

Crunching numbers to decode biological processes

So many steps can go awry to disrupt a biological process and lead to errors. The StoNets project aims to determine how cells deal with disruptive factors and maintain stability. It combines experimental data with theory and mathematical models.



Mihaela Zavolan, professor for Computational & Systems Biology at the Biozentrum of the University of Basel, is in charge of the new StoNets RTD Project.

Whether we are trudging through the bitter cold or sitting on a sofa in a warm room – in both situations our skin cells function normally. “In a way, this is astonishing”, points out Mihaela Zavolan from the Biozentrum in Basel. Temperature has a direct influence on the processes that take place within cells. For instance, when a gene is read and transcribed into so-called mRNA, the latter takes on a different three-dimensional structure depending on the temperature. Yet, despite such changes at the molecular level, the cell as a whole manages to remain stable.

“There must be mechanisms capable of dealing with the fluctuations and preserving stability”, explains Zavolan, for there are other disruptive factors, besides temperature. Every biological process comprises a large number of steps, involving numerous molecules which need to be in the right place at the right time. There are many ways things can go awry, leading the process down a completely different track. “This is not like a maze, in which there is only one entrance and one exit”, emphasizes Zavolan.

A tiny molecule of great significance

In the StoNets RTD Project, Mihaela Zavolan aims to study the extent of the influence of disruptive factors on various biological processes and how cells deal with such situations and maintain stability.

In one of the sub-projects, the research team will closely examine the function of so-called microRNAs. These tiny molecules control the length of time an mRNA persists in a cell and consequently how often its information is translated into a protein. “MicroRNAs play a central role in controlling processes such as cell division and differentiation”, explains Mihaela Zavolan.

“Computer models help us understand biological processes that are extremely complex.”

It is not known how microRNA and mRNA find each other, what precise consequences the interaction has and or how the interplay of these molecules varies under the influence of temperature fluctuations and other factors. This is one of several biological processes that the StoNets team plans on studying during the next four years.

Different disciplines, one goal

Within the StoNets project, molecular biologists and biochemists will work closely with computer scientists and mathematicians. “The development of theories and the mathemat-

ical models based on experimental data that we obtain in our labs play a central role in our work”, explains Zavolan.

Interdisciplinarity begins with the project leader. Mihaela Zavolan first studied medicine. “But I quickly realized that, as a physician, I would only observe and interpret symptoms in order to treat patients. Yet I wanted to understand the causes of diseases”, the scientist tells us. This is why she studied computer science after obtaining her degree in medicine. Ever since, she has strived to understand biological processes by expressing them in numbers and formulas and by developing models. “Many biological processes are so complex that we are unable to understand them without the help of computer models.”

From experiment to theory

Nevertheless, computer calculations cannot replace experiments in the laboratory. Quite the opposite: a good model requires a considerable amount of accurate data. Based on this information, one can then develop a hypothesis and formulate mathematical models that will describe the relation between the various components of a biological process. “As soon as we have developed a model, we can specifically vary different values and determine how these modifications affect the process”, explains the scientist. Subsequently, an experiment is performed to determine whether the behavior in the model coincides with that observed in the test tube.

“There is a brisk back-and-forth between experiment and theory, and accordingly also between scientists working in different fields”, says Zavolan. When she took up her professorship at the Biozentrum in Basel, she was forced to fall back on data from

other research groups for her models. But since four years she has her own small laboratory and a team of technicians and biologists. “Now we can coordinate experiments and models much more efficiently”, adds a pleased Mihaela Zavolan.

Quantifying biology

According to Zavolan, molecular biology has long been a purely descriptive science, unlike physics and chemistry, fields that have since their beginnings combined theory and experiments. The reason for this is that “in chemistry, processes involving a small number of different molecules interacting with each other are typically studied.” A biological system such as a cell, on the other

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hand, often includes up to 100,000 different molecules, most of which are only present in very small quantities.

Many experiments are therefore, in a first step, aimed at determining whether or not a specific molecule is involved in a given process. Once it is known which molecule is present at which stage and in which concentration in a cell, it is possible to investigate its role in a given process thanks to mathematical models. Zavolan is convinced that “these models will allow us to take biology to a new level, turning this field into a quantitative science.”

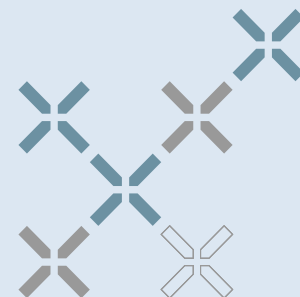
StoNets at a glance

Principal Investigator: Prof. Mihaela Zavolan

Research groups:

- Prof. Mihaela Zavolan, Biozentrum, University of Basel – Computational RNA biology
- Prof. Felix Naef, EPF Lausanne – Computational systems biology
- Prof. Erik van Nimwegen, Biozentrum, University of Basel – Computational modeling of regulatory networks
- Prof. David Gatfield, University of Lausanne – RNA biology
- Prof. Attila Becskei, Biozentrum, University of Basel – Systems biology of regulatory circuits
- Prof. Matthias Lutolf, EPF Lausanne – Stem cell bioengineering

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StoNets

Controlling and Exploiting Stochasticity in Gene Regulatory Networks