ERCIM NEWS

Special:
The Digital Patient

Contents

Next issue: July 2007
Special theme: Service-oriented Computing

Universitas Varsoviensis

PLERCIM

Universitas Wratislaviensis

Poland Joins ERCIM

In January 2007, two major Polish universities – the University of Warsaw and the University of Wroclaw – established together a new research consortium, 'PLERCIM', which will represent Poland in the ERCIM. PLERCIM will initiate and coordinate future cooperation between Polish and European researchers in applied mathematics and informatics within ERCIM activities.

The Scientific Council of PLERCIM consists of four scholars – two from the University of Warsaw (Prof. Jerzy Tiuryn and Dr. Hung Son Nguyen) and two from the University of Wroclaw (Prof. Leszek Pacholski and Dr. Hab. Marek Piotrów). Both universities also have their representatives in ERCIM bodies: the Board of Directors (Prof. Jerzy Tiuryn), the Executive Committee (Dr. Hab. Marek Piotrów) and the Editorial Board of ERCIM News (Dr. Hung Son Nguyen).

"ERCIM should give the scientific community of Polish mathematicians and informaticians a stimulus to foster engagement and international cooperation with leading research institutions of Europe in the corresponding areas of research", said Jerzy Tiuryn, president of PLERCIM. "This engagement is anticipated on several levels: access to high-quality post docs, involvement in the existing research working groups of ERCIM, a possibility of creating international working groups within ERCIM in the scientific areas of mathematics and informatics, which are strategic for the Polish research institutions, and easier involvement in international research teams in connection with the European Union's 7th Research Framework Programme. I believe that our joining of ERCIM will be mutually beneficial. I am looking forward to this cooperation."

PLERCIM will host the 2007 ERCIM autumn meetings in Warsaw on 21-23 October.

Link:
http://www.plercim.pl/

Please contact:
Radosław Siedliński
PLERCIM Office
Warsaw University
E-mail: r.siedlinski@mimuw.edu.pl

The University of Warsaw

The University of Warsaw (Universitas Varsoviensis, est. 1817), is the largest university in Poland. It teaches over 56 000 undergraduate students and around 2100 PhD students in nineteen faculties. About 11 000 students graduate from the university every year. It offers a broad range of courses taught in Polish and English in 76 areas of study.

The nineteen faculties of the university are:
- Applied Linguistics and East-Slavonic Philology
- Applied Social Sciences and Resocialization
- Biology
- Chemistry
- Economic Sciences
- Education
- Geography and Regional Studies
- Geology
- History
- Journalism and Political Science
- Law and Administration
- Management
- Mathematics, Informatics and Mechanics
- Modern Languages
- Oriental Studies
- Philosophy and Sociology
- Physics
- Polish Studies
- Psychology.

Auditorium Novum, Warsaw University.

There are around 850 professors and 2000 scientists involved in teaching and research.

The Faculty of Mathematics, Informatics and Mechanics, with almost 170 faculty members and researchers, is engaged in a wide spectrum of research areas, ranging from pure mathematics and theoretical computer science, to applied mathematics and applied areas of informatics. The Faculty consists of three Institutes: Mathematics (with over ninety faculty members), Informatics (almost fifty faculty members), and Applied Mathematics and Mechanics (with over thirty faculty members). Almost eighty Ph.D. students are involved in various research areas under the supervision of faculty members and researchers. The faculty has the top research category in the Polish government classification.

Traditionally, the Faculty has its strengths in selected areas of Mathematics and Informatics. In addition it is expanding the scope of its research by focusing on some truly multidisciplinary areas such as Financial Mathematics and Computational Biology. An independent Section of Economic, Financial and Insurance Mathematics consists of faculty members

from two of the three Institutes: Mathematics, and Applied Mathematics and Mechanics.

There are close to 1500 students at the Faculty attending a wide variety of courses. There are nearly 250 lectures offered each year at the undergraduate, master and doctoral levels. They cover numerous topics in computer science - both theoretically and practically oriented - and in pure, applied and financial mathematics. The Faculty also offers basic courses in mathematics and informatics for about 2000 undergraduate students at Economics, Management, Chemistry, Physics, Biology, Geography, Geology and Education Faculties.

Basic Areas of Research: algebra and number theory, algebraic geometry, algebraic topology, algorithms and data structures, concurrency and communication, dynamical systems, theory of vector fields and their singularities, geometry, logic in computer science, mathematical analysis and differential equations, mathematical logic, probability, semantics and formal specifications, topology and set theory.

Applied Areas of Research: artificial intelligence, machine learning, knowledge discovery and data mining, biomathematics and game theory, computational biology and bioinformatics, databases, financial mathematics, multiagent systems, numerical analysis, software engineering, statistics and applied probability, theory and applications of PDE's and functional analysis.

Links:
Warsaw University: http://www.uw.edu.pl/en
Faculty of Mathematics, Informatics and Mechanics: http://www.mimuw.edu.pl/english

The University of Wroclaw

The University of Wroclaw (Universitas Vratislaviensis, est. 1702) is the largest university in the south-western part of Poland called Lower Silesia. It teaches over 40 000 undergraduate students and about 1300 PhD students in ten faculties. About 9000 students graduate from the university every year. The university offers a broad range of courses taught in Polish and English in over seventy areas of study.

The ten faculties of the university are:
• Biological Sciences
• Biotechnology
• Chemistry
• Earth Science and Environmental Management
• History and Pedagogy
• Law, Administration and Economics
• Mathematics and Computer Science
• Philology
• Physics and Astronomy
• Social Sciences.

There are about 500 professors and 1300 scientists involved in teaching and research.

The Faculty of Mathematics and Computer Science consists of two parts: the Mathematical Institute and the Institute of Computer Science. It teaches 870 undergraduate students in

The Aula Leopoldina in the main building of the Wroclaw University.

mathematics, 520 undergraduate students in computer science and 50 students in PhD programmes in both disciplines.

The Faculty has the top research category in the Polish government classification. With about forty professors and eighty other scientists it bundles its research and teaching capacities in many areas crucial to the development of the information society. Currently, the Faculty is involved in six EU grants and nine grants from the Polish Ministry of Science.

Research in the Institute of Computer Science involves the following groups and areas:
• Programming Languages Group: theory of programming languages, theory of automata, symbolic computations, fundamentals of Internet security, software engineering and computer graphics.
• Computational Complexity and Algorithms Group: approximation algorithms, probabilistic algorithms, online algorithms, parallel, distributed and mobile computations, cryptology and computational complexity.
• Numerical Methods Group: computational statistics, continued fractions, finance data analysis, numerical integration, numerical methods of differential equations, optimization methods, computation with recurrence relations, special functions and orthogonal polynomials.

Research in the Mathematical Institute is focused on: harmonic analysis, partial differential equations, differential and metric geometry, applied probability and statistics, foundations of mathematics, mathematical logic, model theory, measure theory, algebra and number theory.

Links:
University of Wroclaw:
http://www.promocja.uni.wroc.pl/prospectus
Institute of Mathematics: www.math.uni.wroc.pl/
Institute of Computer Science:
http://www.ii.uni.wroc.pl/cms/en/main_page

EUROPEAN AND CHINESE COOPERATION ON GRID

ERCIM Coordinates European-Chinese Grid Cooperation Effort

The European Commission entrusted ERCIM with the coordination of 'EchoGrid', a project to foster collaboration between the European Union and China in Grid computing research and technologies by developing short-, mid- and long-term visions in the Grid computing field.

Thanks to the substantial investments and the numerous initiatives launched at the national and European levels, Europe has succeeded in getting a leading worldwide position in Grids. China has well established programs and a critical mass of researchers in the Grid technological area. Most of the application areas have similarities or well defined boundaries that match European Grid areas. This has been demonstrated during two workshops organised in Beijing and in Shanghai in June 2005 and February 2006 by the Grid@Asia project. EchoGrid will build on this experience to develop a collaboration roadmap that identifies common areas of interest and opportunities for collaboration on Grid technologies between the EU and China. In the frame of the programme, ERCIM will organise a set of workshops on strategic topics open to researchers and engineers from both academia and industry to define a better view of the research and development activities in China and Europe. A mobility programme is also planned to encourage exchange of personnel across countries and institutions.

The major outcome are roadmaps developing a shared European and Chinese vision (3, 5 and 10 years terms) of future Grid research perspectives. It is epected that the roadmaps lead to a joint technological and research agenda and to long-term collaborations between key Grid initiatives in the EU and China.

Partners
The project consortium is composed of five Chinese and five European partners. The Europan partners are: ERCIM EEIG; the National Technical University of Athens, Greece; ATOS Origin SAE, Spain; Engineering Ingegneria Informatica S.p.A, Italy; THALES, France. The Chinese partners are: Beihang University; Institute of Computing Technology, Chinese Academy of Sciences; Computer Network Information Center, Chinese Academy of Sciences; National University of Defence Technology; and Huawei Technologies Co.,Ltd .

First International Conference
A first joint EchoGrid and EUChinaGRID international conference will be held on 24-25 April 2007 at the Institute of Computing Technology, Chinese Academy of Science in Beijing, China. The conference will be followed by a two days tutorial on ProActive at the SuperComputing Centre, CAS coorganised with the Sino French Lab in Computer Science, Automation and Applied Mathematics (LIAMA) on 26-27 April.

This conference will present complementarities between European and Chinese initiatives and disseminate the goals and foreseen activities of EchoGRID. The conference promotes cross-fertilisation between Grid-related projects and initiatives in Europe and China by interacting with top Grid research and industrial communities, exchange experiences and best practices for Grid middleware and applications interoperability. Programme highlights include topics such as 'Enterprise Challenges with Grids', 'Interoperability, New Programming Paradigms/SOA', 'New Priorities for Management in Grids', and 'Ongoing Research versus Enterprise Achievements'. The programme also features a live demo and poster session, as well as a roundtable on future collaborative scenarios led by experts at the forefront of Grid technologies.

Links:
EchoGrid: http://echogrid.ercim.org/
Grid@Asia: http://gridatasia.ercim.org/
EU ChinaGrid: http://www.euchinagrid.org/
Grid Technologies in the IST Programme:
http://cordis.europa.eu/ist/grids/

Please contact:
Bruno Le Dantec, ERCIM office
E-mail: bruno.le_dantec@ercim.org

New ERCIM Working Group on 'e-Mobility'

by Torsten Braun

A new ERCIM Working Group 'eMobility' was established in January 2007. The main research areas are mobile applications and services, middleware for mobile communications, security mechanisms, network architectures, technologies, and protocols for wireless and mobile communications. The working group aims to encourage collaborations and information exchange among researchers in the area of both mobile services and wireless communication systems.

The eMobility working group is closely related to the topics addressed by the eMobility European Technology Platform (ETP). Several members of the eMobility working group are already members of the eMobility ETP. To complement the activities of the eMobility ETP, the ERCIM working group eMobility focuses on more theoretical basic research issues. The working group aims to have a longer term research scope and rather address research topics that might become practically important in ten to fifteen years. Also, the lifetime of the working group should be rather in a longer time-scale, exceeding project or research framework lifetimes significantly. A major difference compared to the eMobility ETP is that the topics addressed by the ERCIM

working group eMobility should not be limited to any commercial constraints and also have a stronger focus on social and environmental interests. The working group is mainly driven by public research organizations and academia, while the eMobility ETP is driven by the major industry companies active in mobile communications. The eMobility working group should also allow for the investigation on disruptive technologies to drive the evolution of today's mobile applications and wireless technologies.

The eMobility working group intends to organize meetings as well as workshops and to encourage collaboration among participating institutions. Other objectives are dissemination and discussion of research results as well as the participation in the ERCIM Alain Bensoussan Fellowship Programme. Since several involved organizations are interested in experimental research based on test-beds, it is planned to share such test-beds for experimental research activities. The eMobility working group also aims to develop a strategic basic research agenda and project proposals (for example in FP7) in the area of mobile and wireless communications.

ERCIM instititutes participating in the eMobility working group include CNR, CWI, FNRS/FWO, FORTH, NTNU, SARIT, SICS and SpaRCIM. In addition, several other universities and research organizations already joined the working group: University of Cantabria and University of Granada (Spain), TNO (The Netherlands), Czech Technical University Prague (Czech Republic), Tampere University of Technology (Finland), University of Coimbra (Portugal), Demokritos University of Thrace (Greece), Politecnico di Bari (Italy), Karlstad University (Sweden). During the kick-off meeting on 27 October 2006, in Basel, Switzerland, Prof. Torsten Braun from the University of Bern/SARIT and Prof. Dimitri Konstantas from the University of Geneva/SARIT have been elected as chair and deputy chair, respectively. Dr. Markus Wulff from the University of Bern will act as a secretary general.

A presentation about the new working group has been given by Torsten Braun at a networking session organized by the eMobility ETP during the IST 2006 conference in Helsinki on 22 November 2006. A working group meeting was held at the University of Malaga on 15 February 2007, co-located with a COST 290 action meeting. The main goal of this working group meeting was to prepare the eMobility workshop to be held at the University of Coimbra on May 21, 2007, co-located with the 5th International Conference on Wired/Wireless Internet Communications. More information about the working group and the upcoming workshop including the call for papers is available at http://www.emobility.unibe.ch.

Scientists interested in joining the working group should contact the working group coordinator.

Link:
http://www.emobility.unibe.ch/

Please contact:
Torsten Braun, eMobility WG coordinator
University of Bern
E-mail: braun@iam.unibe.ch

Increase your FP7 Potential with the ERCIM Office

From Proposal Preparation to Successful Project Management
ERCIM is offering to assist you in preparing FP7 ICT research proposals, and in managing ICT projects by carrying out the administrative and financial coordination. ERCIM's expertise has been a key success factor in getting innovative ICT research proposals funded across the different European Framework Programmes (for a detailed list of projects coordinated by ERCIM, see http://www.ercim.org/activity/projects/).

The ERCIM Office is open to cooperation with all research institutions. Yet, in order for the ERCIM Office to participate in a proposal, a minimum of three ERCIM members must be involved in a proposed project consortium. This is an excellent way to complement a proposed consortium to include highly qualified researchers in related areas of expertise.

How to Benefit from ERCIM's Expertise?
At the heart of every successful proposal is an idea. Contact ERCIM to present your project idea. An internal evaluation panel of experts will review your project idea and will systematically give you its feedback within one week. Based on this feedback, the ERCIM Office will decide whether to commit to your proposal.

If ERCIM expresses an interest in participating, the ERCIM Office will assist the scientific coordinator by assuming the role of the administrative and financial coordinator. From experience, this is a real asset for a project as it allows the scientific coordinator to focus entirely on technical and scientific management. All decisions concerning the proposal organisation or preparation are taken in cooperation with the scientific coordinator, who remains at the heart of the proposal. The ERCIM Office then coordinates the entire proposal preparation, up to submission to the European Commission.

If the proposal is evaluated positively, ERCIM will guide the proposal across the following steps: hearing - negotiation - consortium agreement preparation - contract signature - management .

How much will it cost?
ERCIM is a partner like any other, motivated by the nature and scientific content of the proposal. Whether successful or not, ERCIM's coordination of the proposal and ERCIM's contribution to the writing of the proposal are *entirely free*.

Yet, if the proposal is successful, ERCIM will ensure the administrative and financial coordination of the project, receiving a standard 4-6% of total project financing for management of the consortium activities.

Successful Project Management
When ensuring the administrative and financial coordination, the ERCIM Office will provide support to the scientific coordinator and to the project as a whole by implementing a reliable management based on a wide array of communication and collaborative tools.

For more information, please contact:
Rémi Ronchaud, ERCIM office
E-mail: remi.ronchaud@ercim.org

W3C WORLD WIDE WEB consortium

HTML Activity Relaunched - Developers and Browser Vendors to Shape HTML Future

Recognizing the importance of an open forum for the development of the predominant Web content technology, W3C invites browser vendors, application developers, and content designers to help design the next version of HTML by participating in the new W3C HTML Working Group. Based on significant input from the design and developer communities within and outside the W3C Membership, W3C has chartered the group to conduct its work in public and to solicit broad participation from W3C Members and non-Members alike.

"HTML started simply, with structured markup, no licensing requirements, and the ability to link to anything. More than anything, this simplicity and openness has led to its tremendous and continued success," explained Tim Berners-Lee, W3C director and inventor of HTML. "It's time to revisit the standard and see what we can do to meet the current community needs, and to do so effectively with commitments from browser manufacturers in a visible and open way."

In addition to the new HTML and XHTML 2 Working Groups, W3C is also pleased to recharter the HTML Coordination Group and charter the Forms Working Group. The Forms Working Group will continue work on the XForms architecture, which has seen significant adoption in a variety of platforms.

Links:
HTML Activity: http://www.w3.org/html/
HTML Working Group: http://www.w3.org/html/wg/

Mobile Web May Help Bridge the Digital Divide

W3C has published a report from the Workshop on the Mobile Web in Developing Countries, held in Bangalore, India in December 2006. Workshop participants discussed the needs and challenges facing people in developing economies who use a mobile phone as the primary and often sole platform for accessing the Web. Participants included mobile handset manufacturers, browser developers, software companies, local Indian companies and universities, and organizations working on information technology projects in rural communities in India and Africa. The report presents their findings and proposed next steps.

Link:
http://www.w3.org/2006/07/MWI-EC/exec_summary

Two New Groups in W3C's Incubator Activity

The W3C Incubator Activity fosters rapid development, on a time scale of a year or less, of new Web-related concepts. Target concepts include innovative ideas for specifications, guidelines, and applications that are not (or not yet) clear candidates for development and more thorough scrutiny under the current W3C Recommendation Track. Two new Incubator Groups (XG) were created:

• **Incubator Group to Analyze Semantic Web Services**
The SWS Testbed Incubator Group's mission is to develop a standard methodology for evaluating Semantic Web Services based upon a standard set of problems and develop a public repository of such problems. This XG is sponsored by W3C Members Wright State University, Stanford University, DERI University of Innsbruck, and the National University of Galway, Ireland.
• **Incubator Group to Focus on Uncertain Knowledge**
The Uncertainty Reasoning for the World Wide Web Incubator Group was created to better define the challenge of working with incomplete knowledge. The group expects to identify the elements of uncertainty, produce use cases, and create the fundamentals of a way to represent and reason when truth or falsehood is inapplicable or unknown. The group is sponsored by W3C Members Image, Video and Multimedia Systems Lab, McDonald Bradley, MITRE, National ICT Australia (NICTA), the University of Amsterdam and the University of Bristol.

Links:
http://www.w3.org/2005/Incubator/swsc/
http://www.w3.org/2005/Incubator/urw3/

Workshop on Declarative Models of Distributed Web Applications

5-6 June 2007, Dublin, Ireland

The aim of this workshop is to look at the potential for applying declarative techniques to describing Web applications, as a whole rather than just the markup downloaded to each device. The workshop seeks to guide future W3C work on Ubiquitous Web Applications through joint discussions with experts in the areas of user interface and application modeling, and security and usability, on the potential role of declarative approaches for reducing the costs of building Web applications in the face of increasing varieties of devices in the home, office and mobile environments, and demand for greater interactivity and richer access to device capabilities. W3C membership is not required in order to participate in the Workshop, and registration is free.

Link:
http://www.w3.org/2007/02/dmdwa-ws/

Tim Berners-Lee Spoke on Future of the Web to US Congress

Tim Berners-Lee, W3C Director, testified on the future of the World Wide Web before the Subcommittee on Telecommunications and the Internet, Committee on Energy & Commerce, U.S. House of Representatives, on 1 March 2007. Chairman Edward Markey invited Berners-Lee as the sole witness for the first in a series on the Digital Future of the United States. Confronted with current U.S. policy questions, Tim Berners-Lee explained the success of the Web, described its three essential features: universality, open standards, and the separation of layers, and provided a view of its future.

Links:
Tim Berners-Lee testimony:
http://dig.csail.mit.edu/2007/03/01-ushouse-future-of-the-web.html
Hearing and archived webcast:
http://energycommerce.house.gov/cmte_mtgs/110-ti_hrg.030107.WorldWideWeb.shtml

Latest W3C Recommendations

- WebCGM 2.0
  30 January 2007, David Cruikshank, Lofton Henderson, Benoit Bezaire
- XQuery 1.0 and XPath 2.0 Data Model (XDM)
  23 January 2007, Jonathan Marsh, Ashok Malhotra, Norman Walsh, Mary Fernández, Marton Nagy
- XQuery 1.0 and XPath 2.0 Functions and Operators
  23 January 2007, Jim Melton, Ashok Malhotra, Norman Walsh
- XML Path Language (XPath) 2.0
  23 January 2007, Mary F. Fernández, Michael Kay, Scott Boag, Jérôme Siméon, Jonathan Robie, Anders Berglund, Don Chamberlin
- XQuery 1.0: An XML Query Language
  23 January 2007, Mary F. Fernández, Daniela Florescu, Don Chamberlin, Jonathan Robie, Jérôme Siméon, Scott Boag
- XQuery 1.0 and XPath 2.0 Formal Semantics
  23 January 2007, Mary Fernández, Peter Fankhauser, Ashok Malhotra, Michael Rys, Jérôme Siméon, Kristoffer Rose, Philip Wadler, Denise Draper
- XML Syntax for XQuery 1.0 (XQueryX)
  23 January 2007, Subramanian Muralidhar, Jim Melton
- XSLT 2.0 and XQuery 1.0 Serialization
  23 January 2007, Joanne Tong, Michael Kay, Norman Walsh, Scott Boag, Henry Zongaro
- XSL Transformations (XSLT) Version 2.0
  23 January 2007, Michael Kay

Link:
http://www.w3.org/TR/

W3C Mobile Web Initiative at 3GSM World Congress 2007

Tim Berners-Lee, W3C Director and inventor of the Web, opened the 3GSM World Congress - the world premier mobile industry event - with a keynote address at the Mobile Innovation Forum in Barcelona, Spain on Monday 12 February. Berners-Lee spoke on the role of innovation and open-

Tim Berners Lee addresses the Mobile Innovation Forum

ness in the Web's success, and how the W3C Mobile Web Initiative brings mobile telephony into convergence with the Web and aids in bridging the digital divide.

Advancing its goal to make browsing the Web from mobile devices a reality, W3C recently launched two MWI groups: the MWI Device Description Working Group is rechartered to enable the development of globally accessible data and service repositories for use in content adaptation, and the new MWI Test Suites Working Group is to help create a strong foundation for the mobile Web through the development of a set of test suites targeted at browsers. The latter group is specifically supported by the 3GWeb project of the European Commission's IST Program.

W3C team staffed a booth in the 3GSM'07 exhibition. The latest achievements of W3C's mobile Web work were presented, and visitors were able to learn how to mobilize Web content following the Mobile Web Best Practices (MWBP) guidelines and using its associated online checker. A popular handout were the MWBP flipcards, which is a set of cards summarizing the guidelines of that document in ten themes.

Links:
Keynote address:
http://www.w3.org/2007/Talks/0222-3gsm-tbl/text.html
W3C Mobile Web Initiative: http://www.w3.org/Mobile/
Mobile Web Best Practices (MWBP):
http://www.w3.org/TR/mobile-bp/
MWBP flipards:
http://www.w3.org/2007/02/mwbp_flip_cards
MWBP online checker: http://validator.w3.org/mobile/

Introduction to the Special Theme

The Digital Patient

by Ioannis Tollis and Nicholas Ayache

Initiated by the European Commission as a major multidisciplinary scientific challenge, the Virtual Physiological Human (VPH) aims to develop robust, in silico models of human physiology and pathology. The desired outcomes include the identification of novel diagnostic biomarkers, the optimization of clinical decision-making and the discovery of innovative therapies. In this way, individualized models of human function could serve as virtual testbeds for a better understanding of pathophysiological processes (ie the disturbance of normal mechanical, physical and biochemical functions), as well as

Computational modelling of pathologies of the central nervous system. See article "The Digital Patient in Clinical Neuroscience" on page 18.

evaluating potential therapeutical strategies in silico.

This scientific direction is reflected in the recent calls for projects for the European Union's 7th Framework Programme on VPH, which will target:
• patient-specific computational modelling and simulation of organs or systems targeting specific clinical needs such as prediction of diseases
• data integration and knowledge extraction, and most importantly
• clinical applications and demonstration of the tangible benefits of patient-specific computational models.

This European initiative will give rise to new environments for predictive, individualized, evidence-based, more effective and safer healthcare. In addition, better therapy and the modelling of adverse drug

effects will reduce medical errors and improve patient safety.

However, in developing such patient-specific models it is crucial to implement multi-layered models that describe different properties (eg electrical, mechanical and biochemical), and appropriate image analysis and data assimilation tools to identify their specific parameters from patient images. An ultimate goal is to meaningfully integrate these models to describe/model/mimic some life function, rather than individual properties, at different scales; for example, from cellular

dynamics to organ function. To realize this ambitious scientific vision it will be necessary to address a number of challenges related both to infrastructure and data management, computational issues, validation and legal ethical issues.

A new ERCIM Working Group for Pathophysiology Modelling

In order to contribute to the European effort on the Virtual Physiological Human a new ERCIM Working Group (WG) on the Digital Patient was created. This WG facilitates multidisciplinary research in this domain, with a special emphasis on:

• computational frameworks for modelling and simulation of pathophysiological human function at multiple levels (from molecular/genetic to tissue/organ)
• multiparameter and multilevel data and information visualization, as well as

tools and novel interaction paradigms relevant for this domain (eg for mixed reality such as tumour growth simulation in real 3D patient data), and user interfaces for specific medical applications (eg educational GUIs for training in 3D simulations)
• the image analysis and data assimilation issues related to coupling/fusion of anatomical models with imaging data of tissue properties (eg X-rays, US, CT, MRI, PET, SPECT, optical imaging etc).

The ERCIM WG on the Digital Patient intends to promote interaction between the relevant ERCIM R&D groups, and to facilitate cross-fertilization and synergistic activities in collaboration with other groups and initiatives such as the Euro-physiome initiative currently funded by the European Commission.

To date, many ERCIM (and non-ERCIM) members have joined this effort. The last WG meeting was held in Nice in October 2006, and identified three interesting research directions:

1) Cardiovascular Modelling
Cardiovascular modelling is important for the therapy planning and guidance of cardiovascular therapies. An example is Atrial and Ventricular Radio-Frequency ablation for the surgical treatment of atrial/ventricular flutters or fibrillations. The therapy consists of burning cardiac cells that are causing pathological electrical pathways. Prior to burning the cardiac tissue, the cardiologist must precisely locate the pathological cardiac cells by reading electrical signals measured by more than ten electrodes inserted through an endovascular procedure. The real-time interpretation of those signals requires significant training, and the planning and execution of the therapy could be made more efficient with the use of electrophysiological models.

Another important example is Cardiac Resynchronization Therapy. Resynchronization therapy artificially stimulates the myocardium through implanted electrodes in order to limit the ventricular dysfunction caused by asynchronous ventricular contraction. Although a number of cardiac

The article "Towards an Individualised Physiological Model of the Musculoskeletal System" on page 26 presents advances in developing functional musculoskeletal models.

A position-tracked interactive display for the co-located visualization of medical images and simulation results. See article on page 22 about interactive simulation and visualization for cancer treatment planning with Grid-based technology.

resynchronization therapeutic strategies exist (regarding the selection of the number, location and delay between those electrodes), nearly 30% show no real improvement in cardiac function. It is therefore plausible that a thorough planning of CRT based on a personalized cardiac model could greatly assist the cardiologist in deciding the optimal strategy.

2) Musculoskeletal Modelling

Musculoskeletal modelling aims to predict musculoskeletal behaviour (eg bone kinematics, tissue deformation, tissue degeneration and tissue reconstruction) from the morphology, kinematical constraints, mechanical constraints or neuromuscular impulses. In addition to applications in orthopaedics (eg early detection of osteoarthritis, prosthesis design, osteotomy planning, tendon lengthening and ligament reconstruction), this would be of use in kinesiology for movement optimization (eg reduction of tennis elbow), rehabilitation and ergonomics (eg minimization of physical fatigue under specific constraints). From the physiological point of view, a link between large-scale studies (anatomy-based virtual humans animated from motion capture and EMG) and small-scale studies (deformation analysis due to local fibre actuation) has not yet been achieved. Bridging those domains through computationally efficient and scalable mechanical simulation methods is a major challenge.

3) Oncology Modelling

Oncology modelling focuses on the simulation of tumour growth and/or the response of tumours and physiological tissues to different therapeutic regimes (eg chemotherapy, radiotherapy or combined therapy). In this way, the optimal therapy decision for individual patients can be selected on the basis of the best 'simulated therapy' outcome. For this to be successful, it is crucial to test these models against reality and thus assess their usefulness in clinical practice. From a purely technical perspective, the challenges include: the development/refinement of a number of hybrid discrete Monte Carlo/cellular automata and continuous differential equation simulation models of normal tumour growth and response to therapeutic modalities; image analysis tools such as geometrical normalization (eg 3D MRI before and after therapy); extraction of relevant information (eg accurate tumour delineation also considering liquefaction during therapy); normalization and quantification from images (eg differential gene expression, tissue density); and visualization. The main clinical applications are glioma and nephroblastoma (Wilm's tumour). These applications have been selected on the basis of existing work, experience and ongoing clinical collaborations in relevant projects. The ultimate goal is to optimize the therapeutic strategy by conducting, in a patient-specific setting, in silico experiments on tumour growth and tumour and normal tissue response to therapeutic schemes.

This wide range of research interests was the inspiration behind the proposal for a special theme on the Digital Patient for ERCIM News. This issue features articles addressing either European projects or specific scientific achievements related to the VPH. A number of articles deal with applications of 'Pathophysiology modelling' (at the organ level), mainly in the three areas previously described. However, in order to build multidimensional models of the human function, it is essential to extract information from all possible scales. This is addressed by articles on the subtopic 'Data analysis and imaging' in this special theme. Several articles address 'System biology modelling', since modelling at smaller scales (cellular and even molecular) is an essential part of a 'holistic' VPH. Lastly, the article by Vincent Duffy deals with Digital Human Modelling for perception-based safety design.

Links:

White Paper on the Virtual Physiological Human: http://europa.eu.int/information_society/activities/health/docs/events/barcelona2005/ec-vph-white-paper2005nov.pdf

ERCIM Digital Patient Working Group: http://www.ercim.org/wg/Digital_Patient/

Europhysiome initiative: http://www.europhysiome.org

Please contact:
Ioannis Tollis
ICS-FORTH, Greece
E-mail: tollis@ics.forth.gr

Nicholas Ayache
INRIA, France
E-mail: nicholas.ayache@inria.fr

The Virtual Physiological Human
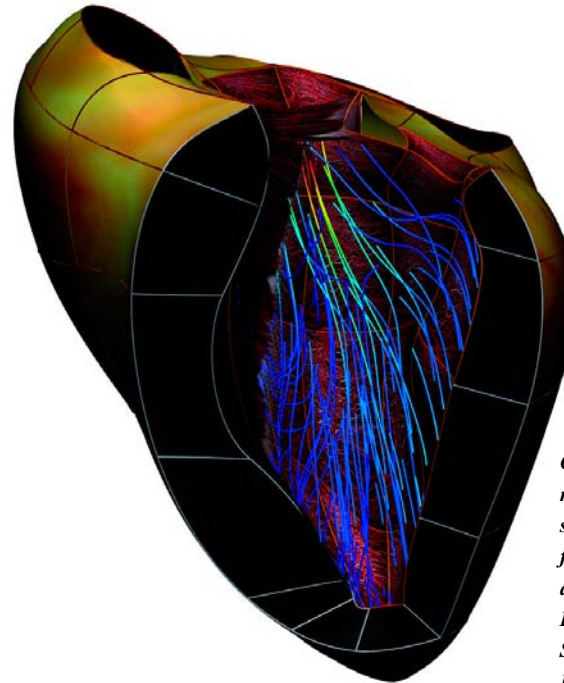
by Marco Viceconti

The Virtual Physiological Human (VPH) is a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system.

A group of genetically identical inbred mice are stabilized under identical conditions; half of them are then subjected to mild (0.3 g; g=acceleration of gravity) whole-body mechanical vibrations for a few minutes per day. After a few days, the transcriptional activity of hundreds of genes related to the musculoskeletal apparatus becomes significantly different between the two groups of mice. To explain this observation, we need to find the systemic relationship that links the accelerations experienced by the mouse's body with the transcriptional activity of its genes.

Today, biomedical research faces many problems similar to the one above, which involve a level of complexity for which the traditional approach is inadequate. This approach is based on the subdivision of biological systems in some way – by dimensional scales (body, organ, tissue, cell, molecule), by scientific disciplines (biology, physiology, biophysics, bioengineering), or by anatomical subsystems (cardiovascular, musculoskeletal, gastrointestinal etc). However, these artificial subdivisions make it impossible to unravel the systemic nature that governs many of the physical manifestations of the human body.

Scientific exploration of the human body has already dramatically improved the length and quality of the life for a significant proportion of humanity. In order to continue this exploration, it will be necessary to complement the traditional approach with an integrative approach that combines observations, theories and predictions across the temporal and dimensional scales, across the scientific disciplines, and across the anatomical subsystems, all of which reflect the rather artificial divisions described.

This realization, shared by the vast majority of experts in the field, has given rise to a number of initiatives such as integrative biology, systems biology and study of the physiome. We believe that this integrative approach requires a

Oxford-Auckland multiscale model of a human heart, representing the anatomy, the muscles fibres orientation and the hemodynamics. Image courtesy of David Nordsletten and Nic Smith, University Computing Laboratory, University of Oxford.

radical transformation of the way in which biomedical research is conducted. It is necessary to create a framework within which observations and measurements from a variety of sources can be collected, shared and combined in many different ways.

This framework should allow experts from a variety of disciplines to work collaboratively to analyse these observations and develop systemic hypotheses. It should also make it possible to combine predictive models defined at different scales or with different methods or with different levels of detail, in order to make the hypotheses concrete, and to allow their validity to be tested against existing results.

Current investigations of the human body pretend that it is a jigsaw puzzle made of a trillion pieces, and we are trying to understand the whole picture by looking only at a single piece orperhaps a few closely interconnected pieces. It no surprise, therefore, that we are not finding it easy.

In contrast, the scope of the EuroPhysiome Initiative is to promote the devel-

opment of the Virtual Physiological Human (VPH), a methodological and technological framework that will enable investigations of the human body to consider it as a single (though hugely complex) system.

The Virtual Physiological Human is the frame within which we can finally start to put all of the pieces together, and it is the glue that can connect them. The Virtual Physiological Human will not itself be the whole picture, but it represents our best pathway towards forming that picture at some time in the future.

We claim that, given sufficient resources over the next ten years, the European Research System can develop the methodological and technological framework called the Virtual Physiological Human..

A Strategy for the EuroPhysiome

The STEP ('A Strategy for the Euro-Physiome') coordination action of this roadmap is to explicitly identify the essential requirements for developing the VPH and to specify what the objectives of this collective effort should be.

In addition, the document describes the current state of knowledge; the challenges that the development of the VPH poses; the material, environmental, societal and other barriers that we will need to overcome; and the impact that we predict the VPH will have on research, industry, clinical practice and society at large.

Specifically, the framework of methods and technology representing the VPH will have to possess three fundamental attributes:
- *descriptive:* the framework should allow observations made in laboratories, in hospitals and in the field, at a variety of locations worldwide, to be collected, catalogued, organized, shared and combined in any suitable way

- *integrative:* the framework should enable experts to analyse these observations collaboratively and to develop systemic hypotheses that involve the knowledge of multiple scientific disciplines
- *predictive:* the framework should make it possible to interconnect predictive models defined at different scales, with different methods, and with different levels of detail, into systemic networks that provide a concretization of those systemic hypotheses; it should also make it possible to verify their validity by comparison with other clinical or laboratory observations.

For more information on the VPH and on how the community of experts coor-

dinated by the STEP action plans to pursue this ambitious goal, please refer to the VPH Research Road Map. If you would like to participate in the further development of this collective vision and receive all the recent news about the VPH and related initiatives, you are invited to join the Biomed Town Internet community.

Links:
http://www.europhysiome.org/
http://www.europhysiome.org/RoadMap
http://www.biomedtown.org/

Please contact:
Marco Viceconti
Istituti Ortopedici Rizzoli, Italy
Tel: +39 051 6366865
E-mail: viceconti@tecno.ior.it

Modelling the Pathophysiological Human Brain Function

by Vangelis Sakkalis and Ioannis G. Tollis

Recent research has exploited graph theory in the development and implementation of an advanced electroencephalogram (EEG) analysis framework for modelling and visualizing cognitive brain functions under normal or pathological conditions. There is special interest in using graph theory to study brain networks, since it offers a unique perspective to the study of local and distributed brain interactions.

Most brain disorders and cognitive brain functions remain largely unresolved. Imaging modalities like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are valuable tools in identifying activations localized to specific brain regions (lobes). However, in comparison to classical electrophysiological techniques like the EEG, which capture the electrical activity that define neuronal communication, they represent indirect measures of neural activity and are characterized by rather poor temporal responses. All of these approaches focus on identifying the exact location of activations in the brain, which is a vital step towards understanding the brain's internal function. Modelling dynamic and synchronization phenomena in the brain will hopefully explain 'how' psychological mechanisms function.

Cognitive tasks require the integration and constant interaction of widely distributed neuronal areas over the brain. The study of functional relationships

and synchronization between pairs of brain regions has therefore been one of the main aims of the EEG. A variety of analysis frameworks are available that are able to capture such interdependences, ranging from linear (ie correlation and coherence) to nonlinear chaos-related ones (ie phase and generalized synchronization). Their application in the area of brain analysis is based on the assumption that the higher the synchronization, the stronger the functional relationships between the related brain regions. They are extensively used in studying the interrelationships between different cortical regions with respect to sensory stimulation, voluntary movements, the effects of drugs and a wide range of clinical and cognitive problems and tasks. In particular, higher frequency bands (ie gamma bands) are believed to reveal large-scale oscillations that enter into precise phase-locking over a limited period of time. This is often referred to as a phase-synchrony phenomenon. Another example is thought to be the genesis of epileptic

phenomena, where synchrony has long been considered to be an important factor. Chaotic descriptors of the EEG were found to change through the different sleep stages and during the performance of various cognitive tasks. Nevertheless, such techniques may reveal linear and nonlinear structures that are hidden to the neurophysiologist, for whom visual signal trace inspection still remains the main diagnostic tool.

Using the interdependence methods and measures discussed in the previous paragraph, one is able to characterize and measure the coupling of complex brain networks by means of graph theory. Graph theoretical measures and visualizations provide the tools with which to study and model both local and long-range brain interactions. Measuring some basic properties of a complex network is the first step towards understanding its structure. The next step is the creation of a simulated version with similar properties, ie a mathe-

During a working memory task in a high-frequency (gamma) band, a 'healthy' network (left) appears to have significantly different graph properties to a 'schizophrenic' one (right). These disturbances are more prominent for the connections of the frontal and temporal lobes. Increased thickness of edges denotes stronger interdependence between adjacent pairs of EEG channels. The channels belonging to the same lobe are painted with the same colour.

matical model with a topology of statistical properties similar to the brain.

With this in mind, our first application was a study of the 'disconnection syndrome' as proposed for schizophrenia, using graph theoretical measures and visualization. An experiment on working memory was undertaken using the gamma band (the EEG frequency of around 40 Hz), which is activated during the connecting activity (ie the 'binding' of the neurons). We analysed multichannel EEG data collected from twenty stabilized patients with schizophrenia and controls, and the spatial pattern of functional connectivity was assessed by computing the wavelet coherence of EEGs. This method, as with other synchronization measures, yields a statistical coherence measure ranging from 0 to 1, which is an indication of how strongly a specific electrode is correlated with every other electrode. Thus, we obtain an NxN coherence matrix C with entries ranging from 0 to 1 formulated per task and subject. In order to obtain a graph from a coherence matrix, it must first be converted

into an NxN binary adjacency matrix, A. To achieve that we define a variable called the threshold T, such that $T \in [0, 1]$. The value $A(i,j)$ is either 1 or 0, indicating the presence or absence respectively of an edge between channels i and j. That is, $A(i,j) = 1$ if $C(i,j) > T$, otherwise it is equal to 0.

Using graph theoretical analysis we found that the integration related to the 'binding' phenomenon, as expressed by the high-frequency gamma band, is reduced overall in schizophrenics.

In the future, higher cognitive functions like mathematical reasoning and common pathologies such as epilepsy will be investigated. Brain modelling will be further elucidated by investigating brain functional graphs during the evolution from neonate to early childhood.

The era of bioinformatics poses many challenging computational problems. Graph theory together with the advent of nonlinear synchronization algorithms point towards the synergistic research and development of quantita-

tive techniques in the area of EEG signal analysis and visualization, which gives us an extra window of understanding into how the brain works.

This work was initiated from the Institute of Computer Science – FORTH in collaboration with the Technical University of Crete (TUC). Most of the synchronization algorithm implementations took place in the context of the BIOPATTERN Network of Excellence EU project (http://www.biopattern.org). Physical and clinical reasoning was performed in collaboration with the Clinical Neurophysiology Laboratory (Faculty of Medicine) of the University of Crete in Greece.

Link:
http://www.ics.forth.gr/bmi/

Please contact:
Vangelis Sakkalis and Ioannis G. Tollis
ICS-FORTH, Greece
Tel: +30 2810 391448
E-mail: sakkalis@ics.forth.gr,
tollis@ics.forth.gr

From Riemannian Geometry to Computational Anatomy of the Brain
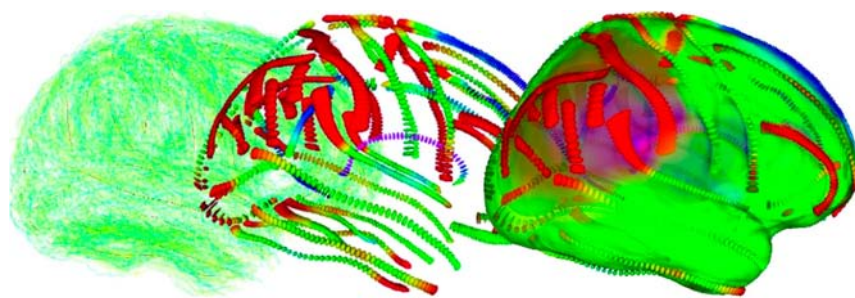
by Xavier Pennec

Understanding and modelling the individual anatomy of the brain and its variability over a population is made difficult by the absence of physical models for comparing different subjects, the complexity of shapes, and the high number of degrees of freedom implied. This also raises the need for statistics on objects like curves, surfaces and deformations that do not belong to standard Euclidean spaces. Applications are very important both in neuroscience, to minimize the influence of the anatomical variability in functional group analyses, and in medical imaging, to better drive the adaptation of generic models of the anatomy (atlas) into patient-specific data.

The shape of the brain differs greatly from one subject to another. At the scale of decimetres, a few tens of cortical folds (sulci) separating the main brain areas can be found consistently in all subjects, although they are geometrically very variable. At lower scales, however, many more sulci can be only

From sulcal lines in a population to the brain variability; (left) sulcal lines of eighty subjects in green with the mean sulcal lines in red; (middle) variability measured along the mean sulcal lines (covariance matrix at one sigma); (right) the colour encodes the amount of variability everywhere on the cortex after the extrapolation of the variability tensors onto the whole 3D space. Images realized by P. Fillard.

partially matched across subjects and it is difficult to speak about their homology. Computational anatomy, an emerging discipline at the interface of geometry, statistics and image analysis, aims to analyse and model this type of biological variability at the population scale. The goal is not only to model the normal mean anatomy and its normal variations among a population, but also to discover morphological differences between normal and pathological populations, and possibly to detect, model and classify pathologies from structural abnormalities. Another goal is to correlate this variability information with other functional, genetic or structural information (eg fibre bundles extracted from diffusion tensor images). Important applica-

tions include the spatial normalization of subjects in neuroscience (ie mapping all the anatomies into a common reference system) and atlas-to-patient registration in order to map generic knowledge to patient-specific data. Computational anatomy is currently a very active research field, as exemplified by the very successful workshop on the Mathematical Foundations of Computational Anatomy (MFCA'06), organized in September 2006 in conjunction with the conference MICCAI'06.

Many geometrical and physically based registration methods exist that can faithfully deal with intra-patient deformations. However, the absence of physical models relating the anatomy of different subjects leads to a reliance on statistics to learn the geometrical relationship from many observations. The method is to identify anatomically representative geometric features (points, tensors, curves, surfaces, volume transformations), and to model their statistical distribution. This can be done, for instance,

via a mean shape and covariance structure after a group-wise matching. However, the features usually belong to curved manifolds rather than to Euclidean spaces, which precludes the use of classical linear statistics. For instance, the average of points on a sphere is located inside the sphere and not on its surface. We were among the first to propose a consistent set of statistical tools to work on Riemannian manifolds (mean value, covariance matrix, Normal law, Mahalanobis distance) along with efficient algorithms and tractable approximations for small variances. We used this framework with P. Fillard to infer anatomical variability in the context of the INRIA-associated team BrainAtlas with P. Thompson at LONI. We proposed to model the variability of the brain from a dataset of precisely delineated anatomical structures (sulcal lines) on the cerebral cortex. We model the first- and second-order moments of sulci by an average sulcal curve and a sparse field of covariance tensors along these curves. The covariance matrices are then extrapolated to the whole brain using a harmonic diffusion PDE on the manifold of tensor fields. As a result, we obtain a dense 3D variability map, which proves to be in accordance with previously published results on smaller samples of subjects. Statistical tests demonstrated that our model was globally able to recover the missing information. Preliminary results on the correlation between local and distant displacements indicate that the displacement of the symmetric point is correlated. Other long-distance correlations also appear, but their statistical significance still needs to be established.

Another way to gather statistics on inter-subject brain variability is to perform multiple deformable registrations between a reference image and subject

images. We recently proposed a consistent mathematical framework called Riemannian elasticity to learn the shape deformation metric from a set of registrations and to use the result as a regularization penalization for new non-rigid registrations. First experiments indicate that the method is sound and effective. Other methods are currently being investigated by other groups. However, due to the very high complexity of the problem, each team is targeting specific aspects with different types of anatomical features and different statistical methods. In order to compare and combine wherever possible the algorithmic solutions and the databases for the statistical estimation, we recently initiated the INRIA Cooperative Research Initiative BrainVar with the Neurospin initia-

tive (http://www.neurospin.org) and several other groups in France including LENA (laboratory for cognitive neurosciences and cerebral imaging at Hopital la Pitié-Salpêtrière, Paris), the Visages (vision, action and information management system in health) INRIA-INSERM reserach team at Rennes (http://www.irisa.fr/visages/visages-eng.html), LSIS (laboratory of information science and systems), Marseilles, and CMLA (centre for mathematics and its applications, Ecole Normale Superieure de Cachan). We plan to investigate many sources of information: cortical landmarks like sulcal ribbons and gyri, the surface of internal structures or fibre pathways mapped from DTI. Individually, these sources of information provide only a partial and biased

view of the whole variability. Thus, we expect to observe a good agreement in some areas, and complementary measures in other areas. This will most probably lead in the near future to new neuroanatomical findings and more robust medical image analysis applications.

Links:
http://www-sop.inria.fr/asclepios/
The ARC BrainVar:
http://www-sop.inria.fr/asclepios/projects/ARCBrainVar/

Please contact:
Xavier Pennec
INRIA, France
Tel: +33 4 92 38 76 64
E-mail: xavier.pennec@sophia.inria.fr

Understanding Cerebral Aneurysms – The @neurIST Project

by Alejandro F. Frangi, Aurelio Ruiz and Martin Hofmann-Apitius

The @neurIST project will develop a vertical and integrative approach to knowledge discovery, personalized risk assessment, patient guideline generation and treatment design. The project will have a big impact on the way that cerebral aneurysms are understood and handled and will provide a reusable and scalable approach to other diseases.

In common with almost every form of knowledge, the volume of data describing human disease processes, including their understanding, diagnosis and management, is growing exponentially. The data are increasingly heterogeneous in form, including textual, image and other symbolic structures. They are also hugely diverse in context, from global guidelines based on the broadest epidemiological studies, through knowledge gained from disease-specific scientific studies, both in vitro and in vivo, to individual patient-specific data.

The data also spans all length scales, from molecular, through cellular, to tissue, organ and patient representations. In recent years huge breakthroughs have occurred in the description of the human genome and in our understanding of its connection to disease processes through functional genomics studies.

The huge volume of this information and its rate of growth represent an unprecedented data management challenge. In particular it is often impossible

for an individual, whether a clinician responsible for patient management, or a physicist or engineer developing a new generation of imaging or interventional devices, to understand and assimilate this knowledge. It is increasingly evident that new methods are required to manage, integrate and interrogate the data in a manner that is accessible to the end user.

Scalable and Reusable Concepts address a concrete Clinical Challenge

Although vertical integration across data structures and across length scales is the primary theme of this project, there is also horizontal integration at every level of abstraction, from access to information sources, evidence processing, knowledge representation, structuring and fusion. While for the purposes of this project and for obvious practical reasons the focus is on one (carefully selected) disease process, our aim is to create an integrative approach that is scalable and reusable for other disease processes. The chosen clinical application of this project is that of

cerebral aneurysms and hemorrhagic stroke. While having an intrinsic importance due to its societal impact, this disease also has a number of interesting challenges that make it attractive as a proof of concept of the envisaged approach. Additionally, it is our belief that such a level of focus is necessary to credibly address the expected vertical integration and to identify clear exploitation paths. The latter exist both in industrial contexts (eg decision-support systems and advanced design of medical devices) and medical contexts, supporting further research and knowledge discovery (eg linking the molecular level of a disease with the disease process itself)

@neurIST is working towards:
• developing a novel IT-enabled system for cerebral aneurysm management
• identifying and collecting all publicly available, relevant and strategically important data for scientific studies
• delivering a rich, multiscale information-processing chain that will provi-

de new diagnostic indexes and insight into the process of aneurysm development and rupture

- developing a set of scalable and reusable integrative suites and demonstrating their value for revolutionizing the understanding and management of cerebral aneurysm

- providing an ICT-system for developing, integrating and sharing biomedical knowledge related to cerebral aneurysm as required by the integrative suites. The @neurIST infrastructure will not only support computationally demanding tasks such as complex modelling and simulation but will also enable access to health data distributed in public and protected databases distributed all over the world

- inspiring and promoting the development of corresponding systems for other disease processes by demonstrating the personal and economic impact of IT-enabled information integration in the context of cerebral aneurysm management.

Although this Integrated Project is primarily concerned with vertical integration of biomedical data, many of the developed concepts have obvious implications and applications along the lines of the roadmap initiative STEP (A Strategy Towards the Europhysiome), which was funded as a concerted action

Virtual Physiological Human for Cerebral Aneurysms

Current understanding of cerebrovascular aneurysm disease combined with modern imaging technology will increasingly reveal silent lesions as found during clinical exams. With a prevalence of 2-3% and a rupture risk in the order of 1/10 000 people annually, treatment of this disease would benefit significantly from an integrated approach and the development of a personalized risk assessment strategy. Integration of multiple clinical data and the use of Grid-based IST systems may provide a platform from which to tackle this problem. This will reduce health care costs by optimally targeting the relevant patient population, thus avoiding unnecessary and potentially risky interventions and improving methods of minimally invasive treatment.

in the same call as @neurIST. In particular it provides a platform for the demonstration of the benefits and viability of the "in silico model of a human being (virtual human)…[merging] a top-down approach starting from the models of body parts and organs with a bottom-up approach that models molecular interactions, pathways and cells taking into account existing research activities." We believe that @neurIST is a pragmatic and concrete exemplar of the Virtual Physical Human concept as well as a transitional project from the Sixth to the Seventh Framework Programme.

Links:
http://www.aneurist.org
http://www.europhysiome.org
http://www.ninds.nih.gov/disorders/cerebral_aneurysm
http://www.bafound.org

Please contact:
Alejandro F. Frangi
Pompeu Fabra University, Barcelona, Spain
Tel: +34 93 542 1451
E-mail: alejandro.frangi@upf.edu

One of the aspects being developed within @neurIST is image-based subject-specific computational fluid dynamics (CFD) of cerebral aneurysms, which is used to understand the role of blood flow in the rupture process. The picture shows CFD simulations (streamlines colour-coding velocity magnitude) in four subjects (1-4) who bear mirror aneurysms in the Circle of Willis (ie aneurysms symmetrically placed in the cerebral circulation). In each subject, the aneurysms are comparable in shape, type and location, and genetic and systemic factors are identical. However, one of them ruptures (a) and the other does not (b). The complex processing chain developed in the context of the project will help in understanding whether flow conditions differ and how they can be used to define surrogates of risk of rupture in a patient-specific manner. Images are courtesy of Dr. A. Radaelli from UPF and were produced in collaboration with NAT/HGC, HCPB and GMU, using ANSYS CFX solver.

The Digital Patient in Clinical Neuroscience: The 'VISAGES' Point of View

by Christian Barillot

Activities of 'VisAGeS' - a research team jointly affiliated to INSERM (National Institute of Health and Scientific Research) and INRIA - are focused on computational modelling of pathologies of the central nervous system. The team addresses a number of general problems: the conception of the surgical room of the future, achieving a better understanding of normal and pathological behaviour of the brain and other organs, and the promotion and support of virtual organizations of biomedical actors by means of HealthGrid technologies.

New in vivo physiological sensors are making it possible to acquire complementary anatomical (structural) and physiological (functional) information from patients. However, this increase in the quantity of information available for purposes of diagnosis and treatment is only of benefit if researchers and physicians are able to interpret it meaningfully. Traditional methods of using these data are often sub-optimal, implying that much valuable information is still neglected during medical decision processes.

In this context, we are focusing our efforts on producing new processing algorithms in the field of neuro-informatics and clinical neurosciences. This involves the development of computational modelling procedures in medical image computing, computer-assisted interventions and the management of distributed and heterogeneous neurological information. We focus our medical application objectives on pathologies of the central nervous system, with a particular effort on multiple sclerosis (MS) and image-guided neurosurgery.

The 'Digital Patient' in Multiple Sclerosis

Today, magnetic resonance imaging (MRI) is widely used for disease diagnosis, patient follow-up, monitoring of therapies, and more generally for the understanding of the natural history of MS. MRI allows abnormalities in MS to be seen with high sensitivity, but is non-specific. Clinical observations are inherently subjective, show poor inter- and intra-observer reliability, and have limited sensitivity. These drawbacks are particularly critical when dealing with hundreds of subjects as in clinical trials. On the other hand, such large-scale studies, involving multiple subjects, image modalities, time points and acquisition centres, naturally require automated
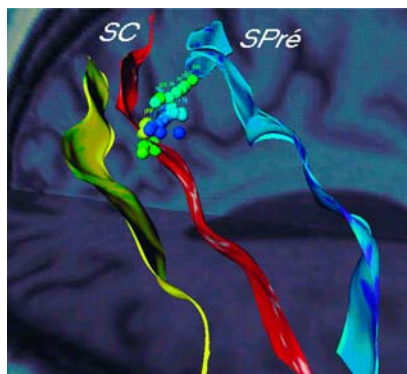

Figure 1: Volumetric representation of sulci from the central region with the representation of somatosensory activation acquired on MEG.

image-processing pipelines for the efficient computation of MR biomarkers from spatio-temporal and multiple MR sequence images.

It is expected that neuroimaging will play a critical role in defining in vivo MS lesion patterns. Making a distinction between MS lesion patterns, and between the early and late stages of MS, is important for a better understanding of the natural history of MS and even more for the appropriate selection and monitoring of drug treatment in MS patients. MRI has a low specificity for defining focal MS pathological changes, but allows highly sensitive detection of both focused and widespread diffuse pathologies in apparently normal white

and grey matter. Some of our major ongoing research issues in neuroimaging of MS lesions concern the definition of new neuroimaging biomarkers for tracking the evolution of the pathology from high-dimensional data (eg MRI). This includes the use of imaging specific to white matter, like Diffusion Tensor imaging (DT-MRI); cell-labelling neuroimaging (eg from MRI or Positron Emission Tomography - PET); and the comparison of MR and PET data using standard and experimental MR contrast agents and radio-labelled PET tracers for activated microglia (eg Ultra Small Particle Iron Oxide or the selective peripheral benzodiazepine antagonist PK 11195). The ultimate objective is to develop cell-specific and quantitative imaging markers and thereby improve routine clinical in vivo characterization of MS pathology.

The 'Digital Patient' in Image-Guided Neurosurgery

Image-guided neurosurgical procedures rely on complex pre-operative planning and intra-operative environments. This includes various multimodal examinations: anatomical, vascular and functional explorations for brain surgery and an increasing number of computer-assisted systems situated in the operating room. Using an image-guided surgery system, a rigid fusion between the patient's head and the preoperative images is determined. Unfortunately,
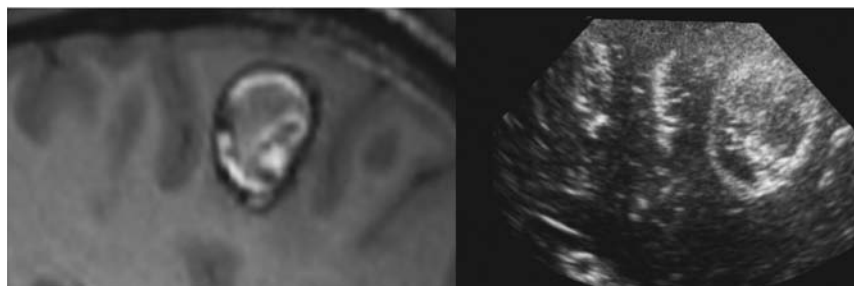

Figure 2: Registration of intraoperative ultrasound with pre-operative MRI.
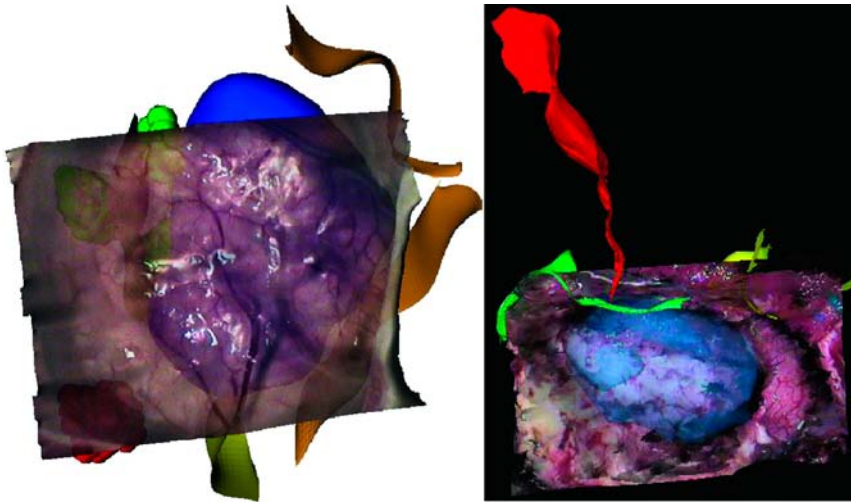
Figure 3: Surface based intraoperative reconstruction after dura opening (right) and tumor resection (left).

the assumption of this rigid registration only holds at the beginning of the procedure, since soft tissues tend to deform during surgery. This is a common problem in many image-guided interventions, but the particular case of neurosurgical procedures can be considered as a representative case. Brain shift is one manifestation of this problem but other tissue deformations can occur and must be taken into account for a more realistic predictive work.

To do so, one possibility is to deform the anatomical and functional images according to the estimated real deformation. This requires intra-operative imaging, and we have recently introduced 3D video reconstruction and 3D ultrasound (3DUS) as a possible intra-operative modality for neurosurgery. These modalities have a minimal effect on operating room logistics and are therefore readily accepted by neurosurgeons. Additional sensors will shortly be available in the operating room; among their functions are molecular data acquisition or in vivo 3D optical imaging and microscopy. Nevertheless, the integration of these new intra-oper-

ative sensors is nontrivial. As mentioned above, one of the most challenging aspects concerns the problem of image fusion between the intra- and pre-operative data, which includes the mathematical modelling of matter dissipation during surgery. Another issue concerns the temporal resolution of images, which is not always adapted to the deformations that must be estimated. For instance, intra-operative images cannot be continuously acquired since this would interfere too much with the operative conditions. This implies the merging of different observations gathered at different time scales during surgery (typically, video and 3D ultrasound or intra-operative MRI).

For these two projects we are working within the INRIA international associated team NEUROMIME, which associates the Visages team with Louis Collins' group at the Montreal Neurological Institute of McGill University.

Links:
http://www.irisa.fr/visages
http://www.irisa.fr/visages/documents/FormulaireNeurOMIMe.html

Please contact:
Christian Barillot
Unit/Project VISAGES,
INRIA/INSERM, France
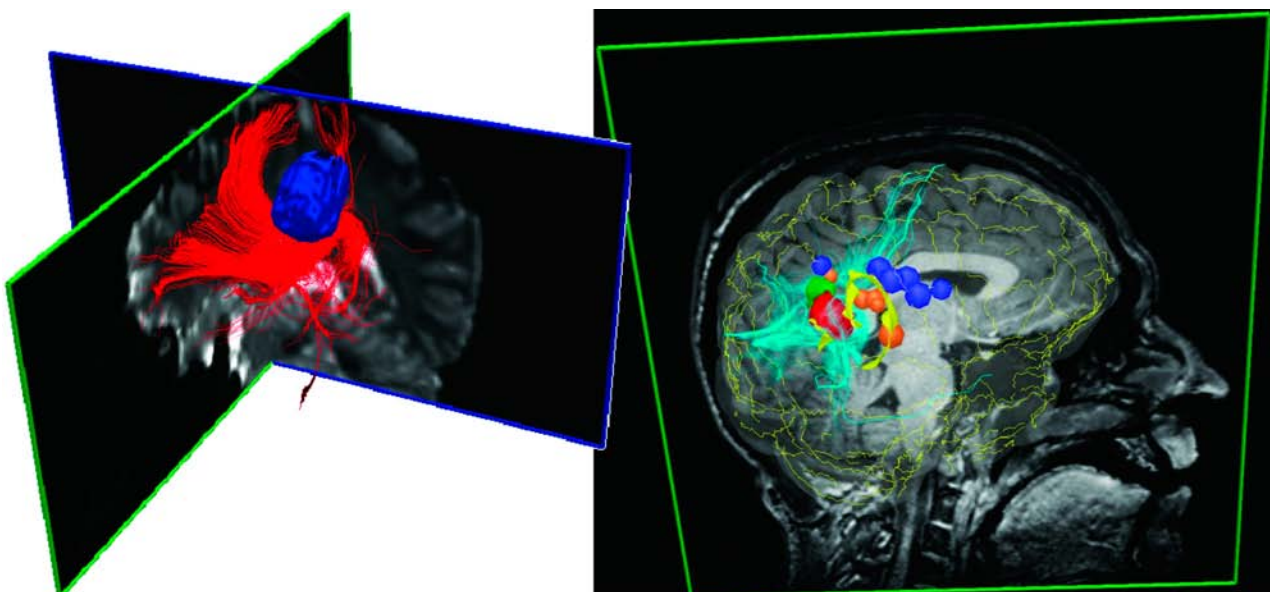Tel: +33 2 99847505
E-mail: Christian.Barillot@irisa.fr

Figure 4: Combination of multimodal pre-surgical data outlining low grade lesions surrounded by fibers bundles (right: with fMRI markers as balls and sulci ribbons).

Computational Brain Tumours

by Olivier Clatz, Ender Konukoglu, Pierre-Yves Bondiau, Simon Warfield, Hervé Delingette and Nicholas Ayache

Computational models of brain tumor have gained attention among scientists in the last decade. Equations describing these models now include different components of the growth: cell proliferation, migration through the tissue and expansion. Recent efforts were devoted to the inclusion of patient-specific data into the model. Simulation results demonstrate a good correlation with radiological observations and allow for new perspectives in neuro-oncology.
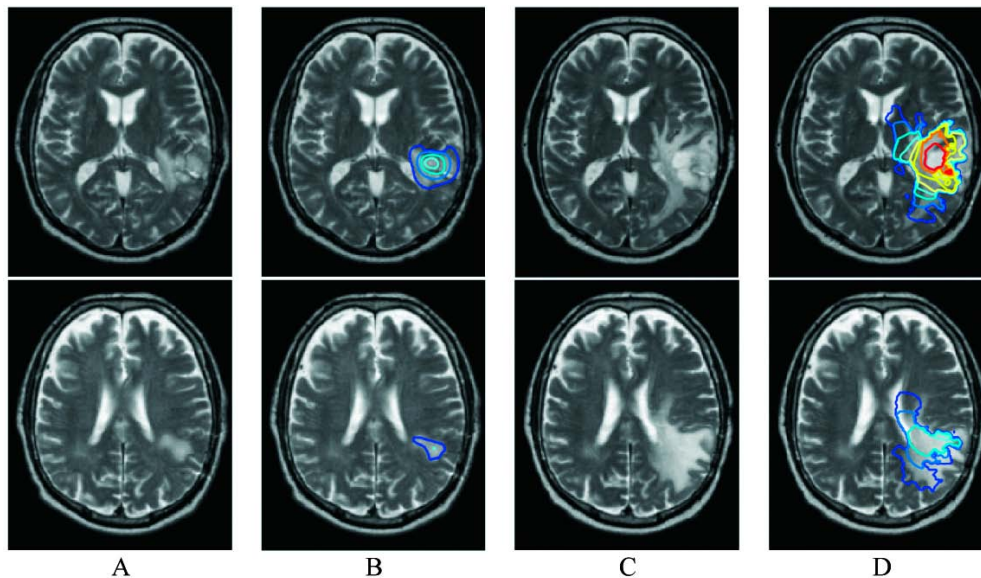

Figure 1: Tumor growth simulation based on patient images. (A) T2 MRI of the patient in March 2002 (two different slices are shown). (B) MRI A with superimposed iso-densities of tumor cells used as initial conditions for the model. (C) T2 MRI of the same patient in September 2002 (6 months later). (D) MRI C with superimposed iso-densities of tumor cells simulated with model. Real tumor -C- and simulated tumor -D- show similar growth patterns.

Brain tumors show a complex pattern of growth at a cellular level. At histological scale, two major mechanisms are responsible for the invasion of the tumor: infiltration and expansion. Infiltrating tumor cells are isolated cells that invade the brain through a diffusion process. This diffusion tends to follow white matter fibers. Expansion describes the coherent growth of the tumor mass, pushing surrounding structures away. Most of the diffusive brain tumors (known as gliomas) share these 2 patterns of growth, with different proportions depending on their grade.

Biomathematical Models

Different mathematical models have been developed at different scales to model the growth of gliomas. For example, cellular automata describe the evolution of tumors at the microscopic scale. The models we develop in the Asclepios project of INRIA Sophia Antipolis describe the tumor at the macroscopic scale, corresponding to the observation scale in medical images. In our model, the evolution of tumor cell density is described with a reaction-diffusion equation. This equation involves two parameters: ρ and D, which respec-

tively control the speed of cell division and diffusion into the tissue. In our case, the diffusion tensor D takes into account the anisotropic invasion of tumor cells in the white matter fibers. This equation is coupled to a mechanical equation to model the mass effect of the tumor. It is important to notice that the numbers of parameters have intentionally been kept small in this model, to minimize the number of unknowns to fit to the data.

These two equations completely describe the three components of the tumor growth: proliferation, diffusion and expansion. Different properties are set according to the different tissues of the brain, identified on MR images of the patient. Specific boundary conditions prevent tumor cells from diffusing through the skull and ventricles. This personalized model allow for a realistic simulation of the tumor growth with respect to observations (see Figure 1).

Figure 2. Application of the model to radiotherapy on a synthetic case. (A) Red: segmentation of the visible tumor in the image. White line: contour of the region targeted with radiotherapy. A constant margin of 1.5cm is used. (B) Estimated distribution of tumor cells computed with the model. The estimated distribution of tumor cells is highly inhomogeneous. (C) Blue: area invaded by the tumor and targeted by radiotherapy. Yellow: estimated healthy tissue targeted by radiotherapy. Green: invaded area of the brain that may be targeted by radiotherapy. The model could be used to adapt the targeted volume to apply the radiotherapy dose to the blue and green regions only.

Applications

In the context of the associated team CompuTumor and the European project Health-e-Child, we are currently developing methods to identify model parameters based on radiological images of the patient. These methods allow for a personalized and quantitative diagnostic of the pathology. Such information could influence the therapeutic strategy: a very diffusive tumor (high D, low ρ) may be better treated with extended radiotherapy and chemotherapy, while surgery seems more adapted to expansive -but less diffusive- tumors.

This model could also provide information that cannot be quantified by MRI. Indeed, it allows for the estimation of the local tumor cell density, where the MR image only shows a detection threshold. By better defining the invisible part of the tumor, this may open new possibilities for the treatment of these tumors with radiotherapy. Figure 2 presents a synthetic example of the application of the model to radiotherapy. The simulated virtual tumor of this example illustrates the improvement in the radiotherapy margin definition in the case where the extension of tumor cells matches that simulated with a growth model.

Please contact:
Olivier Clatz
INRIA, France
E-mail: olivier.clatz@sophia.inria.fr

Towards Virtual Oncology

by Georgios Stamatakos

Approaching biology as the physical science of living matter dictates the development of a parsimonious mathematical and computational formulation of multiscale biological phenomena. Such a long-term endeavour must be collaborative on a worldwide scale. The combination of cancer biology with in silico oncology can serve as a valuable paradigm for such a process. Here we outline simulation results on the response of tumorous and normal tissues to therapeutic schemes. These simulations were developed over the last decade by the In Silico Oncology Group at the National Technical University of Athens.
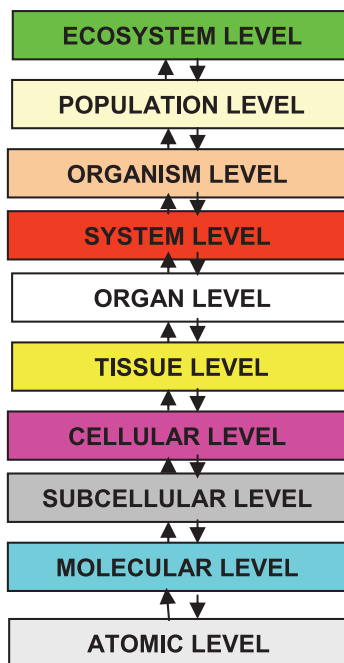
The remarkable rate of accumulation of both experimental and observational (clinical) knowledge pertaining to living matter dictates the formulation of a parsimonious system of 'laws' that are somewhat analogous to Newton's 'Mathematical Principles of Natural Philosophy'. This seems to be a necessary step if a rational, coherent and transparent understanding of the biological phenomena is to be sought. Such a system would consist of a finite yet considerable number of principles and would refer to all levels of biocomplexity (see Figure 1), since according to Denis Noble a privileged level of causality does not appear to exist. The experimental, observational and theoretical study of cancer, a markedly multiscale biological phenomenon of obvious clinical importance, may be viewed as an excellent ground for the establishment of a number of such multiscale laws. Their formulation might well be achieved in a combination of discrete and continuous mathematical terms.

In Silico Oncology and the Problem of Cancer Predictability

The emerging field of in silico (computational) oncology has already provided

The ten levels of biocomplexity.

some plausible descriptions of several biological mechanisms, both continuous and discrete in nature, that characterize cancer. Obviously cancer is far from being a purely deterministic phenomenon. Instead it seems to behave like a mixture of deterministic (eg

sequence of cell-cycle phases) and stochastic (eg radiation cell-kill probability) processes. Stochastic aspects should therefore always be taken into account. Nevertheless, as more critical knowledge becomes available, the more deterministic the cancer phenomenon appears to become. An illustrative example supporting this hypothesis is that more detailed knowledge of the genetic status of a tumour may lead to a better prediction of its response to therapeutic interventions, and thus to apparently more deterministic tumour behaviour.

Based on these ideas, the In Silico Oncology Group (ISOG) in the Institute of Communication and Computer Systems (ICCS) at the National Technical University of Athens (NTUA) has developed a number of hybrid discrete Monte Carlo/cellular automata and continuous differential equation simulation models of tumour growth, and of the response of tumour and normal tissues to therapeutic modalities. The models range from tumour growth and radiotherapy response in vitro, to the clinical tumour response, to radiotherapeutic and chemotherapeutic schemes in vivo,

based among other things on actual imaging data. Processed molecular data is used in order to perturb the radiobiological or pharmacodynamic cell-kill parameters about their population-based mean values. At the heart of the proposed simulation approach lies a prototype system of quantizing cell clusters included within each geometrical cell of a discretizing mesh, which covers the anatomic area of interest. Cell-cycle phase durations and imaging-based metabolism distribution define the quantization equivalence classes considered. Several algorithms have been developed so as to simulate various macroscopic mechanisms such as tumour expansion or shrinkage and mechanical boundary conditions, as well as the effects of particular drugs (eg temozolomide) and radiation on the tumorous and normal tissue under consideration.

A number of the models developed, which mainly refer to imageable glioblastomas, have already been clinically validated to a substantial degree by exploiting the outcomes of pertinent clinical trials. Long-term clinical testing and adaptation procedures are in progress. The response of treatment-affected normal tissues in radiotherapeutic schemes has also been addressed for certain cases. Currently, a substantial extension of the simulation models to cases of nephroblastoma (Wilm's tumour) and breast cancer is being performed within the frame of the EC-funded project ACGT (Advancing Clinico-Genomic Trials on cancer), in collaboration with several European institutions including the Foundation for Research and Technology Hellas, Heraklion, in Greece. Of particular clinical importance is the tight collaboration with the Paediatric Haematology and Oncology Clinic of the University of Saarland in Germany, and Belgium's Institut Jules Bordet, located in Brussels. The whole effort is also supported by the NIH-NCI-funded Center for the Development of a Virtual Tumor (CviT), based in Massachusetts, USA. It is worth noting the remarkably collaborative character of this and other complementary research efforts on a global scale.

It is expected that the type of model described here will provide clinicians and researchers with the option of running virtual experiments to optimize cancer treatment strategies based on the specific molecular, histopathologic, imaging and historical data of individual patients. A deeper understanding of the cancer disease at a molecular level and at the same time of the related macroscopic phenomena is a further intermediate goal of considerable importance.

Links:
In Silico Ontology group, NTUA:
http://www.in-silico-oncology.iccs.ntua.gr

ACGT project: http://www.eu-acgt.org/

Center for the Development of a
Virtual Tumor: https://www.cvit.org/

Please contact:
Georgios Stamatakos
National Technical University of
Athens, Greece
Tel: + 30 210 772 2288
E-mail: gestam@central.ntua.gr

Interactive Simulation and Visualization for Cancer Treatment Planning with Grid-Based Technology

by Robert G. Belleman, Michael Scarpa and Bram Stolk

Can virtual reality help to understand tumour growth? Researchers at the Section Computational Science of the University of Amsterdam (UvA), SARA Computing and Networking Services (SARA) in the Netherlands and the In-Silico Oncology Group of the National Technical University of Athens (NTUA) have combined interactive Virtual Reality visualization with in-silico tumour simulation models to better comprehend tumour growth and optimize the planning of treatment schemes.

Visualization is often used in situations where data analysis algorithms for the detection of features in scientific data are too limited or do not even exist. It exploits the researcher's visual acuity, cognitive abilities, expertise and experience in recognizing patterns. One of its application areas is computer simulation. Simulation results are often represented by abstract mathematical structures, and visualization is used to convert these into pictures.

At the core of every simulation is a mathematical model that is evaluated by a computer. Invariably, a computer simulation model is defined by a number of parameters that control the behaviour of the simulation, and which are therefore of crucial importance to the model developer and the end-user of the model.

Awareness of a model's behaviour is greatly enhanced when a researcher is given the ability to control a simulation by interactively manipulating the model's parameters. Such an interactive system aids in exploring the behaviour of a simulation because parameter changes are immediately visible. This provides a feedback-response mecha-

nism allowing a researcher to use the visualization to plan a response.

Tumour Growth Simulation
In the EU-funded project 'Advancing Clinico-Genomic Trials (ACGT) on Cancer', researchers collaborate to combine interactive visualization, virtual reality technology and in-silico tumour growth simulations into an interactive environment. This can be used to explore simulated predictions of tumour growth and treatment response. The architecture constructed in ACGT consists of a Grid-based distributed computing and software framework. It

Figure 1: The Personal Space Station (PSS) offers stereoscopic visualization and direct interaction by means of tracked objects. Picture: UvA.

allows in-silico tumour simulation models, interactive visualization methods and other data sources to be combined into an interactive visual exploration environment.

In-silico tumour simulation models combine tumour information obtained from medical imaging techniques (CT, MRI, PET and ultrasound) with mathematical models that predict the growth of tumours or the response to chemotherapy or radiation therapy. The simulation models produce spatiotemporal predictions of the composition and morphology (form) of the tumour over the course of time. These predictions provide clinicians with valuable information on the most effective treatment out of several alternatives, as well as detailed parameters on the optimal composition of a treatment scheme, including the total treatment period, the type of drug(s), dose, and interval between treatments. A treatment is defined by several parameters; each of these has a range of possible values, and is influenced by the others. When a new clinical trial is defined, simulation models help to define the initial parameters that predict the treatment most likely to be most effective.

Interactive Visual Exploration

Tumour growth simulation results are used in different ways. Each scenario has different visualization and interaction requirements, which sometimes call for unconventional graphical displays to effectively assist researchers to

achieve their goals. Researchers at UvA and SARA have designed a Highly Interactive Framework for Interactive Visual Exploration (HIFIVE); this abstracts interactive visualization applications from graphical displays and user interfaces, so that they can be used on many types of graphical displays, each with their own set of user interfaces. This allows interactive visual exploration applications to be used in a wide variety of scenarios.

For example, finding the optimal combination of parameters for a certain treatment is difficult. As no analytical method exists for finding this optimum, the ACGT environment is used to perform a large number of simulations for combinations of parameters that are thought to be most successful. The

Figure 2: A position-tracked interactive display for the co-located visualization of medical images and simulation results. Displays like this can be a powerful planning and navigational tool in surgical treatments. Picture: UvA.

results of these simulations are presented in a stereoscopic visualization environment called the Personal Space Station (PSS), developed by Personal Space Technologies in the Netherlands. The PSS represents the simulation results in 4D (3D + time) and allows a researcher to 'reach in' and explore the visualized results hands-on, simply by manipulating optically tracked handheld objects. The combination of 4D visualization with intuitive interaction methods allows researchers to explore the different outcomes and make adjustments to optimize treatment parameters.

Patient-specific treatments are optimized with the help of an interactive handheld display. It combines simulation results with information obtained from additional medical image sources, including anatomical scans (CT, MRI, ultrasound), functional scans (fMRI, PET) and advanced imaging techniques such as Diffusion-Weighted Imaging (DWI). Combined with tractography, they are used to infer the connectivity of the brain. Through the simultaneous visualization of simulation results and medical images, this co-located tracked display provides surgeons with a powerful planning and navigational tool that can be used in the case of surgical treatment, such as tumour resection.

Overall, the combination of the ACGT Grid infrastructure with the HIFIVE framework provides a unique distributed computing architecture that offers support for high-performance and responsive interactive simulation and visualization applications.

Links:
http://www.science.uva.nl/research/scs/
http://www.eu-acgt.org/

Please contact:
Robert G. Belleman
University of Amsterdam,
the Netherlands
Tel: +31 20 525 7462
E-mail: robbel@science.uva.nl

Patient-Tailored Cancer Therapeutics – The Tempo Project

by Jean Clairambault, François Fages and Sylvain Soliman

'Temporal Genomics for Tailored Chronotherapeutics' (Tempo), is a European project partly funded by the European Union's FP6-LifeSciHealth programme. The project investigates the possibility of individual cancer therapeutics by genetic profiling of cellular drug processing mechanisms and their circadian rhythms.

The main principle that guides Tempo is the exploitation of individual variations (genetic polymorphism) encountered in biological mechanisms. These govern the cell metabolism of anticancer drugs, and particularly those mechanisms that are dependent on the molecular circadian clock, to adapt time-scheduled drug delivery regimens (eg using programmable pumps) for individual patients. Every single patient will belong, according to his genetic enzymatic profile, to one in a limited number of dynamic classes or clusters - ideally between three and five - to be defined after biological measurements of toxicity obtained by blood and tissue samples. And his or her class or cluster will determine his or her personal drug delivery regimen.
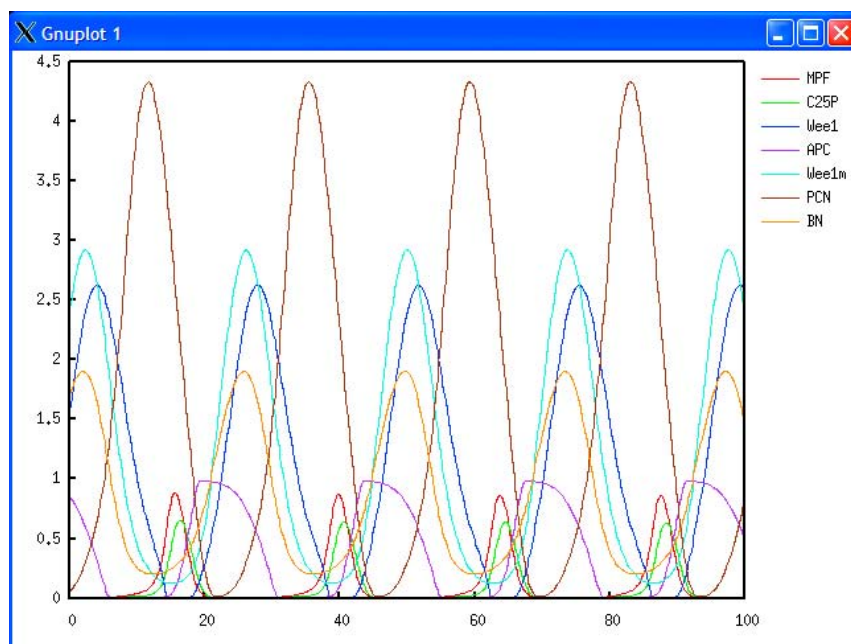
Tempo is a Specifically Targeted Research European Project (STREP) and has been running since October 2006. It has a relatively short duration of three years. It involves the investigation of drug processing mechanisms in several laboratory rodent strains. Both genders are used, with each bearing one of several different types of implantable tumour. The drug processing mechanisms will be studied at regularly spaced time points (four or six) during 24 hour spans, so as to identify the influence of circadian rhythms.

The aim of the project is to optimize the delivery of two anticancer drugs. One of these is already in use in everyday cancer clinics, but has significant toxic side effects. The other is a more recent discovery and belongs to a new class of drugs: the cyclin-dependent kinase inhibitors (CDKIs). Initial investigations into the enzymatic activation and degradation systems of these two drugs, irinotecan (initially isolated from the Chinese tree Camptotheca acuminata) and seliciclib (isolated from starfish oocytes), will be performed on laboratory rodents by looking at the genomic expression, protein concentration and enzymatic activities of the cell mechanisms. Finally, molecular and physiological human descriptive variables will be gathered in patients with the aim of obtaining theoretically optimal drug delivery time schedules for these two drugs separately.

The project includes a work package dedicated to data integration and mathe-

Simulation of the entrainment in period of the cell cycle by the circadian cycle through Wee1.

matical modelling, which is managed by INRIA in the research teams 'Bang' and 'Contraintes' at Rocquencourt. Models will be designed both at the individual cell and cell population levels. At the individual cell level, ODE models will be developed in the BIOCHAM environment for molecular systems biology (see http://contraintes.inria.fr/BIOCHAM). These will describe the interrelations between the cell division cycle and the circadian clock, and the pharmacokinetic-pharmacodynamic (PK-PD) mechanisms of drug activity with their genetic polymorphism and circadian variations. At the cell population level, age-structured PDE models of homogeneous cell populations (healthy or tumorous), subject to renewal, will be developed and analysed as targets of cytotoxic drugs. The pharmacological control of the growth of the cell populations under study will be analysed both by a global cell population number and a Malthus exponent for each tissue represented.

Future activities to be developed from this project include the investigation of other anticancer drugs and their synergies, and the definition of optimized chronotherapeutic strategies, individualized for patients in order to minimize unwanted toxic side effects on healthy tissues and to overcome the occurrence of drug resistance.

The Tempo project will be developed in conjunction with other running FP6 European projects to which members of the Tempo consortium already belong, and which are dedicated to modelling of either cancer (M3CSTGT: http://calvino.polito.it/~mcrtn) or drug development (BIOSIM: htttp://biosim.fysik.dtu.dk:8080/biosim/index.jsp).

The project is coordinated by Francis Lévi (INSERM U 776 'Biological Rhythms and Cancers', Paul-Brousse Hospital, Villejuif, Fance). Associated teams of researchers are from fundamental biology and clinical oncology, studying the cell division cycle, pharmacogenomics, or circadian chronobiology at CNRS, INSERM and European universities, with INRIA teams dedicated to mathematical and systems biology, and SMEs accustomed to applied mathematical modelling for pharmaceutical industries and drug delivery device technology.

Towards an Individualised Physiological Model of the Musculoskeletal System

by Nadia Magnenat-Thalmann and Benjamin Gilles

In the framework of two projects we present problems and advances in developing functional musculoskeletal models.

Since 2002, Prof. Nadia Magnenat-Thalmann of the Swiss National Center of Competence in Research Co-Me has been leading a project on interactive clinical visualization for hip joint examination. The goals of this research are to build a 3D patient-specific functional model of the hip joint, and to develop interactive tools allowing clinicians to examine hip behaviour. Such tools will be invaluable aids in diagnosis and treatment planning, particularly for osteoarthritis and impingement syndrome pathologies. While MIRALab is taking care of the modelling and clinical visualization, two Swiss partners – VRLab-EPFL and MEMcenter ISTB (University of Bern) – are responsible for scalable mechanical simulation methods. Medical consulting is ensured through extensive collaboration with radiologists and orthopaedists from the University Hospital of Geneva and Inselspital Orthopaedics – University Hospital of Bern.

Prof. Nadia Magnenat-Thalmann is also project coordinator of the European Marie-Curie Research Training Network called 3D Anatomical Human. Having commenced in 2006, its objective is to train a body of researchers in the various domains involving the modelling/simulation of the human musculoskeletal system. More explicitly, we aim at reducing the current fragmentation in musculoskeletal research by providing a bridge for partners from different domains of expertise: Medical Imaging (INRIA-Asclepios, University College London); Biomechanics (SMI-Aalborg University, LTM-Istituti Ortopedici Rizzoli); Computer Graphics & Animation (MIRALab, VRLab-EPFL, CRS4); and Knowledge Management (STARLab-Vrije Universiteit Brussel). MIRALab collaborates with two ERCIM partners (VRLab-EPFL and INRIA-Asclepios) in the domains of musculoskeletal modelling from Magnetic Resonance Imaging (MRI) and fast biomechanical simulation.

Musculoskeletal disorders are the commonest and most notorious causes of severe long-term pain and physical disability, and affect hundreds of millions of people throughout the world (www.boneandjointdecade.org). An advanced understanding of the musculoskeletal system and its disorders is absolutely necessary in order to improve prevention and treatment. Three pathological levels can be distinguished: the first is directly related to tissue geometry (eg bone fracture, muscle/tendon/ligament injuries); the second is related to musculoskeletal function (eg joint degeneration, movement restriction); and the third is related to neuromuscular control (eg cerebral palsy). The ability to predict musculoskeletal behaviour from morphology, kinematical constraints, mechanical constraints or neuromuscular impulses would have a great impact on current medical practice. In addition to applications in orthopaedics (eg early detection of osteoarthritis, prosthesis design, osteotomy planning, tendon lengthening, ligament reconstruction), this would aid in the kinesiology science for movement optimization (eg reduction of tennis elbow), rehabilitation and ergonomics (eg minimization of physical fatigue under specific constraints).

Data acquisition modalities are becoming increasingly precise, available and standardized, as well as less and less invasive. In the course of their work, radiologists are required to analyse large amounts of data related to musculoskeletal anatomy, kinematics, dynamics, mechanics and physiology, and must therefore manage and visualize information at increasing levels of complexity. Individualized modelling of organs deals with shape, structure (fibre direction) and motion/deformation extraction from images. The specificity of the musculoskeletal system is complex due to the relatively large spatial scale and the large number of interrelated organs. Regarding the musculoskeletal simulation aspect, researchers face geometrical, mechanical, chemical and physiological complexity: a variety of events can occur at very different spatial scales (eg micro versus macro mechanical interactions) and temporal scales (eg muscle actuation versus muscle longitudinal changes). Consequently, the study of

musculoskeletal functioning has been compartmentalized into various disciplines, though these are not independent, resulting in partial and oversimplified models (eg precise mechanical models of a single tissue, complete limb model using simplified muscle action lines and simplified skeletons etc). A higher and unified level of simulation (co-simulation level) taking into account large scales (eg anatomy-based virtual humans animated from motion capture and electromyography) as well as small scales (eg deformations due to local fibre actuation) is not yet available. This would be of major benefit in linking the different disciplines, and would allow a better understanding and a more accurate simulation of the musculoskeletal system. This in turn would lead to new applications in the field (eg post-surgical predictions, functional prosthesis).

To bridge modelling and simulation levels requires on the one hand fast and well-constrained (mostly geometric and surface-based) segmentation methods and on the other hand, accurate predictive methods (physical and volumetric models). To guarantee the efficiency and the accuracy of segmentation methods, these latter are taken into account in the clinical protocol that drives MRI data acquisition. Within particle-system frameworks we propose geometric/physically-based techniques to reconstruct and parameterize mechanical models from image data. Passive characterization of tissue through mechanical testing is carried out and incorporated in the model, along with motion capture, electromyography (EMG) and force-plate data. Since mechanical models manage volumetric meshes, equivalences between surface and volumetric meshes are studied through intermediate medial representations. The multi-organ and multi-tissue nature of the problem involves a fast handling of collisions/contacts, and multi-resolution meshes are required to allow a scalable control of the complexity. Moreover, in order to meet timing constraints during interactive tasks, new rendering techniques have been developed. Finally, to fuse multimodal data, to combine redundant information (eg MRI-based models and motion, and motion-capture data), and to insure completion of sparse data, we use a high-level representation (medical ontology). This also permits medically relevant data management (eg visualization tools for clinicians) and analysis (eg subject comparison and statistical analysis).

Links:
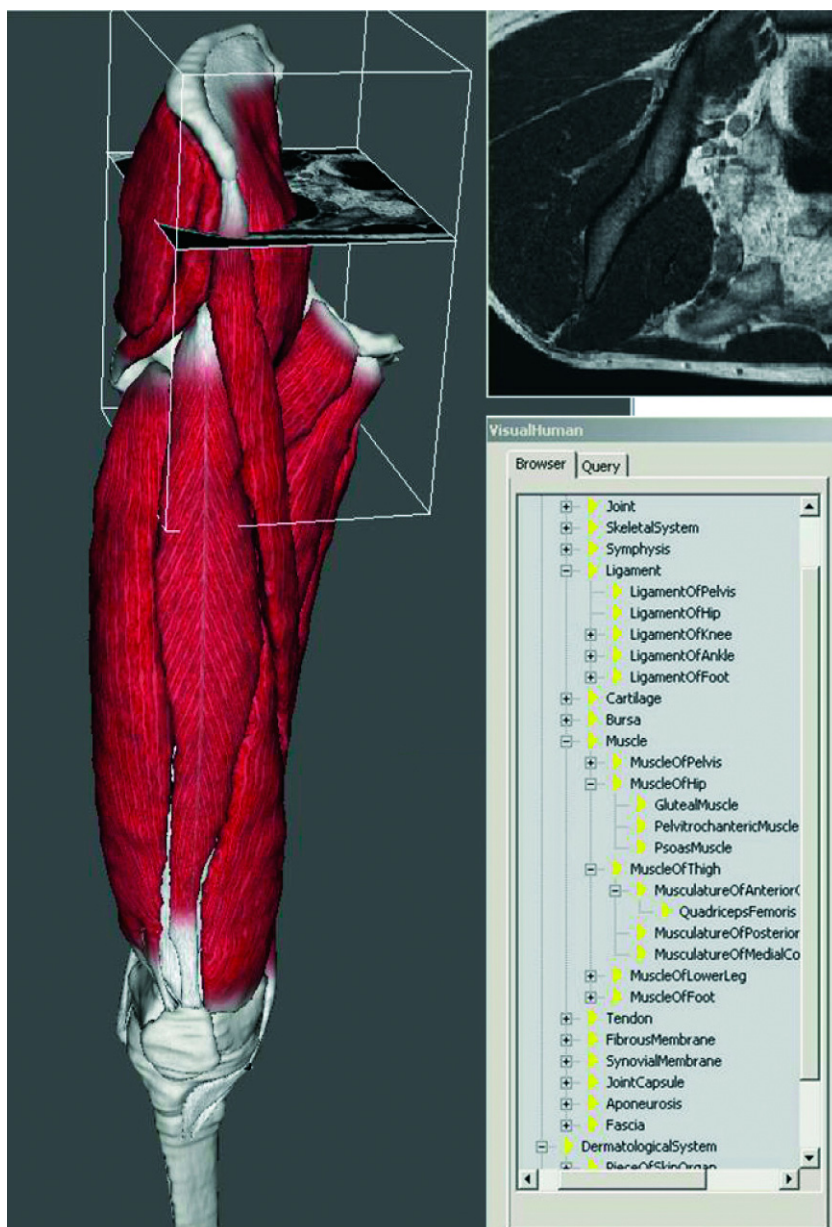http://www.co-me.ch
http://3dah.miralab.unige.ch

Please contact:
Nadia Magnenat-Thalmann
MIRALab – University of Geneva, Switzerland
Tel: +41 22 379 77 69
E-mail: thalmann@miralab.unige.ch

Benjamin Gilles
MIRALab – University of Geneva, Switzerland
Tel: +41 22 379 77 69
E-mail: gilles@miralab.unige.ch

Ontology-based framework for musculoskeletal modelling, simulation and visualization.

Combined Statistical Model of Bone Shape and Biomechanical Properties for Evidence-Based Orthopaedic Implant Design

by Miguel A. González Ballester, Philippe Büchler and Nils Reimers

Researchers at the MEM Research Center (Institute for Surgical Technology and Biomechanics, University of Bern), in collaboration with Stryker Osteosynthesis, are constructing advanced statistical digital models of bone shape and biomechanical properties. These models will lead to the design of a new breed of orthopaedic implants that will guarantee an optimal fit for the whole range of patients.

Current design processes for orthopaedic implants rely on very limited information about the shape of the target bone. Such information may be in the form of a small set of shape parameters (eg lengths and angles) derived from the existing literature, which fails to capture the complexity of real anatomical shapes. Alternatively, tests on cadaver bones can be performed. However, extrapolating the findings reached by such tests to the whole target population can lead to implants that may fit some patients, but not others. The importance of determining a range of implants that fit most of the population is paramount, both from a clinical and an economic perspective.

For this reason, the current project uses novel population-based design methods to develop market-specific trauma implants. Our technology allows a compact model that represents the range of shape variation encountered in a set of different 3D shapes (in this case bones) to be automatically built. Statistical analysis techniques are employed to determine the average bone shape in a given population, as well as the shape distribution around this average in the form of principal components of shape variation. From such a distribution it is possible to generate new virtual shapes, and in particular to create a set of models representing, for example, 95% of the shape variability in the population.

During this project, we have extended our ability to analyse the surface shape of anatomies to also include internal structures and bone density information. This results in a compact statistical description of the variability in bone shape and density, and the correlation between them. To this end, novel methodological contributions are being developed, tested and applied to the particular case of bone modelling. As a side product of this development, it is possible to generate realistic synthetic image data sets for further virtual testing and assessment of the anchoring performance of the developed implants.

For this project, a large database of computer tomography (CT) scans of bones from different populations is being constructed. Statistical analysis is performed and it is then possible to generate new bone instances covering a representative cross-section of the population. This includes both the bone surface, which will be used to contour an optimally fitting implant, as well as bone mineral density, to allow the best positioning for fixation to be determined.

The biomechanical behaviour of the bone/implant construct will also be taken into consideration during the design process. Advanced finite element analysis (FEA) has been coupled with the statistical models of bone shape and density previously created to evaluate implant design across a population. Initial evaluations will focus on the implant strength and primary function. Then, since it is well known that the mechanical environment around the fracture site strongly influences the healing process, mechanical parameters important for the fracture healing will be calculated. By sampling the statistical model, which contains the variation in shape and bone density across the

How to make an implant "fit" a majority of a population?

Selection of a target population — Averaged bone shape of the population — Statistical shape variation (95% of the population) — Implant design — Biomechanical evaluation of the implant accross the population

Population-based orthopaedic implant design and virtual testing.

population, and performing the FEA experiment as described above on each instance, we are able to reconstruct the statistical distribution of biomechanical properties across the population. These results will allow the selection of an implant that will create the optimal mechanical conditions for bone healing.

In short, in this project we are developing and applying technology that will lead to better implant design, in terms of both morphology and biomechanical performance. This is achieved by building digital models of human anatomy and biomechanical properties, which allow virtual implant testing to be performed across a target population.

This project is funded by the Swiss Innovation Promotion Agency (CTI/KTI) and the Swiss National Science Foundation (SNSF), through the National Center of Competence in Research on Computer-Aided and Image-Guided Medical Interventions (NCCR Co-Me).

Please contact:
Miguel A. González Ballester
MEM Research Center,
University of Bern
Tel: +41 316315950
E-mail:
miguel.gonzalez@MEMcenter.unibe.ch

Model Based System for Computer Assisted Knee Surgery

by Gábor Renner and György Szántó

A computer aided system has been developed for the support of orthopedic surgery. The system provides a wide range of facilities for the design, control and navigation of clinical interventions, primarily aimed at knee surgery. For the purposes of pre-operative planning and the control during the operation, the system builds 3D models of the anatomical structures based on individual image sequences of the patient. The flexible structure enables the system to be configured to different orthopedic operations. The first application is prepared for knee ligament surgery (anterior cruciate ligament reconstruction). The work has been accomplished by a team composed of the R/D staff of SZTAKI and the Orthopedic Department of the Semmelweis University, Budapest.

The knee joint is one of the most important components of the human motion system. Knowledge of the geometrical properties of the internal surfaces (condyles) and their functionality is crucial in understanding the complex behaviour of the knee. The discovery of these internal features is imperative for successful medical intervention in pathological cases of the knee.

Traditional medical examinations can only provide limited information about the complex and hidden structures of the knee. Modern medical imaging technologies (CT, magnetic resonance imaging etc) provide advanced tools with which to investigate the morphological properties. This is extremely important for acquiring in vivo information during different motion phases of the knee. However, the raw data directly provided by these imaging techniques represent only two-dimensional (2D) pictures of the anatomical objects. Conversion of the 2D image sequences into precise 3D representations suitable for detailed motion analysis is a challenging job. This can only be achieved with the help of computer-based methods of image analysis, geometrical modelling and reconstruction.

The work accomplished was primarily based on information stored as magnetic resonance (MR) sequences. Image analysis methods (eg fast marching, active contour) were applied to detect the boundaries of the anatomical structures, and these contours were used to

Figure 1:
Active surfaces of the femur and tibia.

build a precise static 3D model. Several methods and programs were developed to analyse the shape properties of the contacting elements of the knee. However, the exploration of the dynamic behaviour of the knee requires information to be acquired and stored in different motion phases of the joint. In order to handle the data in one common coordinate system, different registration algorithms were developed. (Figure 1 shows the shape of the femur and tibia reconstructed from MR slices and highlights the active surfaces.)

In addition to a scientific exploration of the geometry of the knee, the main purposes of this study were to support the development of knee prostheses with a new geometry, and to create various tools for computer assisted knee surgery. In the following some details of the surgical system are described. Such systems provide the means to assist the pre-operative design to allow minimal invasion and continuous control with the required precision during surgery. We are firmly convinced that a proper solution must largely rely on the permanent availability of realistic images and

computer generated 3D models of the anatomical elements.

The surgical system is implemented as a framework that integrates the most important design and navigation functions and enables fast adaptation to different kinds of clinical tasks. The flexible architecture of the system is a key feature that will allow it to be modified for other application areas (eg dental and cranial surgery). The system architecture facilitates the definition, creation and manipulation of clinical tools used during computer assisted surgery (eg surgical devices, drills, hooks, active and passive sensors, motion tracking cameras, calibration and navigation devices) together with the previously gained MR images and 3D geometric models. These tools can be placed into any arbitrary position and

recalculated runtime, according to the hierarchical topology. The local 3D spaces are mapped to arbitrary other spaces within the hierarchical topology through a series of 3D transformations. A wide range of visualization features is available to the surgeon through the graphical user interface, allowing the actual state of the system components to be monitored. Figure 2 shows the components of a typical system.

The first experimental application of our surgical navigation system was configured to meet the requirements of anterior cruciate ligament (ACL) reconstruction operations. ACL reconstruction is a frequent surgical intervention to replace the ligament torn because of excessive load during sport or an accident. The use of the computer-assisted navigation system offers significant

the knee. Proper placement of the cruciate ligament is very important to prevent both over- and undertension of the replacement tendon.

Programs have been developed to support pre-operative calculation and analysis of the variation in ligament length during motion, and to provide tools for graphical representation. Figure 3 shows nearly optimal positioning of the fixing points on the tibia (T) and on the reconstructed surface of the femur (F). The femur surface is colour-coded according to the relative change of the distance between the fixed tibia point and the varying femur points during flexion.

In addition to the above geometrical calculations, the clinical system incorporates tools for setting up, registering,
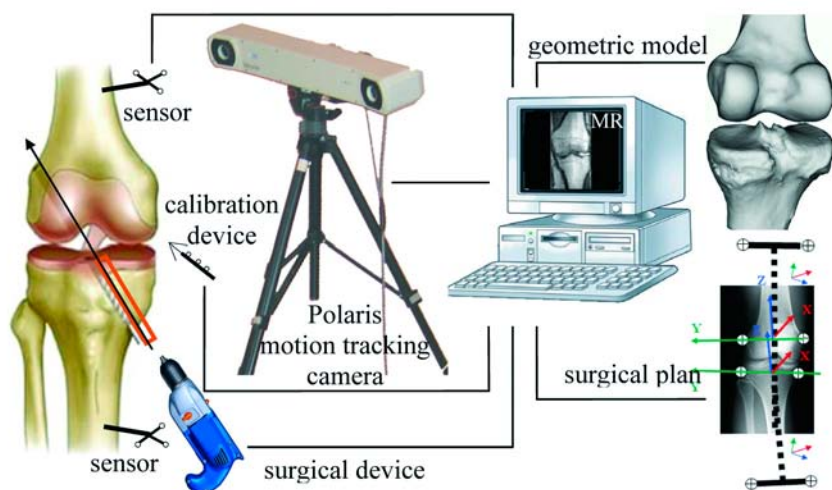

Figure 2: Typical system set-up.

Figure 3: Optimization of the ligament position.

jointly moved after a series of well-defined registration steps.

The system components used during navigation are arranged in a common hierarchical topology that is represented by a flexible tree structure. The root of the tree is the global space and the objects with their own coordinate system represent the nodes. The structure of the tree expresses the relationship between the embedded coordinate systems assigned to the objects. Some elements can be fixed to the global space, and by adding, deleting or reconfiguring elements, the whole tree structure can be modified. The associated local/global position and orientation values are

advantages compared to traditional surgery. For instance, minimal surgical invasion is required, the ideal location of the replacement ligament can be well defined during the pre-operative design phase, and the position and orientation of the surgical devices can constantly be monitored and controlled during operation. This technique assumes the availability of a precise 3D model of the knee based on the MR data of the patient, and appropriate procedures for performing the necessary geometrical calculations. One of the key problems is to define the fixing points of the ligament to the tibia and femur with the condition that the length of the ligament is constant during the normal flexion of

configuring and controlling the navigation facilities, the operating environment etc, as defined in appropriate medical protocols. Due to its flexible architecture, the system can easily be reconfigured to other kinds of orthopedic interventions.

Please contact:
Gábor Renner
SZTAKI, Hungary
Tel: +36 1 279 6152
E-mail: renner@sztaki.hu

György Szántó
SZTAKI, Hungary
Tel: +36 1 279 6187
E-mail: szanto@sztaki.hu

CardioSense3D:
Electromechanical Modelling of the Heart for Personalized Diagnosis and Therapy

by Hervé Delingette, Maxime Sermesant, Nicholas Ayache, Dominique Chapelle, Miguel Fernandez, Jean-Fréderic Gerbeau and Michel Sorine

The CardioSense3D action is an INRIA initiative that aims to develop a patient-specific simulation of cardiac activity that is suitable for clinical applications. This simulation includes a coupled model of the electrophysiological and mechanical behaviour of the heart, whose parameters are estimated based on the medical images and signals acquired on a given patient.

There is an irreversible evolution of medical practice toward more quantitative and personalized decision procedures for prevention, diagnosis and therapy, based on ever larger and more complex sets of measurements. This deep trend has led to a crucial need to produce a new type of so-called computational model of the anatomy and the physiology of the human body, which is able to explain the observations, detect abnormalities, predict evolutions, and to simulate and evaluate therapies.

The simulation of the heart is the subject of growing attention due to the impact of cardiovascular diseases in industrialized nations and to the high complexity of the cardiac function. Indeed, formulating a computational model of the cardiac function of a specific patient represents a great challenge due to the intrinsic physiological complexity of the underlying phenomena, which combine tissue mechanics, fluid dynamics, electrophysiology, energetic metabolism and cardiovascular regulation. Another source of difficulties lies in the partial information on cardiac function available for a specific patient through acquired signals and images.

CardioSense3D

To tackle these challenges, a four-year Large Initiative Action was launched in 2005 and funded by the French national research centre INRIA, focusing on the electromechanical modelling of the heart. This action relies on the expertise of four INRIA research teams (Asclepios, Reo, Macs and Sisyphe, previously known as SOSSO2) covering the fields of medical image analysis, computational structural and fluid dynamics, numerical analysis and control. It is also a collaborative framework that involves clinical centres such as the Guy's Hospital London, the Laboratory of Cardio-Energetics at the National Institutes of Health and the Hospital Henri Mondor. These and other partners are listed on the Web site of the project.

A prime objective of the CardioSense3D project is to build a personalized cardiac simulator with identifiable parameters, which links four different physiological phenomena: electrophysiology, mechanical contraction and relaxation, myocardium perfusion and cardiac metabolism. In building patient-specific cardiac models, the complexity of these models is constrained to match that of the available observations. Furthermore, an impor-

Figure 1: Long axis (top row) and short axis (bottom row) views of an electromechanical heart model during end diastole (left column), ventricular depolarization (middle column) and end systole (right column).

Figure 2: Fibre tracking performed on an average canine heart built from nine images.

Figure 3: Three regions of an electromechanical model of the heart have been set with different contractility parameters; a data assimilation technique has been used to recover those parameters.

tant research activity in the CardioSense3D action lies in the conception of data assimilation software that can estimate patient-specific parameters and state variables from given signals or images of the cardiac activity.

The current CardioSense3D model includes a simulation of the electrical depolarization and repolarization of the cardiac tissues through a set of macroscopic reaction-diffusion equations. This electrical activity can be synchronized with the actual ECG (electrocardiogram) of the patient, and creates a mechanical contraction and an active relaxation that are modelled by a set of partial differential equations.

We have shown that this model can be interactively adjusted to the actual geometrical, mechanical or electrical properties of a patient's heart through the use of conventional or tagged magnetic resonance images and some in vivo electrophysiological measurements. The average direction of the myocardium fibres is also integrated into this model, because it plays an important role in both the electrical and mechanical modelling. Even more interestingly, the model can then be used to study the effect of locally modifying some electrical or mechanical properties in order to better predict the effect of a therapy or the evolution of a pathology.
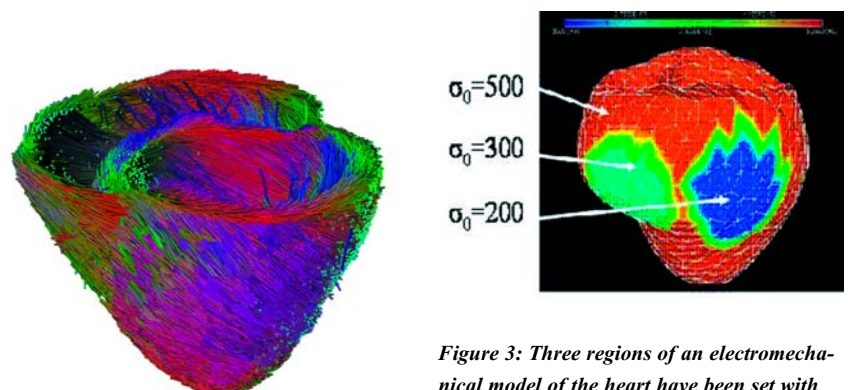
We believe that this kind of model of a dynamic organ could be used in the future to better plan or train a number of medical gestures; for instance, in radio-frequency ablation procedures for the positioning of pacemaker stimulation probes.

Link:
http://www.inria.fr/CardioSense3D

Please contact:
Hervé Delingette
INRIA, France
Tel: +33 4 92 38 76 60
E-mail:
Herve.Delingette@sophia.inria.fr

Development of a New Hyperthermia Treatment Planning Tool

by Esra Neufeld

Hyperthermia is a promising treatment modality for various types of cancer. The difficulty of administering high-quality patient-specific treatment has so far hindered the acceptance of hyperthermia in most countries. Can a new approach for treatment-planning tools help?

Hyperthermia is a promising, relatively new treatment modality for various types of cancer. The technique involves heating the tumour using electromagnetic (EM) fields, generally using antenna arrays to focus the energy. Despite its tremendous proven potential, the treatment has so far failed to gain widespread acceptance. One of the reasons could be the difficulty of administering good treatment, which involves reliably heating the entire tumour while reducing energy deposition in healthy tissue. This is due to the complexity of the applicators (antenna arrays with many degrees of freedom) and the nonstraightforward relationship between the settings and the resulting temperature distribution. A reliable treatment-planning tool could not only solve this problem but help to visualize what actually takes place inside the patient, thereby increasing the acceptance of hyperthermia.

Treatment planning (TP) for hyperthermia involves the following steps: generating an individual patient model, simulating the EM field distributions induced by the various antennae, determining the resulting temperature increase while optimizing the antenna settings and finally calculating the effect at the cellular level. The treatment-planning tool has to permit modeling and planning with a very high level of detail, accuracy and reliability. This is necessary to reduce hotspots and guarantee good coverage of the tumour area.

The Foundation for Research on Information Technologies in Society (IT'IS) and various research partners have started developing such a treatment-planning platform. The planning tool is based on the SEMCAD X software co-developed by IT'IS: a software optimized for studying electromagnetic field distributions in complex models, and induced temperature changes, especially in living tissue. Furthermore, we are developing generators and applicator hardware that enable precise computer control of the antenna array excitation, and hence heating, whilst providing reliable feedback.

Segmentation
The first step towards generating patient-specific treatment is to have a detailed model of the patient. A toolbox is being developed that allows the flexible combination of various segmentation techniques ranging from fully automatic to highly interactive. This is necessary to enable the toolbox to work with various types of input data (CT/MRI) of potentially low quality. Furthermore, there is no general-purpose automatic segmentation method that can handle all of the types of tissues that must be identified for reliable TP. The toolbox will contain pre- and postprocessing methods to remove noise, close holes and extract surfaces. Provision of interaction types tailored to the specific segmentation methods is critical. The segmentation must be a simple task performable by technical staff in hospitals.

EM Simulation
The patient model is then loaded into the simulation environment. Solvers have been developed that can handle complex models of both the patient and the applicator. Generally, the finite-difference time-domain method (FDTD) is used, as it is ideally suited to these types of inhomogeneous models. Dedicated FDTD hardware accelerator cards are used to reduce the simulation time. Special techniques such as conformal sub-

cell models, ADI (Alternating Direction Implicit) and transient excitations are employed to reduce numerical errors and speed up the simulations.
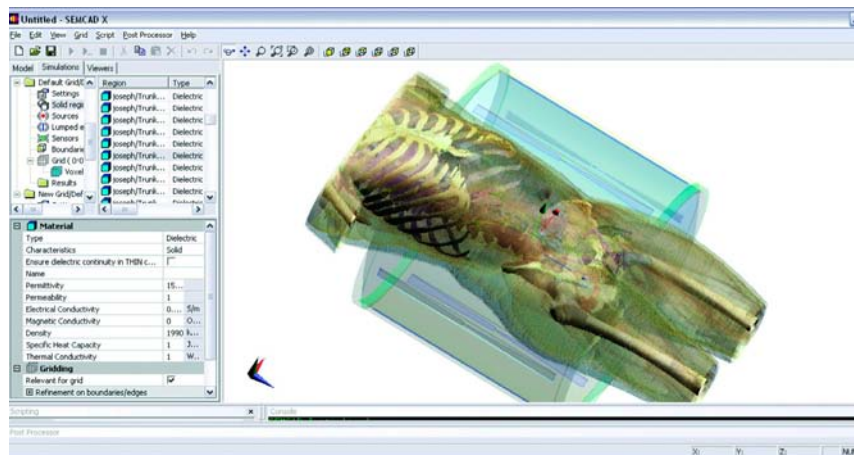
Thermal Simulation

Since it is the temperature increase that causes the increased cell death in tumours, it is important to determine not only the EM field but also the temperature distribution. The main challenge here is to correctly account for perfusion cooling. For this, the bioheat equation with temperature and time-dependent tissue parameters is solved. However, in order to account for the discreteness of blood vessels and the directivity of blood flow, an improved model is being developed. It couples the continuous 3D simulation to a pseudo-1D simulation of the vessel tree and uses information about the location and orientation of the nearest vessel to determine a tensorial effective heat conductivity.

Effect Assessment

Various methods for quantifying tissue damage are being studied. These include using an Arrhenius model that can account for the transient behaviour of the temperature increase and a CEM43 dose concept.

Optimization

Finally, a fast and generalized eigenvalue method is used to determine the optimal antenna steering parameters. Both temperature and EM energy distributions can be optimized. Multiple targets can be assigned individual heating priorities, and sensitive regions can be

Model of a Sigma-60 applicator (BSD) in the SEMCAD X simulation environment.

specified. Information about hotspots (both simulated and experienced by the patient) can be used to come up with a modified treatment plan.

A cooperative effort with the Computer Science Department of the University of Basel is exploring new possibilities arising from recent advances in nonlinear optimization. A new interior point method will be devised that will allow the optimization of nonlinear models for temperature increases on large rectangular grids as they appear in FDTD. Together with the hyperthermia unit of the Erasmus MC in Rotterdam, the practical use of such a treatment-planning tool is being explored. An additional collaboration is studying the development of new applicators and the use of simulation software to help create new devices.

To validate the planning software, extensive experiments are planned. These will include building phantoms and measurement devices as well as using MRI thermometry to monitor the treatment of real patients. Close cooperation with the University hospital in Geneva and the MRI group of the Kinderspital in Zürich has been established.

It is hoped that these advances in the reliability of treatment-planning software will increase the quality of hyperthermia treatments and encourage physicians to apply the technique more widely.

Please contact:
Esra Neufeld
IT'IS Foundation, Switzerland
Tel: +41 44 2459698
E-mail: neufeld@itis.ethz.ch

megNet®: Visualization and Modelling Environment for Translational Medicine

by Matej Orešič, Jyrki Lötjönen and Catherine Bounsaythip

There has long been a consensus that there is a pressing need to bridge the gap between basic and clinical sciences, to ensure that basic research discoveries of potential relevance to patient care are effectively applied. This is a formidable challenge to implement. One of the key problems is the lack of a framework or model that would link clinically relevant information to the knowledge obtained across multiple disciplines, experimental platforms and biological systems.

The overall objective of our project is to develop a comprehensive visualization and modelling framework to enable a multi-level integration of biological and clinical data. The primary focus areas are:

- multi-level biomedical data integration using a conceptual space approach
- linking medical image data with molecular pathway level information
- cross-species phenotype mappings and translational biomarkers.

This project gathers people across several domains at VTT, including systems biology, signal processing, medical imaging, data mining and software engineering. The research has been performed in close cooperation with med-

Cross-Species Mapping for Translational Medicine: Type 1 Diabetes Pathogenesis and Prediction

Type 1 diabetes (T1D) is the most prominent metabolic-endocrine disease among children in the western world. Since 2005 we have been involved in the Finnish Type 1 Diabetes Prediction and Prevention Study (DIPP), a large birth cohort study, in order to identify novel molecular markers that characterize the development of dia-betes-associated autoimmunity and progression towards overt clinical T1D.

Much of the current knowledge on T1D was obtained using preclinical models, and establishing the direct clinical relevance of these findings has been difficult. Not surprisingly, over one hundred therapies successfully tested in preclinical models have so far proved unsuccessful in a clinical setting, and at present there is still no cure for the disease.

This problem of translation of knowledge from preclinical models to successful therapies is one of the key bottlenecks in today's pharmaceutical pipelines. We addressed this challenge by initiating a project called 'In silico models of disease pathogenesis and therapy' (TRANSCENDO™). The objective of the project is to generate a translational biomarker bridge between the large-scale molecular pro-filing in a clinical setting to molecular profiles obtained in a preclinical setting, with the primary focus on T1D. The model will enable us to link knowledge on molecular pathways related to T1D pathogenesis, as well as to develop and test new therapies for disease prevention and treatment.

While the TRANSCENDO™ strategy provides a methodology for a comprehensive translational medicine implementation, it also addresses the issue of a true system-ic integration of cell-, tissue-, or cross-organ-specific information, including mole-cular pathways. The megNet® environment has been used to enrich our statistical model based on longitudinal molecular profiles in clinical and preclinical settings, with vast amounts of information on molecular pathways and physiology.

ical experts. The conceptual space approach was developed in collaboration with the Computational Cognitive Systems group at Helsinki University of Technology.

Beyond the current Semantic Web: A Novel Conceptual Approach to Tackling the Complexity of Knowled-ge Representation

Most current approaches to life science data integration are conceptually based on methods that were developed when information was scarce. With the pace at which data volumes are increasing, these approaches face the challenge of evolving concepts and context sensitiv-ity. For a knowledge model to be adap-tive, it must support emergence of new concepts and knowledge structures in a context-specific manner.

Conceptual spaces have recently emerged as a flexible framework to tackle the problem of context-based con-cept formation and evolution. The theory of conceptual spaces combines elements from other theories in cognitive science, psychology and linguistics. It is based on the topological analysis of the infor-mation space that enables similarity to be modelled and computed in a natural way, using appropriate metrics. The information space can embed many other spaces, which makes the paradigm suitable for tackling the problem of multi-scale data integration in systems biology.

Metabolome: Sensitive Readout of Human Physiology

Metabolomics has recently emerged as one of the key platforms for medical systems biology and translational research. Patterns of metabolites (small molecules) in biofluids and tissues reflect the homeostasis of the organism. The human metabolome is affected by factors such as lifestyle, nutrition and gut microbiota, which are of particular relevance to complex diseases believed to be due to interactions between genetic factors and the environment.

Metabolites are also common across species, unlike other levels of molecular biology, and hence might represent the best chance of cross-species biomarkers.
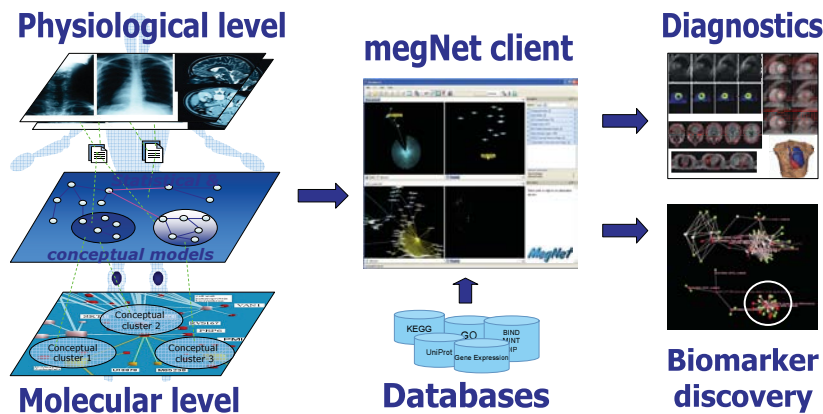
We applied the metabolomics strategy in multiple clinical and preclinical studies. The metabolic profiles obtained in these studies contain valuable information about clinical phenotypes, which can be utilized as a link between the human physiological level and local alterations of molecular pathways.

Integrating Pathways and Medical Images

The conceptual space framework is well suited to the integration with molecular-level information of complex clinical data such as medical images. The soft-ware tool that we have developed, meg-NET®, implements the conceptual space approach for mining and visualiz-ing life science and medical data by uti-lizing state-of-the-art 3D techniques, mathematical modelling techniques, and contextualization (see Figure).

The essential part of our data integra-tion strategy is the highly automated and accurate image quantification accomplished by our image analysis tool. Statistical models can thus be developed to cluster disease-related phenotypes based on image data, as has already been performed using molecu-lar profiling techniques. Mappings between the medical image level and molecular profiles and networks can be established in two ways: either based on statistical models, which are optimal if data at multiple levels is available from the same individuals, or based on matching the clinical annotations using biomedical ontologies.

As a case study, we have been collecting a large number of cardiac magnetic reso-nance images and other clinical data related to dilated cardiomyopathy caused by Lamin A/C mutation. Serum samples from a clinical trial have been collected from the same individuals for metabolomics analyses. This data is complemented by the establishment of molecular networks based on published microarray data related to the topic, as well as by the integration of relevant molecular interaction networks using the megNet® environment. In a typical megNet® query, the user inputs biologi-cal entities and concepts, such as "Lipoxygenase AND Lamin A/C muta-

Physiological level

megNet client

Diagnostics

Molecular level

conceptual models

Conceptual cluster 2

Conceptual cluster 1

Conceptual cluster 3

Databases

KEGG

GO

BIND

UniProt

Gene Expression

MINT

IP

Biomarker discovery

Conceptual approach to data integration and modelling, implemented using the megNet® software. Both statistical and semantic models are utilized to enable systemic integration of data across multiple levels. The platform also enables integration of models and knowledge across multiple species.

tion AND females", from which a network of relations in clinical and biological databases is built and visualized.

Perspectives

Our conceptual space strategy, implemented using the megNet® environment, has already demonstrated its potential in clinical applications. We believe that our approach will be very useful in building complex in silico models at the level of human physiology, making mappings across multiple levels of biological organization and

across multiple knowledge domains a feasible task.

One of the emergent challenges in life science and medical knowledge management is how to deal with the dynamics in biological systems, that is, how to encode the inherent dynamic properties of biological systems for the purpose of data mining and modelling. It is obvious that modelling at all levels, from quantum processes to physiology and environment, is computationally unfeasible. We believe that the conceptual spaces

approach could help in establishing the relevant components of the system to be included in the models.

Since conceptual spaces are a powerful approach to build metaphors across different knowledge domains, one could also envision the applications of the approach outside the life science domain. We have recently initiated one such project, aiming to use agent-based modelling of biological cells in order to develop more flexible computing tools.

Please contact:
Matej Orešič
VTT Technical Research Centre of Finland
Tel: +358 20 722 4491
E-mail: matej.oresic@vtt.fi

In Vivo Microscopy for Real-Time Structural and Functional Cellular Imaging

by Tom Vercauteren, Aymeric Perchant and Nicholas Ayache

Fibered confocal microscopy allows the acquisition of in vivo and in situ images at the cellular level, in combination with standard endoscopic procedures or needle biopsies for solid organs. This makes it a promising tool for clinical molecular imaging, an activity aiming at in vivo characterization and measurement of biological processes. Confocal microscopy images represent a new source of information for developing patient-specific digital models that integrate knowledge of cellular dynamics. This is also an unrivaled technique for refining digital patient models down to the microscopic level.

Current medical practice is moving towards more quantitative and personalized methods of diagnosis and decision-making. This has led to a need for more complex and detailed patient-specific digital models. The resolution at which the model is described is important and may vary from macroscopic to microscopic and even molecular scales, ideally through multiscale descriptions. As these individualized models start to inte-

grate knowledge of cellular dynamics, it becomes crucial to acquire patient-specific information at the cellular level.

The goal of the cooperation between the Asclepios research group at INRIA Sophia Antipolis and the company Mauna Kea Technologies (MKT), Paris, is to develop advanced image analysis tools capable of extracting the

pertinent information from in vivo confocal microscopy images. This is a first step towards the integration of individualized cellular dynamics information in the physiological models we develop at Asclepios.

Fibered Confocal Microscopy

Mauna Kea Technologies' Cellvizio® family of endo-microscopes rely on a unique approach for the in vivo and in
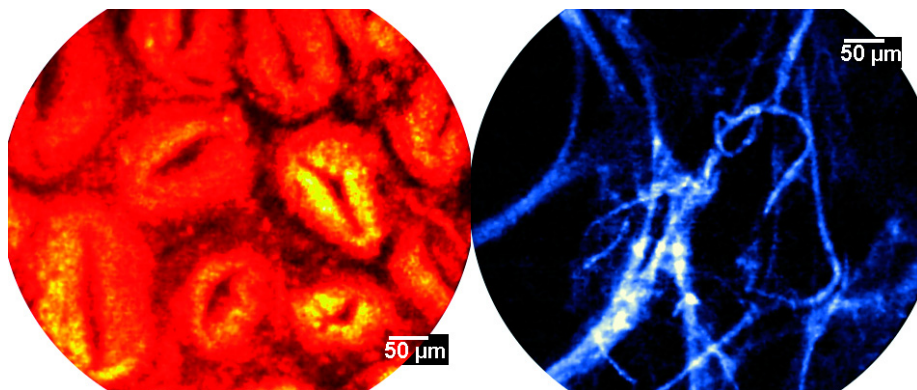
Figure 1: Fibered confocal microscopy allows the clinician to perform micron-scale resolution optical biopsies and to diagnose the state of a tissue in vivo and in real time. Left: Normal gastric pits. Courtesy: PD. Dr. A. Meining, Klinikum rechts der Isar, Munich. Right: Alveolar Network. Courtesy: Pr. L. Thiberville, CHU Charles Nicolle, Rouen.

situ exploration of living organisms. Simply stated, this involves putting a microscope objective at the end of an ultra-thin, three meter long optic fiber.

The Cellvizio® acquires image sequences of microscopic resolution, displays them in real time and enables live measurements. The confocal miniprobe, one of the Cellvizio®'s three components, is a custom-built highly advanced optical imaging probe incorporating a proprietary fiber bundle and objective lens technology. Coupled to the laser scanning unit, the sophisticated image processing software renders real-time dynamic image sequences with a lateral resolution as fine as 2.5μm and a field of view of up to 600μm at 12 frames per second.

This specific imaging modality raises certain image processing problems. For example the raw data generated by the instrument shows geometric distortions and a non-uniform honeycomb pattern due to the modulation of the fiber optic bundle. This makes the data impracticable for automated analysis if left untreated. Algorithms that take on the image reconstruction task in real time have thus been developed in order to provide high-quality, smooth-motion video sequences.

Bridging the Gap between Micro- and Macroscopic Scales

Fibered confocal microscopy can unveil in real time the cellular structure of the observed tissue. However, as interesting as dynamic sequences may be during the time of the medical procedure or biological experiment, it is necessary to have an efficient representation of the entire imaged region. Mosaicing techniques can be used to provide this representation. However classical algo-
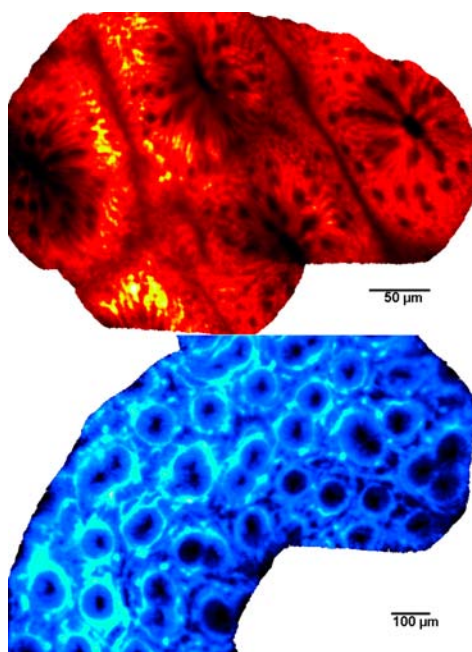

Figure 2: Mosaic reconstructions can increase the field of view while enhancing the image definition. Top: Healthy colonic mucosa (26 images). Bottom: Microscopic colitis (98 images). Courtesy: PD. Dr. A. Meining, Klinikum rechts der Isar, Munich.

rithms do not take into account the characteristics of fibered confocal microscopy, namely motion distortions, irregularly sampled frames and non-rigid deformations of the imaged tissue. This is why specific novel algorithms were developed.

With these mosaics, quantitative and statistical analysis becomes possible over a wide field of view. The quality of the data that can be used to build cellular-level patient-specific models is thus improved. Moreover, mosaicing for microscopic images is a means of bridging the gap between microscopic and macroscopic scales. The combination of Cellvizio® and image processing therefore provides a unique way to build patient-specific digital models at the microscopic scale.

Please contact:
Tom Vercauteren, Aymeric Perchant
Mauna Kea Technologies, Paris,
France
Tel: +33 1 48 24 11 43
E-mail: tom@maunakeatech.com,
aymeric@maunakeatech.com

Nicholas Ayache
Asclepios project team, INRIA, Sophia
Antipolis, France
Tel: +33 4 92 38 76 60
E-mail:
nicholas.ayache@sophia.inria.fr

Extraction and Deployment of New Features
for Cardiac Shape and Function Representation

by Sara Colantonio, Davide Moroni and Ovidio Salvetti

Researchers in the EU HEARTFAID consortium are undertaking an investigation into the extraction and deployment of new features for the representation of cardiac shape and function.

The ISTI-CNR 'Signals and Images' Laboratory is currently involved in a challenging research activity concerning cardiac image analysis. This is taking place in the context of the EU-funded project HEARTFAID. This project aims at providing a knowledge-based platform of services for supporting the clinical management of heart failure. Here we report the preliminary results of our investigation.

The analysis of deformation patterns in the heart is of key importance in understanding its functional properties and assessing its state of health. Image analysis modalities provide an invaluable aid when studying complex cardiac structures. However, image sequences contain a huge amount of high-dimensional data (two or three spatial dimensions plus time), which cannot be fully exploited without the help of suitable tools for image processing and pattern recognition. Furthermore, the growing number of imaging perspectives and modalities provide multi-source information on the anatomical structures, electromagnetic activity, dynamic perfusion and metabolism, strain and blood flow of the heart, which must somehow be combined into an overall picture. There is thus a pressing need for a unifying framework for cardiac dynamic analysis.

Cardiac modelling seems to be the natural answer. An abstract representation of the heart is built and can be instantiated to the particular anatomy under examination, with the aim of extracting shape and functional parameters. In addition, cardiac modelling can enable a sophisticated quantitative assessment of heart pathologies, for which present clinical practice uses only semi-quantitative (and to some extent subjective) measurements.

In the clinical management of heart failure patients, the study of segmental wall motion and dyssynchrony characterization are so far the main areas in which image processing has proven useful or even essential. In particular, dyssynchrony, which refers to incoordinate wall motion due to activation delay, is a complex phenomenon whose origins are to be tracked back to electrical conduction disturbances that affect both regional and global functions of the heart. Despite its relevance, the only dyssynchrony marker that has received some consensus is an ECG-derived parameter, yet this is poorly correlated to the outcome of resynchronization therapy. We believe that cardiac modelling would provide more insight into the problem by conveying novel representation features and suitable tools for their scientific visualization. Ultimately, dyssynchrony characterization may be translated via the extracted features into a statistical pattern-recognition problem, thus allowing for new methods of quantification.

With this goal in mind, we investigated approaches that describe periodically deforming structures identified in 3D image sequences (MRI, ultrafast CT etc) in a compact but faithful fashion. An encoding of this type would be useful to build up a reference database for similarity searches or data mining procedures.

Of course an essential step in characterizing deformable structures is their initial localization and reconstruction from an image sequence. We addressed this preliminary but highly nontrivial problem by developing a two-stage procedure, based on fuzzy clustering and Artificial Neural Networks (ANNs), for the identification and reconstruction of the deformable structure of interest.

Figure 1: The two-stage method for structure reconstruction. In the first stage the structure is localized in the image domain: homogeneous regions, obtained by cluster analysis, are labelled and their behaviour throughout a whole deformation cycle is analysed in order to identify periodically deforming structures. In the second stage precise contours are obtained by means of a dedicated artificial neural network.

Figure 2: Left ventricle wall thickness plotted as an attribute of epicardial surface at end-diastole (left) and end-systole (right).

The reconstructed structures represent the underlying geometry of the organ, which is further enriched by computing local attribute functions, describing its functional properties. A model normalization procedure is then applied to solve issues of data compression, enable easy comparison of deformable structures belonging to different patients and, finally, to identify the most salient features. Both Fourier and wavelet transforms with respect to time are considered, in order to get an overall encoding of the whole deformation cycle.

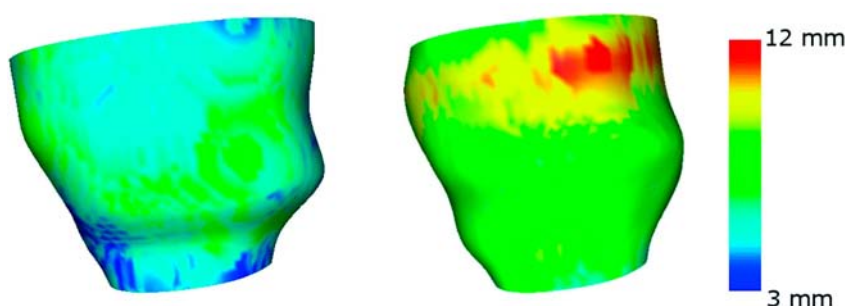Future activities will involve fine tuning of the encoding with respect to the characterization of wall motion and dyssynchrony, with the goal of identifying meaningful nontraditional descriptors. In this setting, the HEARTFAID platform could provide a unique opportunity to start their comparative evaluation.

The HEARTFAID consortium consists of four technological research institutes (University of Calabria-Italy, the coordinator; FORTH-Greece; ISTI-CNR-Italy and Rudjer Boskovic Institute-Croatia), four medical partners (University of Milano Bicocca-Italy, Istituto Auxologico-Italy, University Magna Graecia-Italy and Jagiellonian University Medical College-Poland), and three industrial partners (FORTHnet SA-Greece, Synapsis-Italy and VMWS-UK). The project began in February 2006 and will run for three years.

Links:
HEARTFAID project
http://www.heartfaid.org/

Signals & Images Laboratory, ISTI-CNR:
http://www.isti.cnr.it/
ResearchUnits/Labs/si-lab/

Please contact:
Davide Moroni
ISTI-CNR, Italy
Tel: +39 050 315 3130
E-mail: davide.moroni@isti.cnr.it

Multilevel Analysis and Information Extraction Considerations for Validating 4D Models of Human Pathophysiology

by Kostas Marias, Thanassis Margaritis and Ioannis G. Tollis

In order to assess the clinical importance of models of human pathology (eg cancer), it is necessary to validate them with pre- and post-treatment clinical data. This in turn requires that the size and shape of the tumour, along with structural and physiological information, be determined with high resolution, accuracy and precision. ICS-FORTH has been involved in several research projects addressing image analysis, with the aim of defining optimal methods to robustly extract multiscale anatomical and functional information related to the underlying pathology. This information can be used to initialize and validate models of pathophysiology and to test simulations and predictions of the success of therapeutic regimes.

Imaging techniques in the field of medicine have focused on providing anatomical information, particularly relating to human bones, dense tissue and arteries. PET and functional MRI allow the study of various pathological processes via radio-labelled tracers (PET) or pharmaco-kinetic models in contrast-enhanced (CE) MRI. The whole field of molecular medicine and molecular imaging is opening up new possibilities for targeted assessment of disease and disease mechanisms. In addition, microarray imaging has created exciting possibilities for measuring gene differential expression and defining new disease biomarkers.

In order to improve existing models of human pathophysiology it is essential to robustly extract multiscale information, both anatomical and physiological. For example, consider the importance to cancer modelling of determining genetic profile changes and global changes in tumour size and density, through the analysis of temporal biomedical data. In many cases, common problems arise over different scales (eg geometrical inconsistencies over time). It is therefore important to develop generic tools for multiscale temporal analysis so that time-dependent pathophysiological information can be robustly extracted and visualized. Such information is crucial for initializing, inspiring and validating 4D models of human functions. For example, in the case of in silico models of cancer, 3D voxels should be classified as 'proliferating', 'necrotic', etc.

From the imaging standpoint it is essential to stress two points. First, there is a need for a holistic understanding of pathophysiology and this clearly implies a multidisciplinary approach. To this end, molecular and genetic imaging offers unique opportunities to better understand pathophysiology on smaller scales, and to build multilevel models.

Second, it is necessary for the extraction of pathophysiological information to pre-process biomedical data at all possible scales (eg medical images, microarray scans). Thus, multiscale information extraction is necessary to 'individualize' a given model. This concept is schematically illustrated in Figure 1, where the extracted multilevel temporal information (eg from microarrays, CE-MRI and mammography) is driven into the corresponding multilevel model of breast cancer.

FORTH has been involved in several aspects of multimodal information extraction (see publication list), and is currently participating in the cancer modelling WP of the ACGT IP project.

Some areas of research include:

Extracting regions of interest from bio-medical data: Several algorithms have been developed for identifying important structures and features from biomedical images. For example, tumour segmentation is achieved using pharmacokinetic models of gadolinium uptake with contrast-enhanced MRI and microarray spot segmentation through a combination of the two different information channels, ie Cy3 and Cy5.

Geometrical normalization: A number of algorithms have been developed for aligning temporal biomedical data from the same patient, in order to correct geometrical distortions and allow the robust extraction of pathophysiological parameters. Such algorithms can be widely applied, from breast cancer to newer applications such as molecular imaging (eg for correcting time-dependent geometries in 2D molecular optical imaging studies) and microarray imaging (for aligning different channels prior to computing differential expressions).

Intensity normalization: Biomedical measurements often 'mask' true underlying physiological properties due to the image formation process. The non-linearities introduced by varying imaging conditions may significantly alter the image intensity profile and reduce the efficiency of generic analysis algorithms. This is a well-known problem in cancer imaging (eg mammography). In
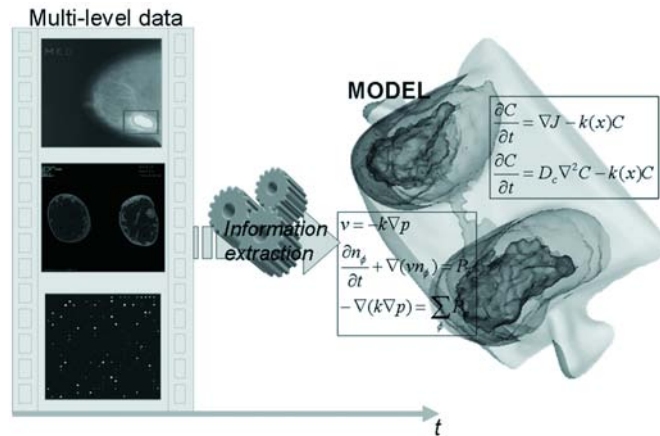

Figure 1: Extraction of multiscale temporal pathophysiological information for computing 'individualized' models of pathophysiology.

microarray imaging, several nonlinearities in the experimental process render the measured expression values prone to variability, and often to poor reproducibility.

FORTH ICS and IMBB have co-developed algorithms for normalizing microarray values. This was done by exploiting the fact that the gene expression values (eg from the Cy3 and Cy5 matrices) should ideally follow a linear trend, and considering a 'ground truth' subset of imaged genes that is known a priori to be the same in both channels (Cy3 and Cy5).

Visualization: This is a fundamental aspect of biomedical data information fusion that is typically less well addressed in the literature, but which can dramatically increase the clinical utility of a solution if implemented intelligently. To develop patient-specific models it is important to implement appropriate tools for information visualization at all levels, from gene networks to cellular processes and organ function. To this end, FORTH-ICS has developed novel tools and algorithms for visualizing complex biological networks.

Links:
http://www.ics.forth.gr/bmi/publications.jsp
http://www.ics.forth.gr/~kmarias/publications.htm
http://www.eu-acgt.org/

Please contact:
Kostas Marias
ICS-FORTH, Greece
Tel: +30 2810 391672
E-mail: kmarias@ics.forth.gr

High-Throughput Analysis of Gene Expression Data for Personalized Medicine

by Filippo Geraci, Mauro Leoncini, Manuela Montangero, Marco Pellegrini and Maria Elena Renda

A new approach to the analysis of large data sets resulting from microarray experiments yields high-quality results that are orders of magnitude faster than competing state-of-the-art approaches. This overcomes a significant performance bottleneck normally evident in such complex systems.

Modern personalized medicine relies heavily on molecular analysis and imaging, and so requires a range of support systems that include integrated health information systems, digital models for personalized simulations, and advanced diagnostic systems. Technology is of greatest use to decision makers if it is able to produce clear and useful indications in an accurate and timely manner.

Advances in microarray technology have reached a stage where it is possible to 'watch' simultaneously the activation state of all the genes of a given biological entity under a variety of external stimuli (drugs, diseases, toxins etc). The analysis of the gene expression data complements the better-known analysis of the individual variations in the genetic code.

To use a computer programming analogy, in order to understand the work-

ings of a piece of code in a computer, it is often necessary to look at internal changes during execution, rather than just looking at the program as an isolated static piece of text. This is even truer in biology since it is by now clear that the genetic code, though very important, is just one ingredient in a far more complex biological mechanism.

Our research fits neatly within the 'Digital Human Modelling' initiative since it removes technical obstacles standing in the way of the personalization of digital models. Ideally we should strive for a different model for each individual human being. In practice we should collect as much information as possible related to a single human being, at different levels, so as to be able to fine-tune our existing generalist models. On the one hand, we are living in the 'age of data', and existing technology is able to produce a deluge of data related to a single patient: data on organs, tissues, and as far down as the molecular level. On the other hand, a burden is placed on our data processing capabilities that is only partially alleviated by advances in hardware performance. Our aim is to identify and tackle algorithmic bottlenecks blocking the pipeline that connects data collection with useful simulation and diagnostics.

Gene expression data from a single microarray experiment can trace the activities of a number of genes ranging from a few thousands to hundreds of thousands under hundreds of stimuli. Moreover large laboratories of pharmaceutical companies already perform tens of thousands of experiments each year (eg research labs at Merck & Co, Inc undertook roughly forty thousand microarray experiments in 2006).
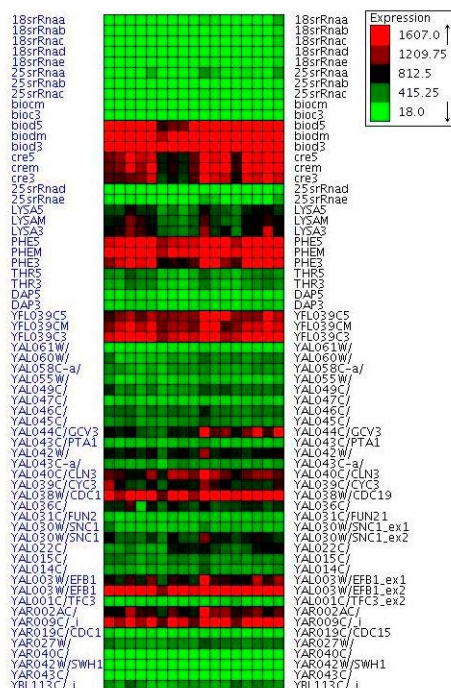
In order to extract useful information from this amount of data it is customary to apply the clustering unsupervised learning technique. This involves automatically grouping together genes with a similar expression profile. The human analyst then has the simplified task of checking a few dozen groups (clusters) of genes, instead of thousands of individual genes.

Unfortunately existing state-of-the-art clustering methodologies cannot cope with this data deluge. Some do not scale well to such large data sets, requiring hours or days of computation on power-ful workstations. Others are unable to determine critical parameters automatically such as the optimal number of clusters, and thus rely on educated guesses or rote repetitions.

Our project is developing and demonstrating the effectiveness of a new class of clustering algorithms that are able to cope with massive data sets in a fraction of the time needed by current state-of-the-art techniques. In addition, these algorithms can retain or even improve the quality of the output, and can detect automatically the optimal number of clusters. We have already attained improvements in speed of up to a factor of ten to twenty on relatively small data sets of six thousand genes. We employ techniques from computational geometry developed for clustering points in metric spaces coupled with information theoretic optimality criteria.

In a parallel research activity, this methodology has been already successfully applied to information retrieval on textual data. Our approach has been validated by comparing our results with the well-known annotated gene list for yeast (Saccharomyces cerevisiae), maintained by the Gene Ontology Consortium.

Future activities involve the application of our techniques to specific medical problems related to the analysis of tumour growth. One of the most important discoveries in recent years has been that many types of cancer result from genomic changes acquired by somatic cells during their lifetime. Moreover, tumour growth evolves in a series of stages, each with characteristic features and metabolic mechanisms. Thus a complete description, modelling and prediction can be made only by collecting large amounts of data over time, at the molecular level (gene expressions), the tissue level (via medical imaging

Clustering of a yeast gene expression data set. The clusters are the groups of contiguous homogeneously coloured rows. The figure is produced using the Expander tool.

technology) and the clinical level. Current models of tumour growth will be greatly improved by the integration, correlation and cross-validation of molecular, imaging and clinical data.

This research is carried out in Pisa at the Institute for Informatics and Telematics of the Italian Research Council (IIT-CNR), by a team composed of researchers from IIT-CNR and the Department of Information Engineering of the University of Modena and Reggio Emilia. The activity began in 2006 as part of the CNR Bioinformatics Inter-Departmental Project. This research benefits greatly from the exchange of ideas taking place within the recently formed ERCIM Digital Patient Working Group.

Please contact:
Marco Pellegrini
IIT-CNR, Italy
Tel: +39 050 315 2410
E-mail: marco.pellegrini@iit.cnr.it
http://www.iit.cnr.it/staff/marco.pellegrini/

Causal Data Mining in Bioinformatics

by Ioannis Tsamardinos

What gene's expression is causing another one to be expressed? Which combination of mutations is causing disease? Knowledge of causal relations is paramount in simulating the digital patient, understanding the mechanisms of disease, designing drugs and treating patients. Recent theoretical and algorithmic advances in the discovery of causal relations from observational data promise to boost our biomedical knowledge.

Perhaps the most basic scientific tool for advancing knowledge is the randomized controlled experiment, where a quantity A (eg smoking) is manipulated in a controlled manner on a random population and the effects are measured on a quantity B (eg development of lung cancer). A significant portion of classical statistics is concerned with soundly inferring from the measurements of the experiment whether or not A (probabilistically) causes B. Unfortunately, particularly in biomedicine, such experiments are often costly (in terms of both time and money), unethical, or even impossible. Nevertheless, a wealth of observational data is often available to researchers; the issue is then to identify the most useful probable causal hypotheses on which to focus.

The induction of causal relations from observational data has traditionally been an anathema in statistics. Data analysts in bioinformatics commonly state their results in a covered way: "the function of protein A is related to the function of protein B", "… our analysis has identified the relevant genes for the expression of gene B". Behind the use of the terms 'related' and 'relevant' is typically implied more than a statistical association: a causal relation. Correlation is not causation; yet the existence of some correlations and the absence of others can lead us to induce under some fairly broad conditions the existence or absence of certain causal relations. Since the end of the'80s, the work on formal theories of causality and causal
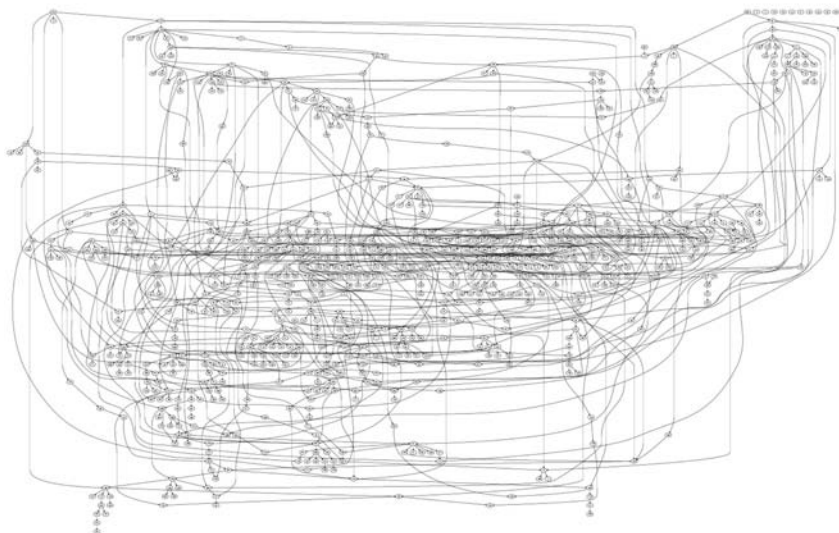

Figure 1: A Bayesian Network induced from gene expression data on the Spellman yeast cell cycle dataset using the Sparse Candidate algorithm; it consists of 801 nodes corresponding to 800 gene expression levels and the cell-cycle time.
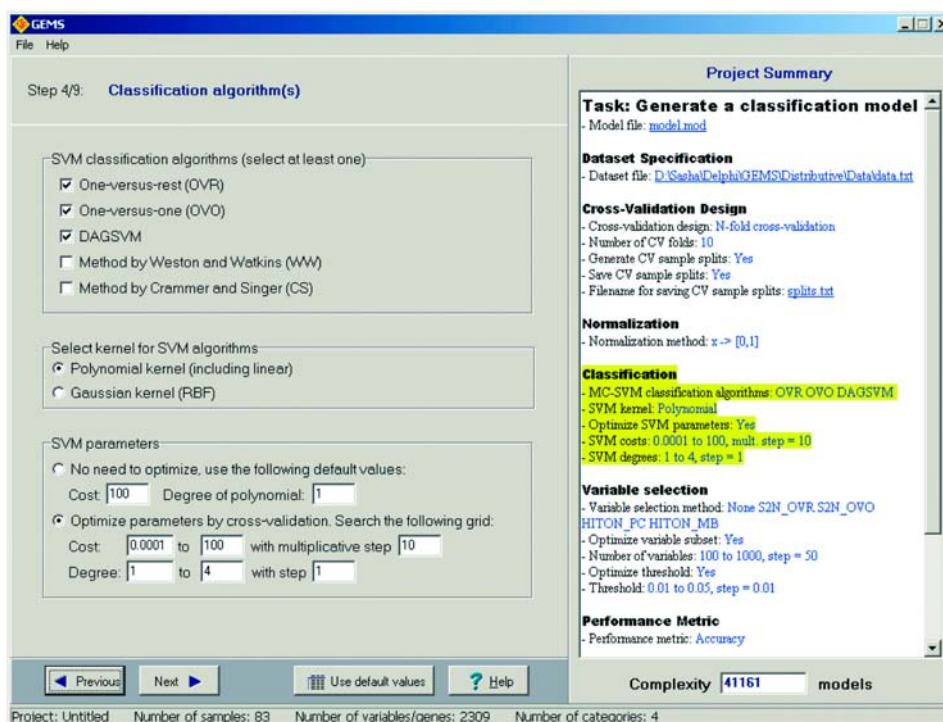

Figure 2: A screen of the Gene Expression Model Selector, a tool for automating the mining and predictive modelling of gene expression data using multi-category Support Vector Machines and Markov-Blanket-based algorithms for variable selection.

induction by Spirtes, Glymour, Pearl, Cooper and others has been gaining ground. In 2003, Clive Granger won the Nobel Prize in Economics for his work on the causal analysis of observational economic time series, giving more respectability to the field. Several articles have already appeared in the bioinformatics literature employing causal techniques, and related conferences and workshops (such as the recent NIPS workshop on causal feature selection) have been held.

Several theories of causality have corresponding graphical means for representing causal relations, such as Structural Equation Models and the more recent Causal Bayesian Networks (see Figure 1). Algorithms exist for inducing such networks from observational data. Our recent work has extended learning Bayesian Networks with tens of thousands of variables and unprecedented accuracy. In addition, a growing body of our work is focused on causal variable selection: when the time available or the number of variables does not permit the construction of the full Bayesian Network, algorithms can identify the local causal neighbourhood of a vari-

able of interest in reasonable time, for example, the causes and effects of the expression levels of a gene. The causal local neighbourhood (related to the concept of the Markov Blanket) is under some conditions the smallest variable subset required for optimal prediction. Our algorithms often outperform traditional non-causal variable selection algorithms for prediction, and in addition the selected variables have known causal relations to the target. Our group, along with other researchers, is carrying out theoretical work to accompany this algorithmic work. This includes looking at the conditions under which the relations found correspond to causal relations, lifting or changing the set of assumptions for causal discovery and extending it to different types of data. Algorithms now exist for identifying hidden (unobserved) variables that cause (change the distribution of) the variable of interest, that explicitly model selection bias, model feedback loops and other interesting situations.

We have developed a couple of tools for applying causal data-mining techniques to real data. The first is Causal Explorer, a library of algorithms for learning

Bayesian Networks and identifying the causal neighbourhood of a target variable. The second is the Gene Expression Model Selector or GEMS, which automates the mining of gene expression data with the option of using some of the causal methods mentioned above.

In moving to the Institute of Computer Science at the Foundation for Research and Technology, Hellas and the Biomedical Informatics Laboratory, I will be extending this line of work in several dimensions. In our plans are new algorithms, more theoretical results, and enhanced tools for inducing and mining causality; in addition, the application of such methods to biomedical data to answer specific biological questions. In particular, for the Digital Patient, our methods could identify from data the factors that need to be modeled in order to simulate the development of a disease or a human subsystem malfunction.

Please contact:
Ioannis Tsamardinos
ICS-FORTH, Greece
Tel: +30 2810 391 617
E-mail: tsamard@ics.forth.gr

Desktop Virtual Reality for 3D and 4D Medical and Biological Data Analysis

by Jurriaan D. Mulder

The Personal Space Station (PSS™) brings Virtual Reality (VR) to the desktop of the medical and scientific professional. Its purpose is to make VR more useful and accessible for the effective analysis of 3D and 4D data in medical and biological research. To this end, PS-Tech in the Netherlands and CWI are developing and improving new techniques and methods for the application of VR in 3D and 4D data analysis.

Three-dimensional (3D) and time-dependent (4D) datasets are becoming increasingly important in medicine, microscopy, and biology. Such a vast amount of information implies a need for fast, accurate and cost-effective analysis. Visualization - the ability to present complex data as multidimensional images - combined with direct control over that data in VR provides a tool to satisfy that need. In a VR environment the data is presented truly in 3D and users can interact with the data directly in the 3D space. However, traditional VR systems tend to be bulky, difficult to use, and expensive, and their

use has therefore been mainly limited to dedicated VR centres. In other words, the use of VR remained beyond the scope of most medical and biological scientists.
The Personal Space Station was developed at CWI, and is now also commercially available from the CWI spin-off company Personal Space Technologies (PS-Tech) in Amsterdam. The PSS™ is a desktop interface that allows the researcher to interact with 3D and 4D images in a natural and intuitive manner, under normal office working conditions. About the size of a child's school desk, the PSS™ is portable, yet still

large enough to create a virtual environment in the user's personal space. The images are presented to the researcher using a head-tracked, stereoscopic display. In addition, the researcher can control, explore and interact with the data directly in 3D and 4D. Therefore, both the viewing and the interaction with the data are achieved in a transparent and intuitive manner, allowing the researcher to focus on the analysis instead of the user interface.

The PSS™ is now progressing from a scientific concept to a device for medical and biological data analysis. 3D

and 4D datasets from ultrasound, MRI, MRA, CTA and confocal microscopy can be analysed and explored in VR. The user holds a dataset - like a 4D ultrasound dataset of a heart - in one hand and can orientate and position it. The other hand is used to interact with the dataset for manipulation, like slicing, dicing, and pointing. Next to the 3D interaction tools the user has standard 2D tools like a mouse and keyboard. Depending on the task the user selects the appropriate tool (eg menu operations using 2D tools, positioning a data set using 3D tools). The ability to select the right kind of tool for the task at hand not only simplifies the process of working with 3D data, but it also simplifies application development.

Scientists at research institutes, universities and academic hospitals are working with CWI and Personal Space Technologies to create the PSS™ applications needed for the analysis of complex medical and biological data. At the Academic Medical Center (AMC) in Amsterdam, the PSS™ will be used to analyse 4D ultrasound data of quantitatively complex (patho)physiological processes and the effects of genetic background and therapeutic intervention. Processes such as tumour development, atherosclerotic plaque formation in blood vessels, the development of the heart and the effects of genetic background and therapeutic strategies on these processes can be studied effectively in 4D.

At the University of Amsterdam, the PSS™ is used in live-cell imaging to facilitate visualization and analysis of large 3D and 4D data sets obtained with the microscope unit. A controlled light-exposure microscopy (CLEM) microscopy unit combined with the PSS™ is the chosen method that
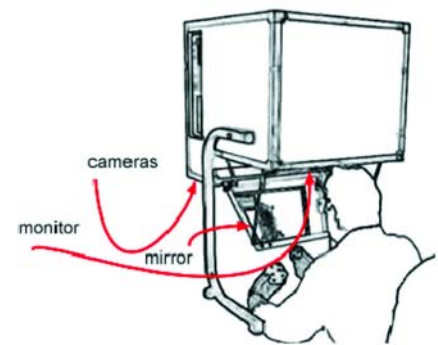

Figure 1: The PSS explained. In the PSS the user holds the image in his hands and manipulates it with tangible interaction devices. The user looks at the monitor via a mirror. This enables the user to bring his hands into the same environment as the virtual 3D-objects without interrupting the visual image. With the use of a custom optical tracking system, the user can interact with the 3D images using wireless, tangible interaction devices. Therefore, interaction with virtual objects can take place in a direct, natural and intuitive way. Hand-eye coordination and 'proprioception' (the subconscious perception of the position of muscles and joints) are used to the full. The user is 'attracted' by the objects he sees; his natural reaction is usually to grab and manipulate them.

enables time-resolved study of fluorescently labelled cells to gain insight into cell dynamic processes. This methodology will allow delicate intracellular processes such as DNA repair, protein aggregation and transport to be more easily studied.

The PSS™ is also used for the analysis and modelling of 3D vascular data, ultrasound analysis in cardiology, brain research, neurosurgery and medical education. With the development of these applications, and the close cooperation between CWI, Personal Space Technologies and the medical and biological research institutes and universities, VR is being brought into the world of the medical and biological professional. The ultimate goal of the project is to bring 3D visualization and interaction within reach of all users of com-

plex 3D and 4D data sets. To achieve this, further research and development is needed in several fields, including human-computer interaction, tracking and display, large dataset management, and automated and interactive image segmentation methods. CWI and PS-Tech will continue to cooperate with scientists from different fields and application areas to continuously improve and develop new techniques and methods for the application of VR in 3D and 4D data analysis.

Link:
http://www.ps-tech.com

Please contact:
Jurriaan Mulder
Personal Space Technologies
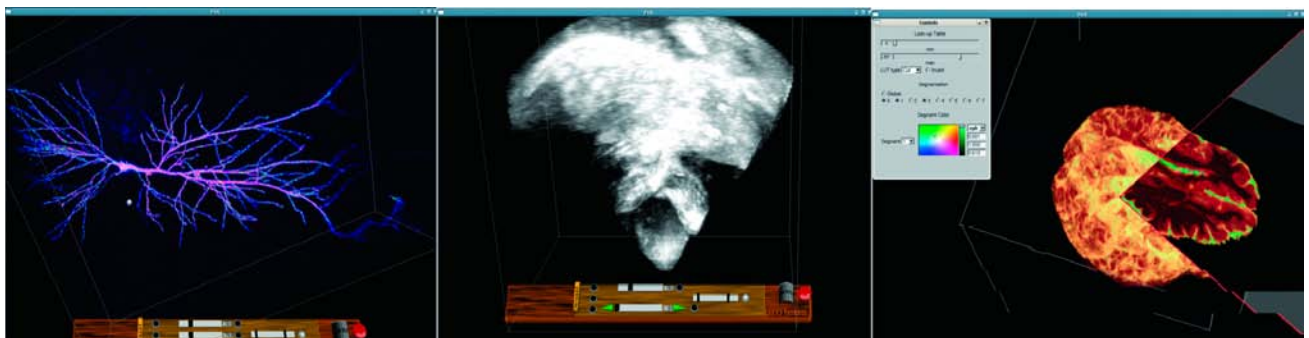Tel: +31 20 3311 214
E-mail: mullie@ps-tech.com

Figure 2: Some examples of interaction and visualization in the PSS. From left: 3D and 4D microscopy; Cardiology, 3D and 4D Ultrasound; Brain Research, segmented CT data.

New Digital Speech Processing Strategies for Cochlea Implants

by Frank Klefenz

The human auditory system processes very complex audio signals and deduces meaningful information like speech and music. Conventional speech processors for cochlea implants use mathematically based information-coding strategies. In a new approach being investigated by researchers at the Fraunhofer Institute for Digital Media Technology (IDMT), the human auditory system is digitally modelled as naturally as possible. This leads to a better understanding of the neural representation of sounds and their subsequent processing.

A cochlea implant is controlled by its dedicated speech processor, which specifically triggers electric stimuli according to the speech coding strategy. To make this speech coding easier and more natural, research efforts have recently been invested in the development of analogue silicon cochleas.

Some Analogue Very Large Scale Integrated Circuits have been evaluated as speech processors for cochlea implants. Even micro-engineered approaches exist, which implement the cochlea as a hydromechanical system on a physical substrate. Even the signal-transducing sensor units – the inner hair cells – have been micro-engineered on a physical substrate.

Fraunhofer IDMT took a slightly different approach to solving the underlying partial differential equations of the mathematically described cochlea definition in a digital computer system. The cochlea and the sensor model are coupled. The structure and function of the outer ear, the middle ear, the cochlea, the inner hair cells, the spiral ganglion cells and higher cognitive maps for vowel recognition and sound-source localization are modelled and physiologically parameterized, taking psychoacoustic phenomena into account.

The audio signal transduction process is very complex. The audio signal, consisting of sound pressure fluctuations in the air, is converted to movements of the tympanic membrane. This is mechanically coupled to a group of tiny bones in the middle ear, the hammer, the anvil and the stirrup, which cause the fluid-filled cochlea to vibrate. Sensing the fluid velocity along the basilar membrane, the inner hair cells convert this into the release of neurotransmitter vesicles. The neurotransmitters diffuse through the synaptic cleft of the adherent spiral ganglion cells and bind to the receptor ligand sites of the cells' ion channels. The triggering of an electric postsynaptic potential at the spiral ganglion cell is modelled according to the Hodgkin-Huxley rate kinetic equations. The auditory system model therefore directly produces the stimuli patterns for the electrodes of the cochlea implant in a spatio-temporal fashion.

In Figure 1, the stimuli patterns for the conventional advanced combinational encoder (ACE) speech processor strategy are shown on the left. On the right, the stimuli patterns are shown for the

a) Stimulation pattern obtained for the speech token /a/ /k/ /a/ for the ACE
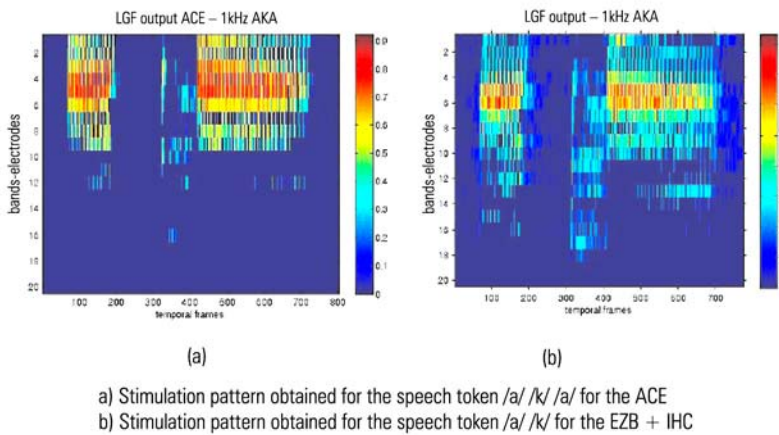b) Stimulation pattern obtained for the speech token /a/ /k/ for the EZB + IHC

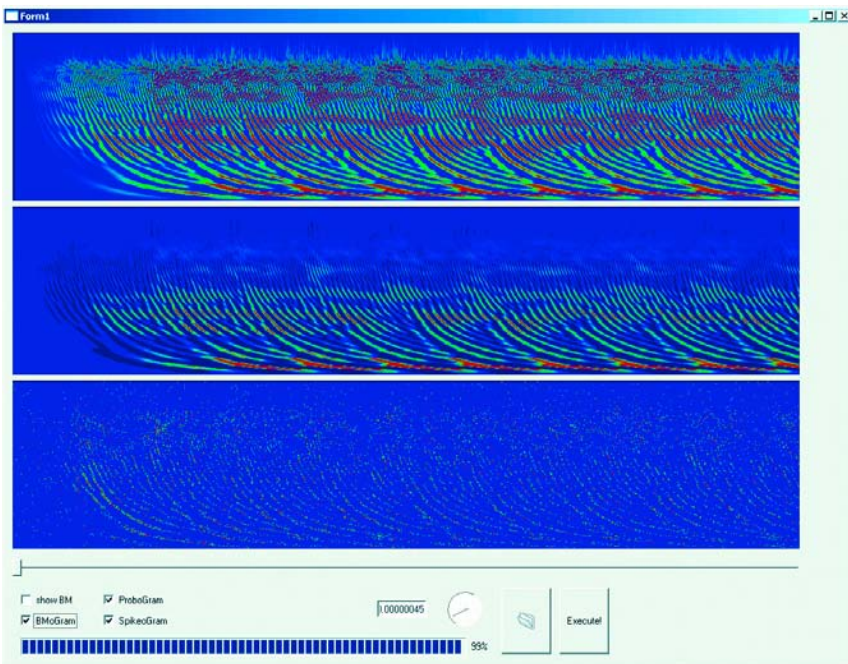*Figure 1: Comparison of stimuli patterns for two different speech-coding strategies.*

Figure 2: Simulation results of the Fraunhofer IDMT model for the vowel /a/.
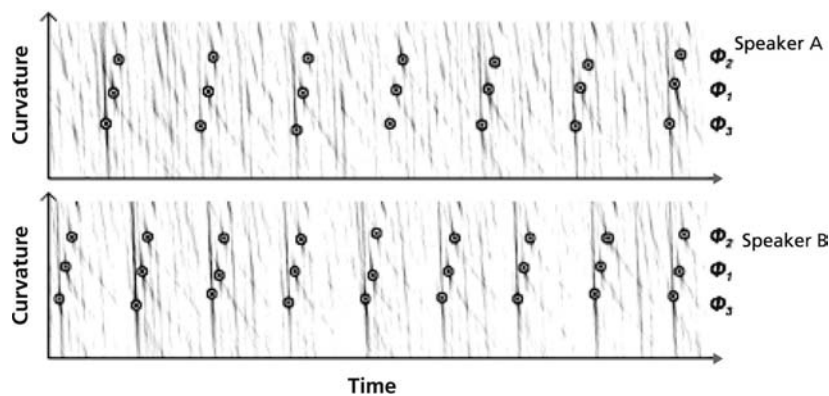
Figure 3: Regularly shaped pattern of the vowel /a/ after being processed in the computational map.

new strategy. The latter differ significantly from existing speech-processing coding strategies such as ACE and spectral peak (SPEAK). In Figure 2, the basilar membrane movement is shown in the upper part for the vowel /a/. The middle part shows the neurotransmitter vesicle release probability, and the lower part shows the actually released neurotransmitter vesicles. This strategy computes typical delays in the propagation of signals from apex to helicotrema, which is not reflected in the other strategies. Vowels are coded in

this neural representation as bundles of pulse spiking trains of hyperbolic shape. We have found a solution to detect these delay trajectories using a Hubel-Wiesel type computational map. For instance, the vesicle release representation of vowel /a/ undergoes a mathematical transformation, allowing the differences between individual voices to be compensated for. Figure 3 shows the transformed result of the vowel /a/ for two different speakers; the three-point structure is very regular and very similar for both speakers.

This research continues with the aim of improving the system in detail. and allowing it to function in real-time. This will mean that the digital system can be used without prestored stimuli; field tests with several patients will then be run. The computer model will be parameterized, so that the system can be fine-tuned and will be adaptable to the patients' needs. The system's performance will be monitored by an automatic speech recognizer that delivers a quality measure of speech intelligibility.

These tests, which are done at the Hearing Research Center in Hannover, Germany, serve to evaluate the system and to compare its performance in terms of speech intelligibility to existing speech processors.

Link:
http://www.idmt.fraunhofer.de

Please contact:
Frank Klefenz
Fraunhofer Institute for Digital Media Technology IDMT, Germany
Tel: +49 3677 467 216
E-mail: klz@idmt.fraunhofer.de

Oranges-In-A-Box Simulations help to Classify Brain Tissues from MRI

by Hugo Schnack

Magnetic resonance imaging (MRI) is a very useful tool for in vivo detection of possible morphological differences in the brains of psychiatric patients as compared to healthy persons. Due to the relatively large size of the voxels - the 3D pixels that make up the images - classification is difficult. Simulated 'orange-in-a-box' images can help to improve the classification algorithms.

The brains of psychiatric patients may be different from those of healthy people in size and shape; this could be a cause or a result of the disease. One way to investigate this is making MRI brain scans of patients and control subjects. The information in the images is quantified by segmenting them. The voxels – the building blocks of the images – are attributed to different tissue classes. The three main brain-tissue types of interest are grey matter (neurons, mainly in the cortical surface), white matter (connecting fibres), and cerebrospinal fluid (CSF). The latter is not a real tissue: rather it is the fluid surrounding the brain and filling several

holes in the brain (see Figure 1, left and middle). The cortical surface is thin (~ 2mm) and highly folded, and therefore most voxels (of size ~ 1mm^3) that sample the cortex are only partly filled with grey matter, with the rest being CSF or white matter. These voxels have a brightness somewhere between the brightnesses of the pure tissues, and this so-called partial-volume effect hinders a straightforward classification of MR brain images. The reason for this is that segmentation algorithms must simultaneously estimate intrinsic tissue parameters (means and variances of their brightness distributions) and tissue volume fractions of the voxels,

depending on the morphology of the brain.

An MRI brain tissue segmentation algorithm should produce reliable estimates of the tissue distributions and volumes. In particular, for analysis of images from patients and control subjects, the algorithm should be unbiased in classification of images of brains with different morphology.

Our goal was to test the robustness of our segmentation algorithm: how much influence does the structure of the brain have on the estimation of the intrinsic tissue properties, ie the intensity

means? Since the true tissue distributions of real MR brain images are unknown, we designed a model that simulates images with three tissues and with different structural organizations, mimicking the relevant properties of the natural situation as much as possible. The brain tissue is modelled as a collection of white matter spheres with a grey

reflecting atrophy. Some randomness is added to each orange's parameter value in order to model the variation of cortical properties throughout the brain. Finally, noise is added to the image. Any number of oranges can be created.

We used these images of oranges to test our tissue classification algorithm. The

This was successful, and the calculated tissue volumes were equal to the modelled volumes within 1-2%. Then we ran our algorithm on a series of simulations in which we varied the average packing distance or peel thickness in a regular way, creating small to large, but realistic, numbers of partial-volume voxels, in order to test the influence of the structure on the classification results. The influence turned out to be minimal – about 1% of the mean grey matter intensity and 3% of the grey/white contrast – for a wide range of distances.

Sagittal slice (left) of an MR image of a human brain, where the white matter shows up brightest, the grey matter is grey, and the CSF is dark; (middle) an enlargement of the red box from the left image, with the intermediate brightnesses at the borders between the different tissues clearly visible; (right) slice of a simulated oranges-in-a-box image. The spheres have white matter cores (radius ~ 3mm), grey matter peels of about 2mm, and are floating in a sea of CSF. Picture: Hugo Schnack.

matter peel (the cortex): 'oranges'. The oranges are placed in a sea of CSF (see right picture of the figure). The parameters to be varied are the size of the white matter cores and the grey matter peel thicknesses, reflecting brain size and cortical thickness respectively. Furthermore the distances between the oranges can be varied from densely packed to not touching at all, the latter

algorithm analyses the intensity histograms of the images and gives probabilistic segments, ie for each voxel a probability of being grey matter, white matter, or CSF is calculated.

First we ran our classification algorithm on several simulated images to test if it could find within a certain precision the simulated intrinsic tissue parameters.

In conclusion, although MR brain images and our oranges-in-a-box appear quite different, the latter are in fact surprisingly suitable as realistic test images for tissue classification algorithms.

This research project was carried out by Hugo Schnack and Rachel Brouwer of the neuroimaging section of the Rudolf Magnus Institute of Neuroscience. This is located in the Department of Psychiatry at the University Medical Center Utrecht, in the Netherlands.
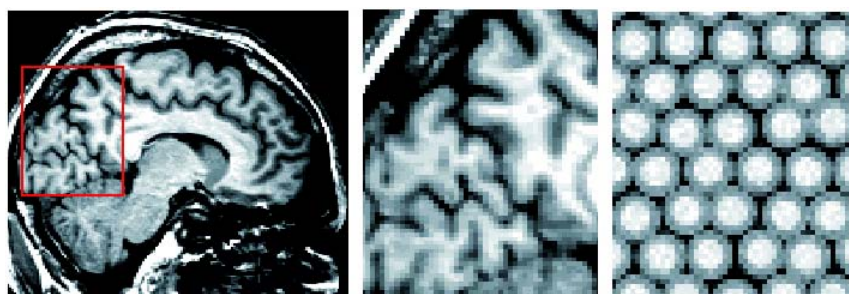
Link:
http://www.smri.nl

Please contact:
Hugo Schnack
University Medical Center Utrecht, the Netherlands
Tel.: +31 30 2508459
E-mail: hschnack@azu.nl

Digital Biological Cell

by Tomáš Bílý and Michal Karásek

Can mathematicians describe digital cells in the same way they can mimic the behaviour of biological systems? It appears that digital cells can mimic some behavioural properties, while others are being intensively studied. From some level of approximation, we can use this knowledge to connect the predictive power of these digital cell models to the methods commonly used in clinical general practice.

When we refer to a digital biological object, we usually mean a mathematical or computer model of a real object. We shall use the adjective 'digital' in this sense. The digitization of the biological cells of digital patients and organisms is the main paradigm of theoretical biology and medicine. It is a crucial instrument for predicting the behaviour of biological systems over scales ranging

from nanometres to the whole organism. Researchers at the 'Seminar on Mathematical and Computer Predictions of Cell Behaviour', which has been held for over a decade at the Department of Applied Mathematics (KAM) at Charles University, Prague, Czech Republic, are working on a digital cell project. There are two main streams of research. In the first, we

invent mathematical models of a universal digital cell that can mimic certain important aspects of eukaryotic biological cells. In the second, we study these models collaboratively using interactive well-behaved simulation programs called virtual laboratories.

From a mathematical point of view, we are using multiscale hybrid continuous-

discrete models; these are based on reaction-diffusion models ruled by partial differential equations on the finest hierarchical level (small spatial scales and short time intervals), and discrete agent-based models with universal rules (some based on metabolic control ruling) on coarser levels. Our actual research target is to produce qualitative models and understand their combinatorial properties.

A virtual laboratory is a special simulation program with the following characteristics. It is designed as an implementation of a mathematical model and its behaviour is restricted by the validity of the model rules. The actions of model entities can be modified by changing the parameters of its environment and/or the entities' interaction rules. Although realistic behaviour is not fundamental, parameterization helps in looking for biological plausibility. In addition, incremental parametrical changes allow researchers to identify important stable and dividing situations. For consistency in simulation it is determined that virtual experiments are always (ceteris paribus) repeatable with the same results. Visualization of the virtual laboratory output is absolutely necessary.

Moreover, the concept of the virtual laboratory is a natural way to explain an abstract experiment in an interpersonal communication. Using a number of prepared experiments allows a better understanding of our digital cell models, and facilitates both general identification with problems and model behaviour orientation. According to our experience, using a visual form of information is crucial for interdisciplinary communication.

Our virtual laboratory design makes it possible for an experimenter to change model parameters easily, which with adequate visualization also enables the use of the laboratory as an educational tool. Either alone or under supervision, users can modify the parameters of an experiment and follow the corresponding changes in simulation behaviour. Collaboration in teams is supported and recommended.

We have implemented ligand-based models of neural network growth dynamics, immune cell dynamics (eg allergic reactions or different blood-
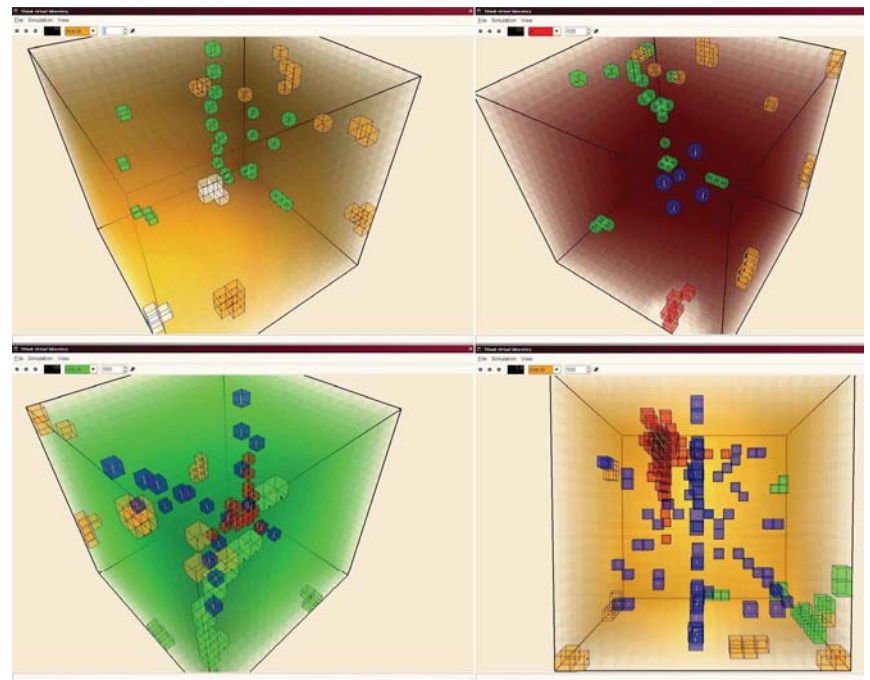

Figure 1: Simulation and visualization of immune cell dynamics.

type reactions) and the morphogenetic formation of shapes. We have compared the results of simulations with biological experiments and it seems that certain qualitative properties of the biological experiments can be successfully simulated.

Several objectives will be addressed in our future work. First, the modularization of our virtual laboratory system will be improved. Second, we will run larger virtual experiments in order to simulate some simple digital organisms and thus explore more combinatorial properties. Finally, we will perform more quantitative virtual experiments and then get it closer to clinical general practice.

Please contact:
Tomáš Bílý
Charles University, KAM MFF - CRCIM
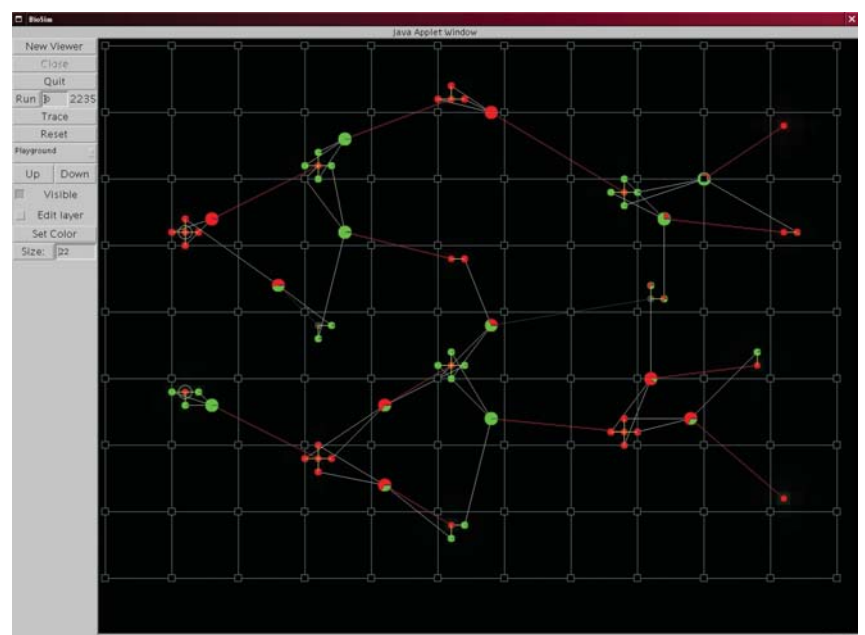Tel: +420 221914261
E-mail: tomby@kam.mff.cuni.cz

Figure 2: Simulation and visualization of neural network growth dynamics.

An Interactive Computational Framework for Integrative Biology

by Lakshmi Sastry and Srikanth Nagella

The Integrative Biology (IB) project, funded by EPSRC, is nearing completion with the building of a customized Grid framework. This is being used to run large multi-scale models, from cellular to whole organ simulations, to manage a growing database of in-vitro experimental data and simulation results, and to support advanced visualization for interactive data analysis with comparison and assimilation of experimental and observed data. The services offered by the computational framework are based on the requirements of two application areas: arrhythmia and cancer. Computational and experimental biologists are using the prototype infrastructure, thereby aiding the STFC computer scientists in improving the framework and its services.

Heart disease and cancer represent the two biggest diseases in the West, and hence have become the focus of intense research within the biomedical community. Computer simulation of whole organs offers the potential to improve our understanding of the causes of these conditions, and eventually to develop new treatment regimes and drugs to reduce their threat to life. The Integrative Biology (IB) project brings together a team uniquely qualified to tackle these problems. It includes researchers from the universities of Oxford, Auckland, the STFC (Science and Technology Facilities Council), Sheffield, Birmingham and Nottingham, University College London, and Leeds. One aspect of this work is the computer simulation of whole organs based on molecular- and cellular-level models, and this requires the application of large-scale computational and data management resources. Another major aspect is the provision of advanced visualization services that allow real-time interactive data analysis on the Grid.

The main components of the Integrative Biology Grid are as follows.
Security access: the Grid Security Infrastructure is employed throughout. The IB project has successfully promoted the Grid computing model and its certificate-based authentication and authorization, not only to computational scientists but also to biologists whose experience of complex computing paradigms is minimal.

Data management: the use of the Storage Resource Broker for data storage and the use of metadata catalogues for browsing and retrieval have been built into the infrastructure. The complexities are hidden behind user-friendly interfaces within familiar tools.

Interactive access: fundamental to successful analysis and the extension of existing models is the scientist's ability to interactively control, or 'steer', simulations as they are executing. Such experimentation increases understanding the correlation between the parameters under investigation and provides an
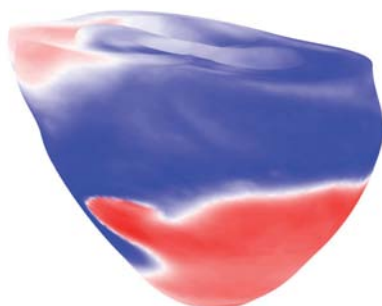

Figure 1: Simulation of the action potential and re-entry on the ventricular section of the heart visualized as geometry.

Figure 2: 3D image reconstructed from high-resolution MRI data (1024x1024 pixels and 1440 slices).

opportunity for collaboration with colleagues and peers, promoting both the sharing of knowledge and an understanding of the models and the results being produced. A useful dialogue can be established between those working on systems of different scales - from single cells to multi-cell and whole organ models – so that a holistic understanding of the chemical, biological and functional processes of diseases can be achieved. The IB interactive services include an elaborate image-based computational steering infrastructure built using the gViz steering library. The steering parameters are bound to appropriate image icons that are placed within the graphics window. A pull-architecture is used to interact with the remote simulation, supporting in situ decisions that are guided by a visual inspection of intermediate data. This image-based steering is developed as a generic portable library usable with OpenGL-based desktop tools. The communication protocols are standards-based and portable.

Visualization: advanced visualization services are built to handle extremely large datasets close to where the data is stored or generated. These include building 3D images from 2D MRI and histology data, 3D isosurfaces, server-side animation generation and viewpoint-dependent animations. Tailor-made generation and rendering services can render up to 0.5GB of data in high resolution and in close to real-time. The results can be sent to the user's desktop using public-domain open-software stacks.

User interfaces: desktop application toolkits familiar to scientists are used to realize interfaces to job submission, workflow, data management, visualiza-

tion and analysis utilities, and are offered as an integrated data analysis framework. Scientists see an incremental addition in functionality to the tools that they have found effective for their data analysis. This adoption is an essential factor in encouraging widespread take-up of the emerging Integrative Biology Grid.

Virtual Research Environment: the IB services are also deployed within a Virtual Research Environment (VRE) built using portal technologies in the sister project IBVRE. The collaborative research tools built as services within that project will be exported into the main IB project through the generic IB interface.

Links:
http://www.integrativebiology.ox.ac.uk/
http://www.vre.ox.ac.uk/ibvre/

Please contact:
Lakshmi Sastry
Science and Technology Facilities
Council, e-Science Centre, UK
Tel: +44 1235 446892
E-mail: m.sastry@rl.ac.uk

Delving Beneath the Skin

by Mike Holcombe

Systems biology, an integrated research field involving experimental biology and computational modelling, takes a systems-level view of biological phenomena without losing the detail and complexity that is inherent in all biological systems. I call this the 'in virtuo' approach (in preference to 'in silico' which seems to imply a specific computational technology). Two investigations are discussed: one looking at how part of the innate immune system works, and the other at how skin seems to heal wounds.

Our key approach to modelling in this area is to start at the bottom and work up. This is in contrast to more traditional approaches that are based on the use of differential equations of various types and which take a top-down approach. Biological systems are composed of many different types of coherent components that communicate with each other in a variety of ways, and develop structures and functions as emergent phenomena. The interesting thing about these systems is that there is no overall control centre; that is, the systems organize themselves according to their hard-wired instructions and the laws of physics and geometry.

One factor with this type of modelling, known as agent-based or individual-based modelling, is that a massive number of components must be modelled – often into the millions – and this requires significant computational resources. Each component is designed as a software 'agent' with its own life cycle, functional behaviour and structural form. These agents communicate with one another through many different communication channels; these may be chemical signals, physical contact and so on. This approach views each agent as a communicating 'X-machine' – a fully general model with many attractive and convenient properties. We try to

model the agents as accurately as possible using all the experimental techniques of molecular biology, and to then put them all together in simulations. We continuously track the position of every agent, since where it is and what it is near has a fundamental effect on what it does. For example, if we are modelling at the cellular level and a particular cell is ready to divide, it cannot do so if it is surrounded by other cells and there is no space into which it can 'expand'. Validation must be done experimentally in a continuous manner.

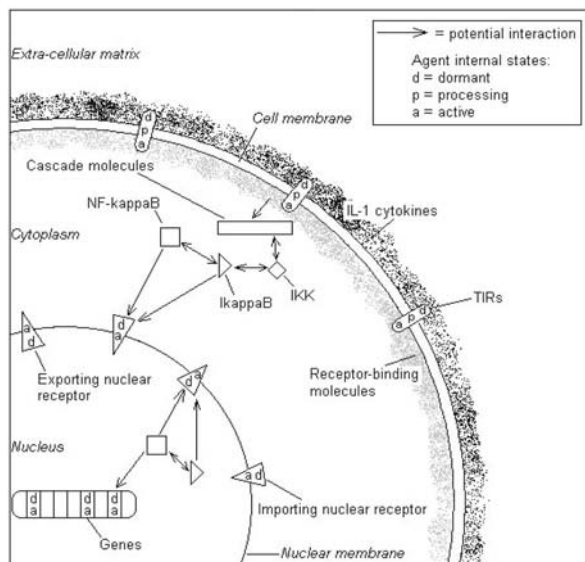We have developed a framework FLAME (Flexible Agent–based Model-

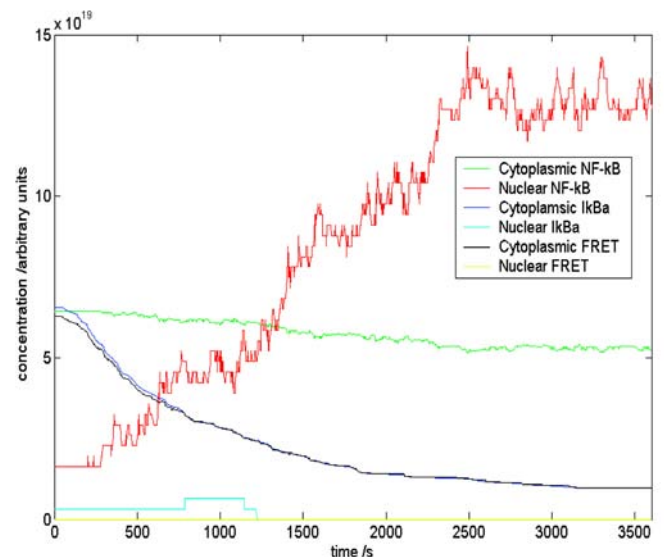*Figure 1: A schematic of the NF-k B pathway in a cell.*

Figure 2: Trace of the numbers of key molecules in the pathway over time.
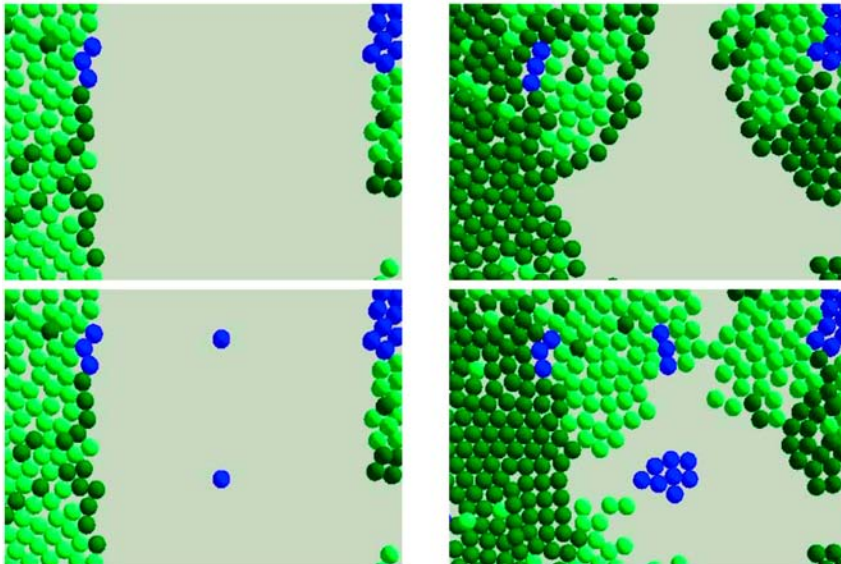
Figure 3: Simulations showing (top) the growth of keratinocytes with low numbers of seeded stem cells (blue), and (bottom) the effect of seeding stem cells in the spaces between the tissue.
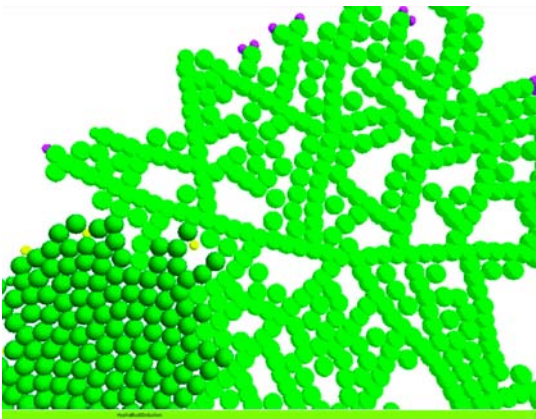

Figure 4: An image from a simulation of the different phases of the life cycle of an important fungal pathogen of humans, Candida albicans.

ling Environment) that allows for the simple definition of the agents and their environments, and compiles straight to highly optimized code for running on parallel computers.

The first example is the NF-κB system – a vital part of the innate immune system. In this system the NF-κB molecules are bound to other molecules such as IkBα and the onset of infection causes them to separate and the NF-κB molecules then move into the nucleus and switch on a number of key genes. The agents in this model are varied and in some cases short-lived. For a biochemical pathway, this means that anything from a molecule to a signalling receptor to an entire chain of interactions can be modelled as an agent, thus providing a modular and extensible modelling framework that allows abstraction of detail as necessary.

In this model, molecular agents diffuse through the cell, binding and dissociating from other molecules, receptors and cell structures in accord with signals they send and receive from surrounding agents. Every agent is represented by a complete computational model, the communicating stream X-machine. This provides an intuitive and rigorous basis on which to model the functional behaviour of systems in a flexible and extensible manner. An important feature is the memory of each agent's X-machine, which contains its physical location, meaning that the number of states required to model the system is manageably small. It is essential that the agents are both biologically plausible as entities and that their behaviour is based on experimental measurements. In the model, as in reality, molecular interactions are local events that depend only on the position and current state of the molecules involved, where the state of a molecule is whether or not it is already bound. The physics of a molecule is modelled according to specific agent-based characteristics, including which types of interaction are possible.

If two molecules may interact according to the rules, they must satisfy criteria on their state and proximity, derived from standard rate constants. If interaction occurs, the state of each agent changes to a 'bound' state, which can be reversed through random thermal separation.

Not only is this the most detailed and accurate model of this pathway so far, but it has led to a new biological discovery. There had been some evidence that the ratio of one of the key molecules IκBα to NF-κB was three times what was 'needed'. Where was all this excess IkBα? The model predicted that it could be sequestered with actin filaments, and recent experiments have produced significant data that confirms this.

The second case study involves the process of skin healing. The Epitheliome project is part of the Human Physiome Project, and aims to integrate computational and biological models of the social behaviour of cells within epithelial tissue. We aim to develop a computational model of cell behaviour within the context of tissue architecture, differentiation, wound repair and malignancy.

Factors in the model include cell division (agent proliferation) and cell death; physical space (the cells cannot divide if there is no room); intracell communication; cell role changes according to age and circumstance; and other variables like nutrient uptake, immune response, calcium and physical force.

We have investigated the simulation and the tissue culture of stem cells and how they develop into tissue. The simulations have demonstrated that the distribution of the Keratinocyte stem cells determines to a large extent how successful the repair will be. For instance, new cells will fail to spread if there are large gaps between them, because the growth factor signal from the stem cells is too dilute.

Link:
FLAME (Flexible Agent–based Modelling Environment):
http://www.flame.ac.uk

Please contact:
Mike Holcombe
University of Sheffield, UK
E-mail: m.holcombe@dcs.shef.ac.uk

The Impact of Systems Biology on the Digital Patient

by Martin Reczko, Panayiota Poirazi, Anastasis Oulas, Eleftheria Tzamali, Maria Manioudaki, Vassilis Tsiaras and Ioannis Tollis

Substantial advances in predictive, preventive and personalized (PPP) medicine are starting to emerge from computational simulations of complex networked models of metabolism ranging to the molecular level of detail. From the systems biology perspective of the digital patient, diseases are perturbations of biological networks through defective genes or environmental stimuli, and therapies are the interventions needed to restore these networks to their normal states. The Bioinformatics group at FORTH Heraklion is developing novel computational methods for identifying new parts of these networks both from genomic sequences and from metabolite time-series, and to generate meaningful visualizations of them.

Our bioinformatics activities are collaborations between the Biomedical Informatics Lab of the Institute of Computer Science and the Computational Biology Lab of the Institute of Molecular Biology and Biotechnology. The common goal is the data-driven discovery of novel regulatory networks. In most cases, these networks are related to various diseases. One specific focus is the study of the interferon signalling network and its interplay with clinically relevant pathogens such as Cytomegalovirus. In particular, we are developing computational methods to investigate the role in various diseases of a novel class of small regulatory genes called microRNA (miRNA).

Large parts of the general regulatory network operating with miRNAs are not yet known. We have therefore developed a computational pipeline to extract novel miRNAs from the human genome, using support vector machines trained on features of known miRNAs as the central classification method. In collaboration with the Universities of Pennsylvania and Toronto, we experimentally verified the actual expression of a large number of these miRNAs in many different human tissues. Subsequently, the regulatory function of these miRNAs can be partially predicted by computational methods in order to unfold the underlying regulatory network. To visualize these and other types of regulatory networks that contain genes annotated by the Gene Ontology project, we developed a visualization tool using circular drawings and treemaps (see Figure 1).
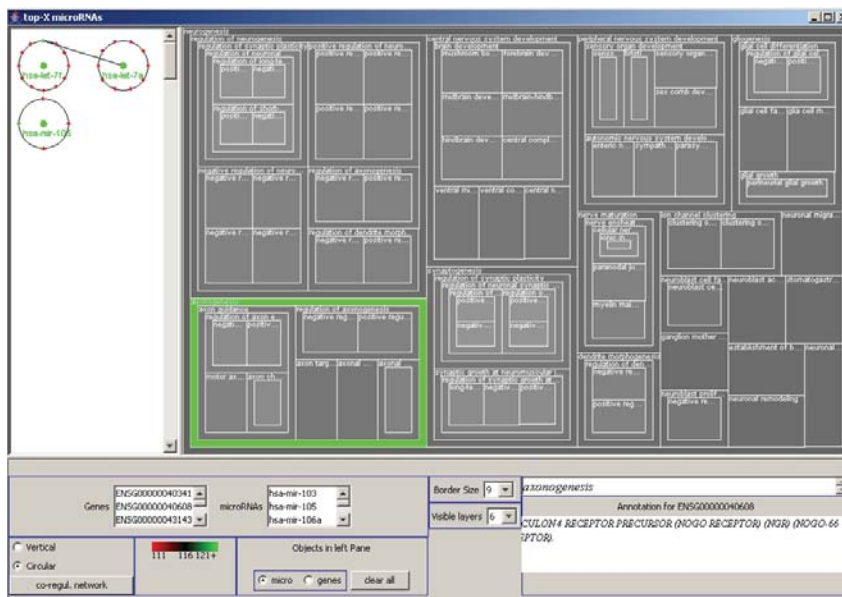
In developing methods to identify regulatory networks, we use time series of metabolite concentrations in yeast cells exposed to various types of environmental stress. At a higher level of detail we aim to identify the static modular organization of these networks, where the modules are defined as groups of co-regulated genes contributing to one specific biological function. We try to detect the kind of interrelations that govern each module, and the rules for interactions between modules. Initially we use gene expression data in conjunction with several statistical approaches, such as linear and higher-order correlation functions.

Figure 1: Circular drawing of genes regulated by microRNAs (left) and treemap visualization of the Gene Ontology categories of these genes (right).
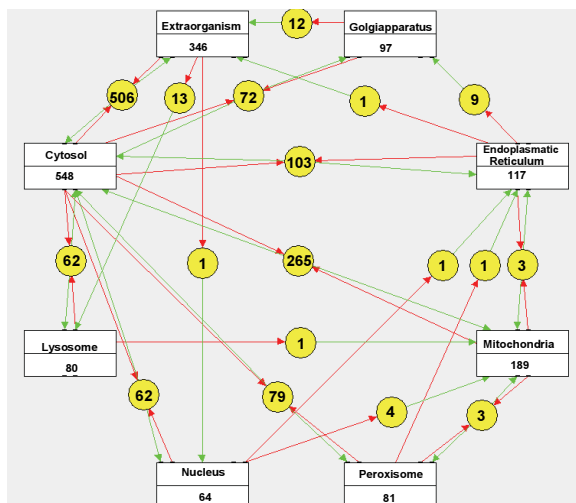

Figure 2: A visualization of the reactions between subcellular compartments of the first global reconstruction of the human metabolic network from the BIGG database (bigg.ucsd.edu). The number of chemical substances are specified in each the compartment box and the number of reactions between compartments are given in the circles. Reactant edges are shown in red and product edges in green.

More accurate network models emulate the dynamic behaviour of all observable metabolites and have already been used to predict the presence of as yet unknown biological elements; for example, an unknown activating 'modifier' in human colon carcinoma cells that might act as a novel therapeutic target. To derive these types of networks from time series we employ evolutionary optimization methods.

An example of the most successful multilevel model with a wide temporal and spatial range is the virtual heart that recently extended the spatiotemporal detail of the simulations to the level of fixed subcellular modules. Now the first in silico reconstructions of the complete human metabolic network have become available for this and many other predictive models for human diseases.

Figure 2 shows one possible visualization of the reactions in this network; we designed this using the Cytoscape tool. Apart from leading to fundamental advances in biology, these models will have a direct practical value in future medicine for the integration, analysis and classification of data.

This work is supported by the EU-funded projects INFOBIOMED and ACGT, and by the action 8.3.1 (Reinforcement Programme of Human Research Manpower). It is also assisted by the project PrognoChip, which is itself funded by the operational programme 'competitiveness' of the Greek General Secretariat for Research and Technology.

Links:
http://www.ics.forth.gr/bmi
http://www.imbb.forth.gr/groups/computational.html
http://infobiomed.org

Please contact:
Martin Reczko
ICS-FORTH, Greece
E-mail: reczko@ics.forth.gr

Digital Human Modeling and Perception-Based Safety Design

by Vincent G. Duffy

The 'Digital Human Modeling and Perception-Based Safety Design' project is intended to minimize or reduce the need for physical prototyping in design. Researchers at Purdue University from across different colleges have the opportunity to work collaboratively on projects in this area through the Regenstrief Center for Healthcare Engineering and Discovery Park. The work has origins in automotive, aerospace and military vehicle design.

A digital human model is created by inserting a digital representation of the human into a simulation or virtual environment; this is then used to explore issues of safety and/or performance. The model enables researchers to visualize situations of interest, and the virtual environment incorporates all of the necessary mathematics or science to ensure rigour. Perception-based safety design applies fundamentals of human factors and ergonomics to the optimal design of products and processes in various application domains, including manufacturing, automotive, military and healthcare.

This work began in 1996 as an extension of research in virtual environments. Later, results on digital human modeling (DHM) were presented by Purdue researchers at the IIE Applied Ergonomics Conference and the Society of Automotive Engineers Conference on Digital Human Modeling for Design in 2004 and 2005. Some early fundamental research can be found in papers presented at the international conference on Computer-Aided Ergonomics and Safety and at the Human Factors and Ergonomics Society annual conference.

These recent projects on virtual interactive design, which began in 2003, give consideration to both cognitive and physical aspects of the virtual interaction. Motion capture is integrated with virtual reality as an input to some commercially available computer-aided ergonomics models. Additional research leading to new models will provide more robust predictions, including consideration of the dynamic aspects of work for improved safety and risk predictions.

Successes in DHM-related research led to funding from UGS, Nissan, General Motors and the U.S. Army. The current affiliation with the Regenstrief Center for Healthcare Engineering at Purdue University is driving a number of new research initiatives and academic endeavours, including editing the forthcoming Handbook of Digital Human Modeling and organizing the 1st International Conference on Digital Human Modeling, to be held in Beijing, China in July '07.

Opportunities for the systematic application of engineering principles to healthcare delivery include simulations and predictions of healthcare outcomes. By considering human physiological and psychological factors during virtual interactive design, we can determine the likelihood of injury or error given certain workplace conditions and task requirements. Future activities and cooperation with ERCIM will provide opportunities for larger-scale Digital Patient models. Informed by molecular and genetic data, these will provide better predictions and thus have a positive impact on the clinical outcomes of individuals.

Links:
https://engineering.purdue.edu/IE
http://discoverypark.purdue.edu/wps/portal/rchedev

Please contact:
Vincent G. Duffy
Purdue University, USA
Tel: +1 765 496 6658
E-mail: duffy@purdue.edu

Semantic Interoperability in the Structured Electronic Health Record

by Petr Hanzlíček, Petra Přečková and Jana Zvárová

The electronic health record (EHR) is defined as a repository of information regarding the health of a subject of care, which exists in computer-processable form, stored and transmitted securely, and accessible by multiple authorized users. Its primary purpose is the support of efficient, high-quality integrated health care, independent of the place and time of health care delivery. To achieve these objectives, the semantic interoperability between information systems of different health care providers is a key issue.

The EuroMISE Centre is located in the Czech Republic and is based in the Department of Medical Informatics at the Institute of Computer Science, AS CR. Development of the EHR started here in 2000 and was based on experience from existing standards (CEN/TC251 European Standardization of Health Informatics) and several European projects. The proposed system should combine structured data storage with free text and the possibility of dynamic extension and modification of the set of collected attributes without any change of the database structure. The main goal of the research in this field was to suggest common general principles to increase the quality of EHR systems, to simplify data sharing and data migration among various EHR systems and to help overcome the classical free-text-based information stored in a medical record. The suggested solutions were implemented in a pilot application named the 'MUltimedia Distributed Record' (MUDR).

The MUDR EHR is based on a three-layer architecture: the database layer, the application layer and the user interface layer. Because of the requirement of a dynamically extensible and modifiable set of collected attributes, the classical relational database structure with columns corresponding to the gathered variables was not suitable as a basis for the information storage. Instead, the solution is based on two main structures described by tools of a graph theory. The set of collected attributes and relations among them are stored in a directed graph structure called the knowledge base. The vertices of the graph describe the collected attributes, while the graph edges describe the relations among attributes. The dominant edge of the type 'inferior' defines the main hierarchical tree structure of the knowledge base. Another hierarchical
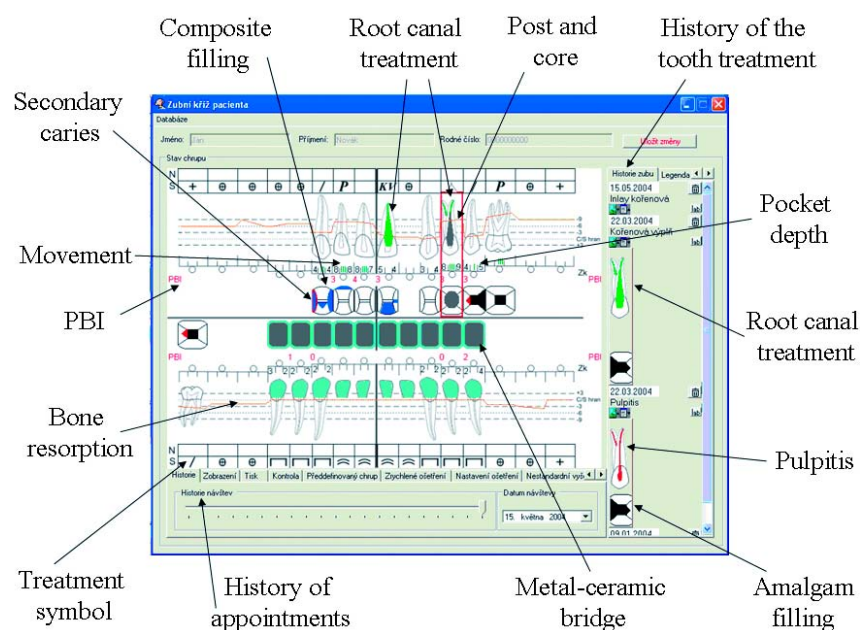

Figure 1: The special interactive user interface for data storage in dental medicine.

graph structure named 'data-files' is used to store the patient data. Each tree in the graph describes the data of one patient. Each vertex in the tree describes one instance of the medical concept from the knowledge base. The values are physically stored in separate tables according to the physical data type. Knowledge of cardiology and dental medicine was gathered for MUDR EHR, and the special interactive user interface was developed in dental medicine according to requirements of physicians.

The knowledge base content for the pilot project implementation in cardiology was prepared as a set of approximately 150 important medical concepts, named the Minimal Data Model for Cardiology patients (MDMC). This model was prepared by consensus of Czech professionals in the field of cardiology

as the basic data set necessary for an examination of a cardiology patient.

Terminology and Classification Systems

Since uniqueness of term definitions and their precise denomination are necessary in order to prepare the EHR, we found that our classification of medical terms was not optimal. Insufficient standardization in medical terminology represents one of the prevailing problems in processing of any kind of medical-related data.

Various classification systems, nomenclatures, thesauri and ontologies have been developed to solve this problem, but the process is complicated by the existence of more than one hundred incompatible systems. The most extensive current project that supports conversions between major international

classification systems and records relations among terms in heterogeneous sources is the Unified Medical Language System (UMLS).

During development of the MUDR EHR and MDMC, which was supported by the 1ET200300413 project of the AS CR, the UMLS Knowledge Source Server was used to evaluate the applicability of international nomenclatures in the Czech medical terminology. During the analysis we found that approximately 85% of MDMC concepts are included in at least one classification system. More than 50% are included in SNOMED Clinical Terms.

The concepts may be divided into five classes. Trouble-free concepts can be mapped directly. Partially problematic concepts have several mapping possibilities to various synonyms, which differ slightly in their meanings and usually in their classification codes. Concepts may also be too general or too narrow, such that classification systems contain only concepts of a narrower or wider meaning. There are also concepts that cannot be mapped to any of the classification systems.

Close cooperation with specialists is therefore required. It is often necessary to choose the right standardized synonym to substitute for a certain technical term. Sometimes it may be better to describe a non-coded term by several coding terms and include their semantic relations. In some cases it may be possible to add a certain concept into an upcoming revision of a certain coding system. However, sometimes the restricted interoperability is inevitable.

The structured electronic health documentation is a necessary requirement for modern information systems in health care. It provides intelligent decision-support tools and information-processing techniques and results in improved reliability, accuracy and effectiveness of health care. Use of international standards and nomenclatures is the first and essential step towards interoperability of heterogeneous systems of EHRs.

Link:
http://www.euromise.org/

Please contact:
Petr Hanzlíček
EuroMISE Centre
Institute of Computer Science AS CR, Prague / CRCIM, Czech Republic
Tel: +420 26605 3788
E-mail: hanzlicek@euromise.cz

Adaptive Patient Scheduling with Dynamic Resource Usage

by Ivan B. Vermeulen, Sander M. Bohte and Han La Poutré

Can patient planning be more efficient? The Computational Intelligence and Multiagent Games (SEN4) research group at CWI uses software agents and smart, adaptive algorithms to improve hospital patient scheduling and to better match patients' appointments to their own preferences.

The aging populations in the western world are placing an increasing demand on health-care services, and the provision of efficient yet high-quality care is a prime concern for providers. Key health-care providers like hospitals want to provide their patients with high levels of service, such as short waiting times and the ability to make appointments that fit the needs of individual patients. At the same time, the scarce hospital resources should be used with the highest possible efficiency, in order to keep health care affordable.

As is known from both theory and practice, low access time to resources usually comes at the expense of resource capacity. The premise of our work is to combine improvements in logistics with smart, adaptive IT approaches. This can give lower access times by using more flexible resource allocation, while maintaining and possibly even increasing effective resource usage.
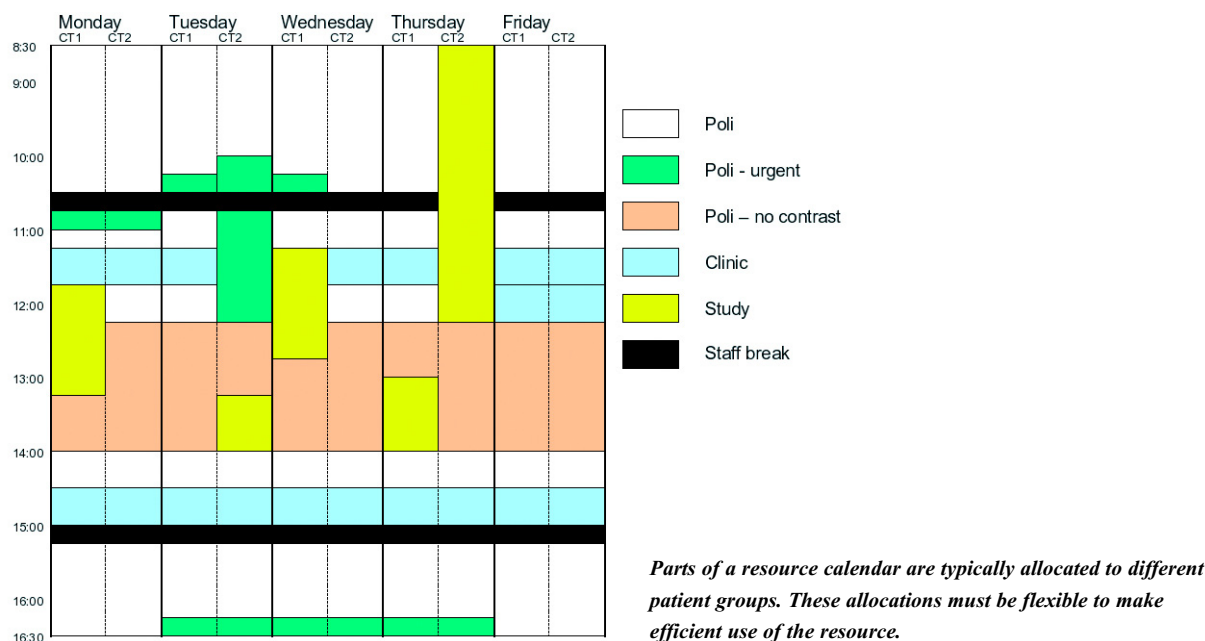
Efficient scheduling of patient appointments on expensive resources is a complex and dynamic task. Traditional approaches to logistical improvement are usually not suited to the medical domain. In most hospitals, the internally distributed authority makes it difficult to implement efficient scheduling between many departments. This can partly be explained by different operating procedures for different medical disciplines, and partly by the existing professional culture. Furthermore, scheduling decisions must be made dependent on the individual patient's specific attributes, such as the level of urgency.

In cooperation with the Amsterdam Medical Center, a large university hospital in Amsterdam, we analysed and modelled the distributed patient scheduling problem. From these models and discussions with experts, we are deriving approaches to improve the scheduling flexibility and efficiency for bottleneck resources, while respecting the typical organization style of hospitals and medical constraints.

We find that most bottleneck resources in hospitals are shared by several patient groups, where each patient group has its own distinct properties. For example, there are various groups of 'inpatients' (admitted to the hospital) and 'outpatients' (not admitted), with different levels of urgency. The total resource capacity is allocated to these groups, explicitly or implicitly (see figure). Due to fluctuations in demand, this allocation must be flexible in order to make efficient use of the resources.

To complicate matters further, many outpatients must be scheduled for more than one diagnostic test. The outpatient department has to make appointments for these tests with the various auxiliary departments. A combination of tests might for instance be an imaging technique – like CT, MRI or echo – with an additional test (function/endoscopic/

Parts of a resource calendar are typically allocated to different patient groups. These allocations must be flexible to make efficient use of the resource.

punction). Each of the departments involved wants to fit the appointment into their own local schedule. At the same time, the outpatient department wants to schedule the combination of appointments within a limited time and to provide its patients with a high level of service by coordinating the various appointments, scheduling them, for example, in the same part of the day. Currently, coordination between departments to schedule combined appointments is too labour intensive and too dependent on the restricted time available to the operator.

From our case study, the labour-intensive nature of scheduling is obvious, even though electronic calendar-systems are widely applied to allocate hospital resources. In general, these systems just store patient appointments, while as in many hospitals, the actual patient scheduling is done manually by human schedulers. They either check the calendar for an available slot, or use the search function of the calendar system to find available timeslots.

To improve on this highly constrained scheduling practice, we have developed an agent system where each party – like doctors, patients and resources – is represented by a software entity – the agent

– that autonomously acts on behalf of its owner. Given the distributed and decentralized nature of hospital patient scheduling, the use of such a distributed mechanism for scheduling seems a natural fit. Each agent 'knows' the preferences and constraints of its owner.

To increase efficiency while reconciling patients' potentially conflicting preferences, we developed a Multi-agent Pareto Appointment EXchanging algorithm (MPAEX). In MPAEX, agents acting on behalf of individual patients attempt to exchange the time-slots of the initial appointments with better appointments occupied by other patients. The other patient's agent accepts a proposed exchange of appointments if the resulting schedule is not worse for that patient. Guaranteeing 'not worse' for schedule changes means that patients have an incentive to cooperate, which is an important requirement in practice. In simulations, we show that when (re)scheduling patients using MPAEX, the collective overall waiting time for patients is improved.

Furthermore we have developed an adaptive approach to automatically optimize resource calendars. Our approach makes the allocation of capac-

ity to different patient groups flexible and adaptive to the current and expected future situation. To maintain high performance levels, our system regularly exchanges capacity between different patient groups. Additionally, opening hours for resources can be altered to achieve high capacity usage, while maintaining key performance goals such as waiting time.

In our current work, therefore, we are focusing on improving the scheduling of combination appointments for hospital patients. Most importantly, we aim to improve the service provided to patients by facilitating same-day appointments and by taking the patients' preferences into account, all the while using resources with a high level of efficiency.

Technology to Assist the Sick, the Elderly and People with Disabilities

by Loriano Galeotti, Matteo Paoletti, Andrea Vannucci, Stefano Diciotti, Massimo Carradori, Massimo Pistolesi and Carlo Marchesi

We consider a digital patient to be a person who is part of a community that is well acquainted with advanced technology, and is open also to medical applications. This project aims to make such patients capable of managing assistive technology devices for monitoring their health conditions, and also to train and improve their opportunities for social contact.

Defining Operating Ambients

The immediate goal of this study is the definition of design criteria for a portable, personal piece of equipment that could help people with physical impairments (eg due to age or disease) by augmenting their ability to communicate. Technology could also improve the independence of such people by allowing them to practice autonomous social interaction. However, the success of an assistive device depends on a good level of cooperation between the patients and the professional who trains them in its use.

This project faces the human factor issues in an original way, recruiting students from high school as caregiver volunteers, under teachers' and professional caregivers supervision. Students have shown a natural attitude to provide effective help, so this cooperation appear to be a major factor for success.
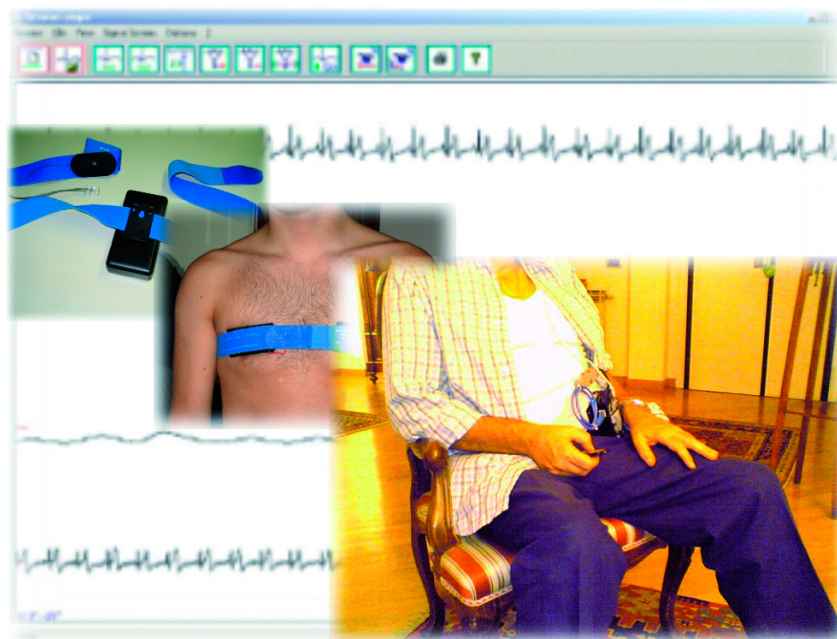
We can say that the final goal of providing patients with significant help is the the transformation of their impairment into a diverse ability. The achievement of this goal is conditioned by human factors. This issue widens further the patients' needs. These observations lead us to introduce the ambient as a scalable entity by which context is defined through typical requirements, rather than costly and possibly unpredictable individual requirements.

We have introduced a hierarchy of ambients to represent the global, distributed system of services in a standardized way, taking into account communication between home, the doctor's office and emergency units.

The first ambient (the domestic ambient) is closely tied to patient needs, while the definition of communication between patient and doctor (low-risk ambient) and patient and hospital (emergency ambient) could easily be conceived as part of a standard service network. These latter two thus belong to the digital citizen concept rather than the digital patient. Design of the first ambient required specific attention, since it contains the contextual data, while the design of service networks involve general-purpose specifications.

The portable processing and radio-transmitting unit, showing the sensor-carrying belt, its position over the thorax.

The COMPASS Project

The domestic ambient supplies data, which are analysed following two main paths. Real-time software is used for signal acquisition and processing, alarm generation and patient/doctor cooperation, where the main aim is to provide emergency assistance. Batch processing is used for data mining, knowledge discovery and decision-making support, where the main aim is to detect and treat chronic disease.

Particular care has been dedicated to any operation affecting the quality of the acquired data, including the problem of heterogeneous data, which is typical of the medical field. We built our research from the bottom up, developing original algorithms for signal processing and defining criteria for data access.

In particular, algorithm performance is enhanced by using a priori knowledge derived from physiology, individual data patient records and the experience available in the BIM Lab and partners.

Partners

This project has involved a variety of partners, chosen for their complementary backgrounds:
- BIM Lab (Bioingegneria e Informatica Medica), Department of Systems and Computer science,

Florence University
(hardware/software design)
- AIAS (Associazione Italiana Assistenza Spastici) association (rehabilitation, assistance)
- ITIS (Istituto Tecnico Industriale Statale) 'Fedi' Technical High School of Pistoia
- Department of Critical Care, Florence University (protocol definitions and clinical procedures)
- ISIA (Istituto Superiore per le Industrie Artistiche) Higher Institute for Artistic Industry of Florence (design of wearable setup).

Conclusions and Perspectives

We believe our research and experience have led to the development of effective new equipment for continuously monitoring multi-channel vital signs over extended periods of time. This is assured by embedding the sensors in a simple wearable setup. The digital patient will emerge from this experience if we are able to document that the unique features of COMPASS are providing specific help. In other words, our digital patients will be confident and comfortable enough with their own portable vital-sign monitors to reduce medical interventions and possibly hospital admissions. For people with disabilities, we are planning to validate the organization model and to evaluate its application in other places.

In conclusion, we expect that the project will answer the following crucial questions:
- Are 'ambients' a proper approach to unify the organization of those who care for the patients?
- Will the continuing experience at AIAS and in Florence show the final correct specification for personal monitors under each aspect (hw/sw, ergonomic, procedures, interfaces..)?
- Is it possible to combine system reliability with aesthetic and ergonomic values?
- Is the enthusiastic, fresh approach of high-school students a major factor in the success of the project?
- Finally, will the project provide validated protocols for patient monitoring and assistance for people with disabilities?

Link:
http://www.dsi.unifi.it/bim

Please contact:
Loriano Galeotti
Florence University, Italy
Tel: +39 0554796464
E-mail: galeotti@dsi.unifi.it

Matteo Paoletti
Florence University, Italy
Tel: +39 0554796464
E-mail: paoletti@dsi.unifi.it

Carlo Marchesi
Florence University, Italy
Tel: +39 0554796255
E-mail: marchesi@dsi.unifi.it

OLDES: A Low-Cost System for Caring for the Elderly

by Massimo Busuoli

With the number of senior citizens in the EU dramatically increasing, the burden in terms of public expense rises concomitantly. This is the motivation behind OLDES (Older peoples' e-services at home), a three-year project funded by the Information Society Technologies Programme of the European Union.

Today an increasing number of elderly people are living alone, in many cases with no families helping them and not enough money to afford private carers. The goal of OLDES is to plan and implement an easy-to-use, low-cost innovative technological platform. The platform will be tested by 100 elderly people in Italy (ten of them affected by heart disease) and a sample of diabetic patients in Prague.

This project is strongly supported by the Bologna Town Council. Its Health Department believes that the welfare model must be rapidly renewed, making the most of new technologies and high-tech devices to offer tele-medicine, tele-assistance, tele-entertainment and tele-company services to a wider number of se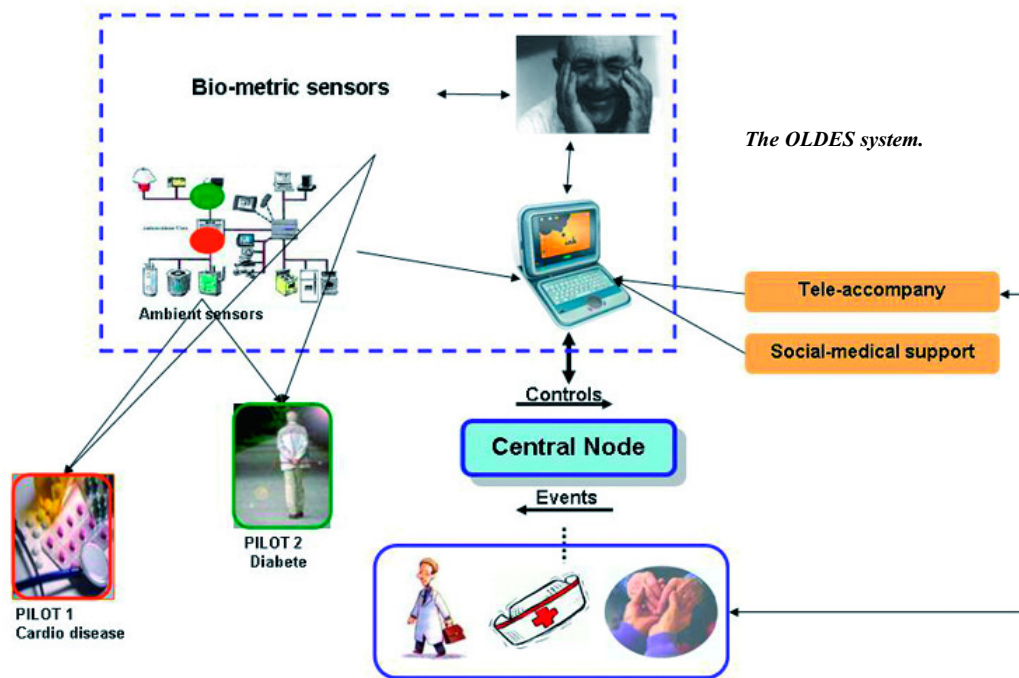nior citizens. The aim is to augment the number of people assisted by public services, even if public resources decrease as the number of elderly increases.

OLDES is considering three main categories for care – entertainment and companionship, clinical monitoring, and domestic monitoring. The project will define an innovative and alternative welfare system in which technology will be customized according to user needs and employed on a large scale. In the OLDES vision, the future will see all elderly people who live in cities and suburban areas being tele-assisted. This would contribute greatly to a simplification and systemization of social services and would save public money. The technology proposed by OLDES represents a cost-effective and humane solution that will allow the elderly and their families to live more serenely in their own homes.

OLDES will be an easy-to-use, plug-and-play system with different costing levels, according to the profile of the person assisted. A base level will be available for everyone, which includes communication and tele-company and which will be simply based on a low-cost PC and open-source software with a target price of around €100 per person (corresponding to Negroponte's paradigm of a $100 device).

The intermediate level will involve the addition of simple sensors (eg to measure the ambient temperature) for the management of generic monitoring situations (eg very hot periods in the sum-

The OLDES system.

mer). Finally, an upper and tailored level will include health-monitoring sensors depending on the health profile of the user.

The starting point will be the construction of usage scenarios, which will help to produce results that are of wider interest and applicability on a European scale. For this reason, OLDES will perform a market study based on two strategies. These are the development and progressive refinement of a set of generic usage and provision models, and a service-component approach to the packaging of technical developments to ensure maximum flexibility and configurability.

For products and services that support the provision of social care, market analysis and exploitation planning is more complex than when commercializing a device or testing a medical or therapeutic procedure. In order to address the diversity that exists in the context, provision and funding of care services, the project will generate a set of care delivery models that are grounded in practice but are sufficiently generic to provide a framework for the deployment of the OLDES components. These models are an essential component of the broader OLDES

architecture, and their evolution and refinement is a process that will continue throughout the life of the project. They are both conceptual and descriptive but must also provide quantitative data upon which service and business planning can be based.

The usage and provision models provide one mechanism for addressing the diversity of the OLDES 'market'. To maximize the flexibility and therefore the exploitability of the OLDES products, it is also required that our technical outputs are packaged appropriately into highly configurable service components. We use the term 'service' both in the sense of client service to older people and also in the sense of technical service components as part of a systems infrastructure. The service-oriented approach employs a simulation and interactive development strategy by which real service components replace simulated ones in an evolving reference implementation.

The combination of an essentially infrastructural service-oriented approach and the potential for innovation and change mean that conventional market analysis models are of limited applicability to OLDES. These assume that evidence of demand, as opposed to

latent need, can be readily elicited through conventional market research techniques. Such approaches are not only of limited applicability to public service contexts but can actually be misleading. Conventional market analysis can only operate in the incremental development mode and cannot cope with propositions that may, for example, fundamentally change the shape of the provision value chain.

The approach to be adopted by OLDES is of incremental development, client and user participation and the use of animation and simulation in a reference implementation context. This design should ensure that possibilities for change remain open while development is, at all stages, grounded in the realities of social care, the cultures and economies of the specific pilot contexts, and as wide a range as possible of other European public service contexts.

Link:
http://www.oldes.eu

Please contact:
Massimo Busuoli
OLDES project coordinator
ENEA EU Liaison Office, Bruxelles
E-mail:
massimo.busuoli@bruxelles.enea.it

Mobile Health Assistant

by Christian Weigand and Janina Schmidt

The Mobile Health Assistant has been developed by Fraunhofer researchers to provide support for patients with chronic illnesses. Comfortable and easy to use, the Assistant is designed to aid patients 24/7 a week.

The Mobile Health Assistant is a piece of technology that employs sensors and telemonitoring services to tailor therapy to individual patients. Based on continuously measured vital parameters, the services can include a personal trainer, who gives tips for a balanced diet or provides an exercise plan via a mobile device (smartphone). While we initially focused on patients with cardiovascular diseases and unclear syncopes, we have also found the Assistant to be useful in the support of patients suffering from adiposity, hypertony and other diseases. These patients require data on their heart rate, blood oxygen saturation, blood pressure and pulse.

The Mobile Health Assistant comprises a sensor shirt and a wrist-worn plethysmograph (a device to measure SpO_2, blood flow and heart rate.). The shirt is designed to be worn both day and night. We meet hygienic requirements by using elastane fabric, which can be washed in standard washing machines at 60°C. Four special electrodes are integrated in the shirt: one on each shoulder and two at the bottom of the costal arch. The so-called 'dry electrodes' were specially designed for the shirt, and make special electrode fixation or contact gel superfluous. The shirt also contains a three-lead Einthoven electrocardiogram (ECG), processed by a flexible electronic circuit board. The gathered data can be also stored and wirelessly transmitted via a Bluetooth connection. While several cables are required for the connection between the electrodes and the ECG electronics, these connections are integrated in the fabric of the shirt and cannot be felt. As shown in the figure, the shirt can be worn discreetly under everyday clothes, even during a physical workout.
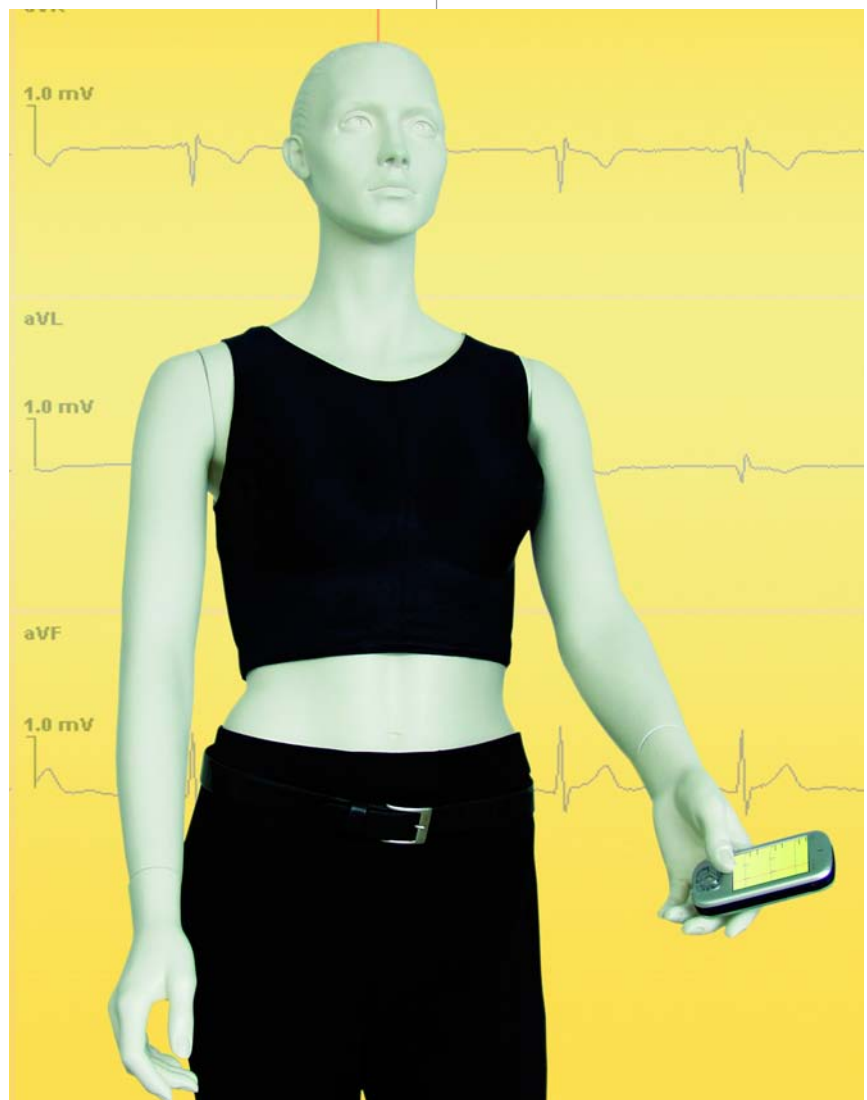
Currently, a pulsoximeter is employed to measure the oxygen saturation of the blood. The sensor front-end is embedded in a finger clip, which is applied to a fingertip. Like the ECG data, the data gathered by the pulsoxymeter are transmitted wirelessly via Bluetooth. A standard smartphone with a Bluetooth interface is used to connect with the two sensors and record their data. In the near future, the front-end will be integrated with the plethysmograph wristband, making the finger clip no longer necessary.

The pulsoximeter not only measures oxygen saturation but also provides the pulse wave curve. Combining the pulse curve with peak data from one of the ECG leads, the so-called pulse transit time can be calculated. Based on this value we are able to estimate an equivalent for the diastolic and systolic blood pressure. The calculations are done by an application on the smartphone, and require a precision of one millisecond. This is achieved by using special Bluetooth modules in both sensors that are able to synchronize the measured data. The smartphone does not require a special Bluetooth module.

The smartphone continuously shows the patient the values of blood pressure, pulse and oxygen saturation. Via the GPRS or UMTS capabilities of the smartphone, the whole data set can be transferred to an internet-based server.

ECG-Shirt with dry electrodes woven into the elastic fibers of a sensor shirt and flexible electronic circuit board.

This allows the physician in charge, the insurance company, the hospital or personal trainer to monitor the patient's data via an Internet browser. The Internet communication is encrypted and meets the security requirements of the German government. The data is stored as an electronic health record; the patient then has ownership and control of this record..

The patient's self-determination and freedom of decision are reflected in the treatment of choice. Patients can choose the simple observation of vital data, can request a response from a physician concerning his condition or can communicate via smartphone with the doctor and discuss further steps of therapy. A doctor's response can range from mere medical consultation to a call for the ambulance. This means that patients are free to decide to what degree the system affects their lives.

The Mobile Health Assistant merges two projects: 'senSAVE®', undertaken by five Fraunhofer Institutes (Fraunhofer FIT (St. Augustin), Fraunhofer IAO (Stuttgart), Fraunhofer IBMT (St. Ingbert), Fraunhofer IIS (Erlangen) and Fraunhofer IPMS (Dresden)), and the 'digital patient assistant' project at the Fraunhofer ISST (Dortmund).

The Mobile Health Assistant was presented at CeBIT 2007.

Please contact:
Christian Weigand
Fraunhofer Institute for Integrated Circuits IIS, Germany
Tel: +49 9131 776 7341
E-mail:
christian.weigand@iis.fraunhofer.de

Janina Schmidt
Fraunhofer Institute for Integrated Circuits IIS, Germany
Tel: +49 9131 776 7311
E-mail:
janina.schmidt@iis.fraunhofer.de

Research Institute Supporting Electronic Governance

by Zoltán Tóth

Promoting the fast and efficient development of the Information Society is a major objective of the Hungarian Academy of Sciences (HAS). Accordingly, in January 2006 SZTAKI, the Computer and Automation Research Institute of the HAS, established the E-governance Competence Centre (ECC), dedicated to developing and promoting applications for e-administration.

The foundation of ECC was motivated by the fact that no independent professional organisation existed in Hungary to provide joint expertise in legal, administrative, and technical issues simultaneously; such an organization is essential in building and promoting general e-administration.

The department carries out complex tasks. Its essential objectives are the following:
• research on theoretical issues of e-administration and to make proposals for governmental and municipal organs
• consultation with and education for users of e-administration
• elaboration of research and development projects and proposals
• preparation of publications and e-learning syllabuses.

Recently, the ECC undertook two projects. We defined the conditions necessary to establish a new person (client) identification system, including a proposal for a new data protection law to be placed on a new constitutional basis. Hungary has accepted the data protection proposals of the European Union, meaning there are legal difficulties in connecting databases containing client data with each other.

Our other project was the elaboration of the theoretical basis of the public administration infrastructure, which enables the widespread use of electronic administration and electronic signatures. According to the Hungarian law, electronic documents can be issued by the authorities only if qualified electronic signatures are attached. In Hungary, four certificate authorities offer electronic signatures, but due to legal difficulties, none is able to provide qualified electronic signatures.

Governmental executives have made it clear that there is a strong demand for our work. In order to improve and expand the prepared proposals, we organized a conference at the Institute for Legal Studies of the Hungarian Academy of Sciences.

In the period 2007-2013, the European Union will place at Hungary's disposal a development fund worth 22.4 billion euro from the Structural and Cohesion Funds. However, the developments will not be financed exclusively by the EU, and must be complemented by domestic funds. For utilizing this financial fund, the Hungarian Government developed a strategic document for the EU, namely, the New Hungary Development Plan (NHDP). We participated in the preparation of this plan, in the State Reform Operational Programme, and in the Electronic Administration Operational Programme. The latter two programmes describe the detailed objectives of the NHDP. Recently, we have contributed to the Action Plans that belong to the Operational Programs for the Prime Minister's Office and for the National Development Agency.

In the second semester of 2006 we established the ECC Presentation and Education Centre. Here we present proven e-governmental applications for governmental and municipal organizations. This activity will be expanded both quantitatively and methodologically, since in 2007 the number of market participants in the e-government sector will increase from fourteen to

more than twenty. As a qualitative improvement, we will commence operating an ASP (Application Service Provider) centre in 2007, which will provide qualified e-governmental applications for e-municipalities.

At the request of governmental executives, we established a Hungarian-Austrian workgroup, which collects and presents international experience in developing and using citizen e-cards. In Austria each citizen has his/her own multipurpose e-identity card, and we would like to implement a similar initiative in Hungary.

Since we consider the wide-ranging familiarization and acceptance of the results of e-governance to be especially important, we organize conferences and other programmes, and prepare professional e-learning materials. Among other things, we have organized several conferences with the aim of improving the e-governance knowledge of the civil service, and have completed the first two professional educational DVDs in the 'Electronic Governance' e-learning series.

Our experience in e-governance and the methodologies that we will develop in the near future will make it possible to catch up with those countries where computer techniques are widely used. Moreover, these experiences can be handed over to other similar countries, making them valuable in international relations.

The ECC Presentation and Education Centre.

Please contact:
Zoltán Tóth
SZTAKI, Hungary
Tel: +36 1 2796245
E-mail: tothz@sztaki.hu

The Bridge Project: Cooperation between Europe and China to Develop Grid Applications

by Gilbert Kalb

Launched with a kick-off meeting in Southampton on 25 January, the Bridge Grid Project is designed to encourage bilateral research and industrial development that will enhance and integrate Grid-enabled technology for industrial cooperation between Europe and China.

The Bridge project builds on major Grid efforts on both sides. The European part is based on the SIMDAT project (Data Grids for Process and Product Development using Numerical Simulation and Knowledge Discovery), which joins forces for product development and production process design using Grid services. CN Grid, a similar project with comparable objectives, was launched in China in 2002. While SIMDAT uses

GRIA (GRID Resources for Industrial Applications), GN Grid is based on GOS (Grid Operation System). Both are independent developments.

The two systems have attracted wide support from industrial players using Grid technology and consequently large investments in their respective countries. Bridge intends to combine the two worlds through interoperability. IT Inno-

vation from Southampton and Beihang University from Beijing will work on the underlying infrastructure. These partners played a significant role in the original development of the two systems.

Application Scenarios
Showcase applications for the new interoperable Grid platform were chosen from three different fields. They will show a general proof of concept

and will simultaneously help to shape the infrastructure through their specific needs and requirements.

Aviation: EADS on the European side and AVIC II from China will use the infrastructure developed in Bridge for various simulations of improved designs, for example of aircraft wings. A work package concerned with this development is led by the company LMS (Belgium). LMS will adapt and improve the Grid middleware with the support of Fraunhofer SCAI.

Meteorology: The European Center for Medium-Range Weather Forecasts (EDMWF) together with the Chinese National Meteorological Information Center (NMIC) will use Bridge infrastructure for faster and more precise predictions of weather-related phenomena and disasters. The Deutsche Wetterdienst (DWD) will support them in developing this application scenario.

Drug Discovery: InforSense (UK) and the Shanghai Institute for Medical Material (SIMM) will use Bridge-based workflows to improve their development of new drugs for fighting bird flu, dengue fever and malaria. Docking tools from both partners will run on the interoperable middleware provided with the Bridge infrastructure.

Each of these applications has a high demand for computing intensive services and a special need for cooperation between Europe and China.

Fraunhofer Gesellschaft is responsible for the overall management of the Bridge project, and is providing special tools to improve the performance of the aviation and pharmaceutical applications. The Bridge project is supported by the European Union, with 1.7 billion euro for 24 months.

Link:
http://www.bridge-grid.eu/

Please contact:
Gilbert Kalb
Fraunhofer-Gesellschaft, Germany
Tel: +49 2241 142244
E-mail: gilbert.kalb@zv.fraunhofer.de

DELOS-MultiMatch Workshop on Ontology-Driven Interoperability for Cultural Heritage Digital Objects

by Vittore Casarosa and Carol Peters

Nearly forty researchers and practitioners in the IT and cultural heritage sectors participated in a one-day workshop on "Semantic-driven Interoperability for Digital Objects in the Cultural Heritage Domain". The workshop was organised as a joint DELOS – MultiMatch event in conjunction with the DELOS Conference, held in Tirrenia, Pisa, 13-15 February 2006.

Interoperability is a hot topic within the digital library and distributed information retrieval research communities. This is also evidenced by the fact that the European Commission has just set up a working group on Interoperability and Multilinguism as part of the i2010 digital library initiative. The DELOS Network of Excellence and the MultiMatch specific targeted research project both have strong interests in this area. For this reason, it was thus decided to organise a joint DELOS – MultiMatch workshop in order to investigate the current state-of-the-art, and discuss those issues that currently hinder the widespread adoption of standards and impede interoperability.

The goal of Multimatch is to develop a system that will enable users to explore and interact with online cultural heritage (CH) content across media types and language boundaries (see ERCIM News 66, July 2006). This means that the project is acquiring large volumes of heterogeneous domain-specific data both directly from CH content providers but also via focussed web crawling. This data must be processed and categorised. The original idea for the workshop thus resulted from early discussions within MultiMatch aimed at defining of the most appropriate metadata schema and conceptual framework for the project. It was felt that it could be very beneficial to be able to exchange ideas and experiences with people working on similar problems.

DELOS has long been concerned with questions concerning interoperability and has published a comprehensive report on Semantic Interoperability in Digital Library Systems (publicly available on the DELOS website). The DELOS conference offered the perfect venue for this workshop and a number of experts in the field (both theoreticians and practitioners) were thus invited in order to share their expertise and experiences and advise the MultiMatch group.

The workshop opened with a brief presentation by Neil Ireson (University of Sheffield) in which he illustrated the main factors impacting on the definition of the MultiMatch knowledge representation framework, the problems currently being addressed and the solutions being considered. The aim was to set the context for the following discussions.

The remainder of the morning session was dedicated to the keynote talks. Martin Doerr (FORTH, Crete), Maja □umer (University of Ljubljana) and Chrisa Tsinaraki (Technical University of Crete) presented three of the best known existing conceptual frameworks (CIDOC-CRM, FRBR and MPEG-7) and some of the relationships between them. These talks were followed by a lively panel discussion, moderated by Stavros Christodoulakis, aimed at investigating how these frameworks can be made interoperable. During this discussion, Martin Doerr pointed out that in his opinion there is a fundamental con-

fusion between the schema and the ontology levels: ontologies are about the underlying concepts, schemas are concerned with the data. In his opinion there is no reason not to agree on the concepts and a common vision should be possible. Doerr stressed that an ontology such as CIDOC is neutral, it only tells the implementers what kind of reasoning and what relationships are possible, but it is up to them to decide to what level of detail they wish to go. And as a first step, it is essential to start by understanding what kind of queries are to be supported by the reference framework adopted. Chrisa Tsinaraki stated that although ontologies are developed for specific communities it is also important to aim for widely adopted generic standards – ontologies cannot be just domain-specific but must fit into an overall vision of the world

The first session in the afternoon was dedicated to a series of position statements by a number of projects and institutions working in the CH domain. The EDLProject, TEL, MICHAEL, BRICKS, IMAGINATION, EPOCH plus the Dutch Cultural Heritage Institution briefly presented the problems they are currently facing in this area and/or

the solutions they are adopting. The last speaker presented the perspective of the Text Encoding Initiative, the work being done by the TEI Ontologies SIG working group and the problems this group has faced when trying to map from a TEI document to a model conforming to CIDOC-CRM.

The final session of the workshop began with a presentation of the objectives of the recently formed EC Interoperability Group by Stefan Gradmann (University of Hamburg). This triggered a discussion of the main issues that had emerged during the day, again moderated by Stavros Christodoulakis. Points raised included:
• how do you combine different reference models?
• how do you handle very heterogeneous data?
• what kind of queries do users really want?
• how can you handle incomplete and uncertain information, eg information crawled from the web?

Many participants felt that there is a conflict between the needs of the real world (ie achieving interoperability between schemata) and the conceptual

level. What is needed is a common conceptual reference framework comprehensive enough to cover the multitude of detail required, while being, at the same time, both sufficiently simple to use and amenable to the application of automatic population techniques. There was general consensus that with the current state-of-the-art, it is difficult to envisage being able to achieve this goal. The working notes and presentations of the workshop can be found on both the DELOS and the MultiMatch websites.

The DELOS Network of Excellence on Digital Libraries is managed by ERCIM.

Links:
http://www.delos.info
http://www.multimatch.eu

Please contact:
Vittore Casarosa, ISTI-CNR, Italy
Tel: +39 050 3153115
E-mail: vittore.casarosa@isti.cnr.it

Carol Peters, ISTI-CNR, Italy
Tel: +39 050 3152897
E-mail: carol.peters@isti.cnr.it

EU-US Workshop on "Secure, Dependable and Trusted ICT Infrastructures"

by James Clarke

An EU-US workshop on research in 'Cyber Trust: System Dependability and Security' was held in Dublin, Ireland on November 15th and 16th, 2006. This article presents the themes discussed and the main workshop conclusions.

Secure and reliable information and communication systems and networks play a key role for a healthy growth of the Information Society. Today, the global character of the Internet and other ICT Infrastructures, the scale of security & trust problems we are facing and the related research challenges to address call for intense international cooperation research activities.

An international workshop was thus held in Dublin, Ireland on November 15th and 16th, 2006 on research in "Cyber Trust: System Dependability & Security". Its aim was to gain an understanding of the priority of mutual

critical issues and promising dependability and security research directions, and to foster collaboration between EU, US and other developed country's research communities. The workshop was attended by 60 delegates from the EU and the US, along with representatives from Canada, Australia and Japan. It was co-organised by the IST-FP6 Co-ordination Action SecurIST, Unit INFSO-F5 "Security" of the European Commission's Directorate General Information Society and Media, US National Science Foundation (NSF), Department of Homeland Security (DHS) and the University of Illinois.

The workshop was structured around six thematic panel sessions. Discussions held enabled the identification of a number of challenges and research priorities in ICT Trust, Security and Dependability (TSD) and triggered planning of some joint EU-US actions to address them.

The workshop themes and their conclusions were the following:

1. Architecture and design issues for TSD of Future Networked Systems
Future emerging networked ICT systems will be large-scale, complex mixed mode environments consisting of

diverse computing, communication & storage capacities. They will be based on the model of service-centric computing, systems of embedded systems and a mix of classical computers and embedded systems on the Internet. The discussion focussed around the new TSD attributes that such future ICT systems should be endowed with. These include trustworthiness and resilience, protocols, languages, metrics, internet routing paradigms, security provision technologies (cryptology, trusted functionality, multi-modal biometry, etc.), adaptive detection, diagnosis, run-time response mechanisms and stochastic security in core/access networks from an end-to-end perspective. For these new systems, there is a need to specify not only the underlying service semantics but also the TSD semantics and metrics for designing resilient architectures and secure network protocols and for detecting and measuring any anomalous behaviour.

2. Scalability and context-awareness for TSD of Future Networked Systems.

Discussions focused on multi-layered, scalable and context-aware approaches to make future networked systems secure and dependable. The main conclusions focussed on the need to extend scalability from all perspectives (hardware, software and systems) through better, realistic abstractions and by focusing on three phases of a system's lifecycle: (a) capturing network functionality, system performance and end-users requirements (b) System design, and (c) System evaluation and testing. Other discussions focussed on: development of a formal authorization engineering framework to increase the authorization capability limits required in order to support multiple administrative domains; automated fault detection and remediation techniques for application on a massive and growing scale; and, support of health management of autonomic system-of-systems approaches that enable automated fault detection and remediation on a massive scale.

3. Security and privacy in dynamic wireless networks of evolving systems composed of ad hoc coalitions of large numbers of sensors and devices for new personalized services.

The main conclusions focussed on addressing the lack of a security infrastructure, of threat models and of adequate security evaluation techniques for dynamic wireless networks. The main research directions identified to address this challenge were: testing methods and threat models; security infrastructure akin to tethered networks; federation of security policies and mechanisms across multiple domains; adaptive systems based on context; trust management while giving users more control over choosing risk levels and adaptable context; and, usability of security systems, especially in complex heterogeneous sensor systems.

4. Modelling, simulation, predictive evaluation, assurance cases for evaluating the TSD of networked systems.

The main issues addressed under this theme were verification and evaluation frameworks related to (possibly) Internet-scale applications and to particular networks and networked systems. There is a need to consider the wider socio-technical aspects and interdependencies as well as their semantic learning and understanding dimensions. There is also a need to use assurance cases and claim semantics from and for different stakeholders' viewpoints in order to communicate assumptions and agree on system security. When developing the above further, scenario building and use case generation would enhance understanding and inclusion of test data. There is a need here to develop and use standard metrics for incremental security improvements and probabilistic approaches for radical security improvements and for reducing stakeholders' interdependencies.

6. Monitoring, operational assessment, auditing for evaluating the TSD of Networked Systems.

Discussions focused on dynamic and online methods of analysis and evaluation and on real time assessment frameworks, including attacks observed, observation mechanisms, audits, measurement and decision making tools, etc. It is imperative to start now with the challenges associated with metrics, measurements and analysis, even with limited systems and goals, to gain a better understanding for threat characterization, prediction, observation, instrumentation and data collection. On-line measurements are needed to control and adapt, in particular, to put in place network information sharing techniques at all levels (including attacks observed, keystrokes of users, network traffic capture in an anonymous fashion and oth-

ers). There must also be put in place more incentives for the provision and sharing of data, which is needed to ensure sufficient context that would permit replication through experiments.

6. Establishment of interconnected and/or common test-beds.

Issues discussed include: opportunities for interconnecting existing experimental facilities and building joint benchmarks; test scenarios and interconnected test-beds for supporting the testing and evaluation of new dependability and security architectures; and, technologies, protocols, and privacy protection mechanisms, together with support towards global standards. Examples of identified potential shared test-beds include a test-bed for software and services to allow experimentation at the application and services level or a test-bed for dynamic wireless and sensor networks. The first would open up valuable opportunities for innovative Small and Medium sized Enterprises and Academics to venture into service-oriented solutions. For wireless and sensor network test beds, there are some stand-alone test beds already available but the issue that must be explored is to how to federate them taking into account cross testing, mobility aspects and security policies as users move in and out of different environments.

The full workshop report, all presentations and position papers are available on http://www.securitytaskforce.eu.

Link:
IST-FP6 SecurIST Coordination Action: http://www.securitytaskforce.eu

Please contact:
James Clarke
SecurIST contact point
Waterford Institute of Technology,
Telecommunications Software
and Systems Group, Ireland
E-mail: jclarke@tssg.org

CSCLP 2007:
Annual ERCIM Workshop on Constraint Solving and Constraint Logic Programming

Rocquencourt, France, 7-8 June 2007

This workshop is organized as the 12th meeting of the ERCIM Working Group on Constraints, co-ordinated by Francois Fages. The workshop is co-located with the French speaking days on Constraint Programming JFPC'07

The workshop will cover all aspects of constraint and logic programming, including foundational issues, implementation techniques, new applications as well as teaching issues. Particular emphasis is on assessing the current state of the art and identifying future directions. We would like to invite authors to submit papers on all aspects of research on constraint and logic programming. Standard research papers, position papers and work-in-progress papers describing current projects are all welcome.

The proceedings of the workshop will be available online. A printed volume of the workshop papers will be given to the participants, free of charge. The workshop is open to all free of charge.

Some limited scholarships may also be available to help students with travel expenses.

More information:
http://contraintes.inria.fr/CSCLP07/

Third International ERCIM Symposium on Software Evolution

Paris, 5 October 2007

The ERCIM Working Group on Software Evolution will organise its third international meeting on Friday 5 October 2007. It will be co-located with the International IEEE Conference on Software Maintenance (ICSM) in Paris, France. The main organisers are Tom Mens and Kim Mens (members of FNRS, Belgium) and Maja D'Hondt (ERCIM fellow and member of INRIA, France).

The aim of the symposium is to gather people from academia and industry to identify and discuss recent advancements and emerging trends in the state-of-the-art in research and prac-

tice in software evolution. Tentative workshop topics include, but are not limited to: application areas of software evolution, software evolution in different development paradigms, technical aspects of software evolution, dynamic adaptation and reconfiguration, software quality improvement, empirical studies of software evolution, evolution of open source software, industrial experience, managerial aspects of software evolution, software process improvement.

Participation to the workshop will be based on the submission of a technical paper or a proposal for tool demonstration (submission deadline: 25 June 2007). Contributions can either be fundamental in nature (eg what are the laws governing software evolution), or can be pragmatic (eg how can we provide evolution support through formalisms, languages, techniques and tools that scale up to industrial-size software applications; what are industrial best practices with reference to software evolution). They can be either narrow or broad in scope, and can be addressed at a short, medium or long term.

All submissions will be subject to peer-review by an international programme committee of experts in the field. Based on this review, authors will be selected for a presentation or demonstration during the workshop. Submitted papers that are of sufficient scientific quality will be published in the Electronic Communications of the EASST, a peer-reviewed scientific open access journal (ISSN 1863-2122).

More information:
http://www.planet-evolution.org/events/evol2007.html
http://w3.umh.ac.be/evol
http://icsm07.ai.univ-paris8.fr/

FMISC 2007 - 12th International Workshop on Formal Methods for Industrial Critical Systems

Berlin, 1-2 July 2007

The aim of the ERCIM FMICS workshop series, which is celebrating its tenth issue, is to provide a forum for researchers who are interested in the development and application of formal methods in industry. In particular, these workshops are intended to bring together scientists and practitioners who are active in the area of formal methods and interested in exchanging their experiences in the industrial usage of these methods. These workshops also strive to promote research and development for the improvement of formal methods and tools for industrial applications.

Topics include, but are not restricted to:
• design, specification, code generation and testing with formal methods
• verification and validation of complex, distributed, real-time systems and embedded systems

- verification and validation methods that aim at circumventing shortcomings of existing methods in respect to their industrial applicability.
- tools for the design and development of formal descriptions
- case studies and project reports on formal methods related projects with industrial participation (eg safety critical systems, mobile systems, object-based distributed systems)
- application of formal methods in standardization and industrial forums.

Workshop proceedings will be available during the workshop. Additional post-workshop proceedings will be published by Springer Verlag in the Lecture Notes in Computer Science series. Revised versions of selected papers will be invited for a special section of Springer's International Journal on Software Tools for Technology Transfer STTT (http://sttt.cs.uni-dortmund.de). The European Association of Software Science and Technology is offering an award to the best FMICS paper.

More information:
http://fmics07.lcc.uma.es/

CoreGRID Symposium

Rennes, France, 27-28 August 2007

The CoreGRID Symposium aims at being the premiere European event on Grid Computing for the dissemination of the results from European and member states initiatives as well as other international projects in Grid research and technologies. The symposium is organized jointly with the Euro-Par 2007 conference. The CoreGRID Symposium will focus on all aspects of Grid computing including service infrastructures and as such will bring together participants from Research and Industry.

The topics include: Applications; Agent-mediated approaches and peer-to-peer technologies; Dynamic composition and orchestration of ubiquitous Grid services; Experimental testbeds; Grid Portals; Grid Services; Grids and Pervasive Computing; Grid Information Systems/Services; Industrial and Business Applications of Grid technologies; Knowledge and data management; Network-centric Grid operating systems; Problem solving environments; Programming models; Resource brokering, management and scheduling; Resource Virtualization; Scalability Issues; Semantic Grid; Service Oriented Architectures; System architectures and middleware systems; Tools; Trust & Security; Validation and take-up of Grid environments and tools

The symposium is organised by the CoreGRID Network of Excellence. It aims at strengthening and advancing scientific and technological excellence in the area of Grid and Peer-to-Peer technologies. CoreGRID is managed by ERCIM.

More information:
http://europar2007.irisa.fr/CoreGRID-symposium.php

Joint DELOS-NSDL Summer School

Digital Libraries for the Digital Librarian
Making the Journey from Traditional to Digital Libraries

Florence, May 28 - June 1, 2007

The DELOS Network of Excellence and the US National Science Digital Library (NSDL) have joined forces in organizing a Summer School addressing some of the common concerns of cultural heritage institutions (such as libraries, archival institutions and museums) as they work together (or should work in the future) with information providers, publishers, publications suppliers to tackle the challenges and opportunities of the digital environment for the knowledge society. The digital medium is radically new for libraries, archives, museums and other information providers and they should undertake a thorough examination of roles and practices in order to address the challenges that this implies. Although there is a continuity of purpose and value of the traditional organisation within these cultural heritage and information institutions, there exists alongside the need of a fundamental re-examination of roles and practices.

The main aim of the School is to provide information professionals who intend to take leadership and responsibilities in the complex world of digital libraries with the knowledge of the technologies and the organizational issues involved in the transition from a traditional organization to a Digital Library, illustrating criteria and methods that exploit the strengths of digital libraries in a socio-economic and interdisciplinary manner.

Distinguished lecturers from Europe and the United States will be addressing the following topics, from three perspectives: the end user, the technologist and the administrator:
- introduction to digital library
- digitizing information
- Digital collections
- organizing the digital library
- describing information
- accessing the repository
- making the library work for users

The school programme also includes a visit to two cultural institutions in Florence with significant digital collections, where the school participants will have the opportunity to experiment with these digital libraries and to listen to the experience of the institutions in setting them up. During the week the participants will also participate in work groups to complete a short assignment about design, implementation and management of a small digital library.

The School will be held at Villa Morghen, in Settignano, on the hills overlooking Florence.

More information:
http://www.delos.info/school-journey

Euro Legal

News digest about the legal information related to Information Technology from European Commission and the development of e-passport in the UK.

The European Commission published the long-awaited Communication from the Commission on the follow-up of the Work Program for better implementation of the Data Protection Directive. The Data Protection Directive set a milestone in the history of the protection of personal data as a fundamental right. Pursuant to Article 33 of the directive, the report concluded there are no legislative revisions needed, though considerable improvements need to be done for the implementation of the directive. Based on the Work Programme for better implementation of the Data Protection Directive, this communication begins with introducing the ten action areas the first report work has been carried out in. Then it went on to assess the present situations of the implementation of the directive. Finally the commission outlines the prospects for the future with policy recommendations.

UK: the Government is considering Proposals to fingerprint children aged 11 to 15 as part of new passport and ID card. From 2008 children aged 16 and over will have to have their fingerprints taken to get the e-passport. In the EU the UK government has argued that children of 5 years of age and above should be fingerprinted for visas as should the children of resident third country nationals. Both the Conservative and Liberal Democrat parties called the idea "sinister". Campaigners have long battled fingerprinting of children in schools. It has been urged that the schools should get parental consent before taking biometric data. Because biometric data has been considered as personal information, and be quite sensitive especially when considering its close link to individuals and its potential to disclose health information. The use of biometric information has raised much privacy concern.

EU: European Court of Justice rejects Sison appeal against denial of access to EU documents (Judgment in case C-266/05 P, 1.2.07). The case concerned the interpretation of the Regulation 1049/2001/EC on public access to EU documents - not the substantive issue of whether Sison should be included in the EU's terrorist list. The European Court of Justice has rejected Professor Jose Maria Sison's appeal against the EU Council's decision to refuse access to the documents putting him in the so-called terrorist list and imposing on him punitive sanctions. By accusing him of terrorism without showing him the so called "sensitive" terrorism list which was used as evidence against him, Prof. Sison claimed that his rights to the presumption of innocence, to due process and to defense continue to be violated. However, Prof. Sison will continue to be protected by the European Convention on Human Rights, especially by its Article 3 which prohibits his forcible transfer to any country where he is at risk of torture, degrading or inhuman treatment or punishment.

By Yue Liu, NRCCL, Oslo, Norway

Warsaw University wins 2007 ACM Programming Contest

A team from Warsaw University won the 31st annual World Finals of the ACM International Collegiate Programming Contest, sponsored by IBM and held at IBM Tokyo Research Lab on 12-16 March 2007.

Photo: Jillian Murphy

Warsaw University - The 2007 world champions in programming.

There were 6,099 teams on six continents in regional contests and 88 teams qualified for the finals. 20 teams were from Europa, 25 from North America, two from Africa/Middle East, 10 from Latin America, and 31 from Asia/South Pacific. The teams were challenged to solve ten highly complex, real-world programming problems - a semester's worth of curriculum - under a grueling five-hour deadline. Warsaw University solved 8 problem sets, in second place was Tsinghua University with 7 solved, the rest solved 6 or less. A Warsaw Universty team won this prestigious world-wide programming champtionship for the second time after 2003.
http://icpc.baylor.edu/icpc/

VTT - Technical Research Centre of Finland joins the OSGi Alliance

The Open Services Gateway Initiative (OSGi) Alliance is a worldwide consortium of ICT companies and research organizations that advances a process to assure interoperability of applications and services based on its component integration platform OSGi. OSGi technology is universal middleware that provides a service-oriented, component-based environment for developers and offers standardized ways to manage the software life cycle. The OSGi specifications define a service oriented architecture (SOA) for networked systems. This architecture significantly reduces the overall complexity of building, maintaining and deploying applications.
http://www.osgi.org/

New Finnish Member on ERCIM's Board of Directors

Tatu Koljonen has followed Seppo Linnainmaa as Finlands's representative on ERCIM's Board of Directors. Tatu Koljonen acts as Vice President, Strategic Research, Information and Communication Technologies at VTT-Technical Research Centre of Finland.

Tatu Koljonen.

CCLRC and PPARC form new Research Council

As of 1 April 2007 CCLRC the ERCIM member organisation in the UK, merged with PPARC (Particle Physics and Astronomy Research Council), bringing together the science and technology for large facilities (including IT) in a new Research Council named STFC: Science and Technology Facilities Council. The role of PPARC has been dominantly funding research grants in particle physics and astronomy but also managing the UK contributions and access to CERN and various astronomical observatories. In addition PPARC has funded CCLRC for some of these activities. The detailed management structure of STFC is under discussion currently. Legal work is underway to transfer the official ERCIM membership of CCLRC to the new organisation.
http://www.scitech.ac.uk/

Agreement on French-German Cooperation in Computer Science

An agreement on French-German cooperation in computer science was signed in Nancy on 7 February 2007. The signing ceremony was marked with a one-day scientific seminar at which scientists from the institutes involved presented current research results. This cooperation agreement will allow scientists of the respective institutes to pursue and intensify their cooperations by proposing joint research activities and by exchanging researchers and students. Moreover, it aims at promoting joint proposals for European research programs. Thus the greater border region, including Luxemburg and the regions of Wallonia, the Saar, and Lorraine has the potential of becoming a region of excellence in computer science.

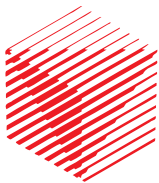*Participants of the signing ceremony.*

The German partners are:
- German Research Center for Artificial Intelligence (DFKI)
- Fraunhofer Institute for Experimental Software Engineering (IESE)
- Max Planck Institut für Informatik
- Max Planck Institut für Software-Systeme
- University of Kaiserslautern
- Saarland University, Saarbrücken.

And on the French side:
- Centre National de Recherche Scientifique
- INRIA
- Institut National Polytechnique de Lorraine
- Université Henri Poincaré Nancy 1
- Université Nancy 2
- Université Paul Verlaine de Metz.

http://www.loria.fr/news/bloc1/a-la-une/signature_franco_allemande/

ERCIM – The European Research Consortium for Informatics and Mathematics is an organisation dedicated to the advancement of European research and development, in information technology and applied mathematics. Its national member institutions aim to foster collaborative work within the European research community and to increase co-operation with European industry.

W3C **ERCIM is the European Host of the World Wide Web Consortium.**

AARIT
Austrian Association for Research in IT
c/o Österreichische Computer Gesellschaft
Wollzeile 1-3, A-1010 Wien, Austria
Tel: +43 1 512 02 35 0, Fax: +43 1 512 02 35 9
http://www.aarit.at/

Consiglio Nazionale delle Ricerche, ISTI-CNR
Area della Ricerca CNR di Pisa,
Via G. Moruzzi 1, 56124 Pisa, Italy
Tel: +39 050 315 2878, Fax: +39 050 315 2810
http://www.isti.cnr.it/

Czech Research Consortium
for Informatics and Mathematics
FI MU, Botanicka 68a, CZ-602 00 Brno, Czech Republic
Tel: +420 2 688 4669, Fax: +420 2 688 4903
http://www.utia.cas.cz/CRCIM/home.html

Centrum voor Wiskunde en Informatica
Kruislaan 413, NL-1098 SJ Amsterdam,
The Netherlands
Tel: +31 20 592 9333, Fax: +31 20 592 4199
http://www.cwi.nl/

Fonds National de la Recherche
6, rue Antoine de Saint-Exupéry, B.P. 1777
L-1017 Luxembourg-Kirchberg
Tel: +352 26 19 25-1, Fax +352 26 1925 35
http://www.fnr.lu/

FWO
Egmontstraat 5
B-1000 Brussels, Belgium
Tel: +32 2 512.9110
http://www.fwo.be/

FNRS
rue d'Egmont 5
B-1000 Brussels, Belgium
Tel: +32 2 504 92 11
http://www.fnrs.be/

Foundation for Research and Technology – Hellas
Institute of Computer Science
P.O. Box 1385, GR-71110 Heraklion, Crete, Greece
Tel: +30 2810 39 16 00, Fax: +30 2810 39 16 01
http://www.ics.forth.gr/

Fraunhofer ICT Alliance
Friedrichstr. 60
10117 Berlin, Germany
Tel: +49 30 726 15 66 0, Fax: +49 30 726 15 66 19
http://www.iuk.fraunhofer.de/

Institut National de Recherche en Informatique
et en Automatique
B.P. 105, F-78153 Le Chesnay, France
Tel: +33 1 3963 5511, Fax: +33 1 3963 5330
http://www.inria.fr/

Irish Universities Association
c/o School of Computing, Dublin City University
Glasnevin, Dublin 9, Ireland
Tel: +3531 7005636, Fax: +3531 7005442
http://ercim.computing.dcu.ie/

Norwegian University of Science and Technology
Faculty of Information Technology, Mathematics and Electrical Engineering, N 7491 Trondheim, Norway
Tel: +47 73 59 80 35, Fax: +47 73 59 36 28
http://www.ntnu.no/

Universitas Varsoviensis
PLERCIM
Universitas Wratislaviensis
Polish Research Consortium for Informatics and Mathematics
Wydział Matematyki, Informatyki i Mechaniki
Uniwersytetu Warszawskiego
ul. Banacha 2, 02-097 Warszawa, Poland
http://www.plercim.pl/

Science and Technology Facilities Council,
Rutherford Appleton Laboratory
Chilton, Didcot, Oxfordshire OX11 0QX, United Kingdom
Tel: +44 1235 82 1900, Fax: +44 1235 44 5385
http://www.scitech.ac.uk/

Spanish Research Consortium for Informatics
and Mathematics c/o Esperanza Marcos, Rey Juan Carlos University,
C/ Tulipan s/n, 28933-Móstoles, Madrid, Spain,
Tel: +34 91 664 74 91, Fax: 34 91 664 74 90
http://www.sparcim.org/

Swedish Institute of Computer Science
Box 1263,
SE-164 29 Kista, Sweden
Tel: +46 8 633 1500, Fax: +46 8 751 72 30
http://www.sics.se/

Swiss Association for Research in Information Technology
c/o Professor Daniel Thalmann, EPFL-VRlab,
CH-1015 Lausanne, Switzerland
Tel +41 21 693 5214, Fax +41 21 693 5328
http://www.sarit.ch/

Magyar Tudományos Akadémia
Számítástechnikai és Automatizálási Kutató Intézet
P.O. Box 63, H-1518 Budapest, Hungary
Tel: +36 1 279 6000, Fax: + 36 1 466 7503
http://www.sztaki.hu/

Technical Research Centre of Finland
PO Box 1000
FIN-02044 VTT, Finland
Tel:+358 207226041, Fax :+207226027
http://www.vtt.fi/