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

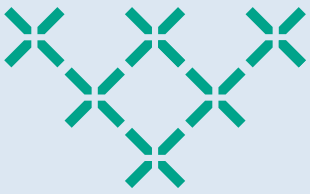
Principal investigator: Prof. Jörg Stelling

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