

# **Report - Scientific Advisory Board Meeting - SystemsX.ch Zurich, December 3-4, 2009**

Fotis Kafatos, Marvin Cassman, Albert Osterhaus and Eugene Butscher  
(affiliations see last page)  
8 December 2009

## **INTRODUCTION:**

### Background

There have been many comments in recent years that biology is at a tipping point. The argument is that the massive increase in understanding of the structure and function of the components of biological systems has led to the possibility of understanding the behavior of complex systems, through the integration of a broad range of knowledge, coupled to computational and modeling approaches. This is the core of SystemsX.ch, and it provides the potential to put Switzerland in the forefront of the new biology of the 21<sup>st</sup> century.

In the 20<sup>th</sup> century biology was driven by chemistry and in the 21<sup>st</sup> it will be driven by mathematics and engineering. It is in this meeting of diverse approaches that the richest yields are to be found. This requires the conjunction of scientists from significantly different disciplines and the concomitant training of young scientists across disciplinary lines. This is a formidable task and one which SystemsX.ch has undertaken.

Indeed, Systems Biology is a scientific revolution of comparable importance to that of molecular biology in a previous era. It marks a major shift from the reductionist phase of Molecular Biology (MB) towards deep understanding of complex systems. During the MB revolution, a small number of institutions paved the way for MB to flourish; primarily Cambridge University and the Institut Pasteur were the pioneers. Similarly there will be other pioneers for Systems Biology. Thus far it seems that these will be the Institute of Systems Biology in Seattle, the Weizmann Institute, Harvard, Stanford, MIT, UCL and SystemsX.ch. It is already a great achievement that Switzerland is one of the leaders of the new scientific revolution. With proper support and persistence, SystemsX.ch could even develop into the top leader in this scientific revolution, and reap the early benefits from it.

We are impressed by the progress you have achieved already. We see more opportunities to consolidate the leadership of CH, by integrating your efforts more deeply, bringing together more intensely Pharma and Academia

facilitating deeper collaborations within CH, but also with other centers (IL, UK) – the collaborative effort with big Pharma that we saw is a very welcome, first important success in this direction.

It is interesting also that in the ERC competitions, CH and IL are the most successful countries per capita; countries that invest, reap success.

PhD program is going well, integrate it more; maybe copy the very successful Example of EMBL's International PhD programme.

## Goals

### *Trans-disciplinary research*

The primary mechanism, that SystemsX.ch uses are the RTDs (Research Technology and Development projects). These are peer-reviewed research projects that require a focus on modeling, particularly of network behavior, for understanding biological properties. The 8 proposals which we heard were with a few exceptions either reasonably close to this goal or were clearly moving toward this outcome. The least mature project was the one dealing with plants. There seemed to be a feeling that broader coverage of biology was needed but this is neither necessary, nor useful at this stage. It is much more important to focus on scientifically important and tractable problems.

The distribution of disciplines in the SystemsX.ch programs shows about 51% in biology and smaller percentages of a number of different fields, with about 30% in quantitative disciplines. This is actually quite a good percentage and SystemsX.ch is to be commended for this balance and vision.

The RTDs cover a large range of scientific areas, with the noticeable absence of the medical sciences. Given the strength of medicine in Switzerland, this continued gap is puzzling. Some effort should be made to remedy this gap.

One consistent and appropriate focus is in the development of tools for quantitative measurements. This is a key issue that relates to the switch from single gene to network approaches and is certainly important. The tools that emerge should have value beyond the individual programs within which they were developed.

Interdisciplinary Pilot Project (IPP) is an extremely useful program. Its value increases if there is an effort to ensure that truly “risky” programs are supported.

In this context risky usually means good ideas without much, or any, preliminary data.

Finally, it is worth thinking about making connections with groups outside Switzerland that have resources that can complement or add to SystemsX.ch (*Microsoft at Trento?*).

### Education

Educational programs are a key component of any new effort and SystemsX.ch appears to have done a good job. The students were all positive about their experiences. There are still some problems, however. The one of most concern to the students seems to be the uncertainty about their ability to get credit for courses taken outside their own institutions. It needs to be determined just how much of a problem this is, but clearly SystemsX.ch should work across individual institutions.

More critically, the apparent limitation of the PhD program to 3 (or 4) years can be a difficulty. After all, students are being asked to become conversant with, at least, two disciplines. This inevitably takes time. This limitation needs to be examined. Interdisciplinary PhD (IPhD) is a valuable program and shouldn't be unnecessarily constrained.

### Industry

Interacting with industry will be difficult until the utility of systems biology for product development becomes more evident. The best way is to have frequent informal interactions of Pharma and SystemsX.ch and allow partnerships to evolve. It is best to allow these collaborations to start without any direct request for funding from industry, even if this means a small contribution by SystemsX.ch. Since single gene defect approaches, even on a genomic scale, are starting to hit a wall, the interest of Pharma will surely mount.

## **CONCLUSION:**

SystemsX.ch is as good as any international systems biology programs, and better than most.

**COMMENTS BY INDIVIDUAL ADVISORY BOARD MEMBERS:****Member (a)**

The overall impression of the Scientific Advisory Board (SAB) about the efforts of the consortium in establishing the Swiss Initiative in Systems Biology is that over the past period major progress has been made in constructing the SystemsX.ch and that the program is already well on its way. The current RTD investigators have indeed bought into this ambitious concept well.

It is worth remembering that:

- Switzerland is a nimble, innovative country;
- Investment in cutting edge and basic science is a successful Swiss tradition;
- Transition from Swiss watches to micro-info systems;
- The more fundamental the discovery, the more powerful it is;
- Systems Biology is the successor of Molecular Biology in a new era.

Regarding the involvement of the Swiss private sector in the SystemsX.ch initiative it was noted that indeed a successful start has been made to get industrial partners on board by having them participate in public- private-partnerships. It was suggested to have the private sector even more actively involved by stimulation of interactions through informal scientific contacts, exchanges of ideas, organization of joint symposia, industry partner clubs etc. This will further stimulate a mutual understanding between the two sectors which will eventually also stimulate the initiation of new collaborations in the field of Systems Biology. This should then benefit from the mutual funding by the SystemsX.ch initiative on the one hand and industry on the other. Both well established companies and SMEs could be involved in such efforts. The establishment of dual positions of industry scientists as e.g. associate professors in university settings where Systems Biology is being carried out in the framework of SystemsX.ch should be seriously considered to further increase such collaborative efforts, which should not be limited to the IPhD or postdoc levels, but preferably involve a continuum from basic training at the bachelor and master levels to the PhD and postdoc positions. In this way not only a useful “fishing pond” of talented scientists would be created for industry in Switzerland, but also a readily accessible outlet for scientific ideas that may make it to the market place. In this light it is important to realize that given the high standard of research in academic medical centers in Switzerland and in order to fully profit from the achievements made in the initiative, it now seems to be the time to encourage the establishment of a more tailor made program that would allow the extension of SystemsX.ch interdisciplinary project

portfolio into the high quality areas of medical research in Switzerland. Specific efforts in this direction by the SystemsX.ch initiative could include targeted calls for proposals and awareness raising activities towards the medical faculties involved in master and PhD programs for MD students and MDs.

One of the major achievements of the SystemsX.ch initiative has been the establishment of a tailor made education system for so-called IPhD students. Since PhD programs are the primary responsibility of the affiliated universities of these students all activities of the SystemsX.ch PhD program are additional. It should be noted that also regular RTD students are eligible to these additional activities. Especially the implementation of the principle of having two mentors from two different and unrelated disciplines of the SystemsX.ch initiative is considered both as a challenge and as an asset and seems to be generally well appreciated by the PhD students. This dual mentorship does secure their introduction in the interdisciplinary approach of the Systems Biology projects that are currently ongoing. It was however also noted that the interdisciplinary character of the projects also poses an extra challenge and time constraint to the PhD students. Therefore it is suggested to have the regular program for SystemsX.ch PhD students extended with an additional year, thus allowing them to master the skills needed for interdisciplinary studies in a more balanced way and also award them for the extra efforts with an additional notification on their bull. Several additional suggestions were made to streamline the successful program even more. Besides the specific courses that have already been installed for the SystemsX.ch PhD students, it would be appreciated if more attention would be paid to career planning, IP and patenting issues and the establishment of an alumni system. Furthermore the existing international fellowship program is well appreciated and its further extension should be considered.

### **Member (b)**

**Note:** this member could not attend the SAB meeting in Zurich. The comments below base on the written documentation provided to the SAB members before the meeting, including *questions (repeated in italic)*

First, I would like to emphasize that overall I have been and continue to be impressed with the SystemsX.ch initiative and the programmatic and early scientific progress being made under its auspices. Specific comments and suggestions in response to the issues addressed to the SAB are below.

## Topics and types of SystemsX.ch projects

*1. Cover the currently running RTDs an appropriate range of systems biology? Are there any topics that are obviously missing which should be considered in a continued phase of SystemsX.ch?*

The range of biological systems being investigated is appropriately diverse. Moreover, if the question is directed at biological systems and models, I think the focus should continue to be on funding the best systems biology, not on efforts to expand the range of biological systems further. Another interpretation of ‘range of systems biology’, however, would focus on the diversity of approaches to systems understanding.

Here a continuing effort should be made to expand and enhance modeling availability. The lack of a significant or believable modeling component has been a recurring reason for failure of RTD applications, for example. The SAB and SEB should discuss the need and ask if there are new ways to enhance the Swiss infrastructure (faculty?) involved in modeling and interested in systems biology. A Modeling Program (which could be decentralized) might provide an additional integrative force within SystemsX.ch could help recruit talented mathematicians and computer scientists to systems biology; and might also prove an important factor in maintaining the Swiss systems biology focus after phase II.

We in the SAB, and the review groups, have had much discussion of the need for modeling, but there is no targeted ‘modeling’ support and development component to Systemsx.ch as yet. SyBIT if I understand it is (rightfully) focused on the critical issues of data sharing and utility. And most if not all of the RTD’s and IPP’s are driven by biology or ‘omics’ technical development. Is there the potential for a modeling consortium or support program as well? In terms of educating future systems biologists, another possibility would be providing financial support/incentives for teaching of formal graduate student classes in modeling.

Companies such as Entelos, as well as some academic groups, have developed standardized mathematical modeling platforms, and used them to model physiologic process of clinical interest: some of these models have proven of significant interest to industry. Thus an organized SystemsX.ch program of support for modeling frameworks could lead to additional industry involvement by facilitating application of Systemsx.ch datasets into models of clinically relevant pathways and disease processes.

Another dimension of systems biology that is largely missing (and not just from SystemsX.ch) is that of environmental (different cell type and cell context)

diversity. Most or all projects focus on measuring many things in a very restricted set of biological conditions...high dimensional ‘omics’ but not high dimensional biology. Yet it is clear that the ‘wiring’ that determines the behavior of a cell or system is a complex function of its environment and recent history. Much could be learned from measuring fewer parameters (as low as 10-20, sufficient to define a ‘cell state’ {Lauffenberger}) in many environments (combinations of stimulatory factors and cells relevant to physiologic or disease states); and from studying the differences in wiring networks in different cell types in diverse environments. This approach has been termed “environomics”. Perhaps we could include a call for environomics projects in future RFA’s, to see if competitive projects emerge.

### **Technology: platforms and innovation**

*2. How do you rate the current integration of technology within the RTDs (including those being rather “TD” than “R”), and the concept of technology platforms? Are changes needed in order to better accommodate this crucial element to systems biology research? Are there technology areas that are not adequately covered? How can the technology needs for the future be better supported?*

I cannot comment on this, as this evaluation will depend upon discussion with the RTD and other leaders.

### **Education**

*3. How can SystemsX.ch efficiently support its partner universities to set up Bachelor and Master Curricula in systems biology? Are there additional training and education opportunities that SystemsX.ch could offer in future?*

I am enthusiastic about the IPhD program, and hope that in discussion this seems as successful and valuable as I imagine. I feel that the budget for co-mentored students should be as large as is needed to support the cohort of qualified students and mentors that apply. Thus I hope the SAB will ask about the ratio of demand to supply here.

I am a fan of postdoctoral training fellowship programs as well; and I urge discussion of a SystemsX.ch postdoctoral program that would offer at least 10-20 fellowships per year. These would provide 1 year, renewable to 2 on progress, fellowships for systems biology projects. Preference could be for mathematicians or computer scientists in biology focused labs; and for biologists in physics or math or modeling groups. The fellowships should not be limited to existing SystemsX.ch labs or programs.

I notice that in the IPhD program, substantial support is given for supplies. While I am not familiar with the structure of Swiss labs, in the US one is quite

excited to have excellent students who are ‘free’ in terms of salary. If there are more good PhD or postdoc proposals that we can fund, I would suggest eliminating the research supplements.

The proposed formal PhD program in systems biology, with a centralized admission/selection process, is also an exciting initiative. I hope this will allow students to rotate through several labs in the first year, to provide them with multiple opportunities to identify compatible systems biology mentors and projects. Moreover, contingent on approval of the proposed project as ‘systems biology’, I suggest that students not be required to select faculty already in the SystemsX.ch mainstream: to the extent they chose others, their efforts will expand the systems biology community.

As mentioned above, I suggest discussion of formalized, multicenter SystemsX.ch incentivized courses and instructional programs in modeling.

### **Public-private partnership**

*4. Getting industry to interact with SystemsX.ch has proved to be a real challenge. Efforts have been made to improve this situation, such as creating the BIP and ISA projects. What else can SystemsX.ch and the community do to attract more private partners? How important do you see the participation of large pharma versus smaller companies in an initiative such as SystemsX.ch?*

Pharma seems still (to their detriment) in love with “target focused” discovery. “Pathway” focused drug discovery is a minor step forward. They are a long way from embracing the reality that, without environomic human systems biology, there is little possibility of predicting clinical outcomes of targeting specific molecules in the absence of prior drugs to the same target. I’d be interested in Rene and Paul’s comments.

While the industry should be interested in systems level understanding, systems biology at the academic level is not sufficiently validated or simple for much direct investment from them within this mindset.

However, given their focus on targets, perhaps pharma would be interested in improved modeling as an approach to predicting target involvement in the context of validated networks. Systems biology offers the possibility of improving predictions about the effects of interfering with specific targets when the target is included in multiple different models (reflecting different cells and environments). Enhanced modeling programs as discussed above could lead to additional industry interactions.

Another technology that might lead to enhanced interaction is chemical systems biology: using complex cell systems (environomic) and associated informatics

approaches to select and optimize drug candidates. However, as discussed above, suitably robust human cell systems environmental approaches are not yet a component of SystemsX.ch.

Small companies and start ups, particularly companies derivative of SystemsX.ch science, may ultimately return greater benefit to the systems biology community.

### **International cooperation**

*5. How would you strengthen international cooperation between SystemsX.ch and other institutions and programs? What is an appropriate framework for an effective collaboration of mutual benefit?*

In addition to the conference and EU grant efforts proposed, providing a means for access to SystemsX.ch advanced technology platforms would encourage European interaction. Standardized open source models and modeling platforms, if sufficiently user friendly, could also foster international interactions with multiple SystemsX.ch initiatives. Finally, success will naturally breed collaboration and interaction.

### **Outlook 2010/2011 and strategic plan 2012-2016**

The organizational and programmatic progress has been impressive given the youth of the SystemsX.ch initiative. It may be too early to evaluate the scientific progress except in a few instances. Overall I find the plan for phase II well justified, and the budget request appropriate. See triage comment below however.

I would support shifting additional funds into educational and training programs (e.g., a postdoc program), if the demand is there.

### **Sustainability (beyond SystemsX.ch)**

*10. How do you see the long term sustainability systems biology research? What are the most important elements for its success?*

This may depend more on the institutionalization of educational and programmatic initiatives than on the specifics of current projects. Core facilities (powerful platform technologies) will also help, as will demonstrably successful RTD's; but in my opinion strong educational (graduate and post-graduate) training programs and interdisciplinary faculty devoted to systems biology will be the glue and the catalyst that grows and sustains the initiative.

**Other comments:**

Need for careful oversight and triage of funded programs:

The funded RTD's propose exciting interdisciplinary science on the large scale required for systems biology. However, during the review of RTD's this year, concern was expressed about committing such large grants to ambitious projects with little preliminary data in support of their feasibility. These large projects will also require exceptional leadership to manage and integrate the inter-institutional, inter-group, and interdisciplinary interactions needed for large scale systems biology project success; and for the most part the ability of the PI's to lead such interdisciplinary teams is unproven. I hope that these RTD's will therefore be monitored closely, with a view toward identifying failures early. One focus of evaluation should be the success of inter-group collaboration and synergy; another should be progress of the teams towards integration of data and experiments into models (when appropriate). SystemsX.ch should accept the proposition that not all of these RTD's can or should be successful: failure of some should free up funds for additional initiatives.

Along the same line, the data integration/informatics efforts under SyBIT (with which I am not familiar) would seem critical to the success of the Swiss systems biology effort as a whole (as opposed to it individual projects and technology programs), since systems biology must ultimately have a language allowing sharing of data and integration of models. This will be a monumental challenge, and the efforts and approaches of SyBIT should be carefully monitored to ensure that as stated "SyBIT is very tightly working with all RTDs in order to achieve its goals, and is seeking collaboration with other national and international projects and groups tackling similar data management issues".

**SAB Members**

Prof. Dr. Fotis Kafatos (chairman)	Chair in Immunogenomics Imperial College London South Kensington Campus London SW7 2AZ UK	f.kafatos@imperial.ac.uk
Prof. Dr. Marvin Cassman	875 Haight Street San Francisco CA 94117 USA	mcassman@sbcglobal.net
Prof. Dr. Eugene Butcher	Department of Pathology Stanford University School of Medicine Stanford, California 94305-5324 USA	Eugene.Butcher@stanford.edu
Prof. Dr. Erin O'Shea	Howard Hughes Medical Institute Harvard University Departments of Molecular and Cellular Biology and Chemical and Chemical Biology Northwest Labs 52 Oxford Street, Room 445.40	Erin_OShea@harvard.edu
Prof. Dr. Albert Osterhaus	Head Department of Virology The Erasmus Medical Center Room Ee 1726 Dr. Molewaterplein 50 NL- 3015GE Rotterdam The Netherlands	a.osterhaus@erasmusmc.nl