ERASysAPP Networking workshops

in systems biology

"Networking of research centres"

Belval, Luxembourg 07-08 October 2015

Organizers: ERASysAPP – ERA-net for Systems Biology Applications (**http://www.erasysapp.eu/**)

Location: Maison du Savoir, 2, avenue de l'Université, L-4365 Esch-sur-Alzette Luxembourg

ERASysApp

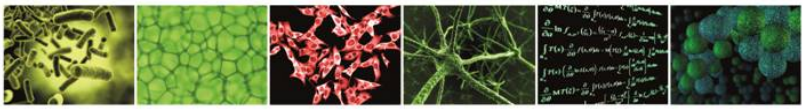
The full title of the ERASysApp (www.erasysapp.eu) project is "Systems Biology Applications – ERASysApp" (app = application, referring to translational systems biology). The project aims to promote multidimensional and complementary European systems biology projects, programmes, and research initiatives with a particular focus on applications. In other words, it aims to stimulate "translational systems biology" research approaches (application-oriented and/or industry-relevant).

Taking past successful developments and achievements into account, ERASysApp continues and builds on work that has been performed by the previously funded successful ERANET on Systems Biology, ERASysBio and its spin-offs ERASysBio+, SysMO and SysMO2 (www.erasysbio.net). This is advantageous, since it allows for the efficient use of past experiences and tangible results of ERASysBio and will guarantee maximal synergism. Apart from setting up joint transnational calls and giving impulses to industry for applying more Systems Biology approaches, ERASysApp focuses on so-called horizontal topics such as improved data management and data sharing, training and networking with national, transnational, and SB initiatives inside and outside the European Research Area (ERA).

Aim of the event

The purpose of the workshop "networking research centres" is to establish networks of research centres, but also to design new and improved formats for such links.

The workshop "Networking of research centres" concentrated on **model systems** and **collaboration mechanisms**.



Outcome and Findings

Workshop Conclusions: Model Systems

Status of model systems

With the breath of Model Systems at disposal each researcher will be faced with a choice of model systems when trying to tackle a specific research question. It is therefore paramount that one develops a clear set of criteria to select a suitable system. Depending on the question, i.e. what we want to know and what we want to do with the model, one will have to test the feasibility of using a specific model and ascertain if the chosen organism that can help understand the problem. Whether we need new model organisms and need to things differently from previous approaches will need to be analysed. There should also be a degree of model driven experimental design.

The members of the workshop felt that talking about *Model Systems* is a little outmoded, dating from a time where it is was harder to generate data and researchers had to concentrate on few organisms. Now the situation has become easier and more models are being established. Currently there is actually a wealth of model systems and the future outlook is so that developing any new model addressing a specific need is possible using new approaches and technologies. Existing models essentially fall into two main categories with the classical real life organisms on the one hand and the computational models on the other hand, where the latter are increasingly coupled to the former.

The classical types of biological models (from 'simple' organisms to human) model systems have been around for a while:

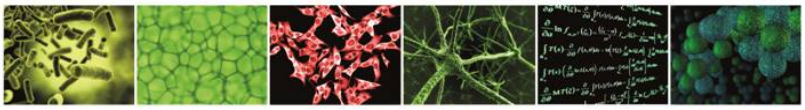
- Bacteria (*E. coli, Lactobacillus*)
- Yeast
- Plant metabolism, virtual leaf, stress and draught models
- Organ and disease driven modeling – mouse and human
- iPS cell derived cell models/organoids

Computational models are increasingly developed, attempting to represent and produce useful data integration from biological models.

Sophisticated experimental models combining cell based models in new environmentally controlled devices such as microfluidics are now coming to the fore.

Recommendation:

- Define the challenges (context-dependent *etc*) and criteria/decision algorithms/guidelines for decision-making in order to be able to decide which model systems are needed for what and why.
- Implement (stepwise) multi-scale model development and validation to get the project started initially and to build momentum.



Multi-Scale Models

There is a clear and particular need to further develop models that bridge the scales (time, space, conservation of regulatory element between organisms) and that foresee the integration with imaging and work on the single cell level. Multi-scale integration are becoming more important and while a few have been around for a while (e.g. 'Noble's heart') others have been developed over recent years (HepatoSys, Virtual Liver, LISYM) and some have found use in the Pharma industry (whole body pharmacokinetics), marking the new trend in medical field for *in silico* clinical trials. The latter is a good example of predictive models which have helped engage the Pharma Industry and more precompetitive collaboration (including - academics!) should be fostered to achieve similar results elsewhere.

Further good examples are needed however to convince industry and academia of the usefulness of such model systems. It is therefore paramount to identify successful implementations of model systems by analysing the outcomes of the projects financed in the frame of the current ERA-Net and previous related initiatives.

The identification of success stories is somewhat difficult as the funding duration is often deemed insufficient to perform a full iteration from generating experimental dataset to the integration into computational model for simulating, and the further experimental work for validation and refinement of the model. An analysis of how long such iteration takes should be performed for various experimental models and the funding timeframe adopted appropriately.

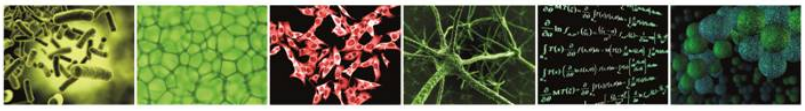
In addition, we are lacking valid mathematical frameworks for multi-scale modeling, that enable scaling and further conceptual research on multi-scale integration is needed. Particular the problem of Interfacing between scales the multi-level integration of the different 'omics' level is still a major problem.

Regarding the interfacing elements between scales it seems that people from other disciplines (e.g. engineering) could bring in new insight and the communication between various research communities need to be stimulated.

An additional need is the development of the ability to transfer or translate the findings and models between organisms (e.g. build on the conservation of regulatory genes). Enabling comparability and interoperability of models within organism and between organisms should therefore be targeted.

Recommendation:

- Define challenges for translational research and corresponding multi-scale models and develop mathematical frameworks for multi-scale models.
- Foster projects to focus on addressing specific interfaces of scales and encourage the interaction of researchers from wide ranging disciplines to address this issue.
- Perform analysis of ERASysapp/SysBio/SysBio+ projects and their achievements to identify 'success stories' and to determine the life cycle of one 'systems biology' iteration.
- Adapt funding timeframe to iteration life cycle



Data Requirement and Standards

In order to build robust models we clearly need high quality experimental data in order to overcome the problems arising from improper experimental design such as missing parameters and values and noise. The enhanced collection and availability of data from human patients (incl. patient history, guiding sampling, cross-hospital protocol, SOs) is needed and should be prioritised while giving the necessary ethical consideration evidently. Generating data for all sorts of scenarios might become unfeasible and a prioritization is needed.

In general, data availability and sharing needs to be stimulated and a change of habits needs to be brought about. Funding agencies and publishers have a role to play by making sure that data is made available by researchers by imposing the necessary requirements and creating incentives particularly in community-driven resources (guidelines of how to generate and to upload need to be made available and pressure applied to follow them in order to publish or to get funding).

However the appropriate handling, labelling and storage of data need to be advocated also in the research labs directly by the principle investigator. This is part of promoting specific academic training in Systems Biology.

Evidently, the simple fact of making data available (e.g. in an Excel sheet) is not sufficient and the adherence to agreed standards should be imposed as well as the relevant documentation and metadata should be provided (e.g. classification of samples, harmonisation/standardisation of values etc). In general the FAIR principles should be implemented making sure that data, operating procedures and models are Findable, Accessible, Interoperable and Reusable (FAIR) fostering thus the free access to data and model tools. The building of reference data and models was also advocated.

The workshop participants noted however that many initiatives on data generation and quality have been started but much has still to be done in the terms of harmonising the various initiatives on standardisation.

Recommendation:

- Develop reward mechanisms for the dissemination of data and models as a complement to the requirements set by Funders and Publishers.
- Encourage the implementation of FAIR principles (through Funders and Publishers)
- Educate students and (early career) researchers in proper data handling and storage and implement these standards in the labs.
- The benchmarking and validation of models and standards by experimentalist and computational groups.

Role of Systems Biology Centres

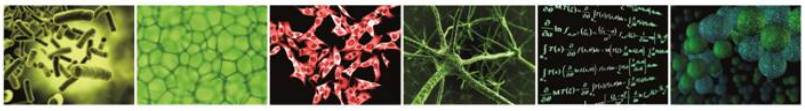
Research centres are seen as specialized hubs or specific focus points (Centers of Excellence) for certain model systems and incubators for cross-community communication. They therefore have a role to play by providing targeted expertise and producing large high quality data sets following

standards. To fulfill this role optimised interaction between wet/dry labs and good dissemination efforts are a base requirement. One of their main missions is also to provide training and education.

However the workshop participants felt that visible international collaborations and interaction remain rare. The centres will need to show more openness towards other centers and the sharing of curated data and models. Initiative such as ISBE (see next chapter) seek to address some of these challenges.

Recommendation:

- Provide further incentives to harmonize and integrate models across centers provide a (virtual) platform for inter-center modelling (see also role of ISBE decribed in next chapter).
- Foster more cross discipline interactions through the organization of workshop, think tanks or bootcamps (see also role of ISBE in next chapter).
- Address IP and legal aspect (esp. in human) that hamper collaborations.



Conclusion on Workshop Conclusion: Collaboration Between Centers of Systems Biology

Current barriers to intensive collaboration between various Systems Biology Centres in Europe

The workshop participants agree that there is essentially no technological barrier to the collaboration between centres but they recognise that in general communication is complex in this very diverse community of communities. The jargon used by biologists is different to that of researchers from an engineering or mathematics background to the extent that education and training to enhance communication is deemed necessary. One stark example of the communication failure between different communities is the often improper cost estimation of the respective contribution of the other partner in interdisciplinary collaborations. Some workshop participants also suggested getting other sciences such as communication scientists involved in the interchanges.

It is important not to dwell too much on the differences between sub-communities however but to identify common ground and similar questions asked by the various actors in the field of systems biology. It would therefore be helpful to have community platforms (e.g. a “Facebook” for systems biologists) which would allow various communities (such as groups working on different scales) to become aware about ongoing initiatives and existing expertise elsewhere. This would provide a “roof” to stimulate interaction between different communities.

The participants of the workshop caution however creating a new platform from scratch but to make use of existing mechanisms (LinkedIn, Researchgate, etc…). In any case it will need to take someone to take the responsibility, develop a well-thought strategy and identify the potential benefits which will motivate people to use the platform.

As already stated in the previous breakout session, the lack of annotated and structured data and the sluggish acceptance of existing community standards is hampering collaborations.

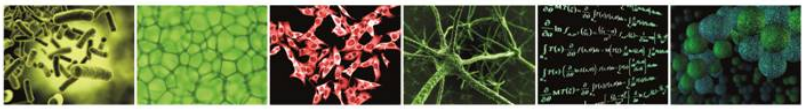
Support by European Infrastructures

The workshop provided the opportunity for the presentation of several initiatives that support collaborations in Systems Biology:

ISBE (project.isbe.eu)

ISBE is a European initiative currently at the end of its preparative phase towards establishing itself as a Europe-wide infrastructure for Systems biology. It aims to interconnect national systems biology centres and make their collective expertise, resources and services easily accessible for all European researchers. The idea is that scientists can easily gain access to various resources and obtain services for model building and model-based systems analysis data drawing on state-of-the-art facilities, data, models, tools.

The national centres in the ISBE network will serve as a first stop shop for interested researchers which will guide them toward the appropriate service provider that can best address the need expressed by the research group.



Further missions of ISBE will be to facilitate state-of-the-art training and to push through FAIRDOM (see below) the development and uptake of standards for biological data, tools and models as well as operating procedures, ensuring that data and models across different laboratories, countries and sectors become combinable and re-usable.

FAIRDOM (fair-dom.org)

FAIRDOM is a joint action of ERA-Net ERASysAPP and European Research Infrastructure ISBE to establish a data and model management service facility for Systems Biology. Its prime mission is to support researchers, students, trainers, funders and publishers by enabling Systems Biology projects to make their Data, Operating procedures and Models, Findable, Accessible, Interoperable and Reusable (FAIR).

FAIRDOM builds on the outcomes of the successful SysMO-DB and SyBIT data management projects, and units their toolset to manage data, models and projects on an open platform which is made available to the research community.

In addition it centrally hosts the public FAIRDOMHub - a "Systems Biology Community Commons" – which functions as a resource for shared and published data, models and methods.

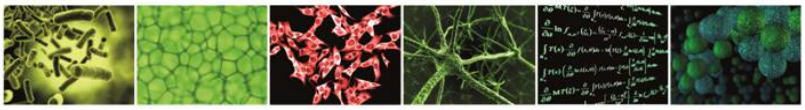
Furthermore it sees itself as a facility of support services for curation, training, and data management planning for the EraSysAPP projects, running workshops and summer schools, and developing a library of standard templates for data, model and SOP management.

EMBL-EBI (European Bioinformatics Institute, www.ebi.ac.uk)

The EBI provides the world's most comprehensive range of freely available and up-to-date molecular databases. The databases are developed through collaborative effort of a worldwide network of scientists and the services provided by EBI allows researchers to share data, perform complex queries and analyse the results in various ways. The guiding principles of the EBI's service provision are that:

- the data and tools are made **open** and freely available,
- the data is **compatible** through the adherence to bioinformatics standards
- the EMBL-EBI resources are **comprehensive** and up to date
- all of the data and most of the software systems are **portable** and can be downloaded and installed locally
- the databases are of **high quality** and enhanced through annotation subjected to rigorous quality control.

In addition EBI acts as a centre providing advanced bioinformatics training to scientists at all levels, from PhD students to independent investigators.



ELIXIR (www.elixir-europe.org)

ELIXIR is a pan-European distributed research infrastructure for life-science information connecting national bioinformatics centres and EMBL-EBI with the aim to support life science research and its translation to medicine, agriculture, bioindustries and society.

ELIXIR unites over 100 of Europe's leading life science organisations in managing and safeguarding the massive amounts of data being generated every day by publicly funded research. The central Hub is funded jointly by ELIXIR member states and the European Commission. The collaboration between the central hub and the nationally funded Nodes are regulated via collaboration agreements.

ELIXIR will provide the facilities necessary for life science researchers - from bench biologists to bioinformaticians - to make the most of our rapidly growing store of information about living systems, which is the foundation on which our understanding of life is built.

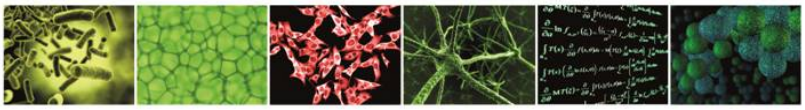
All 4 infrastructures (ISBE, FAIRDOM, EMBLEBI, ELIXIR) provide platforms for data exchange and help address some of the barriers highlighted previously such as applying standards in data management and the training of researchers in the relevant skills (data management, modelling, …). Furthermore that hub and spokes models of ISBE and ELIXIR provides researchers with contact points on the national level which in turn can then provide help on the individual level and facilitate outsourcing to appropriate centre of expertise within the whole network.

Support for Collaboration

Funding is of course essential to fuel collaborations and in particular long term collaborations need dedicated financial support. The building up of the appropriate human resources (fixed or long term contract technical staff) is difficult on normal (often 3 year) project grants and the capacities built up through PhDs and postdocs in the labs often are lost after the project end. In addition enhancing the willingness to share results also requires considerable investments so that the data are being made available in the right format which in itself is not a rewarding job for a research lab. Incentives need to be developed to ensure that labs make these kinds of investments.

One example of successful intensive collaboration/networking between research centres is the cross-project collaboration of the Luxembourg Centre of Systems Biomedicine (LCSB) and the Institute for Systems Biology (ISB) in Seattle which receive considerable funding from government of Luxembourg (approx. 150 M€) which allowed for a sustained support for competence sharing and development of projects making use of their complementary expertise. Further good examples of funding opportunities supporting intensive collaboration are the Innovative Medicines Initiative (IMI, www.imi.europa.eu) which brought about close industry involvement which provides 50% funding (of the total €3.6 billion, €1.425 billion is committed to the programme by European Federation of Pharmaceutical Industries and Associations companies and up to €213 million are committed by other life science industries or organisations) and is chiefly involved in the project definition.

The presence of independent leadership (i.e. leaders which do not run one of the labs part of the consortium) was seen as one success factor for large collaborative efforts. Furthermore these



collaborations need a central budget allocated to management and data management as well as specific funding for the large amount of theoretical work which is needed in most of the projects.

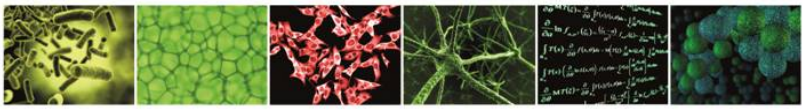
However large project/programme funding is not without criticism and is thought to crowd out smaller seed funding. The need for smaller bottom-up initiative instead of large top-down projects was voiced by the participants of the workshop. Special pilot funding to support small joint initiatives to test out something would be needed also. This could provide the seeding ground for starting up collaborations where currently there are only few initiatives available. Once these collaborations start budding they can seek funding elsewhere (H2020, etc) where they would stand higher chances for funding given the preliminary work achieved together.

The SysMO-DB PALs (Project Area Liaisons) system which foresees modest funding of 5000€ per 'PAL' SysMo (included in project budget) could be regarded as one such low cost success story. The PALs are designated hands-on members of the different SysMO projects who form a user focus group with the aim to facilitate the exchange of new material and experiences within the SysMO and the wider Systems biology community.

The workshop participants felt that more focus needs to be put on the proper project evaluation and monitoring mechanisms post-hoc. There is a feeling that once people have received funding money, the pressure to collaborate decreases and the individual project partners tend to follow their different interests and motivations. Reporting requirements (e.g. for EU funding) often exist but focus on actual performance should be increased. Funding agencies may be reluctant to clearly state however that some of their projects have not performed as expected which may be one of the disincentive for these in depth ex-ante evaluations. It was suggested that the evaluation outcomes should be taken into consideration in future funding decisions or that the part of the project budget should only be provided if the project has managed to achieve a set of criteria that were previously set.

Recommendations

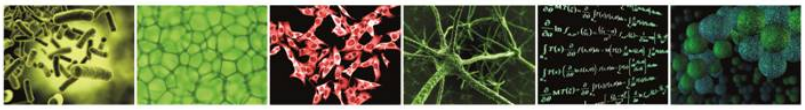
- Build a systems biology community through facilitating exchange and communication between the different sub-communities. Provide appropriate training and a community exchange platform.
- Make use and promote the facilities and services made available by the various European initiatives such as ISBE, FAIRDOM, ELIXIR, EMBL-EBI
- Support collaboration of SB centres on a large scale but also on a small scale by enabling the sharing of facilities, equipment, expertise and exchange of people.
- Enhance ex-post evaluations of funded projects to further stimulate intense collaboration after project approval and avoid project partners 'drifting apart'.



Programme

Workshop "Networking of Research Centres" 07.-08.10.2015.

Day 1: 07.10.2015 / Wednesday		
TIME	**ACTIVITY**	**REMARKS**
12:00 – 13.00	**REGISTRATION & WALKING LUNCH**	**Egils Stalidzans, Frank Glod**
13.00 - 13:15	**WELCOME** Welcome and introduction to ERASysAPP	**Zsuzsanna Nagy**
13.15 - 13:45	**Participants introduction round**	
13.45 - 14:15	**Control systems approaches to uncovering biochemical networks**	**Jorge Goncalves**, Luxembourg Centre for Systems Biomedicine
14.15 - 14:45	**Systems biology approach to study ageing and rejuvenation in the yeast Saccharomyces cerevisiae**	**Marija Cvijovic**, University of Gothenburg
14.45 - 15:15	**Coffee break in POSTER HALL**	
15.15 - 15:30	**Instructions for work in groups on Model systems**	
15.45 - 16:45	**Work in groups on Model systems**	Participants are split in **4 groups**
16:45 - 17:30	**Group reports on Model systems**	
Day 2: 08.10.2015. / Thursday		
8.30 - 9:00	**Welcome Coffee break**	
9.00 - 9:30	**Defragmenting research through sharing expertise and making results additive**	**Roel van Driel**, Dutch NCSB programme
9.30 - 10:00	**Addressing Bioinformatics Challenges for Systems Biology: ELIXIR and EMBL-EBI Bioinformatics Research Infrastructure Provision**	**Rolf Apweiler**, joint associate Director of EMBL-EBI
10.00 10:30	**Work in groups on Collaboration mechanisms**	Participants are split in **4 groups**



10.30 - 11:00	**Coffee break**	
11.00 - 11:45	**Work in groups on Collaboration mechanisms**	Participants are split in **4 groups**
11:45 - 12:30	**Group reports on Collaboration mechanisms**	
12:30h- 14:00	**WALKING LUNCH - End of workshop for**	**"Networking of research centres"**

Description of the breakout sessions

For each of these sessions, delegates have been distributed in 4 groups. For each of the groups, there will be a chair person who will manage the discussion, and a representative from ERASysApp who will act as assistant to the leader by taking notes throughout the session on a computer with overhead projection or a flip chart.

Each breakout group has the time indicated on the programme to discuss the topics defined for the session. The role of the chair person is to lead the discussion, to ensure that all topics are discussed and that all members of the group participate to the discussion. At the end of the session, the chair person with the help of the assistant will summarize the outcomes of the discussion in one powerpoint slide per discussion point, and present these to the other groups (max 10 minutes). This summary will serve as basis for the writing of the report.

Poster Hall sessions

All participating institutions are invited to display a poster identifying its activities. Posters' sessions are scheduled around 15:00 on the first and second days of the workshops (Oct. 7 & 8). This should allow for better identification and networking opportunities during the breaks.

ERASysAPP Organising Committee

Egils Stalidzans (Latvian Academy of Sciences, Latvia)

Frank Glod (National Research Fund, Luxembourg)

Petra Schulte (Project Management Organisation Jülich, Germany)

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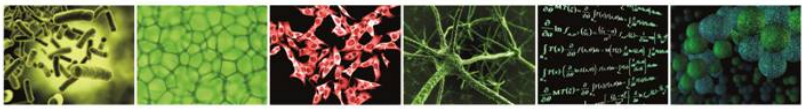
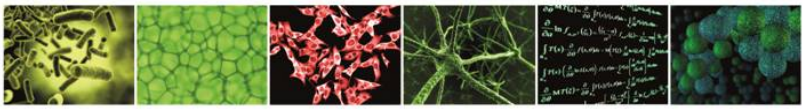


Participants of the ERASysAPP workshop "Networking Research Centers"

First Name	Last Name:	Institution:	Country:
Rolf	Apweiler	EMBL-EBI	UK
Francisco	Azuaje	Luxembourg Institute of Health (LIH)	Luxembourg
Anne	Boeter	ZonMw	Netherlands
Marija	Cvijovic	University of Gothenburg	Sweden
Thomas	Dentzer	Luxinnovation	Luxembourg
Rob	Diemel	ZonMw	Netherlands
Margarida	Gama-Carvalho	BioISI - Institute for Biosystems and Integrative Sciences	Portugal
Frank	GLOD	National Research Fund LUXEMBOURG	Luxembourg
Martin	Golebiewski	HITS gGmbH	Germany
Jorge	Goncalves	LCSB, University of Luxembourg	Luxembourg
Artemis	Hatzigeorgiou	Hellenic Pasteur Institute	Greece
Heidi	Hess	SystemsX.ch	Switzerland
Susanne	Hollmann	University of Potsdam	Germany
Aare	Ignat	ETAg	Estonia
Uldis	Kalnenieks	University of Latvia	Latvia
Yuri	Kogan	Optimata	Israel
Olga	Krebs	Heidelberg Institute for Theoretical Studies	Germany
Andreas	Kremer	ITTM S.A.	Luxembourg
Sylvia	Krobitsch	Juelich Management	Germany
Carole	Linster	University of Luxembourg	Luxembourg



Vitor	Martins Dos Santos	Wageningen University	The Netherlands
Elsa María	Moreda Sánchez	ISCIII	Spain
K. Zsuzsanna	Nagy	Projektträger Jülich	Germany
Maria Manuela	Nogueira	European Institute for Systems Biology and Medicine	France
Styliani	Petroudi	Research Promotion Foundation	Cyprus
Babette	Regierer	LifeGlimmer GmbH	Germany
Berthold	Rutz	European Patent Office	Germany
Venkata	Satagopam	LCSB, University of Luxembourg	Luxembourg
Thomas	Sauter	University of Luxembourg	Luxembourg
Egils	Stalidzans	Latvian Academy of Sciences	Latvia
Simona	Stoian	UEFISCDI- Romania	Romania
Margit	Suuroja	ETAg	Estonia
Eldad	Taub	Optimata	Israel
Roel	van Driel	University of Amsterdam	The Netherlands
Esther	van Zimmeren	University of Antwerp	The Netherlands
Raivo	Vilu	Tallinn University of Technology	Estonia
Daniel	Vonder Mühll	SystemsX.ch	Switzerland
Viorel	Vulturescu	UEFISCDI	Romania
Paul	Wilmes	University of Luxembourg	Luxembourg
Müller	Wolfgang	HITS	Germany