

The CycliX RTD Project

The end is also a new beginning

The life of an organism is based on a number of carefully concerted recurrent processes. How this synchronization is achieved and what happens at the gene level is still largely unknown. The scientists involved in the CycliX project are looking into the secrets of life's cyclic nature.



Cycles take center stage in Nouria Hernandez's research project.

The beginning was not easy. Comprehension problems and therefore disgruntlement within the team arose during the first gatherings of the various research groups. "During these meetings, all the participants reported on the progress achieved in their specific research area. In the beginning, there were situations where someone would explain something and colleagues from other disciplines would not understand what this person was trying to convey", remembers the CycliX RTD Project leader Nouria Hernandez. She is a molecular biology professor at the Center for Integrative Genomics at the University of Lausanne. This is where the said meetings take place and the laboratories in this institute are also where most of the experiments have been performed since this large-scale project was launched in 2009.

Complex subject

Nevertheless, the CycliX team very quickly found a "common language". "This was essential, as we depended on well-functioning teamwork and constructive exchange of thoughts between the various research areas. The intricacy of the subject requires this", explains the biologist. The complexity of the subject is reflected in the starting figures of the experiments: from a single sample, the scientists collect 150 million DNA pieces. The DNA sequence of each fragment is then determined before it can be assigned to one of approximately 20,000 genes. So far, the CycliX team has been able to perform this procedure on more than 200 samples, producing accordingly large amounts of data. These now need to be catalogued and made available for further analysis. "The computer

specialists, mathematicians and physicists in our team are developing made-to-measure database solutions and programs that will enable us to continue our work with the available results", explains the researcher.

Liver cells as a model system

All analyses were performed on mouse liver cells. The CycliX scientists use these as a model system to study three cycles present in all higher organisms. "We wish to understand how the daylight cycle, the nutrient cycle and the cell division cycle are regulated, but also how these three cycles influence each other", says Hernandez, roughly summarizing the project objectives. Although each cycle in itself has already been examined extensively, little is known about the overall genome reactions in the cycles and the corresponding transcription regulation programs. We also know very little about how these are connected and how they influence each other.

By means of an example, Nouria Hernandez illustrates the importance of the orchestration of the cycles within an organism: "During cell division, genetic material is susceptible to damage by free radicals. As radicals are mainly produced during the oxydative phase of the metabolic cycle, organisms such as yeast shift cell division to the non-oxydative phase, during which oxygen consumption is reduced."

The CycliX team hopes to quantitatively and comprehensively define all the genome reactions and transcription programs that characterize each cycle in mammals. The researchers are

particularly interested in understanding how the transcription programs communicate via a common “core” regulation network to guarantee integration and coordination within these three cycles.

Creating different populations

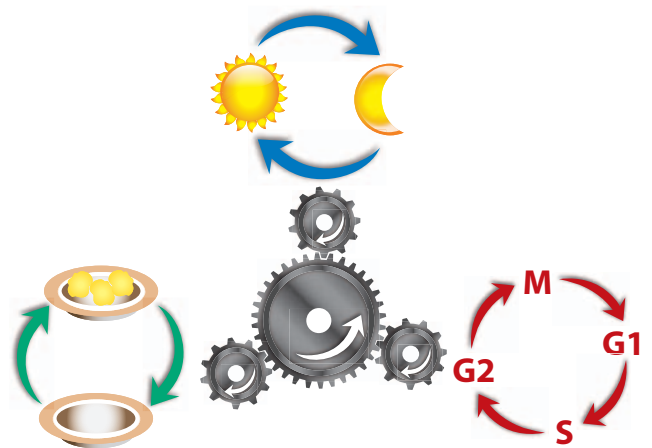
In a first step, the scientists determined the gene activity for each process in each of the three cycles. This endeavor was particularly difficult as all three cycles influence each other and it is not possible to discern whether a given gene activity is related exclusively to one cycle or whether it is the result of an interaction with another cycle. How can one examine an isolated cycle? “We needed to find a way to collect liver cells in which two of the three cycles showed little or no activity”, explains Nouria Hernandez. The complex task of breeding mouse populations that present a single active cycle was also tackled collaboratively by the scientists.

Important milestone has been reached

And now, almost four years later, the CycliX team has reached an important milestone. Very pleased, Hernandez says: “We have succeeded in collecting tissue samples from the various mouse populations. Now we can determine the activity status of 20,000 genes at any given point in time during a cycle.” Thanks to these data, the scientists now possess a multitude of genome activity snapshots in chronological order. These not only indicate when and where modifications of the genetic material take place, they also

enable the researchers to determine which genes promote a cycle and where interfaces between the systems are to be found.

Even though the CycliX RTD Project, partially financed by SystemsX.ch, is slowly coming to an end, the research work in this field will certainly not be discontinued. Confidently looking ahead, Nouria Hernandez says “a follow-up project has already been submitted”. Here, as in any cycle, the end of one thing is also the beginning of another.



The CycliX team is investigating how three common cycles in an organism attune to each other. Illustration: © CycliX

CycliX at a glance

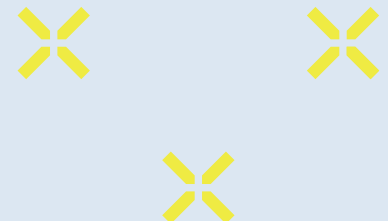
Principal Investigator: Prof. Nouria Hernandez

Research groups:

- Prof. Nouria Hernandez, Center for Integrative Genomics, University of Lausanne – Regulation of Gene Expression
- Dr. Mauro Delorenzi, Center for Integrative Genomics, University of Lausanne – Computational Biology, Models and Statistical Data Analysis
- Prof. Bart Deplancke, Institute of Bioengineering, EPF Lausanne – Systems Biology, Gene Regulatory Code
- Prof. Béatrice Desvergne, Center for Integrative Genomics, University of Lausanne – Lipid Metabolism and Homeostasis in Mammals
- Dr. Nicolas Guex, Vital-IT, University of Lausanne – Computational Biology
- Prof. Winship Herr, Center for Integrative Genomics, University of Lausanne – Regulation of Mammalian Cell Proliferation, Cell Division Cycle
- Prof. Felix Naef, Institute of Bioengineering, School of Life Sciences, EPF Lausanne – Computational Systems Biology, Biological Rhythms
- Dr. Jacques Rougemont, Bioinformatics and Biostatistics Core Facility, EPF Lausanne – Computational Biology, Biostatistics
- Prof. Ueli Schibler, Department of Molecular Biology, University of Geneva – Mammalian Circadian System, Biological Rhythms

Total budget (2009–2013): CHF 9.717 million, including CHF 4.478 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project



CycliX
Transcription
Regulatory Networks
of three Interacting Cycles