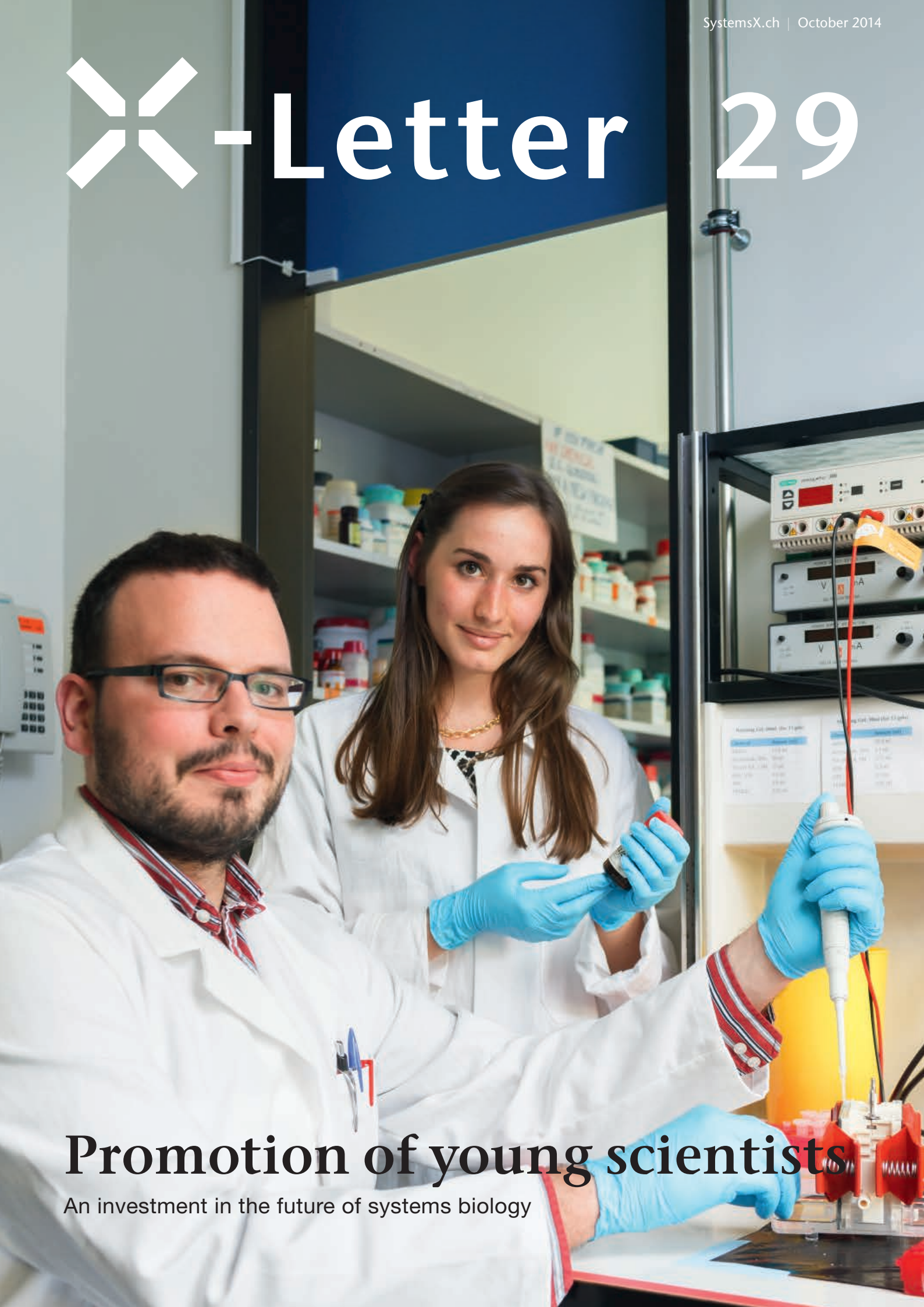
X-Letter 29



Promotion of young scientists

An investment in the future of systems biology

Content

4

10

12

SystemsX.ch
The Swiss Initiative in Systems Biology

Cover: Dimitrios Spiliotopoulos holds a SystemsX.ch Transition Postdoc Fellowship and is involved, jointly with his colleague Lisa Gartenmann, in research at the University of Zurich. Photo: Martin Stollenwerk

Participants of this year's summer school. Photo: David Schweizer

"The new generation of research scientists supported by SystemsX.ch will make a key contribution to shaping the further development of systems biology."

SystemsX.ch has helped to establish systems biology in the Swiss research landscape. Now that the initiative is coming to an end, it is time to firmly anchor this scientific domain. In order for this to succeed in the long run, a new generation of researchers with appropriate training is essential. SystemsX.ch recognised this requirement at an early stage and reacted with targeted measures. These include in particular a comprehensive offer of postgraduate training programmes, as well as support for projects in which doctoral students and postdocs complete their research work in an interdisciplinary environment.

The requirements for education and training have changed immensely since the beginning of the initiative. When SystemsX.ch was launched, most researchers working on systems biology were specialised in a single area: they were trained as biologists, computer scientists, mathematicians, physicists, etc. Today the situation is very different: more and more young scientists have in-depth knowledge in two or more disciplines relevant for systems biology.

SystemsX.ch has made a significant contribution to this change through the support of projects which are directed at the requirements of the new generation of systems biologists. These include in particular the Interdisciplinary PhD Projects (IPhDs) and the Transition Postdoc Fellowships (TPdFs). In the context of an IPhD the doctoral candidates are supervised by two professors from different disciplines. And postdoctoral candidates who have successfully applied for a TPdF are supported in switching from their original subject area to a different one. In this way both types of project help young systems biologists acquire solid competencies in at least two scientific disciplines.

SystemsX.ch also supports the new generation of researchers with tailor-made postgraduate training courses such as retreats and summer schools, as well as with travel grants for visiting selected conferences in Switzerland and abroad. In addition, at the AllSystemsX.ch day, which takes place every year, or at the international SystemsX.ch conferences, the initiative offers young researchers an ideal platform to present their findings to a broad specialist audience.

We are convinced that the new generation of researchers supported by SystemsX.ch will make a key contribution to shaping the further development of systems biology. In this way the scientific initiative will leave a trace way beyond its lifetime.

Eavan Dorcey
Scientific Coordinator, SystemsX.ch

RTD Project MalarX

Together against malaria

MalarX is a prime example of the new generation of SystemsX.ch projects: applied, interdisciplinary research with a strong link to medicine. In this project, the scientists' goal is nothing less than to contribute significantly to the worldwide eradication of malaria.

Volker Heussler has been involved in malaria research for many years.

Malaria does not stop at Europe's doors. As recently as last year, an outbreak occurred in Greece. This comes as no surprise to parasitologist Volker Heussler, a scientist at the Institute of Cell Biology at the University of Bern and a member of the MalarX RTD Project consortium: "Malaria was widespread in Western Europe until the 20th century." He also knows why this disease sporadically flares up in Europe: "As soon as medical care is not fully functional, diagnostics, among other things, are cut back to save costs." Consequently, possible malaria infections remain undetected for many weeks. "This opens the floodgates to the disease", warns Heussler. If infected people are bitten by the Anopheles mosquito during this period, the malaria pathogen spreads before the danger has even been identified.

Millions of new infections

"At our latitudes, only the form of malaria induced by *Plasmodium vivax* is prevalent", explains Volker Heussler. This pathogen is one of four different unicellular parasites, so-called plasmodia, known to cause malaria in humans.

Plasmodium vivax has largely been eradicated at our latitudes but is still the cause of most of the malaria cases in Asia, Latin and South America. "It is estimated that every year 130–400 million infections of *Plasmodium vivax* occur worldwide", says Heussler.

Even though mortality due to this form of malaria is low, it is still a serious disease: "It is like suffering several consecutive, severe bouts of flu." Typical symptoms include feverish episodes caused by toxins released when red blood cells burst.

Heussler explains what happens: "By way of a mosquito bite, the pathogens enter the bloodstream and travel to the liver where they multiply and mature. They then return to the bloodstream and infect red blood cells, where they again multiply until the cells burst." The freely floating parasites can once more be taken up by a mosquito when it bites an infected person, thus completing the cycle of infection.

In *Plasmodium vivax,* this cycle exhibits a distinctive feature: the liver phase can last several months or even years. Thanks to this time lag, the parasite can spend the mosquito-free months in a dormant state in the protected environment of the host organism.

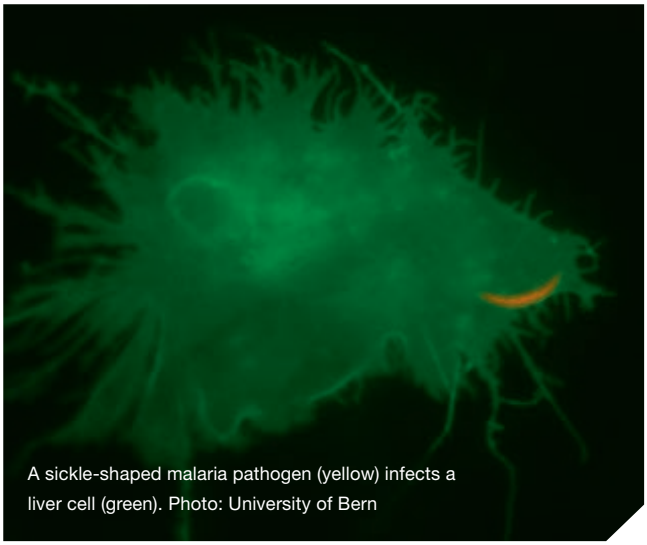
Eliminating parasites without affecting the liver

"To date, most research projects have focused on the blood phase, as it was long thought that this was where the key to new therapeutic approaches would be found", explains Volker Heussler. A mistake, as we now know. "It is not sufficient to kill the plasmodia in the bloodstream. The dormant parasites in the liver must also be eliminated. At present, the dormant phase is still a black box", says the scientist. Especially the events which take place between the parasite and the host cells at the molecular level. For example, experts do not know how the pathogen taps into its host's metabolism for survival. The MalarX RTD Project should help shed light

on this question and determine how the pathogen may be damaged without harming the liver cells.

A major challenge for modeling specialists

The MalarX team can count on project leader Vassily Hatzimanikatis' many years of experience to answer these questions. Hatzimanikatis, a bioengineer at the EPF Lausanne, is specialized in the development of mathematical models for biomedical purposes. But even for him this project presents a special challenge: "Interactions between an intracellular pathogen and the host cell are very complex." The reason for this is the fact that it is not sufficient to integrate the data of two organisms into a single model. The possible interactions between the two also need to be taken into account. Moreover, system biologists are venturing into uncharted territory: "To date, we have looked mainly into the behavior of growing organisms. Here, everything centers on a dormant organism."



A sickle-shaped malaria pathogen (yellow) infects a liver cell (green). Photo: University of Bern

The advantages of interdisciplinary collaborations

In order to be able to work as efficiently as possible, the scientists first develope a model based on the available data. The mathematicians can then formulate possible hypotheses as to how the parasite and liver cells might interact at the molecular level. The plausibility of these assumptions will subsequently be tested in laboratory experiments.

The most important factor in this approach is well-functioning communication between the involved experts. According to Hatzimanikatis, "experience gained during earlier SystemsX.ch projects demonstrates the importance of constant knowledge exchange between the research groups". At the beginning of a project, scientists from a wide variety of research fields need to find a "common language". The project leader is convinced that "in the long term, the advantages of interdisciplinary collaborations will prevail".

International integration and an overarching objective

Not only is MalarX an interdisciplinary project, it is also integrated into the international malaria project network. Experts working in many different countries meet on a regular basis to update each other on the state of their research. Recently, the MalarX team hosted such an event in Lausanne. "Typical competitive thinking is not found among most malaria experts. We are willing to discuss data that has not yet been published", reports Volker Heussler. This is, above all, due to the fact that all involved pursue an overarching objective: to eradicate malaria as quickly as possible.

MalarX at a glance

Principal investigator: Prof. Vassily Hatzimanikatis

Research groups:

- Prof. Vassily Hatzimanikatis, Laboratory of Computational Systems Biotechnology, EPF Lausanne – Mathematical modeling and computational analysis
- Prof. Volker Heussler, Institute of Cell Biology, University of Bern – Biology of Plasmodium liver stage parasites
- Prof. Dominique Soldati-Favre, Departement of Microbiology and Molecular Medicine, Faculty of Medicine, University of Geneva – Genetic manipulation of Plasmodium parasites
- Prof Gerard Hopfgartner, School of Pharmaceutical Sciences, University of Geneva – Metabolomics

Total budget (2014–2018): CHF 5.721 million, including CHF 2.85 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project

MalarX
Systems Medicine of Malaria

Once again, many young scientists attended this year's summer school.

Summer school in retrospect

Summer school 2014 in Kandersteg

This past June the summer school, jointly organized by SystemsX.ch and the SIB Swiss Institute of Bioinformatics, was held in Kandersteg for the second time. Once more, this five-day event was a great success. The 27 international participants were offered a varied program on the subject of "Systems Medicine and its Applications". Each day there were talks by renowned scientists and related hands-on training. A hike to the Oeschinensee completed the event.

Focus on clinical problems

This summer school was geared towards PhD students and postdocs from around the world with expertise in fields such as systems biology, bioinformatics, computer sciences, medicine or biochemistry.

The application of computer-assisted approaches to solving clinical problems took center stage in each class. Therapeutic approaches in personalized medicine were introduced and their various characteristics and potential discussed. In addition to the theoretical and scientific features, the clinical aspect of these approaches was always addressed, including drug development, the promising use of microbiomes and the application of large data sets to techniques such as next generation sequencing (NGS). This high-performance method is used to read sequence information on the DNA strand.

In future, these innovations should help investigate and develop therapies for complex diseases such as cancer and neurological disorders.

From the battle against cancer to data management

As an example, Olivier Michielin, a professor at the University of Lausanne, introduced the participants to the promising uses of NGS in oncology. He is convinced that the knowledge gained in this area will lead to innovative approaches in the development of drugs, capable, for instance, of inhibiting tumor development at the gene level; improvements which will be of great help to patients in the long run.

On the other hand, Timothy W. Clark, a professor at Harvard Medical School, addressed a very different topic in his presentation: the reproducibility and the reliability of scientific data. The computer scientist took a closer look at the problems encoun-

Pieter Borger, University of Basel David Schweizer

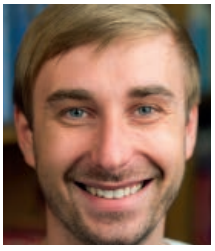
tered in scientific communication. Clark highlighted the important fact that not all data published in scientific journals is available online. In his talk, he also critically analyzed a number of propositions for the implementation of "next-generation" scientific publication concepts.

Norbert Graf, chair of the pediatric oncology clinic at Saarland University, advocated the need for a consensus among internationally renowned data management experts before moving away from the present medical practice in the direction of personalized medicine. According to him, only thereafter is it possible to create an innovative, service-oriented IT infrastructure. He believes that standardization and data bank sharing, as well as data protection and consolidation of patients' rights, are issues that still need to be addressed.

Graf was particularly impressed by the students' contributions to the lively discussion on the topic. "This combined with the very friendly atmosphere, the hospitality and beautiful surroundings made this year's summer school the best one I have ever attended."

"Getting in touch with people from different disciplines broadens and complements your perspective on your own research."

Jasmin Walter, Veterinary Medicine, University of Zurich



"It was great to meet peers and senior scientists, and to communicate with them in both formal and informal environments at the same event."

Stepan Tymoshenko, Industrial Biotechnology, EPF Lausanne

"I liked the event location and the interesting talks and discussions about challenges in medical research."

Nadezda Kryuchkova, Evolutionary Bioinformatics, University of Lausanne

"I liked the diversity of scientific talks and speakers from around the world."

Atul Sethi, Computational Biology and Bioinformatics, ETH Zurich

Michele Fiscella works with mouse cells, sensors and models.

Interdisciplinary PhD Project (IPhD)

Looking into vision

Michele Fiscella is investigating the electric signals sent to the brain by the eye and is working on finding out how they are processed there. Through his findings, this young scientist hopes to contribute to the future development of improved therapies for blind people.

"Experiments are already underway to help blind people recover their eyesight", says Michele Fiscella, a biotechnologist and interdisciplinary PhD student at the ETH Zurich and the Friedrich Miescher Institute for Biomedical Research (FMI). But it is not yet known to what extent the signals sent to the brain by devices such as retinal implants, correspond to those of a healthy retina. "To efficiently heal diseases affecting eyesight, we must first improve our understanding of how vision works in the intact system", explains Fiscella.

Within his interdisciplinary PhD thesis, Fiscella is therefore investigating the activity of so-called ganglion cells. These cells make up part of the retina and act as an interface in vision: they convert visual information from the outside world into electric impulses, called action potentials, and transmit these to the brain.

More precisely, Fiscella is studying the output of a certain subtype of these ganglion cells, the cells that transmit information about movement to the brain. "Thanks to transgenic mouse strains, it is possible to study how the simultaneous signals of these cells are combined and used by the brain", explains the researcher.

Novel high-throughput method

Fiscella, however, needed to develop an adequate method for the recording of the concerted activity of this specific type of cells. One difficulty lay in keeping the retina sample functional for many hours during the measurement process. Support and know-how came from the scientists working in the Neural Circuits Laboratory at the FMI.

As far as measurement methodology was concerned, the young scientist found himself in a more convenient position: he had an extremely powerful detection system at his disposal – a device developed by the Bio Engineering Laboratory at the ETH Zurich, Fiscella's main research group. One distinctive feature of this sensor system is the 3,200 measuring electrodes per square millimeter on its surface, which are sufficient to record the signals of all 2,700 ganglion cells in the corresponding area of the mouse retina. This sensor system is consequently much more efficient for retinal measurements than conventional systems, which have at most 300 electrodes within the same surface area.

"Thanks to the high electrode density, it is possible for us to measure the action potentials of all ganglion cells in a given area

Maja Schaffner

of the retina", explains Fiscella. What's more, the action potentials of every single cell can be extracted and examined separately, if necessary.

Cinema for cells

In order to identify the specific signals which the movement-specialized ganglion cells transmit to the brain in reaction to an outside stimulus, the scientist plays films to the prepared retina cells which are affixed to a sensor chip.

The content of these films is basic: simple white objects moving on a black background. For example, a line progressing slowly from left to right. The movie sessions last several hours, and during this time, thousands of ganglion cells fire their action potentials, providing a coded image of the visual stimulus, in this case the events on the screen.

Models simulate information processing in the brain

"What we ultimately see has been pieced together by the brain, based on signals provided by entire groups of ganglion cells", explains Fiscella. In order to understand how this visual coding happens, and to determine which information is of importance, the scientist has developed various mathematical models with the help of experts in bioinformatics and modeling. He feeds measurement data into the models and looks at how accurately the visual stimulus can be reconstructed.

The search for the best suited model is still underway, but Fiscella hopes to be able to present one by the end of his PhD studies. This model should then provide answers to questions such as "What information does the brain require to correctly perceive the direction of a movement?", "Is it the number of action potentials, or rather their temporal pattern that is important?", or "How do the size and velocity of objects influence ganglion cell signals?".

Fiscella's interdisciplinary PhD project is now coming to an end. "I am very happy that we have reached our goals", he says. With overt enthusiasm the young scientist explains how he has had the opportunity to combine several different disciplines during his IPhD: "I was able to address the scientific issues in a truly interdisciplinary manner and at a systemic level. This is what I call true systems biology!"

The project at a glance

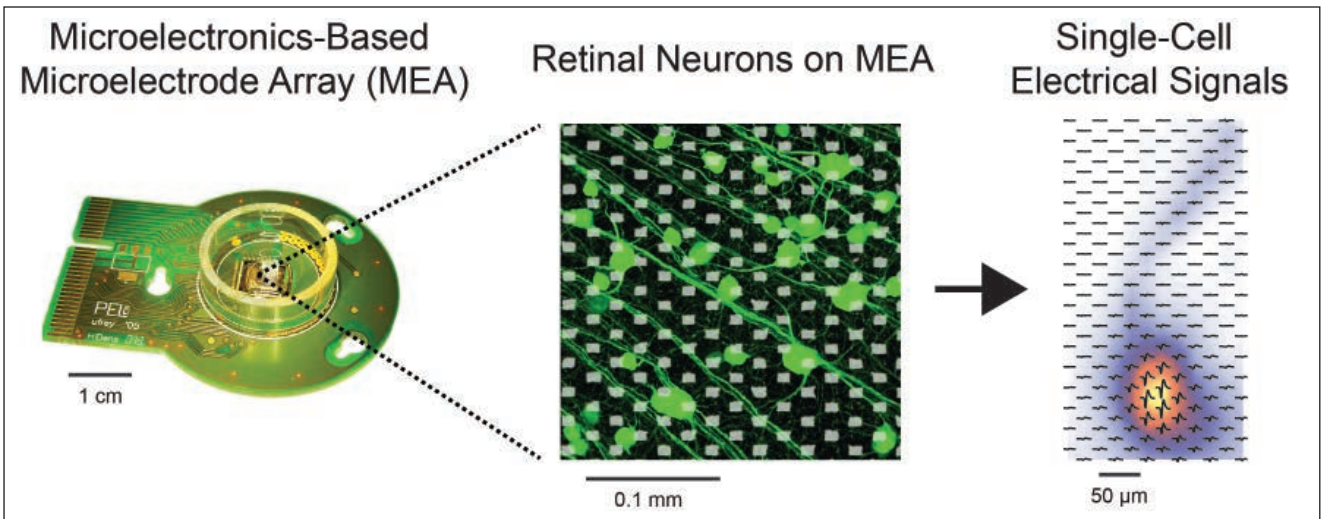
Project title: Microelectronics and genetics to study retinal neuronal circuit dynamics

PhD Student: Michele Fiscella, ETH Zurich, D-BSSE

Advisors: Prof. Andreas Hierlemann, ETH Zurich, D-BSSE; Prof. Botond Roska, Friedrich Miescher Institute for Biomedical Research (FMI)

Project duration: 2009–2013

Project type: Interdisciplinary PhD Project (IPhD)



This sensor system (left) makes it possible to measure action potentials of many cells simultaneously (middle), and to assign the electrical signals to single cells (right). Illustration: Michele Fiscella, ETHZ

Uwe Sauer, chairman of the SystemsX.ch Education Advisory Board

“The SystemsX.ch Advanced Lecture Course is always a big hit.”

In Switzerland, the options for basic and advanced training in the field of systems biology are manifold; a situation that can be ascribed in part to the activities of the SystemsX.ch Education Advisory Board. Its chairman, Uwe Sauer, is pleased with the current situation but also asks himself how the present standard can be maintained after the initiative runs out.

Uwe Sauer advises SystemsX.ch concerning educational questions.

Mr. Sauer, how does SystemsX.ch support young scientists?

Most importantly, SystemsX.ch promotes and supports interdisciplinary research projects. In practice, this means that SystemsX.ch offers young scientists the opportunity to carry out an Interdisciplinary PhD Project (IPhD) or a Transition Postdoc Fellowship (TPdF). The fact that PhD students are coached by two supervisors working in different fields makes IPhD Projects unique. With a TPdF, postdocs change their specialization after their doctorate. This means that someone working in physics, for example, can take their first steps in biology.

How does SystemsX.ch look after researchers once their project has been approved?

The supervisors in each research group take care of most of the specialized training. Additionally, SystemsX.ch regularly organizes

Maja Schaffner Matthias Scholer

retreats lasting several days which focus on the needs of young scientists. Initially, scientific themes took center stage during these events. In the past few years, however, we have moved on to promoting participants' soft skills.

Can you elaborate?

We broach subjects such as the challenges associated with interdisciplinary collaboration, or the difficulties that can arise when working with several mentors. The aim is to teach young scientists to communicate efficiently with various mentors and colleagues, and to act constructively as part of a team.

Are other training opportunities available to young scientists?

Yes, SystemsX.ch organizes and finances additional activities in collaboration with other institutions. One such event is the yearly "Practical Summer Course: Modelling for Systems Biology", which we organize jointly with the Centre for Genomic Regulation in Barcelona. Every other year, we also co-organize a summer school in collaboration with the SIB Swiss Institute of Bioinformatics, and offer an Advanced Lecture Course in Systems Biology with the University of Vienna, which is mainly financed by SystemsX.ch.

Is the main goal of these courses also the development of soft skills?

No, these events focus on high-level scientific training. The courses resemble conferences but are usually held in a smaller setting and are directed towards active learning and interactions between speakers and young scientists. These events also offer the participants many opportunities to socialize and to establish and cultivate their own network.

Do these training opportunities go down well with the young scientists?

The retreats are very popular. My collaborators who attended the last SystemsX.ch retreat came back thoroughly enthused. The SystemsX.ch Advanced Lecture Course is also always a big hit. Last year we were not able to carry out this event, which usually takes place every other year, and some PhD students from Switzerland and Europe even complained.

Does SystemsX.ch also influence university curriculums?

Not directly, as these lie within the responsibility of the universities. But by selectively promoting projects in the area of systems biology, the initiative sustainably influences the Swiss research environment. This is for example reflected by the increased interest in this field of research. Systems biology approaches are being used more and more widely to address scientific problems. Consequently, the need for appropriately trained young scientists is growing continuously. Many universities are aware of this situation and have adapted their curricula accordingly.

For example?

The biology curriculum at the ETH Zurich has recently been revised. Bioinformatics, in-depth statistics and exercises in systems biology are now already taught at the bachelor level. We also offer two degrees in systems biology at the masters level. At the doctorate level, we have established a graduate school for PhD students with the University of Zurich. Within this program, the students are given additional training in systems biology in the form of block courses.

In December 2014, SystemsX.ch will launch its last call for young scientists. How will they be supported thereafter?

For the courses organized or co-organized by SystemsX.ch, we must find new solutions. We might, for instance, be able to integrate the retreats into the graduate school. But we need to find new sponsors for the international Advanced Lecture Course. However, nothing will change regarding the training offered by universities. As to research funding, I am convinced that by the end of the initiative, systems biology will be so well integrated into Swiss research that finding money for planned systems biology projects will no longer be a problem for future young researchers.

The next two SystemsX.ch events for young scientists

In February 9–10, 2015, SystemsX.ch will organize a two-day "Leadership and Management Skills for Postdocs" workshop.

The yearly SystemsX.ch Retreat for PhD students and postdocs will take place March 9–12, 2015.
The title of this event is "Better Results through Diversity".

Detailed information regarding these two events will be published as soon as it is available:
www.systemsx.ch > Events > Educational Events

Pamela Dobay feels at ease at the University of Lausanne.

Portrait of a young scientist

Schumann and systems biology

A dramatic experience in a hospital and the entries in an encyclopedia have lastingly influenced Maria Pamela Dobay's career. Today, this young bioinformatician balances her life between biophysics and "bel canto".

In Manila an unconscious teenager is brought to the emergency room by his family. Surprisingly the physician's first question does not address the patient's medical condition – he enquires about the parents' professional occupations. When the distraught family members reply that the patient's father works in Dubai, the doctor states that under the circumstances, the family will clearly not be able to pay for the young man's treatment. Before leaving the patient's bedside, he advises the family to try a public hospital or take their relative home to die.

Pamela Dobay, a schoolgirl also in need of medical treatment at the time, witnessed this scene – with far-reaching consequences. "At that very moment, I decided that I wanted to prevent such tragedies from happening", explains the now 32-year-old Philippine native. Years later, although she studied biology and computer science rather than medicine, she has remained true to her resolution. "Today, I investigate diseases", says Dobay.

Collected knowledge as a source of inspiration

Unlike the rejected patient, Pamela was in hospital of her own accord on that particular day. "I drank Manila's contaminated tap water, fully aware that I would end up in hospital with an intravenous drip. This way, I was able to escape the girls' boarding school, at least for a short period of time", recalls Dobay. It was difficult for her to make friends with her classmates. While the other girls gossiped about pop stars, fashion and their fellow students, Pamela would retreat to the library: "I used to read an encyclopedia for hours and could not get enough of the illustrations."

The more Pamela read about the great composers, the more she was also attracted to their musical works. "I wanted to become part of that world and learn to play an instrument", says Dobay. She was unable to convince her parents but saw this as no reason to give up: "I taught myself to play the piano and later, I trained to become an opera singer." To this day, singing provides

an important counterbalance to her scientific work. “I sing with a physicist friend on a regular basis”, says Pamela Dobay. Her favorite composers are Brahms, Bellini and Schumann.

Rock music overdose

After she completed her degree in the Philippines, Dobay had only one objective in mind: “I wanted to go to Europe to continue my studies and to be as close as possible to the legacy of the great composers.” Both wishes were granted simultaneously at the Ludwig-Maximilians-Universität Munich: while working on her PhD in biophysics at the renowned university, Dobay had many opportunities to attend classical concerts by well-known artists.

When asked why she is much more interested in classical than pop or rock music, the scientist offers an amusing hypothesis: “My mother always lulled me to sleep with music by The Doors or The Who. That was probably enough rock music to last me a lifetime!”

“My mother always lulled me to sleep with music by The Doors or The Who. That was probably enough rock music to last me a lifetime!”

A big love for music

Her time in Munich was also an important phase of her life for a different reason: “That was where I met my husband who was working as a theoretical physicist in the same group”, she says. And how could it be otherwise: he too is a music lover and a passionate pianist. This does not come as a surprise to the researcher who is convinced that “many scientists are very interested in fine arts and love music”. After her husband completed his project, he returned to Switzerland to take up a new position at the University of Zurich. Dobay followed him shortly after and began working in the area of computer science at the SIB Swiss Institute of Bioinformatics in Lausanne. In the course of her work, she also became familiar with SystemsX.ch and applied for a Transition Postdoc Fellowship (see box).

Suspected of marriage fraud

Yet what has become of her original wish to help sick people? “Despite working with abstract numbers, I never forget that behind all the cancer statistics, there are real patients; I put my whole heart into improving their situation through my work”, she states. Appreciation of her work is of utmost importance to Pamela Dobay. This is why she still resents the Zurich immigration authority’s initial behavior towards her: “The procedure I had to go through in order to take up residence in Switzerland was very impersonal, unlike what I had experienced in Germany. As a citizen of the Philippines, I was suspected of fraudulent marriage, despite my professional achievements. My husband and I had to prove that ours was not a marriage of convenience.”

“Despite working with abstract numbers, I never forget that behind all the cancer statistics, there are real patients."

And where does Dobay plan to be in five years? “I hope to be able to found my own start-up company in the field of medicine”, she explains. Laughing, she adds: “It is probably somewhat late for a professional career as an opera singer.”

The project at a glance

Project title: Applications of network reconstruction, graph theoretic analysis and qualitative modeling to virus-host interaction networks

Applicant: Dr. Pamela Dobay, SIB Swiss Institute of Bioinformatics

Host research group: Dr. Mauro Delorenzi, Bioinformatics Core Facility, SIB Swiss Institute of Bioinformatics

Project duration: 2014–2016

Project type: Transition Postdoc Fellowship (TPdF)

RTD Project MetaNetX

Models in record time

Scientists working on the MetaNetX project are not only trying to comprehensively model metabolic networks, but they are also developing methods to make the creation of these models automated, and therefore quicker. This will be of great benefit to system biologists worldwide.

Jörg Stelling wants to replicate metabolism with mathematical formulas.

Beside microscopes, pipettes, cultures and various measurement devices, mathematical models form the basis of today's systems biology research. "These days you can't get anywhere without modeling", says bioinformatician Jörg Stelling who is a professor in the Department of Biosystems Science and Engineering (D-BSSE) at ETH Zurich, and principle investigator of the RTD Project MetaNetX. Complex systems, like that of a cell's metabolism, can only be described with the aid of such models.

The search for the missing pieces

And this is the goal that MetaNetX also pursues: "We want to encapsulate the metabolic network of a cell in one single model, from the genes and proteins involved all the way to the metabolites", explains Stelling. International publications on metabolic processes serve as a basis for the research. "The published results are like individual puzzle pieces. We're trying to fit them all into one big picture." Nonetheless, many important pieces are still missing, as "even in more thoroughly-researched organisms, half of the metabolic processes remain unknown", says Stelling.

In order to close the gaps, researchers adopt a common systems biology approach: "When we're missing information on connections between two known metabolic components, we model possible interactions. We then examine the most likely hypotheses experimentally", summarizes Stelling.

The big disadvantage of this is that the creation of these models require about half a year. Thanks to MetaNetX, this could soon change. "We've found a way to generate models not only automatically, but within a few hours."

Supported basis of information

Behind this innovative method is a large database in which Stelling and his team have recorded all known data on metabolic processes. Through this the scientists can draw on an already supported basis of information via a software and, with the help of algo-

rithms specifically developed for this, can gather the required data and construct a model. For this process it makes no difference whether one is modeling the metabolism of a plant, bacteria or mammalian cell.

"In order to construct a new model using our method, we still have to feed organism-specific data into the database, and to later fine-tune the automatically generated model", clarifies Stelling.

Off-the-rack models for everyone

The possibility of developing top-quality models in record time is something that the project leader would like to make available to researchers worldwide in the future. "In order that all scientists can benefit from our novel methods, we will make them available via a publicly accessible database", explains Stelling.

Here, the advantages of a large RTD project, in which several institutions are constantly involved, become apparent. "The Swiss Institute of Bioinformatics, one of the MetaNetX project partners, is able to provide the necessary infrastructure and know-how."

Comprehensive approach for relevant predictions

According to Stelling, the approach of the MetaNetX team differs in one respect to that of other previous work in this area: "In our models, we try to imitate the behavior of as many elements of a cell as possible." Stelling is convinced that the more comprehensive the approach is, the more accurate their predictions are.

He illustrates this with an impressive example: "Until now, researchers looking at plant growth have relied on models in which the CO_2-fixing enzyme RuBisCo plays a central role." This protein is thought to be the main factor in plant growth. Conventional models predict an increase of about 40 percent in a plant's biomass when both temperature and CO_2 concentration increase. The prediction from MetaNetX's cell-based models is entirely different: "Our calculations indicate an expected increase in biomass of just 20 percent, given the same conditions." Experimental verification confirms MetaNetX's predictions. "The measurements from field tests support our hypotheses", says Stelling.

This is an indication for the systems biologists that there are other, previously unknown metabolic pathways besides the RuBisCo enzyme that are responsible for CO_2-fixation and plant growth. "We would never have acquired this knowledge, had we only included the behavior of a few single components in our model", emphasizes the researcher.

Positive outlook for the future

In spite of its success, MetaNetX will come to an end this year. Its follow-up project was not approved by the expert committees. Does this mean the end of this research? "We are going to continue our collaboration with the Swiss Institute of Bioinformatics", says the project leader. For the experimental validation of the mathematical predictions of plant growth, Stelling is actively looking for a partner in industry. "We've already held the first, promising discussions", he says. So there's a positive outlook for the future. And that's coming from a scientist who knows a thing or two about predictions.

MetaNetX in overview

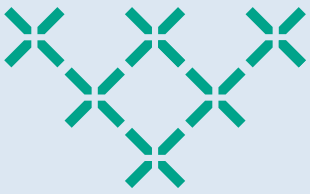
Principal investigator: Prof. Jörg Stelling

Research groups:

- Prof. Jörg Stelling, Department of Biosystems Science and Engineering, ETH Zurich – Development of methods and models
- Prof. Uwe Sauer, Department of Biology, ETH Zurich – Quantitative Metabolite Measurements
- Prof. Wilhelm Gruissem, Department of Biology, ETH Zurich – Plant Physiology and Biotechnology
- Prof. Vassily Hatzimanikatis, Department of Bioengineering, EPF Lausanne – Algorithmic Model Generation
- Prof. Ioannis Xenarios and Dr. Marco Pagni, SIB Swiss Institute of Bioinformatics – Databases and Genomics
- Prof. Donald Kossmann, Department of Computer Science, ETH Zurich – Algorithms and Databases

Total budget (2009–2013): CHF 8.28 million, of which CHF 3.98 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project



MetaNetX
Automated Model Construction and Genome Annotation for Large-Scale Metabolic Networks

9th call for proposals

Supporting young scientists: 24 new projects to be launched

With the 9th call for proposals, SystemsX.ch invited researchers to submit new proposals for Transition Postdoc Fellowships (TPdF) and Interdisciplinary PhD Projects (IPhD). Interested scientists had to send in their applications by the end of April 2014. From the 76 proposals received, the SystemsX.ch Scientific Executive Board and experts from the Swiss National Science Foundation approved 24 new projects.

In the TPdF project category, 7 of the 28 submitted projects will be funded. In the IPhD project category, the experts selected 17 out of 48 proposals.

The aim of the IPhD and TPdF projects is to specifically support young scientists. The 11th call for proposals, to be published in December 2014, will be the final opportunity for submitting an application for a SystemsX.ch project in these two categories (see page 18).

Table 1: The TPdFs approved in 2014.

Title	Principle investigator	Host lab
High-throughput super-resolution imaging reveals contextual effects in gene expression	Douglass, Kyle (EPFL)	Manley, Suliana
Mediation of specificity in mRNA translation by heterogeneous ribosomes	Guimaraes, Joao (UniBas)	Zavolan, Mihaela
System biology of scaling: biophysics of gradient expansion	Merino, Maria Luisa (UniGE)	Gonzalez-Gaitan, Marcos
The thermodynamic underpinnings of enzyme-enzyme interactions and substrate channeling	Noor, Elad (ETHZ)	Sauer, Uwe
Membrane-based memory formation in bacteria: scaling up from single-cell behavior to the dynamics of populations	Schlegel, Susan (ETHZ)	Ackermann, Martin
Exploiting signaling dynamics to overcome robustness of oncogenic networks	SriRamaratnam, Rohitha (UniBas)	Wymann, Matthias
Adaptive noise cancellation in synthetic biomolecular circuits	Zechner, Christoph (ETHZ)	Khammash, Mustafa

New projects for young scientists in an interdisciplinary environment.

Table 2: SystemsX.ch will support the following 17 new IPhD projects.

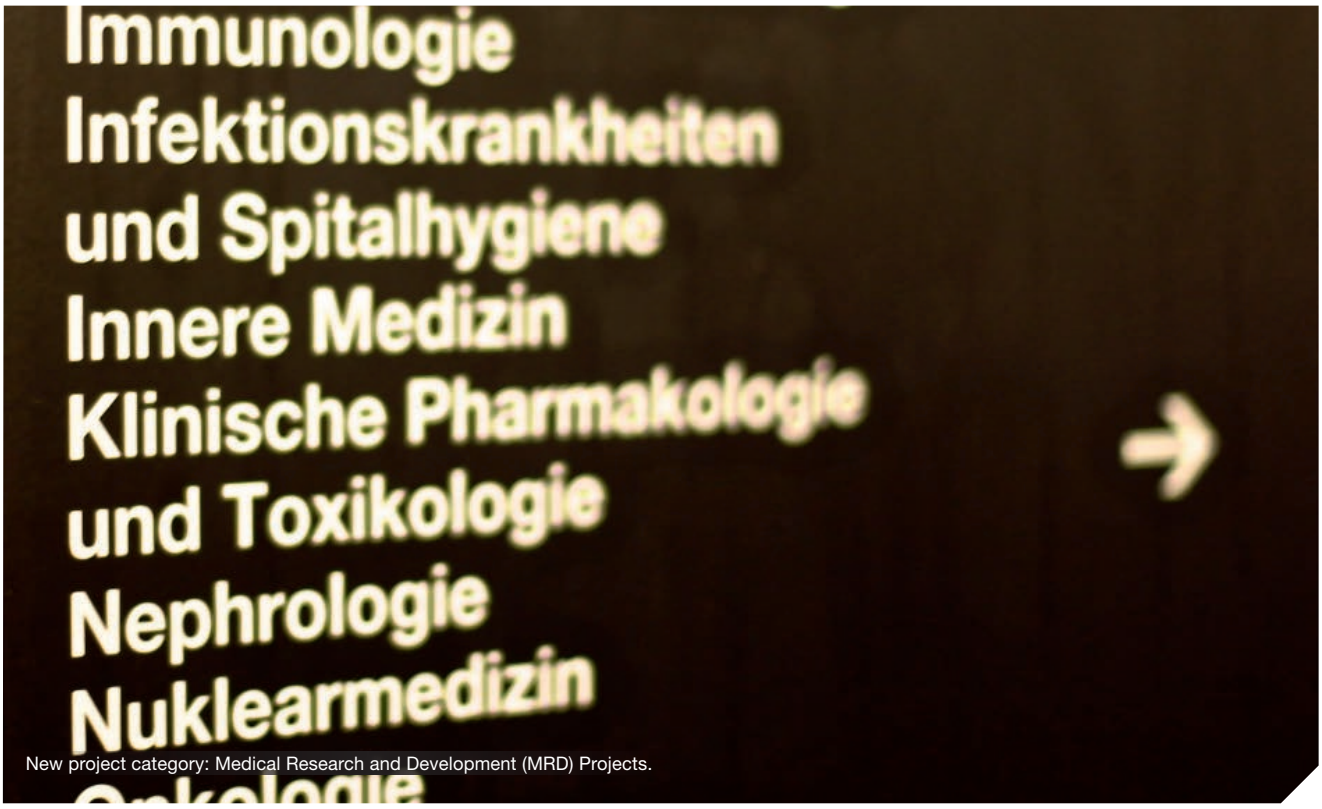
Title	Supervisors
Functional organization of the plant nucleus	Baroux, Célia (UniZH) Grossniklaus, Ueli (UniZH) Majer, Peter (Bitplane AG)
Systematic characterization of the cell biological and mechanical properties of asymmetrically dividing drosophila neuroblasts	Cabernard, Clemens (UniBas) Mueller, Daniel Jobst (ETHZ)
Integrating genomic and physiological data to unravel the functioning of key hub nodes in mammalian regulatory networks: the case of the peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α)	Handschin, Christoph (UniBas) Van Nimwegen, Erik (UniBas)
Prediction error processing in neural networks of the mammalian brain	Helmchen, Fritjof (UniZH) Stephan, Klaas Enno (ETHZ, UniZH)
Systems biology of vision: online identification of visual coding properties of retinal ganglion cells	Hierlemann, Andreas (ETHZ) Roska, Botond (FMI)
Towards in silico organogenesis: inferring and simulating regulatory network dynamics on growing embryonic 3D limb bud domains	Iber, Dagmar (ETHZ) Zeller, Rolf (UniBas)
Spectral deconvolution of SWATH data for peptide identification and deciphering HIV-1 antiviral response mechanisms	Lisacek, Frédérique (SIB) Hopfgartner, Gérard (UniGE)
Comprehensive analysis of transcription factor – promoter interaction in vitro and in vivo	Maerkl, Sebastian Josef (EPFL) Shore, David (UniGE)
Quantification of growth-controlled gene transcription dynamics by live, single-cell imaging	Pelet, Serge (UniL) Shore, David (UniGE)
Computational modeling of pluripotent stem cell transcription factor networks	Schroeder, Timm (ETHZ) Stelling, Joerg (ETHZ)
Metabolic network governing toxoplasma gondii persistence and transmission	Soldati-Favre, Dominique (UniGE) Hatzimanikatis, Vassily (EPFL) Hehl Adrian (UniZH)
Systems analysis of the impact of IFN-lambda signaling on vaccine response	Stelling, Jörg (ETHZ) Egli, Adrian (UniBas)
Input-output relationships underlying transcriptional bursting at the genome-wide level	Suter, David (EPFL) Naef, Felix (EPFL)
Micro2X: micropatterning of microbial communities – tailoring cooperation versus competition	Vorholt, Julia (ETHZ) Zambelli, Tomaso (ETHZ)
Model based inference of age related changes in circadian oscillators	Wegmann, Daniel (UniFR) Ripperger, Jürgen (UniFR)
A computational framework for systems pathology of prostate cancer	Wild, Peter (USZ) Rodriguez Martinez, Maria (IBM Research Laboratory Zurich)
Establishment of in vivo verified molecular networks that control T cell function in chronic infection	Zehn, Dietmar (CHUV) Delorenzi, Mauro (SIB)

Daniel Vonder Mühll Matthias Scholer

10th call for proposals

34 proposals submitted

The 10th call provided for the first time the opportunity for submitting proposals under the new Medical Research and Development (MRD) Projects category, in addition to the familiar Transfer Projects (TF). By the end of July 2014, a total of 34 project applications had been submitted; 30 for MRDs and four for TFs. A Swiss National Science Foundation expert panel and the SystemsX.ch Scientific Executive Board are in the process of examining these applications, and selecting which projects will be supported. The outcome will be announced in November 2014. The funds allotted to each project can amount to a maximum of CHF 2.5 million for MRD projects and CHF 300,000 for TF projects.



New project category: Medical Research and Development (MRD) Projects.

11th call for proposals

Final call in December

The 11th SystemsX.ch call for proposals will be published in December 2014. This is the last opportunity to submit project applications, as the Swiss Initiative in Systems Biology will launch no further calls thereafter.

This final call offers partners in academia and the private sector the chance to submit an application for a Transfer Project (TF). Proposals from potential postdocs for Transition Postdoc Fellowships (TPdF), and joint applications from group leaders working in different fields for Interdisciplinary PhD Projects (IPhD) are also welcome. The submission deadline will be April 30, 2015. The successful project proposals will be announced in summer 2015.

Project categories in the 11th call for proposals

IPhD

Interdisciplinary PhD Project, in which a PhD student is supervised by two supervisors working in different fields.

TPdF

In Transition Postdoc Fellowships the postdocs formulate their own interdisciplinary project application and switch to a complementary discipline that is new to them.

Transfer Project

Interdisciplinary research project, in which teams working in the public-academic sectors collaborate with teams in the private sector (industry, SMEs, hospitals, etc.).

Heide Hess

ERASysAPP: First call for proposals closed

Seven European research projects have been approved

In November 2013, the European research network ERASysAPP launched its first transnational call for project proposals, titled "Transferring Systems Biology Knowledge into Applications". The call was met with great interest; 196 research groups working in nine partner countries, amongst them 18 Swiss teams, submitted a total of 34 project proposals. Seven of them will receive funding over the next few years.

All of the submitted proposals were assessed by an international panel of 48 experts whose main focus was on the quality of the scientific approach. The experts then ranked the research proposals recommended for funding. Based on these recommendations and the available funds, the panel then nominated seven projects which all together will receive more than nine million Euros over the next three years.

Swiss research teams are involved in four of the selected projects: the SysMilk project (Uwe Sauer, ETH Zurich) will deal with microbial communities in kefir. SysVirDrug (Niko Beerenwinkel, ETH Zurich) aims to develop antiviral drugs. SysMetEx (Igor Pivkin, USI) will examine efficient metal extraction using microorganisms, and the MetAPP project (Julia Vorholt, ETH Zurich) will look into the production of biotechnological products from methanol. In total, the Swiss research groups will receive 1.46 million Euros. More information is available at: www.erasysapp.eu > calls > funded-projects > 1st Call

Second transnational call for proposals

In autumn 2014, ERASysAPP will publish its second transnational call for proposals, with the aim of strengthening scientific exchange on a Europe-wide level.
More information can be found at: www.erasysapp.eu > calls

ERASysAPP course: "Data Integration in the Life Sciences"

In partnership with the Lorentz Center in Leiden (Netherlands), ERASysAPP will host a course on data integration from February 2–6, 2015. Over a period of five days, experts will give an overview of different types of data sets, as used in fields such as metabolomics and proteomics. Participants will be shown different approaches for the integration of this data and will practice their application by means of case examples. The aim is to demonstrate how different data sets can be combined to create predictive computer models by choosing appropriate modelling approaches.

Information and application at:
http://www.erasysapp.eu > events

"Personalized Health" – A progress report

At the end of 2012, the SystemsX.ch Board of Directors gathered a task force to develop the concept for a national research initiative focused on public health. The expert panel, including representatives from the Swiss universities and the ETHs as well as clinical research and industry, published its final report in June 2014. This report presents options for coordinating and linking various activities in the area of personalized medicine in Switzerland and defines the measures required to keep our country at the forefront of this cutting-edge research field.

The report "Personalized Health – Report to discuss options and frame for a new Swiss initiative" (in English) can be obtained from the SystemsX.ch Management Office on request: admin@systemsx.ch

Upcoming Events

October 20–23, 2014

2nd International SystemsX.ch Conference on Systems Biology

Lausanne

November 17–20, 2014

Frontiers in Metabolism: From Molecular Physiology to Systems Medicine

Heidelberg, Germany

January 18–20, 2015

Mathematical and Computational Modeling in Life Sciences

Rigi Kulm

February 2–6, 2015

ERASysAPP: Data Integration in the Life Sciences

Leiden, Netherlands

February 9–10, 2015

SystemsX.ch Workshop: Leadership and Management Skills for Postdocs

Gerzensee

March 9–12, 2015

SystemsX.ch Retreat: Better Results through Diversity

Rigi Kaltbad

Imprint

Publisher: SystemsX.ch, Clausiusstr. 45, CLP D 7, CH-8092 Zürich — Contact: admin@systemsx.ch, Phone +41 44 632 42 77, www.systemsx.ch — Editors: Maja Schaffner (mas), Matthias Scholer (msc), Collaboration: Daniel Vonder Mühll (vdm), Heide Hess (hh) — Translation: Frenzis Group, Scitrans.ch — Graphic design and Print: Sihldruck AG, Zürich

Newsletter subscription: communications@systemsx.ch

SystemsX.ch
The Swiss Initiative in Systems Biology