

# Powerful systems biology

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Using new methods, ETH-Zurich researchers have come another step closer towards solving the metabolic puzzle. Credit: Hanne Jarmer, DTU

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 biological control mechanisms.

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 an adaptation 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 show that 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 recognize 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.

**More information:** Buescher JM et al.: Global Network Reorganization During Dynamic Adaptations of *Bacillus subtilis* Metabolism. *Science*, 2012; 335: 1099-1103.

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