SystemsX.ch Newsletter #24
June 2012

X-Letter 24

Welcome to the future!

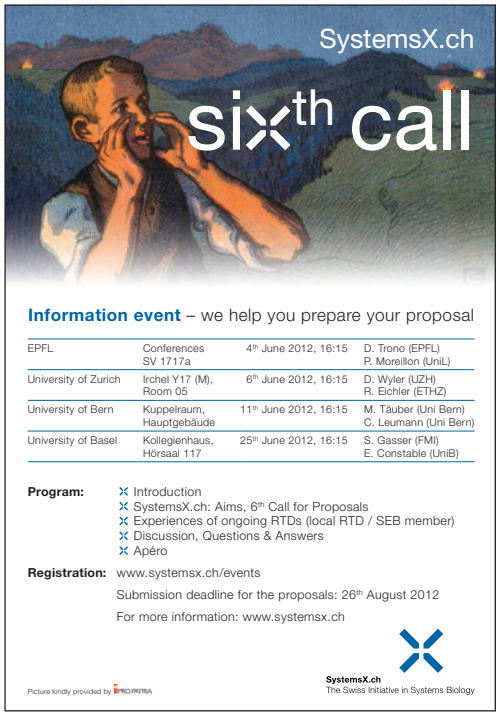
In the last six months SystemsX.ch has published **two new project proposals**.

Consolidation is the motto of the second phase SystemsX.ch. Based on the previous initialization phase (2008–2011), SystemsX.ch will now forge ahead over the next four years and continue to anchor systems biology into Switzerland's research landscape for the long term. An important pillar here is SystemsX.ch's launch of new, innovative research and development projects of various dimensions and orientation.

SystemsX.ch announced its "6th Call" for proposals in March. Interested applicants now have until 26th August to apply for two different types of projects. One is a new generation of the established "Research, Technology and Development Projects" (RTD). Together with Sybit, the IT service and Support project, the previously launched 14 RTD projects are the centerpiece of SystemsX.ch. With a total of 81 million francs, the greater part of SystemsX.ch funding has flowed so far into these major projects.

In addition, the call offers a new type of project with the "Transfer Projects".

In total, around 30 million francs are available for successful applicants in this call. Again, the principle of "matching funds" applies. This means that any institution that receives research funding for a project from SystemsX.ch must inject an equal sum.



Planned information event.

Looking for new RTDs

The search for a further season of RTDs to start in 2013 is officially underway. In addition to the interdisciplinary research, Switzerland's inter-institutional research activities are to be strengthened with these major projects. For this reason, the minimum requirements for

Start of the second half

Daniel Vonder Mühll, Managing Director SystemsX.ch

The first international conference SystemsX.ch last October was a worthy culmination of the first phase of the initiative. After the Swiss National Science Foundation repeatedly expressed praise for the success SystemsX.ch, our next (additional) funding period (2013–2016) is at hand. We'll have more details to impart by autumn. SystemsX.ch projects are expected to be supported until 2018. The «transition year» in 2012 marks halftime, so to speak, for SystemsX.ch. The tender for new RTD and transfer projects make clear what is important in the second half. Based on different types of data floods, we need to:

- **derive new theories with the means of modeling,**
- **actively involve and integrate private companies and hospitals in the consortia, and**
- **pay more attention to medical problems.**

The vision, therefore, means using modeling to be able to make predictions for the tailored treatment of diseases and medical conditions, turning these over to and working with companies and enabling patients to benefit from the treatments.

SystemsX.ch launched many new research projects this year, too.

an RTD project proposal also explicitly prescribe the formation of a consortium of typically three to eight research groups from different disciplines and the involvement of at least two partner institutions. SystemsX.ch also wants to strongly encourage non-biologists, as well as biologists, to take over project management.

Clearly defined project orientation

The new RTD projects should be arranged in such a way that not does not exclusively promote a combination of experimental and theoretical approaches to the description of biological processes. The application of obtained results to clinical research is to be accorded more weight. SystemsX.ch will therefore favor project applications that include the active participation of companies from the private sector in the concept.

Application is not only open to new projects; RTDs initiated in 2008 RTDs can also apply and may be granted a continuation if the project's orientation is adjusted to the newly-defined objectives.

An exciting autumn

In autumn the scientific steering committee (SEB) of SystemsX.ch, together with an international expert committee from the Swiss National Science Foundation (SNF), will select the most suitable project proposals from the submitted entries. SystemsX.ch will check whether the applications meet the objectives of the research initiative, while the SNF representatives will evaluate the quality of each research proposal.

The successful RTD projects will be awarded a contract supported by a maximum of three million francs during a four-year, non-renewable term.

Strengthening collaboration with the private sector

As mentioned in the current call, a new type of project is also on offer, the so-called "Transfer Project". Collaboration between public research institutions and private industry are to be effectively promoted with these projects. The important thing here is that the research aims meet the needs of all partners equally. To ensure this, the leadership of the project is to be balanced by the inclusion of representatives from both public and private institutions.

Selected projects will be supported with a maximum of 300 000 francs for two years. If the project is successful, an additional year can be requested.

"The 5th Call" – Spoilt for choice

SystemsX.ch published its 5th call for proposals last November and interested parties had until the end of January 2012 to submit their research proposals to the Swiss National Science Foundation.

On the one hand, with the "transition post-doc fellowships" the call was aimed at young scientists. On the other, the "Interdisciplinary PhD student project" aimed to make possible and encourage interdisciplinary doctoral theses. Numerous applications arrived in time for the deadline.

In each category SystemsX.ch plans to support approximately 10 projects (cf. Tab1).

Partnerinstitution	Interdisciplinary PhD Projects	Transition Post-doc Fellowship
EPF Lausanne	8	5
ETH Zurich	10	6
FMI Basel	0	1
Uni Basel	1	2
Uni Bern	1	0
Uni Genève	1	1
Uni Lausanne	2	0
USI Lugano	0	1
Uni Zurich	2	1
Total	**25**	**17**

Table 1: Summary of applications submitted for the 5th Call.

Transition Post-doc Fellowships

In this category the search was on for young, ambitious researchers who wish to carry out their own interdisciplinary project independently. The time frame is limited to two years with an option of extension for a third year.

SystemsX.ch supports the researchers by:

- taking over the salary
- covering the cost of supplies for max. 10 000 francs a year. Some basic conditions must be met for this purpose.

The most important of these conditions are:

- a significant part of the interdisciplinary research must comprise quantitative measurements and/or the creation of models for the simulation of biological processes;
- successful applicants must have access to the infrastructure of a SystemsX.ch partner institution for their projects;
- the applicant must find a research group in which he or she has not work before;
- applicants work their way into a – for them – new discipline ("Transition").

The most promising candidates will be invited to present their projects in July 2012 to a panel of representatives of the scientific steering committee (SEB) and the Swiss National Science Foundation (SNF). The the experts will then decide which of the young researchers will be supported with their projects.

The next call for transition post-doctoral fellowships will be published in autumn 2012, and the deadline for submission will be January 2013.

Interdisciplinary PhD Projects (IPhD)

One of SystemX's main tasks includes the promotion and training of future systems biologists. SystemsX.ch therefore regularly launches calls specifically aimed at promoting interdisciplinary doctoral theses.

As in previous calls, the PhD positions funded by the "5th Call" will be positions in which interdisciplinary collaboration in system biologically relevant disciplines (e.g., computer science or engineering, nanotechnology, physics, etc.) is a central component.

For the duration of three years, with an optional, additional year, SystemsX.ch will financially support one doctoral student in a research group by:

- taking over the salary;
- covering the cost of supplies for max. 10 000 francs a year;
- funding of 2000 francs in total to participate in international conferences

In this way SystemsX.ch not only significantly promotes the training of young researchers, but–equally essential for systems biology–also interdisciplinary collaboration and support for promising research.

The next call for IPhD projects will be published in autumn 2012 with an application deadline in January 2013.

Sustainability and innovation

With these calls SystemsX.ch has laid the foundation stone for the burgeoning consolidation phase. Its targeted search for innovative projects not only drives the development of new technology platforms but also guarantees a sustainable integration of systems biology into existing structures. The first step has been taken. The motto is now: full steam ahead into the future.

SystemsX.ch Autumn School

The preparations for SystemsX.ch's Autumn School 2012 are in full swing. The key dates have already been fixed to leave participants time to plan. This year it will take place from the 8th–13th October at the Hotel Bellevue Terminus in Engelberg.

Sybit, SystemsX.ch's own IT project, and its collaborative partner, KNIME, are busy elaborating the course program and tailoring it to the needs of systems biologists. In addition to the basics and an introduction to "IT for Life Science", individual hands-on sessions, for which participants can bring their own data from the laboratory to try out new tools of data analysis are also planned. The type of data is irrelevant. And, in addition to the actual work, there will be time for recreation and Engelberg and the surrounding area offers a range of opportunities.

The Autumn School 2012 program will be shortly be available on our website.

The Autumn School will take place in Engelberg this year.

“To **coalesce a community** takes not just time but also **people with the necessary will** to bring it about.”

Jens Selige has been working since the beginning of the year as Scientific Coordinator at SystemsX.ch. One of his priorities is to strengthen the identity of the research community with SystemsX.ch. To achieve this, he is already planning occasional gatherings where the professional level moves into the background.

What work falls within the remit of SystemsX.ch’s Scientific Coordinator at?

The jobs can be roughly divided into two parts. The first includes lots of administrative tasks. And the other, the creative part, is mainly the planning and design of events in education – doctoral and postdoctoral students – and the science community.

Jens Selige the party animal?

(Laughs) That’ll be the day! No, even if there’s sometimes a cold beer at these social events, the background and the objective is clearly defined and always for the planned events, but also to develop new concepts in this area. For instance, the recently proposed social events.

Can you give us an example?

Yes. At the end of March we organized the first fireside chat in a villa in Zurich. All Zurich based PhD students working within SystemsX.ch were invited. The atmosphere was relaxed and we were able to stimulate discussion on different biologists. Events where the professional, scientific level take something of a back seat are an important supporting measure. To coalesce a community it takes not just time but also people who want to bring it about. With various kinds of events we can create a space where people have time to meet and grow together, so to speak.

The first fire-side meetings ...

You’ve completed extensive training in biotechnology and you can look back on many years of experience in the field of biomedical research. Do you need all that expertise in biological research to accomplish the various administrative tasks?

To fulfill my job description, my experience and know-how of the processes of research establishments are certainly a big advantage. It means that I can also bring the view of a scientist to my work. And, last but not least, my training enables me to answer the scientific questions that arrive in our office.

This is probably also true for the planning and execution of various SystemsX.ch events?

Exactly. After all, one of my tasks is to not merely create the conditions connected to SystemsX.ch’s overall strategy. The core mission of our organization is to build a nationwide, well-networked community of systems biology researchers. This includes nurturing a new generation of systems

... took place in the Hatt Villa in Zurich.

aspects of being a doctoral student. We talked about mutual assistance in research, but also about the support that PhDs could expect from SystemsX.ch. In meetings like these, students don't just get to know one another better. It gives us, from the network organization, a really valuable opportunity to hear directly from the participants and learn from them. An opportunity for them to tell us about their hopes, problems, needs, and expectations. It's not top-down communication that we're cultivating here but a more bottom-up culture.

Do these open fire-side meetings only happen in Zurich?

No. We're also plannings evenings like this in Basel, Lausanne and Geneva. We'll be sending out e-mails a couple of weeks in advance and anyone who's interested can get in touch.

And apart from the fireside chats what other social events are we talking about and are you planning others?

In early May two SystemsX.ch teams took part in the SOLA relay race. Our teams of runners were made up with participants from all sectors of the SystemsX.ch community–our office's director, some PI's, postdocs and graduate students–a really mixed bunch! The feedback was positive and we intend to plan similar events in the future. But I don't want to spoil it by revealing too much. Let's wait and see what we can pull out of the hat!

Participants of the running team at this year's SOLA Stafette: Maxime Auzon-Cape, Gabriella Mosca (both Uni Bern) und Jens Selige (SystemsX.ch).

To come back to the advanced training programs. What plans do you have here?

As in previous years, we're organizing a Summer School this year in the run-up to our Student Retreat. Strictly speaking, though, the former will be more of an Autumn School this year. Both events will be taking place in October in Engelberg. On these occasions the experience and knowledge and professional networking are in the foreground. The program of this multi-day event is not yet determined in detail. The working title of the event is «Practical Data Management and Analysis Methods.» (Editor's note: Details on page 3).

Let's take another look into the future. What are your personal ambitions for SystemsX.ch?

After the first phase, SystemsX.ch already stands on a very solid foundation. Figuratively speaking, the tree has taken root and grown and now we want to bring it to fruition. I believe that what's important, in addition to the output of high-quality research results, is the integration of results into secondary models and projects that takes them further. Another point on my list of priorities is the consolidation of the already existing structures to ensure the sustainability of SystemsX.ch. For my part, I will do everything within my power to achieve these objectives.

Interview Matthias Scholer

Systems Biology of Human Diseases 2012

The "SBHD Conference" took place in Heidelberg this year, for the first time outside of Boston. Apart from supporting the conference as a trans-Atlantic co-organizer, SystemsX.ch also contributed to this event with scientific essays from Martin Fussenegger (D-BSSE) and Ruedi Aebersold (ETH). Active cooperation and networking are to be strengthened – and an "SBHD Conference" on Swiss soil is not inconceivable.

Following the merger of the "Massachusetts Institute of Technology" (MIT) and Harvard Medical School in Boston to form the "Council for Systems Biology in Boston" (CSB²), the SBHD conferences have taken place every year since 2008 under the supervision of Professor Peter Sorger. Meanwhile, with the participation of the "Helmholtz Alliance on Systems Biology", the SBHD has evolved to a transatlantic event, where the focus has increasingly opened up to involve medical and pharmacological systems.

More than 300 systems biologists from around the world participated in the conference, which offered a comprehensive overview of a wide range of topics. The modeling of biological systems was given a forward-looking, application-oriented character concerning medically relevant questions and issues.

Dr. Daniel Vonder Mühll and Dr. Jens Selige represented SystemsX.ch's Management Office at the event. As part of an international network, they made good use of their stay to not only cultivate existing acquaintances but also forge new contacts. Conference participants were able to find out about Switzerland's scientific landscape and the initiative's on-going Systems Biology research programs.

SystemsX.ch thus took a further crucial step towards the international context; not only at the scientific but also at the organizational level towards a broad network of international researchers. sel

Until a few years ago **almost no new antibiotics** were being developed. In the intervening years the alarming increase in bacterial resistance to most drugs has scientists **feverishly looking for new therapeutic approaches**. The "BattleX" team is following **a promising route**.

"Please don't touch anything", warns Dirk Bumann before we enter the lab facilities at the Basel Biozentrum. And with good reason. Because, should we inadvertently take a few of his research objects back home, it could quickly become very uncomfortable. "What we're working with here is Shigella, the causative agent of bacterial dysentery. It's one of the most common diarrheal diseases", says Bumann justifying his warning. He is professor of biology at the center.

Each year, more than 80 million people suffer from the consequences of a Shigella infection and hundreds of thousands do not survive.

Most infections occur either through direct physical contact with infected persons or through the ingestion of contaminated food or water. First symptoms appear between one and four days after the initial infection. Typically, patients are brought down with bloody diarrhea, which results in a great loss of water and they weaken very quickly. This life-threatening development is especially dangerous for children, the elderly and people who are immunocompromised.

In principle, severe cases can be treated with conventional antibiotics. However, like many other species of bacteria, a lot of Shigellae strains are resistant to the most common drugs. This dramatic development has induced many researchers around the world to apply themselves to finding solutions.

The search for new defense strategies against infections is of huge interest to systems biologists as well. After all, the raison d'être for this forward-looking research discipline is to fully understand and recreate the molecular processes within and between biological systems, which, ultimately, is the basic requirement to develop any new therapies.

Dirk Bumann is the pivotman of the RTD-Project «BattleX».

Selective starvation

This is the area in which the RTD project "BattleX" led by Dirk Bumann and his team are working on. "Shigellae are among those bacterial species that penetrate their hosts' cells. They then steal the nutrients from the cells that they require for their replication and virulence. We are now trying to figure out which metabolites are essential to the invaders. Once we have identified these, we can look for ways to disrupt the invasion process". Or, in other words, the agent is to be starved by being cut off from supplies.

It may sound simple but is, in fact, extremely complex. "We chose the relatively well-studied Shigella organism as a study object. What's more, many metabolic pathways in human cells are already known. The molecular interactions between the two different sized networks are so complex that they are hard to understand", is how Bumann attempts to describe the starting position. Without the combination of laboratory experiments and mathematical models, the researchers would never get anywhere. As it is, there is a kind of roundabout-like action between the two methods. On the one hand, results can be interpreted from the studies and classified thanks to the models. On the other, possible associations between individual metabolic steps can first be calculated in models and then the resulting predictions can be checked for accuracy in experiments.

"To achieve its goal BattleX needs experts from a range of disciplines who work closely together", says Bumann. The complexity of the problem is apparent if one superimposes the maps of metabolic interactions that have been studied so far.

Substance pandemonium

Dirk Bumann sheds light on what is seemingly a jungle of countless meta-

bolic processes, "A cell extracts dozens of components from various body fluids in order to maintain its own metabolism, including substances like sugars, vitamins and amino acids". Barely arrived in the cell, a variety of enzymes separates them into their individual parts. In this way, a cell not only gains energy but also all the vital components to produce, for example, proteins for themselves. The result is the production of hundreds of end products and intermediates. "This pandemonium of substances is a paradise for bacteria. You can find just about anything you could possibly need in host cells", enthuses Bumann about the parasitic lifestyle of the Shigellae.

Searching for the ultimate breakdown

The team is focussing on the reactions and interactions that occur while the "nutrient heist" is taking place. Bumann explains, "We must first understand which substances Shigellae remove from the host cells, to what extent and at what stage. Only then can we attempt to interfere with a specific metabolic interaction". As if this task was not already complex enough, there is a further difficulty: "It's not enough to block a single pathway, hoping that this will deactivate the bacteria. If an agent can no longer procure a certain substance, it simply turns to an alternative component". So the search is on for the ultimate source of interference: "The aim is to trigger disastrous consequences for the Shigella with the smallest possible intervention into the cellular metabolic network".

If successful, the team will have found an approach to developing new therapeutics. Faced with the global increase in antibiotic resistance, however, Bumann puts the hope of any speedy solution into perspective. "Even if we succeed in disconnecting the bacteria from the host's metabolism, we are still years away from a clinical application". Because the next step will need to prove the effectiveness of this control strategy in other bacterial species. If it does succeed, however, a collaboration with the development department of a pharmaceutical company would be a future possibility.

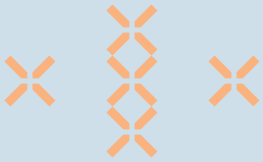
The BattleX-Team

BattleX includes a consortium of seven research groups, of which six are in Switzerland. The seventh member works alternately in Iceland and the USA.

- **Dirk Bumann** Biozentrum, Basel – Shigella Molecular Biology, Modeling, Coordination
- **Bernhard Palsson** University of Iceland, Centre for Systems Biology – Modeling
- **Vassily Hatzimanikatis** EPFL, Lausanne – Modeling
- **Amos Bairoch** CALIPHO, SIB, University of Geneva
- **Ralph Schlapbach** University of Zürich – Data management, Proteomik
- **Julia Vorholt** ETH, Zürich – Metabolomics
- **Cécile Arrieumerlou** Biozentrum, Basel – Shigella Infectional biology, RNAi

BattleX at a glance

Principal Investigator: Prof. Dirk Bumann (Biozentrum, Basel)
Number of research groups: 7
Researchers : Administrators 35:4
Biologists : Non-biologists 22:17 (Administration included)
Total budget (2010–2013): CHF 10.8 Mio, of which CHF 5 Mio von SystemsX.ch



BattleX
Manipulating the Fight between Human Host Cells and intracellular Pathogens

SystemsX.ch from an historical perspective

Alban Frei

At the Chair for the History of Technology at ETH Zurich a doctoral thesis is unfolding on systems biology research in Switzerland. The thesis examines the institutional organization of the richly endowed research initiative, SystemsX.ch, and the scientific and economic context in which it originated.

Among other things the thesis aims to determine how and to what extent research efforts in the field of systems biology change the long-term structures of the partner institutions. At the same time the thesis addresses the importance of paradigmatic change from the reductionist approach of molecular biology to systems biology that reflects the holistic. It also addresses the scientific culture of the new research direction. These four levels–institutional structure, socio-political constellation of epistemic change and cultural practices-furnish the framework of the project.

The knowledge-historical thesis thus offers an external view of the research achievements in the highly dynamic field of systems biology and analyzes these processes within a social and political context. The project is being funded for one year by ETH Zurich and SystemsX.ch initially. It should then be supported by the Swiss National Science Foundation for a further three years.

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Powerful systems biology

An international team of researchers headed by ETH-Zurich scientists has demonstrated for the first time how to extract testable hypotheses from a vast amount of different measurement data for cells that are about to change. The computer methods developed by the researchers help decode extremely complex

Fabio Bergamin

The methods of modern biology have made such leaps in recent years that it is easy to amass vast quantities of measurement data nowadays. Not only have we long been able to decode the genetic material of a living organism; at the same time, we can also determine which genes are activated how strongly in which cells, which cellular regulating molecules are present, which proteins are produced and which metabolic products are present in which concentrations. Far more difficult than collecting the data, however, is analysing it, generating new knowledge from it or proposing new scientific hypotheses. "On the one hand, we are practically drowning in the flood of data in biology-nowadays; on the other hand, we often lack key data," says Uwe Sauer, a professor at the Institute of Molecular Systems Biology.

According to Sauer, new computer methods can help analyse huge amounts of data. Together with Jörg Stelling, a professor at the Department of Biosystems, and an international team of researchers, he has now demonstrated the possibilities computer-aided biology can offer on the bacterium *Bacillus subtilis*.

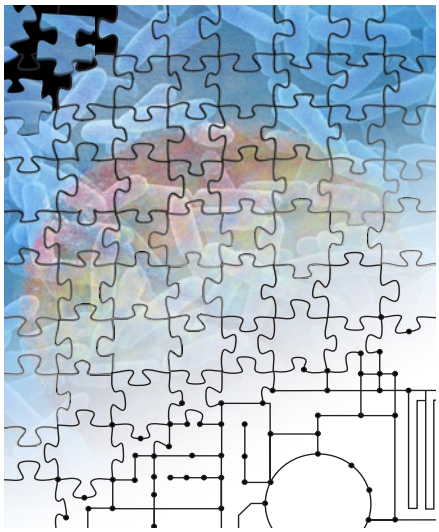
Largest dataset

The researchers began by compiling an extensive collection of hundreds of thousands of specific biological values for the bacterium. What is exceptional about this data pool is that it does not reflect the state of the bacteria at a particular time, but rather a measuring sequence of anadaptation of the micro-organisms to environmental changes over several hours.

The scientists allowed the bacteria to grow on glucose in the lab first before supplementing it with malic acid, which the micro-organisms can use as an alternative nutrient. They then repeated the experiment the other way round. They took all the measurements of the biological parameters available to them at short time intervals, thus generating the largest dataset there currently is for such transitions.

More complex than thought

With the aid of newly developed and existing computer analysis methods, in this dataset the scientists were able to showthat the bacteria alter their metabolism and the basic control mechanisms inside the cell greatly for the comparatively simple adaptation to a new food source,for instance. "The metabolic processes in the bacterium are very strongly linked and nature uses a far more complex control mechanism here than the simplest one possible that is theoretically imaginable," says Stelling. Instead of the expected changes of two handfuls of genes, almost half of the bacterium's 4,000 genes altered their activity.



The researchers were also able to ascertain why *Bacillus subtilis* can adapt much more quickly to malic acid than glucose. Using the computer methods, they were able to recognise genes that effectively act as a brake in the adaptation to glucose because they only adapt their activity slowly to the changed conditions.

Extensive possibilities of systems biology

Thanks to the analysis, the scientists ultimately found a hundred previously unknown regions in the bacterium's genetic material that perform a control function in the organism. And in a series of genes that had not yet been described more precisely until now, they were able to predict a function.

The researchers' main motivation, however, was not to describe the metabolism of *Bacillus subtilis* more precisely, but rather to highlight the possibilities of systems biology with their work. "With our methods, we can recognise all the central biological processes in a cell in the jumble," says Sauer. And they can also be used to decode extremely complex cellular control mechanisms; in other words,also ones that span the entire spectrum of genes, regulating molecules and proteins.

Data and methods publicly accessible

In the next step, they would like to use their methods for a more complex organism than the bacterium, baker's yeast. And eventually they would also like to be able to study mammal cells with it. The methods could also be used to decode important molecules for medical research that can potentially be tackled with medication.

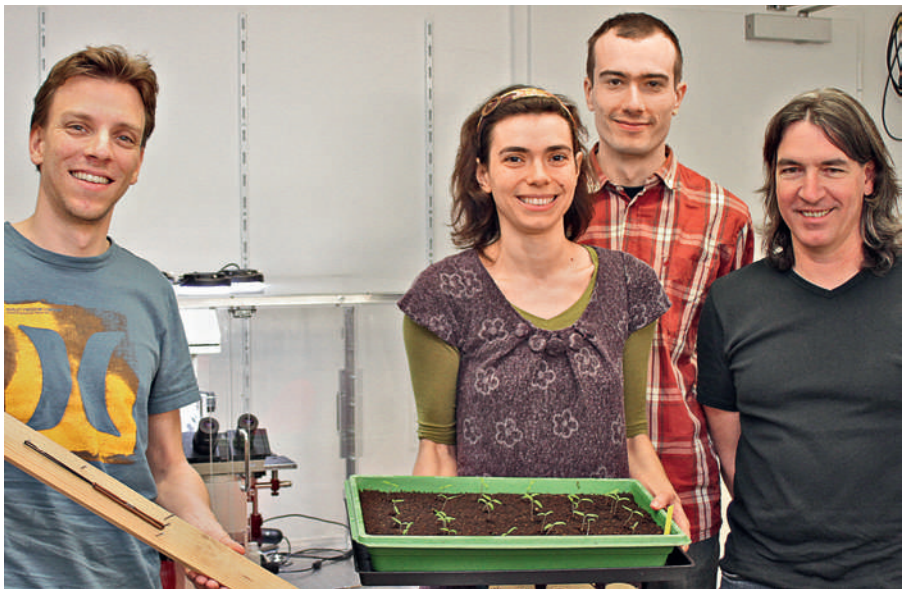
The researchers have made all of their data and tools accessible. "Colleagues can analyse our data with their own methods. And they can use our methods to analyse their own data or develop our methods further," stresses Stelling.

Buescher JM et al.: Global Network Reorganization During Dynamic Adaptations of Bacillus subtilis Metabolism. Science, 2012;335:1099–103.

Hairbands, Tomatoes, and Systems Biology:

Three terms that played an important role in research recently published by the **Institute of Plant Sciences at the University of Bern.** The scientists succeeded in **capturing new insights** into the behavior of **plant cells.**

Stem cells provide a source of founder cells for the plant. Their daughter cells either remain as stem cells or differentiate in order to take on specific functions in tissue or organs.



All the ingredients of the project: scientist,tomato seedlings, hairbands and modern technology. The Team: (from l. to r.) Alain Weber, Anne-Lise Routier, Daniel Kierzkowski, Richard Smith.

In plants the stem cells sit at well-defined vegetation points called meristems. These can be found, for instance, at the tips of the shoots. "The meristem can be divided into a central and a peripheral zone," says Professor Richard Smith. The Canadian is head of the bioinformatics research group that investigated the mechanical properties of these cells. "The stem cells lie in a kind of niche in the central zone. From here, growth causes them to expand into the peripheral zone and this is where, depending on their subsequent function in the plant, they begin to differentiate," says Smith.

While in animals the body plan is already largely determined by the embryonic form, plants continuously shape their form throughout their lives. In order to prevent the organ formation and growth of the plant getting out of control, the tip of the shoot is subject to a number of protective control mechanisms. "We know from previous studies that growth hormones can't induce organs in the stem cell niche. Until now it has been widely assumed that genetic factors were the only thing responsible for this protection," says Smith.

His research team has now succeeded in showing that this is not the case.

Newly-developed software

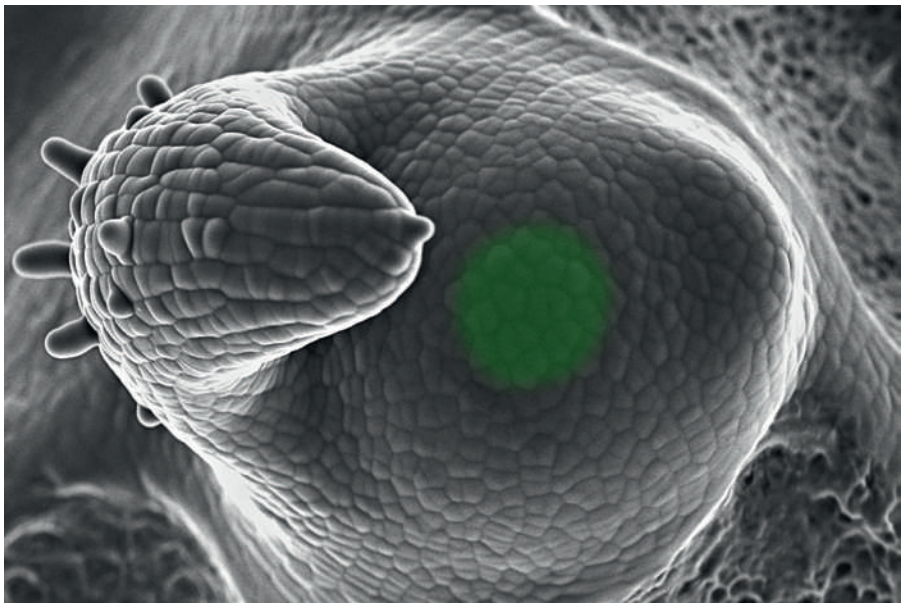
When the Bernese scientists, associates of the SystemsX.ch RTD "Plant Growth" project, investigated the physical aspects and, thus, the forces that act on the cell during plant growth, Richard Smith began to develop his own software (cf. text box). Thanks to this, the team was not only able to quantify the resulting data of the various measurements but were also able to simultaneously visualize the shape changes of the cells. "This meant that we were able to track each and every cell in the meristem over a defined period of time and analyze its behavior under different environmental conditions," explains Smith.

In the process the scientists discovered a previously unknown difference in the central and peripheral cells. While the latter, as expected, expanded considerably in water and shrunk in a salt solution, the stem cells behaved differently; they hardly expanded at all.

Hairbands and tomatoes

To understand the different "zone-dependent" behavior of the meristem cells, the team examined the tips of the shoots of the tomatoes in different osmotic solutions. While the cells in the center did not expand, they could contract considerably. The researchers call this phenomenon non-linear behaviour. In principle, a linear elastic material should stretch or shrink the same for the same change in force. How then was the lack of linearity of the central cells to be interpreted? And is it important to the plant?

First of all, an appropriate mathematical model was needed. Alain Weber, a PhD student and mathematician, developed such a model. "I had to begin with a mathematical description of materials with differing elasticity," says Weber. And this is where the hairbands entered the picture. To illustrate his point he stretches two hairbands, a thick one and a thin one of the same length tied to together in the center. As the band are stretched, at first the thin one stretches more, until it is stretched to the limit and gets much stiffer. At this point the thicker band will stretch more. "We can see how the elongation behavior differs accord-



Scanning electron micrograph of tomato shoot apex, with the stem cell niche marked in green.

MorphoGraphX

Under the name of "MorphoGraphX" Richard Smith developed his own software for the SystemX.ch RTD "Plant Growth" project. The program allows scientists to perform quantitative measurements and visualize the cells under investigation. This open source application is already in use in various other SystemX.ch projects, such as "WingX". According to Smith, MorphoGraphX is the first such application that enables the segmentation of curved surface layers of cells in microscopic images. Smith encourages users to modify the software and tailor it to their respective needs.

More information can be found at: www.MorphoGraphX.org.

ing to the composition of the material. We suppose that the plant stem cells at the shoot tip behave as the thin band, unable to stretch further. In order to investigate this theory, we need to describe them mathematically, so that we can build a model," says Weber.

Protection against uncontrolled growth

The question remained as to what advantage this mechanical property brings the plant? "We believe that it protects the stem cell niche from uncontrolled growth by preventing the hormones from initiating new organs and uncontrolled tissue formation," Smith concludes from the results. The growth and organ formation of a plant is determined not only by genetics, but also by the elasticity of the cell walls.

Without the interaction and close collaboration between scientists from different fields this work would have been practically impossible. "The project is an excellent example of what we understand interdisciplinary research to be. After all, that's the basis of systems biology," says Smith.

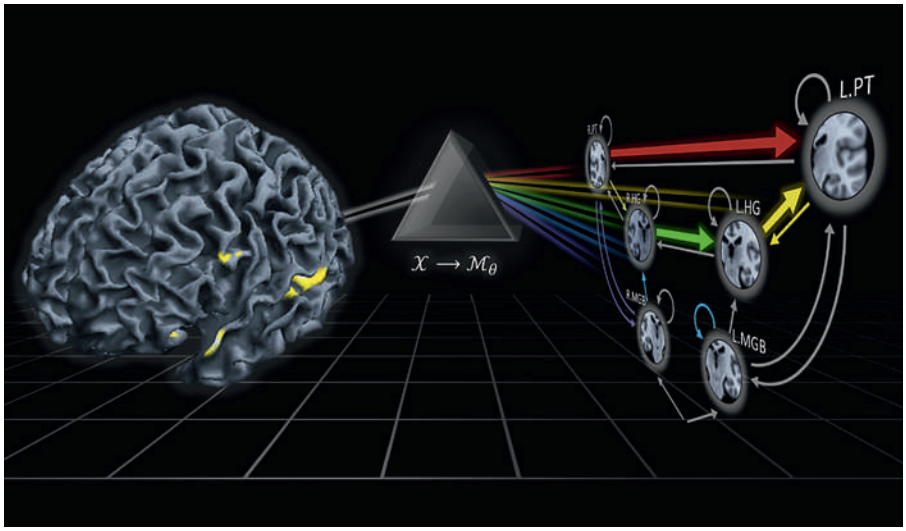
Translational neuromodeling: from imaging science to clinical applications

When mathematical genius John Nash was diagnosed with schizophrenia, the chance for a quick recovery was slim. Medicine in the 1960's simply had no convincing explanations for his condition. Alarmingly, things don't look much better nowadays: depression, addiction, schizophrenia, and other spectrum disorders remain among the toughest challenges for medicine. This is because they are caused by complicated and largely unknown interactions between genes and the environment. Different disease mechanisms may underlie similar, or even identical, symptoms. This means that the effect of any given drug may vary hugely across individuals, resulting in trial-and-error treatment. In addition, conditions whose biological basis is not well-understood may be perceived as particularly stigmatizing.

More specific diagnosis and effective treatment

Most spectrum disorders lack a physiological definition altogether; they are simply described in terms of particular symptoms. This is problematic when these symptoms are caused by different disease mechanisms. Conversely, existing disease classifications frequently group patients with disjoint symptoms

under the same label: a person with delusions and disorganized thought, for instance, can be diagnosed with schizophrenia, just as somebody else suffering from hallucinations and movement problems. Examples such as this one show that the development of more specific diagnoses and more effective treatment will require a better understanding of the pathophysiological mechanisms underlying spectrum disorders.



Mathematical microscopes could help dignose psychiatric disorders.

One step into this direction has recently been taken by Kay Henning Brodersen and Klaas Enno Stephan of ETH Zurich and the University of Zurich. Within the framework of the SystemsX.ch project 'Neurochoice', the two researchers investigate how insights gained from mathematical models of brain function can be translated into clinical applications. "Put simply, we develop 'mathematical microscopes' that allow us to estimate physiological or computational quantities that cannot be measured directly," says Klaas Enno Stephan, director of the newly founded Translational Neuromodeling Unit (TNU) in Zurich. "This allows us to obtain more accurate classifications and gain deeper mechanistic insights into the underlying condition than previous attempts."

Collaboration with a clinical team

To demonstrate the plausibility of their idea, the two scientists collaborated with a clinical team led by Alexander Leff at University College London. They analysed brain activity from two groups of participants: one group of stroke patients that suffered from language impairments; and one group of healthy volunteers. While undergoing functional magnetic resonance imaging (fMRI), participants were asked to passively listen to speech. A mathematical model was then used to assess, separately within each participant, how brain regions involved in speech processing interacted. Notably, none of the brain regions included in the model had been affected by the stroke in the patients. The researchers then asked whether it was possible to automatically detect the presence of a remote lesion from patterns of brain connectivity in the healthy part of the brain. "Using our model of brain function, we were able to diagnose patients with an accuracy of 98%," says Brodersen, first author of the study. "This became possible by tying together dynamic causal models of neuronal dynamics with mathematical techniques from machine learning and Bayesian inference."

Further investigations in other patients planned

In contrast to subtle spectrum disorders, of course, this initial proof-of-principle study concerned a rather salient clinical condition, that is, language impairments caused by a stroke. In the future, Stephan and Brodersen therefore plan to investigate whether their approach might work equally well for those diseases where contemporary medicine is struggling, such as schizophrenia, depression, and addiction. The two researchers hope that their approach will help dissect these spectrum disorders into pathophysiologically well-defined subgroups. Identifying such subgroups would provide an important step towards more specific diagnoses and may eventually predict the most effective treatment for an individual patient.

K. H. Brodersen, T. M. Schofield, A. P. Leff, C. S. Ong, E. I. Lomakina, J. M. Buhmann, K. E. Stephan (2011). Generative embedding for model-based classification of fMRI data. PLoS Computational Biology, 7(6): e1002079.

Newly Founded Translational Neuromodeling Unit


Klaas Enno Stephan

So far, there exist no objective tests for the diagnosis of psychiatric diseases. The mission of the newly founded Translational Neuromodeling Unit (TNU) at University of Zurich and ETH Zurich is to change this. At the TNU, computer scientists and engineers work closely with psychologists and physicians to develop neuronal system models for the analysis of measured brain activity and behavior. These models are used as "mathematical microscopes" for quantification of disease mechanisms in synaptic circuits, with the long-term goal of enabling individualized diagnostics and treatment predictions. The founder and director of the TNU, Prof. Klaas Enno Stephan, is a physician and computational neuroscientist who has been a member of the Neurochoice project in SystemsX.ch since 2008.

SystemsX.ch/BioLAGO – New impulses from the Lake Constance region

BioLAGO life science network

In April 2012 Professor Klaus P. Schäfer, a co-founder of BioLAGO, visited SystemsX.ch. He accepted an invitation from the Management Office, which hopes for new impulses for Switzerland's systems biology community from membership in the Life Science Network.

BioLAGO, a Life Science Network sponsored by a public/private partnership structure, brings together cooperating companies and research institutions situated around the region of Lake Constance from Germany, Switzerland and Austria.

A proposed collaboration between SyBIT and KNIME.com AG, a company now in Zurich, but originating from Constance, is a promising start.

On 25th July 2012 BioLAGO is holding its annual Mini-symposium, "Uni meets Pharma" at the University of Constance. SystemsX.ch will be participating with a contribution from Professor Ernst Hafen.

Jens Selige – the new Scientific Coordinator of SystemsX.ch

- He grew up in Baden-Württemberg
- Education: Degree in Biotechnological Engineering. He received further qualifications for his studies within the framework of a German/French double degree at the Institute of Human Genetics (CNRS) at Montpellier and the Robert Koch Institute in Berlin.
- Research Associate in the preclinical trials of gastroenterology and diabetes research with Altana Pharma AG.
- Admission as International Graduate Fellow at the Universities of Constance and Zurich/ETHZ (IRTG1331). The Chair of Biochemical Pharmacology, Prof. Wendel while doing preclinical research on respiratory diseases at the laboratories of Nycomed GmbH, Constance.
- Postdoctoral research with the Chair of in vitro Toxicology and Biomedicine Professor Marcel Leist, University of Constance.
- Scientific Coordinator of the second Excellence Initiative, University of Constance.
- Since January 2012: Scientific Coordinator of SystemsX.ch.

Glossary of SystemsX.ch

Research, Technology and Development Project (RTD project): SystemsX.ch's flagship project, multi-year duration.

Interdisciplinary Pilot Project (IPP): Research involving risks. One-year duration.

Interdisciplinary Doctorate (IPhD): Duration of 3 to 4 years.

Board of Directors (BoD): SystemsX.ch's highest steering body composed of the presidents, rectors and directors of all participating institutions.

Scientific Executive Board (SEB): Operative committee composed of scientists from the participating institutions.

SystemsX.ch
The Swiss Initiative in Systems Biology

IMPRESSUM

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