Contributed by
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SystemsX.ch: way to go!

"Way to go" refers in all senses to the SystemsX.ch systems biology initiative, a first for Switzerland and involving all its major institutions.

SystemsX.ch is a collaborative effort between over 130 research labs from all major Swiss research institutions. It has received CHF 100 million in federal funds for 2008-2011, aiming to make Switzerland a world leader in systems biology. The "-omics" technologies (proteomics, genomics, etc.) are hot in the world of science, but systems biology is smoking. It combines all the -omics, looking at systems as a whole. The holy grail is to build computer models of processes, cells or organisms that make specific predictions on biological questions (such as what happens if I take this drug?) without anyone going anywhere near a lab rat. To achieve this, there really is a way to go - the scientists at SystemsX.ch reckon the sooner they get stuck in the better!

SystemsX.ch evolved serendipitously. Firstly, Basel Stadt aimed to strengthen its research base. The best way to get a slice of the Swiss federal research pie is to be part of the ETH-domain (*Eidgenössische Technische Hochschule*). There are six such institutions in Switzerland, though none in Basel. This seemed a trifle unfair to Gian-Reto Plattner, former head of research at the Basel University and national parliament member for Basel Stadt. He approached the government with this observation. Eventually a branch of the ETH, the Basel Biosystems Science and Engineering Department (BSSE), was born, run under the auspices of ETH Zurich. Zurich saw the new department as being dedicated to the hip new field of systems biology, and aimed to attract back Swiss proteomics favourite son, Professor Ruedi Aebersold from Seattle. In 2003, the Basel branch was endorsed and Abershold headed home.

Then things got complicated: ETH Zurich, the universities of Zurich and Basel and the Ecole Polytechnique Federale de Lausanne (EPFL) entered an inter-University partnership in systems biology, called "SystemsX". Simultaneously, the universities of Geneva, Lausanne and the EPFL won funding to establish a genomics platform within a National Competence Centre of Research (NCCR). Both SystemsX and the genomics platform were seeking sustained support from the national government to assure continuity. Enough is enough, thought Charles Kleiber, State Secretary for Education and Research. In 2006, it was decided that there be just one Swiss-wide life sciences initiative and one pot of money for 2008-11 to be submitted for approval, under the name "SystemsX.ch". SystemsX.ch would coordinate Swiss systems biology research, encouraging collaboration between institutions to optimise use of resources. The most ambitious Swiss research collaboration ever was the result - something good to come out of politics!

Dr. Daniel Vonder Mühll was given the job of Managing Director of the new .ch entity, nutting out the operational guidelines. "It's not an easy job – every agreement has to go through 11 legal services!" he says. He organised a researcher's market place to work on the funds application for SystemsX.ch to start the ball rolling.

Aebersold, meanwhile, was re-acclimatising to Switzerland. "I'm used to the US system," he says, "it's very straightforward." Luckily, Kleiber's staff were helpful. "They knew how the government functions, and it functions in extremely complicated ways!" says Aebersold. The SystemsX.ch funding proposal generated consisted of just two pages, worth CHF 200 million, in a phone book of CHF 21 billion of science to be passed by the *Nationalrat* and *Staenderat* in 2007. If the book were to get through parliament, the two pages would too. Sure enough, they did. "I doubt anyone read the whole thing!" laughs Aebersold.

How systems biology works

To understand the scientific vision of SystemsX.ch, a closer look at systems biology is needed. Science is a long way from predictive models of biological systems (e.g. us). Scientists only recently decoded the genome - and that was the easy bit. The genome, comprising stretches of DNA code known as genes, is often compared to a book, and like a book it doesn't do very much. It's what the genes encode, the proteins, which actually do the work, and that's a whole new level of complexity. One gene is code for not one protein but often a whole family. You can make a protein using the whole of a gene, or read only part, making a shortened protein. You can cut the protein up, stick bits on it, or even spit it out of the cell. The possibilities are virtually endless. Scientists are a long way from having characterised all the proteins, the "proteome". They can't even say what fraction is done since we simply don't know how many there are.

Once you know all the characters, it's another matter to discover the plot. It's like some sort of super-cluedo: Which protein does what to whom, when, how much and in what "room" of the cell; do they need to dress up in carbohydrates, fats or phosphate groups; do they need accomplices; are others trying to stop them? After all, you can't murder Colonel Mustard if someone has locked you in the cellular toilet. Then, once you've worked out this series of events, or "pathway", you notice it's affected by events from another pathway; in fact many others in the same cell. That cell is then influenced by its neighbours …ultimately by everything going on in the body, directly or indirectly. Systems biology is an approach which aims to take into account this complexity and interconnectivity within biological systems.

Getting started is "very daunting," admits Aebersold, now chair of the

The ETH in Zürich.

scientific executive board of SystemsX.ch. "Committees continually say that the proteome has too many variables. You can say it's too complicated and give up, or you can define a problem you can reasonably approach and keep the caveats in the back of your mind."

One approach could see everyone start on a simple single-cell organism, like yeast, progressing in a concerted fashion until a predicative model of yeast is built, in a sort of yeast CERN. But SystemsX.ch involves collaborations between labs with different specialisations. It's almost as impossible to turn a fly lab-head into a yeast lab-head as it is to turn them into an actual fly. Instead, institutions were asked to put forward their own proposals. "I'm a strong believer in bottom up," says Aebersold, "it means people are interested. The projects have all kinds of flavours and I think that's the exciting part." To date 8 main projects (Research, Technology and Development projects, RTDs) have been accepted.

The SystemsX.ch approach is to start step by step. Aebersold cites the "YeastX" project as being one where significant progress can be expected. Its aim will not be – cannot be – to model the entire yeast in four years. To model even one cell, you need to detect every protein variant and locate it in the cell and the technology isn't advanced enough. YeastX will instead restrict itself to glucose and nitrogen sensing pathways. Since all the proteins involved in these paths are known, you should be able to put all the pieces together into a model.

At the other end of the scale, "LiverX" tackles a whole organ, and will focus on metabolic (energy) pathways involved in insulin resistance. In this case scientists do not know all the players, and a comprehensive model is not the immediate aim. Just identifying a few more proteins and how they fit in can still lead to the discovery of drug targets.

After four years, SystemsX.ch must prove itself worthy of funding after 2011. The Swiss National Science Foundation (SNSF) will monitor scientific quality while the initiative must show achievements in four areas:

- Driving collaboration between universities and research institutes (at least two different institutions must be involved in each RTD project). Institutions must match the money they receive from the government with their own funds to encourage commitment. Additionally, around 30 Interdisciplinary Pilot Projects (high risk projects of one year duration) are planned, fostering collaboration between different disciplines.
- Interacting with industry. An industry day will be held in March next year to fuel interest.
- Educating students and building capacity for the future. An educational program will be run and about 40 Interdisciplinary PhDs (IPhDs) offered.
- Boosting Switzerland's international scientific reputation, allowing it to attract scientists, be involved in international initiatives and win funding.

All this poses considerable challenges. One of the biggest is collaboration. Collaboration is crucial, as systems biology is interdisciplinary: "You can be as clever as you like, but on your own, you'll never get anywhere," says Vonder Mühll. Traditionally, scientists achieve recognition through first-author papers they publish - the famous publish or perish scenario. Scientists are reluctant to share data for fear of being scooped. "It's a huge problem … there's no real solution," says Aebersold. Some journals now start to allow joint first-author papers, he explains, but stresses that "it has to go much further: Students should get credit for datasets they put on the web, or for reviewing papers. Of course, people who hire students also need to change their value system."

Initiating and maintaining industry collaboration is also problematic. "Industry cooperation is unpredictable, they're under enormous short term economic pressure," says Aebersold. There's also academia's antipathy towards industry, finding the subjugation of science to business objectives distasteful. Nevertheless, there has already been some interaction with Novartis and Roche contributed several million francs to a large project in the Centre for Systems Physiology and Metabolic Disease at ETH Zurich.

Systems biology is mind-numbingly complex – perhaps as complex as the Swiss government! However, the SystemsX.ch pioneers believe that the desert can be crossed, experiment by experiment. All of which adds up to what Aebersold calls "a huge experiment for Switzerland." If all goes well, it's not just Switzerland but world science that will benefit and, hopefully, the rest of us.

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