. Quick summary of the different presentations**

Marco Viceconti from the Istituto Ortopedico Rizzoli, Italy, and coordinator of the VPHOP<sup>24</sup> project, introduced the theme of the session and provided an overview of the muscular skeletal diseases and osteoporosis in particular, addressing both clinical and societal implications. He explained how and why the prediction of osteoporotic fractures is complicated, since it is a multi-scale process (from the whole body down to the cells and molecules), and stressed the need to deal with multiple levels in order to develop technology that can predict bone fractures with high accuracy and thus deliver better solutions.

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<sup>24</sup> [www.vphop.eu](http://www.vphop.eu)

Antonie van den Bogert from the Cleveland Clinic Foundation in Ohio, United States, presented an overview of the aims and achievements of the SIMBIOS<sup>25</sup> project in musculoskeletal modelling. SIMBIOS (physics-based *simulation of biological structures*) is based at the NIH Center for Biomedical Computation at Stanford University, California, and musculoskeletal modelling is one of its main focuses. Van den Bogert described the simulation toolkit SimTK<sup>26</sup>, which is stimulating groundbreaking biomedical research by enabling the development and sharing of physics-based models and simulations. The website and infrastructures provide a collaborative environment for user communities of physics-based modelling. Van den Bogert also presented the collaborative work between the Cleveland Clinic and SIMBIOS on concurrent simulations of tissue mechanics and optimal control of movement for applications such as computer-aided design of safer movement strategies (to prevent injury), musculoskeletal surgery, and the design of prosthetic and orthotic devices. He concluded by showing how predictive models of the whole musculoskeletal system can be used to investigate human movement in microgravity, a topic relevant to long-term space missions.

Ryutaro Himeno, from RIKEN, Japan, presented RIKEN's experience in voxel = A **voxel** is a volume element, representing a value on a [regular grid](#) in 3D. This is analogous to a [pixel](#), which represents [2D](#) image data. Voxels are frequently used in the visualization and analysis of [medical](#) and [scientific](#) data. Some [volumetric displays](#) use voxels to describe their resolution)-oriented strategies for multiscale integrative modelling. The presentation focused on RIKEN's development of a petaflop supercomputer (10 petaflops), which is due to become operational in 2012. The supercomputer will have two branches of applications. The first is the "Life Science Grand Challenge" to arrive at a total simulation of living matter. The objective is to arrive at a comprehensive understanding of life phenomena, to create new computer-aided medicine and to develop medical and surgical treatment. Two approaches will be followed: theoretical simulation, with teams for molecular, cell and organ/whole body simulations; and a data-driven approach, with one team for data analysis. Within a few years these four teams plan to complete their models and

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<sup>25</sup> <http://simbios.stanford.edu/>

<sup>26</sup> <http://www.simtk.org>

integrate them into a single software environment, which will be based on the voxel human model. This approach is expected to solve one key issue: the automatic conversion of medical imaging data into predictive models that is needed to make these technologies fully usable in clinical settings. In summary, the mission of this Life Science Grand Challenge is to go directly from medical images to patient-specific simulation.

Fulvia Taddei, from the Istituto Ortopedico Rizzoli, Italy, talked about how multiscale modelling might operate at the body and organ levels to predict the risk of spontaneous fractures. Taddei is involved in VPHOP, an FP7 EU-funded integrated project that focuses on the musculoskeletal system and aims to develop the next-generation technology to fight osteoporosis. She presented the project's work in developing patient-specific probabilistic models at the body-organ level capable of predicting the loading spectrum that patients apply to their bones during daily life. She then discussed the state of the art and the open challenges at body and organ level. These challenges include developing fully validated automatic procedures to predict the risk of femoral and vertebral fracture, and obtaining 3D information on density distribution from less-invasive imaging systems, to include subject-specific information on tissue structure and evolution over time. Taddei also talk about the plan for a clinical and functional assessment, with a clinical study of 100 to 200 patients and an intensive function assessment of 40 to 80 patients. The results of this functional analysis will provide input for the musculoskeletal analysis, which in turn will complete the hypermodel at the organ level.

In the final presentation, Ralph Müller, ETH-Zürich, Switzerland, focused on modelling tissue and cells to predict changes over time to aid the pharmacological treatment of osteoporosis. He showed how multiscale modelling can link clinical observations of organ tissue with laboratory observations of cells and molecules. Müller started with the hypothesis that multiscale computer modelling allows the use of different optimisation goals to reproduce systematically the shape and architecture of bone, giving examples of existing models and simulation on the bone under mechanical stress. Other factors – such as hormones (genetic factors), drugs and biomechanical stress – are important in bone, and he gave different scenarios of bone strength and density for patients with or without bisphosphonate treatment.

The last part of the talk focused on the current need for validation in animal models *in vivo*. In the VPHOP project, Müller and his collaborators will use *in vivo* scanning to follow up the animal models and have a longitudinal *in vivo* study. His conclusion? It is possible to simulate bone modelling and remodelling in health and disease. It is also possible to predict the effects of pharmacological intervention by simply changing cell parameters (though that will require modelling of gene–protein and cell interaction, and better integration of the organ level). And finally, only multiscale approaches can integrate the different levels of hierarchy.

### **3. Discussion & conclusions**

The feedback from the audience was very positive and the presentations were considered very interesting. The audience recognised that musculoskeletal diseases are very important (high incidence and mortality, high burden on healthcare systems) and difficult to study because they are multiscale processes. Current technology cannot cope with the complexity involved. The development of computational models of the musculoskeletal system is extremely relevant to the delivery of predictive tools to improve preventive medicine and treatment. This is an important challenge, to be addressed at a global level.

Some questions were addressed to Antonie van den Bogert on the general approach used in the models presented and the strategy needed to be patient-specific, a direction that all modellers are aiming at. The curation issue was raised, with reference to the needs for models of cellular and metabolic processes relevant for the musculoskeletal system to be curated in the CellML repository. Finally, delegates discussed at length the need to go to full validation of the models (which would require five-year retrospective studies).

# Session 2-2 : Quantitative Imaging Biomarkers for Modelling Health and Disease

**Chair: Gabriel Krestin** (Erasmus Medical Centre)

Rapporteur: **Loukianos Gatzoulis** (European Commission, Unit H1, DG INFSO)

## **1. Summary of the session**

The session focused on the development and validation of quantitative image analysis and modelling methods to extract accurately, robustly and reproducibly anatomical, physiological, biochemical and biophysical parameters from biomedical images, in order to determine the presence and state of a disease, as well as to monitor treatment and follow up. In view of the prominent role of medical imaging in clinical practice and the rapid developments in biomedical imaging technology, biomedical image analysis is a very active and exciting area of research. There are several urgent needs: for computational tools to enable visualisation of imaging data; for the fusion and integrated analysis of data from multiple imaging modalities; for quantitative analysis of biomedical imaging data; and for modelling techniques to interpret the imaging data.

## **2. Quick summary of the different presentations**

Gabriel Krestin, from Erasmus Medical Centre, the Netherlands introduced the theme of the session and explained how the development of medical imaging has brought capabilities to image not only morphology, but also function down to histological and molecular levels. Krestin also provided a definition for biomarkers and indicated the multiple roles of their use, for example, predictive, prognostic, diagnostic, pharmacodynamic and therapeutic. Several successful examples of imaging biomarkers were mentioned, such as liver lesion size in oncology, bone density and fractures in osteoporosis and the percentage of lumen stenosis in

cardiovascular diseases. The validation of imaging biomarkers is associated with a number of challenges. Some refer to the standardisation of procedures, the production and measurement of reference standards, the evaluation of equipment, and the choice of image reconstruction and segmentation algorithms. The goal is to ensure consistent reproducibility and replication, low inter-rater variability, association between biomarker and clinical endpoint, and cost-effective impact on disease management.

Anwar Padhani, Mount Vernon Hospital, United Kingdom, discussed the clinical need, illustrating how imaging biomarkers are used today in clinical practice and drug development. The goal of medical imaging is to improve outcomes, and over the years medical imaging has transformed the way that patients are managed. For example, the invitation alone to breast cancer screening by mammography can lead to 20% reduction in mortality. But there is still a lot of room for improvement in imaging techniques to reduce the false positives and false negatives and to help monitor the response to treatment. Some early indications suggest that contrast-enhanced MRI is almost twice as sensitive as X-ray mammography in breast cancer screening in young women. PET imaging can be used to predict which cancer patients will respond well to treatment. In non-Hodgkin's lymphoma, for instance, alternative therapies could be applied earlier if a patient's lack of response after the first course of chemotherapy could be predicted early.

Medical imaging can also be important in drug development. Contrast-enhanced MRI can indicate whether a drug works, for example, by showing that the drug stops blood flow to a tumour. Imaging can also reveal the effective biological dose for a particular patient (it differs from patient to patient). In conclusion, said Padhani, imaging biomarkers have key decision-making roles in the clinic and in drug development. Yet although biomarkers are continuously being developed and refined at different rates, their validation remains problematic as there are no agreed frameworks for their development.

In his presentation on the development of quantitative imaging biomarkers Wiro Niessen, Erasmus Medical Centre and Delft University of Technology, The Netherlands, emphasised a prerequisite for their acceptance: proof that they are

accurate, reproducible and effective for patient management. The accurate, reproducible extraction and validation of candidate imaging biomarkers from multi-modal imaging data will require quantitative image analysis methods, he said. Niessen gave examples of imaging biomarkers for applications in neurodegenerative diseases, cardiovascular diseases and cellular imaging. For instance, the volume of hippocampus is used as biomarker for Alzheimer's disease, while the degree of lumen stenosis is used as biomarker in cardiovascular diseases. There are efforts to establish the lumen stenosis reliably in quantitative terms with the help of 3D imaging. Cardiovascular imaging has also shifted attention to imaging the vessel wall to identify vulnerable plaques at risk of rupture. Plaque characterisation techniques are applied on imaging data to identify calcified, fibrous and lipid plaque.

Only a few of the new techniques underlying the development of potential imaging biomarkers make it to market, because there is no standardised way to validate them. What is required is a validation framework with standardised evaluation criteria and software to help validate candidate imaging biomarkers, taking advantage of the availability of large image databases, patient characteristics and genetic information.

Hervé Delingette, INRIA, France, discussed image-based modelling and simulation of health and disease, showing how VPH (Virtual Physiological Human) models can be used to extract potential biomarkers. The important thing, said Delingette, is to choose the right level of model complexity. Models need to be compatible with the observation scale in images, while the number of parameters defines whether the model can be personalised or not, he said, giving examples from cardiac and tumour growth modelling. Given the available MR images, the challenges in modelling tumour growth lie in the ability to characterise tumour evolution, predict future progression and personalise therapy. Delingette showed how a multilevel model (encompassing geometry, statistics, biomechanics and physiopathology) can simulate brain tumour growth in 3D, in reasonably good agreement with the growth revealed in MR images. This is, of course, at an early stage of development and further validation is needed with a sufficiently large database of patient data that includes, for each patient, high-resolution MR images taken at several points in time. But the combination *in vivo* medical images with *in silico* models of life to provide

new tools to analyse and simulate tumour evolution, quantify diagnosis and optimise therapy has great potential.

### **3. Discussion & conclusions**

Delegates appreciated the presentations greatly. The discussion that followed focused on validation.

There are problems associated with the validation of biomarkers. First, there is the need to ensure that measurements are made correctly. Second, it is important to establish that what is measured is clinically meaningful. Unfortunately, few researchers are willing to work on the validation of biomarkers. The work is not considered very attractive, yet it is costly and requires extra funding. Funding authorities are not very supportive: while considerable funding for development work is available, funding for translational work into clinical practice is low. Many biomarkers have been developed and are available. The issue now is to translate them into use.

It was recognised that VPH models are interesting, but unless they are clinically validated, they remain simply interesting. Establishing the predictive power of models boils down to their validation. Models are based on validated theories, but patient variability is high and models struggle to describe this variability. To be useful, personalised models need to be seen in conjunction with the original data. A simple one-time mapping from the image-space to the model-space is not desirable.

There is no need necessarily to go for large multi-centre trials. Other, smart methodologies are required to reduce the time it takes to validate biomarkers and models and so shorten the length of drug development trials by a considerable amount of years.

## Session 2-3: Research Infrastructures as a support to Systems Biology approaches

**Chair: Janet Thornton**, European Bioinformatics Institute (EBI)

Rapporteur: **Jean-Emmanuel Faure** (European Commission, Unit B3, DG RTD)

### **1. Summary of the session**

This session was dedicated to exploring system biology's requirements for research infrastructure. Four infrastructure projects were presented: ELIXIR, European Life Sciences Infrastructure for Biological Information, by Janet Thornton; EMAP and DGEMAP, digital atlas and databases of mouse and early human development, by Richard Baldock; EUROCarbDB, a repository of carbohydrate data and associated bioinformatics tools, by William E. Hull; and DEISA, Distributed European Infrastructure for Supercomputing Applications, by Hermann Lederer. These presentations stressed the importance of availability, quantity and quality of data, for the development of models and simulations. They discussed how much data curation, standards, and interoperability are central to this scope. They outlined the need for appropriate and sustainable funding.

### **2. Quick summary of the different presentations**

Janet Thornton, European Bioinformatics Institute, EBI-EMBL, UK, stressed the enormous challenge: the foreseen burst of data is now a reality, in particular with the sequencing of thousands of genomes. There is too much information for the EBI along to preserve, curate and make core data accessible to the scientific community. Other European nodes need to be developed as well as sustainable funding. It is also essential to complement the data with sets of tools to manage and interpret them.

The ELIXIR<sup>27</sup> preparatory phase project based on the ESFRI roadmap<sup>28</sup> (European Strategy Forum for Research Infrastructures), aims to help to build and run a sustainable infrastructure for biological information in Europe. The project is to produce a memorandum of understanding between government agencies, research councils, funding bodies and scientific organisations in the member states.

One important component of the project is the assessment of data resources needed for systems biology (work led by Nicholas Le Novere). Thornton explained the primary knowledge currently seen as necessary: lists of parts (genes, macromolecules, small molecules), intrinsic properties of parts (sequences, structures, activities and functional parameters), contextual properties (amounts and concentrations, locations and distributions), relationships (molecular interactions, functional interactions, hierarchy) and phenotypes (physiological datasets, pathologies). Secondary knowledge such as kinetics, pathways data and quantitative models is needed as well, she said. Many of the primary data are not yet available on a large scale, it is even more challenging to obtain and make accessible secondary knowledge. Last but not least, core software support is required, and standards are an absolute need.

Richard Baldock from the Medical Research Council's Human Genetics Unit, UK, said that data images are being generated on an unprecedented scale. The challenge is to integrate these into resources that can be exploited by the scientific communities. Baldock gave two examples of such integrations. First, he described the Edinburgh Mouse Atlas Project (EMAP<sup>29</sup>), a digital atlas of mouse development and database that is to be a resource for spatially mapped data such as *in situ* gene expression and cell lineage. He also described the Developmental Gene Expression Map (DGEMAP<sup>30</sup>), which is dedicated to the analysis of gene expression patterns in early human development. Baldock also outlined his views about data requirements for systems biology: its data property needs are about spatial and temporal annotation, 2D/3D

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<sup>27</sup> [www.elixir-europe.org](http://www.elixir-europe.org)

<sup>28</sup> <http://cordis.europa.eu/esfri/roadmap.htm>

<sup>29</sup> [genex.hgu.mrc.ac.uk](http://genex.hgu.mrc.ac.uk)

<sup>30</sup> [www.dgemap.org](http://www.dgemap.org)

patterns, quantification, and resolution from the organism to the cellular level; its data access needs relate to being able to directly access, browse and download data, directly access computation, and about interoperability with other resources.

William E. Hull from the German Cancer Research Center presented the European Carbohydrates Databases project (EUROCarbDB<sup>31</sup>), which is designing a large unified data collection for carbohydrates. Standards, rules and formats for collecting the biological and analytical data are being defined, together with good practice and procedures for quality control.

Hermann Lederer from the Rechenzentrum Garching, Max-Planck Gesellschaft, Germany, gave a short presentation indicating that opportunities already exist under the DEISA<sup>32</sup> project (Distributed European Infrastructure for Supercomputing Application) for life sciences researchers to access High-Performance Computing capacities .

### 3. Discussion & conclusions

- Direct access to data and computation is necessary. Data gathered should be openly available to the maximum extent, with the possibility of browsing and downloading them.
- Data repositories are essential for systems biology and need appropriate and sustainable funding.
- The explosion in the quantity of data is a critical challenge. The existing efforts around EBI will not be sufficient: the development of other nodes in Europe will also be necessary to address new types of data.
- An option worth investigating is the idea of “taxing” research projects in life sciences with the objective of systematically reserving funds for data storage, maintenance and access.

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<sup>31</sup> [www.eurocarbdb.org](http://www.eurocarbdb.org)

<sup>32</sup> [www.deisa.eu](http://www.deisa.eu)

- Data curation, standard setting and interoperability are critical issues. Data quality is a topic of concern. In particular, mechanisms should be set to identify the level of data quality.
- Systems biology requires access to both primary knowledge (sequences, structures, concentrations, locations, distributions, interactions, etc.) and secondary knowledge (such as kinetics, pathways data and quantitative models).
- Several efforts address the gathering of primary knowledge. Obtaining and making accessible secondary knowledge is more challenging.

## Session 2-4: Modelling of the Immune System

**Chair: Thomas Höfer**, German Cancer Research Center (DKFZ)

**Rapporteur: Bernard Mulligan**, European Commission, DG RTD

### 1. Summary of the session

This session addressed computational modelling approaches to understanding the huge complexity of the adaptive immune system, which is our safeguard against infection and diseases such as cancer. The immune response is controlled by a complex network of cell–cell interactions and the concerted activation of several cellular pathways. Dysfunction of the immune system can lead to severe autoimmune diseases such as multiple sclerosis.

Three EU projects were presented in this session: SYBILLA<sup>33</sup> by Thomas Höfer, ImmunoGrid<sup>34</sup> by Elda Rossi and MODEL-IN by Gioacchino Natoli.

The SYBILLA project involves strong collaboration between biologists, mathematicians and computational scientists to develop predictive, dynamic modelling of T-cell activation, one of the critical steps in the activation of the immune response. Attention was given to validation of a “virtual T-cell” model in diseases such as multiple sclerosis. The ImmunoGrid project is developing computational models (Grid technologies) to simulate immune processes. Also being developed are tools applicable to clinical immunology that could help in the design of new vaccines and immunotherapies, treatments that work by modulating the immune system. MODEL-IN is a new multidisciplinary network investigating the mechanisms of inflammation. The project will develop new tools, computational and

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<sup>33</sup> <http://www.sybilla-t-cell.de/>

<sup>34</sup> [www.immunogrid.org](http://www.immunogrid.org)

quantitative models of the complex activation cascades leading to the inflammatory response in health and disease.

## **2. Quick summary of the different presentations**

Thomas Höfer from the German Cancer Research Centre, Heidelberg, opened with a brief introduction to the immune system. He stressed that a better understanding of immunity is needed to meet important practical challenges. In the field of infectious diseases, for example, why don't we yet have vaccines for malaria and HIV? What makes a good vaccine? In the case of autoimmune diseases and chronic inflammation, what are the mechanisms behind multiple sclerosis, Type 1 diabetes and rheumatoid arthritis? Why is the incidence of allergies increasing? How can we better prevent and treat allergies? Höfer then went on to give a presentation entitled "Systems Biology of T-cell Activation: Recognising the Unknown", focusing on the Framework Programme 7 project SYBILLA – Systems Biology of T-cell activation in Health and Disease, a worldwide collaboration, including partners in the USA and India. The immune system has to attack and eliminate foreign cells (such as bacteria, viruses) and cancerous cells without harming self-tissues. The main type of cell involved in this decision is the T-cell. Antigen recognition by T-cells involves a complex molecular machinery that computes antigen quality and triggers T-cell activation, proliferation and the adaptive immune response. SYBILLA aims to understand at the system level how T-cells discriminate foreign from self peptides. SYBILLA involves a very close connection between mathematical modelling and experiment. Data obtained in mouse models are being extended to human T cells and to a mouse model of multiple sclerosis.

Elda Rossi from CINECA, Bologna, Italy presented the ImmunoGrid project. ImmunoGrid provides a computer model of the human immune system implemented with Grid technologies. It will establish an infrastructure for the simulation of the immune system that integrates processes at molecular, cellular and organ levels. Rossi pointed out the main problems that prevent computational models of the immune system from being used in practical applications, namely the vast combinatorial complexity of the human immune system, our lack of understanding of specific molecular interactions and the correlation of model parameters to real-

life measurements. Grid computing, she said, can provide the capacity to tackle the challenge of complexity. ImmunoGrid aims to put together a comprehensive simulator for the Virtual Human Immune System. It will standardise concepts for the immune system, bioinformatics tools and information resources to enhance the computational models for pre-clinical and clinical applications. Those models will be validated with experimental data (mice) and the tools will be disseminated to vaccine and immunotherapy researchers and developers. She demonstrated the potential of ImmunoGrid through case studies, including one in which 1,600 cancer vaccine schedules were run for 100 mice. But the high-performance computing needed for ImmunoGrid is not free; finance is a practical barrier to access to the tools developed. ImmunoGrid provides different levels of access, depending on the user.

Gioacchino Natoli from the European Institute of Oncology, Milan, Italy, discussed the immune mechanisms behind inflammation. Chronic inflammation is one of the most important causes of disability and death worldwide. For example, rheumatoid arthritis has a prevalence of about 1% in the Caucasian population. The Model-In project aims to improve our understanding of inflammation, in particular the underlying transcriptional programme and its genomic basis. Mathematical models will be developed to link genomic determinants to transcriptional control of the inflammation process. The project will require technological improvements for *in vivo* and *in vitro* analyses of transcription factors and their binding sites. For example, a novel approach using a UV-laser will be used to cross-link of transcription factors directly to DNA (thus avoiding problems associated with chemical cross-linking). Advanced imaging techniques will be employed to visualise directly the interactions of transcription factors and their binding sites. Mathematical models of the control of gene expression will be tested through *in vivo* perturbation experiments, for example, by using mouse models and cell lines. The project will involve collaboration between molecular biologists, computational scientists, mathematicians and physicists.

### **3. Discussion & conclusions**

The discussion covered various technical issues relating to the projects. A common theme was that the projects involved a synergy between powerful computing approaches and “wet lab” studies of the immune system. Animal models are crucial to test the mathematical models. Advanced computing and statistical methods (statistical mechanics) may be needed to detect and model fast molecular interactions such as the “coming and going” of transcription factors at their binding sites. The systems biology of the immune system necessarily involves dealing with complexity: the field is very much at the interfaces between biology, computing and mathematics. Successful research will involve close and novel types of collaboration between relevant scientific specialists. The need for high-performance computing is evident.

## Session 2-6: European Infrastructure, from experience to challenges

**Chair: Yannick Legré** (HealthGrid)

**Rapporteur: Maria Ramalho Natario** (European Commission, DG INFSO/F3)

### 1. Summary of the session

The session covered three areas: the status of the field; the research challenges; and visions of the future. It began with an overview by Yannick Legré from HealthGrid, France.

The Virtual Physiological Human (VPH), personalised medicine, medical image computing and biomedicine raise new challenges arising from the scale and complexity of the required analysis, for example in studies that require the federation of large data sets or in complex models and processing. Grid technology and the new emerging petaflop facilities are addressing problems related to the manipulation of large data sets over wide computing networks, providing tools for exchanging data and computing power and serving as a vector for structuring the user communities as they enable cross-enterprise collaborations.

This session was devoted to a forward look at the adoption of Grid computing and petaflop facilities for healthcare and biomedical research. It also sought to foster interactions between the scientists, clinicians and industry that are needed to achieve the ambitious goals of the VPH. Speakers reviewed the state-of-the art worldwide and outlined major achievements. They also provided a look at the future developments and challenges in cardiovascular modelling. The focus was the main research challenges required for the adoption and deployment of these

infrastructures into clinical practice. The session closed with a presentation of the results of the SHARE roadmapping project.

## 2. Quick summary of the different presentations

David Manset from Maat France discussed “HealthGrids, From Revolution to Evolution towards the Establishment of an International Infrastructure for Biomedical Research”. From the SHARE Roadmap<sup>35</sup> to Framework Programme 6 e-health and Framework Programme e-infrastructure projects survey, he explained why an international HealthGrid<sup>36</sup> platform is needed to support research collaborations from data sharing, to applications exchange and knowledge consolidation. Finally, Manset introduced a new initiative that attempts to address them by gradually integrating the infrastructures, services, data and knowledge of international infrastructures: the Super Petascale data Infrastructure for Distributed e-health and biomedical Research (SPIDeR<sup>37</sup>).

Antonio Arbona from GridSystems, Spain, talked about his company’s experiences of using Grid technologies in clinical applications. GridSystems and its partners in the FP6 @neurIST project have built an IT system called “@neuSystem”, consisting of applications for clinicians and researchers and a back end that provides data access and storage and computational services.

While the front-end applications are partially adapted to a specific disease taken as a model in the project – cerebral aneurysms – the back end has been implemented around a generic architecture for clinical environments based on Grid technologies and protocols. It supports trust federations between hospitals, research centres, and service providers; secure data access to anonymised textual data, images, and simulations; data transport between institutions; simulation services with automated sensitivity and what-if analysis; massive storage of simulation results; granular access-control policies; and distributed automated workflows among different institutions. Its design was supervised by an ethical committee involving

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<sup>35</sup> <http://eu-share.org/roadmap.html>

<sup>36</sup> [www.healthgrid.org](http://www.healthgrid.org)

<sup>37</sup> [www.spider-simulator.com](http://www.spider-simulator.com)

hospitals and ethics experts. An initial version will be ready by the end of 2008, and the final version by mid 2009.

Thomas Eickermann, from the Research Center Jülich, Germany, looked at PRACE<sup>38</sup>, the Partnership for Advanced Computing in Europe. Its aim: a petaflop computing research infrastructure for European scientists and engineers. To remain internationally competitive, European scientists and engineers must be provided with leadership-class supercomputer systems. PRACE is a preparatory-phase project within Framework Programme 7 that aims to create a persistent pan-European high-performance computing service and infrastructure – to be managed as a single European entity – with capabilities equal to or better than those available in the USA and Japan. The service will comprise three to five superior high-performance computing centres. This presentation introduced the objectives and current status of the PRACE project and its potential benefit for life-science applications.

Mary Kratz from the University of Michigan, United States, introduced an international perspective with a case study of the US HealthGrid<sup>39</sup> community. One of the significant factors driving the HealthGrid, she said, is the demands of the global economy. It will take “nimble interactions” to address the deployment of ICT infrastructure and the capacity of individuals, organisations and society to absorb the changes. There are also big scientific challenges. Kratz described a deeper concern by national leaders that has driven many government programmes to go for public–private partnerships. As the source of new products and services, innovation is directly responsible for the most dynamic sectors of an economy. But history has also shown, she said, that it takes significant public investment to produce the ingredients innovation needs to flourish: new knowledge (research), human capital (education), infrastructure (facilities, laboratories, communications networks), and policies (tax, intellectual property). Kratz showed that we are beginning to see the benefits of public–private partnership investments aimed at stimulating and exploiting technological innovation, such as Grid technologies, in the marketplace.

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<sup>38</sup> [www.prace-project.eu](http://www.prace-project.eu)

<sup>39</sup> <http://usa.healthgrid.org/>

Finally, Tony Solomonides from the University of the West of England, United Kingdom, discussed SHARE, an integrated roadmap for the deployment of HealthGrids in biomedical research and healthcare delivery. The advent of multiscale research – from molecules to populations – and personalised or genomic medicine, together with the need to manage unprecedented volumes of medical knowledge, makes the case for HealthGrid-based solutions very compelling, he said. The SHARE specific support action project was commissioned to explore the opportunities and possibilities of HealthGrid computing for the next ten years or more. It has analysed the technical steps necessary for such deployment and has created a conceptual map of the ethical, legal, social and economic difficulties that arise. These have been tested against a number of existing and commissioned case studies, and the results integrated in a unique road map. Among the conclusions of the project is a need for greater synergy and collaboration between Framework Programme projects as well as the coordination of science policy with the Commission's regulatory activities.

### **3. Discussion & conclusions**

This session attracted a fair number of delegates, given that it was one of the last parallel sessions in the conference. The questions revolved mostly around Grid computing issues. The following are just a few examples of comments from the discussion:

- Grids and e-Infrastructures are profoundly changing the way the health and medical world is working. This is commonly accepted now and everybody is working on the best way to benefit from these changes.
- Shortcomings in data ontologies as well as legal and financial frameworks are slowing down the progress fostered by the use of technology in the advancements of research in Life Sciences.
- High-performance computing is not the main focus at the moment but large simulations of the human heart will need to have access to capability computers (supercomputing)

Some questions raised by the audience were:

- Is there a balance to be made between technology use and medical research content?
- Does the end-user see the whole HealthGrid exercise as far too complex? Is this somehow related to the end-user friendliness of Grids?

It was agreed that the community is now concentrating on data management, and archiving and other ICT-based infrastructure issues were left to future debates.

## Participation statistics

