

How does the alcohol get into the beer?  
By feeding sugar to yeast cells. Scientists working on «**YeastX**» are attempting to fathom the **regulatory processes** that unfold in the cell when the sugar is added – thereby developing a **fundamental modeling concept** to elucidate molecular biological phenomena.

Matthias Scholer «In the meantime we can measure so many things but we're having difficulty keeping up with understanding.» is how Uwe Sauer and Jörg Stelling sum up one of the main problems that Systems Biology research faces. And these two scientists know whereof they speak. After all, together with their respective teams at ETH Zurich, they have been investigating metabolic processes in yeast cells for many years. «Many Systems Biology projects are aimed at finding an answer to a specific question. But as a result, two fundamental mistakes are often made. Either strong simplification is accepted in the development of the corresponding model. Or research begins by collecting as much quantitative data as possible, which one subsequently attempts to integrate into a model. But this simply doesn't work,» explains Sauer. Because biological phenomena have one thing in common; they are devilishly complex, highly dynamic and overlapping. Conceptual models are wholly inadequate to understand such a system. «When one is dealing with biological phenomena a certain mathematical formalism is indispensable. A theoretical analysis of the problem is especially called for in the preliminary phase of the research when more than one explanation for a mechanism exists or where we have bigger knowledge gaps,» expounds Stelling.

#### Efficiency in research

Developing a model before commencing on an experiment brings another benefit: the subsequent research becomes more efficient. «We've got bi-

ologists who understand the problem, analysts who can carry out exact measurements, and theoreticians who can develop models for any given problem,» is how Sauer sums up the situation. This is why the individual parts of a project have to be coordinated. «If you develop a model and have to wait two years for the measuring data or you carry out measurements over a month and then have to wait a year for the matching model it's frustrating for everyone involved,» muses Sauer. If, on the other hand, the focus is on the design of the experiment already in the planning phase of the project, the results then fit the model and make efficient research possible.

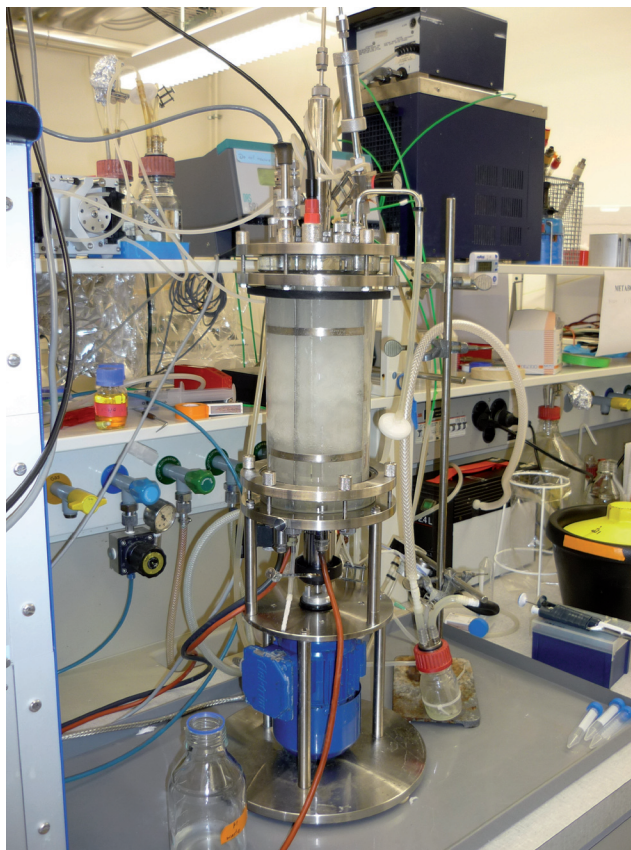
#### Yeast metabolism as a basic model

The SystemsX.ch project YeastX therefore aims to develop, on the theoretical side, a generic basic method. «We're trying to elaborate a modeling approach that can be adapted to many systems biological problems,» explains Sauer. Yeast serves the scientists as a model system, as this organism quickly allows them to put the necessary experiments into effect. Moreover, the results can later be transferred and applied to higher cells.

YeastX teams are concentrating on the nitrogen and glucose metabolism of yeast cells. «With their numerous networked interactions, the meta-

bolic pathways represent the complexity of biological systems,» says Sauer concerning the choice of the research direction.

Even though it has been known for a long time that yeast cells begin alcohol production depending on the glucose concentration in their environment, the molecular interaction between the genes, proteins and metabolites that are involved is still not well understood. «Respected scientists have been working on this problem for the past fifty years. But up until now we have failed to understand in detail how, for instance, the cell measures the level of sugar and how it implements the signal that it triggers,» says Uwe Sauer. «Until now we have been looking at metabolic chains on a molecular level. While the results this has yielded have helped us to understand many process-



Fully operating bioreactor – the basis for the «BIG Y» experiment. Photo: YeastX

es quantitatively and schematically, we're reaching the limits of how far this methodology can take us.»

### Uncertainty and restrictions

The complexity of metabolism poses two fundamental problems for researchers. On the one hand, the possibility of using experimental methods is restricted. On the other, great uncertainty exists when it comes to putting anything forward as a hypothesis on the processes of the signal chains. One consequence of this is that a number of models have to be developed for each problem, which must then be verified in experiments. In order to circumvent this cumbersome procedure, YeastX scientists divide the metabolic pathways into small segments, for which they then determine the most likely hypothesis. «This raises clear expectations, such as the dynamics of signal transmission. In turn, this can then be experimentally investigated.» says Stelling. Should the researchers succeed in developing a conceptual modeling approach

for the regulatory phenomena under investigation, the approach can be applied to many other unanswered system biological questions. Sauer adds, «Whether it's glucose metabolism or organ development. Most biological processes are triggered initially by

a signal that the cell then reacts to.» If researchers in the near future can discover, in detail, how a yeast cell measures the glucose concentration in its environment and then starts to produce alcohol, it would be of great interest, and not only to brewers.



The unflagging navy of the dynamic multiomics experiment («BIG Y»)

Photo: YeastX

## The «YeastX» Team:

The RTD project «YeastX» includes five project heads, each with a different area of responsibility:

- **Uwe Sauer** heads the YeastX project. His team develops new computer supported, quantitative measuring methods to analyze metabolic processes in yeast.
- **Jörg Stelling** is a researcher in bioinformatics at ETH Zurich. His focus is on computer simulations of metabolic pathways and the modeling of dynamic processes in cells and signal transduction.
- **Michael Hall** is a researcher at the Biozentrum of the University of Basel. YeastX benefits from his profound knowledge in the area of signal transmission.
- **John Lygeros** (ETH Zurich) brings his wide experience of control technique from the modeling of complex dynamic systems to the project.
- **Ruedi Aebersold** (ETH Zurich) has worked in the area of quantitative proteomics for many years and his fund of knowledge flows into the project.

### «YeastX – Towards an Understanding of Nutrient Signaling and Metabolic Operation» at a glance



#### YeastX

Towards an Understanding of Nutrient Signaling and Metabolic Operation

Principal Investigator	Prof. Uwe Sauer (ETH Zurich)
Involved research groups	Prof. Ruedi Aebersold (ETHZ), Prof. Joachim Buhmann (ETHZ), Dr. Matthias Heinemann (ETHZ), Prof. John Lygeros (ETHZ), Prof. Matthias Peter (ETHZ), Dr. Bernd Rinn (D-BSSE), Prof. Jörg Stelling (ETHZ), Prof. Andreas Wagner (University of Zurich), Prof. Mike Hall (University of Basel)
Number of research groups	10
Researchers : Administration	30 : 0,5
Biologists : Non-biologists	50 : 50
Total budget (2008-2011)	12'371'000, thereof 5'984'000 CHF from SystemsX.ch