Laboratoire de Physico-Chimie Curie,
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M2 internship proposal

Uncovering molecular mechanisms of developmental tissue coordination with spatiotemporal temperature perturbations

Internship project description

Temperature impacts all biochemical reactions inside a cell. For developing multicellular organisms, temperature fluctuations pose challenges because morphogenetic events depend on both, spatially and temporally coordinated cellular decisions. Despite this, most multicellular systems show a surprising degree of robustness with respect to temperature changes within certain temperature limits. With climate change pushing organisms more and more often towards those limits, it is important to understand how those limits are set, what molecular mechanisms coordinate overall development of an organism and whether there are ways to control these mechanisms.

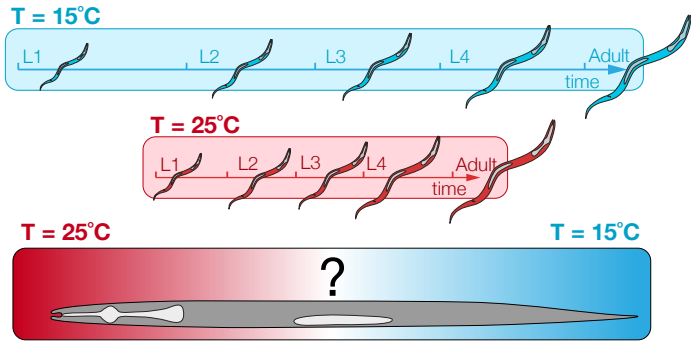

Figure 1. Graphical illustration of the main project idea. The C. elegans larva robustly develops through the four larval stages (L1-L4), almost twice as fast at 25˚C compared to 15˚C. The goal of the project is to uncover compensatory mechanisms that enable this adaptivity of development, by challenging *C. elegans* with a linear temperature gradient and observing gene expression dynamics and cell division timings in the hypodermis before, during, and after perturbation.

To address this question, our team has developed a new experimental setup, that allows us to place a small multicellular model organism (the nematode roundworm *C. elegans*) in a **linear temperature gradient during its larval development**. In our setup, the anterior part (head) of the animal can be maintained at either warmer or colder temperatures compared to the posterior part of the animal while high-resolution live-imaging is performed for several days. Surprisingly, animals develop normally in these extreme conditions, suggesting intercellular and interorgan signaling to achieve and maintain developmental coordination (Schlang et al., in preparation). Similar temperature gradient experiments have been performed with embryos of fruitflies (Lucchetta et al., Nature 2005) and frogs (Anderson et al, Cell Reports 2017), but gave strikingly different results, implying novel molecular mechanism underlying developmental synchrony during the post-embryonic phase of development.

The goal of this internship is to perform the first characterization of molecular players that may mediate tissue synchrony with focus on the *C. elegans* hypodermal stem cells. Using fluorescent reporters for developmental genes and mutants for candidate genes in the insulin and serotonin signaling pathways, the intern will investigate what may help the animal counteract the effects of this extreme environmental condition. Do to so, the student will perform spinning-disc confocal live-microscopy of animals kept in microfluidics device, an analyze various gene expression and cell division synchrony with and without the temperature gradient and how this may be changing in various genetic backgrounds. Additionally, we have recently developed technologies that allow us to visualize and analyze transcription dynamics in developing larva in real-time using the MS2-MCP-GFP tethering system (Kinney & Sahu et al. 2023). The student will use this system to ask whether and how transcriptional kinetics of developmental genes

are affected at different temperatures and how the temperature gradient condition impacts these kinetics.

Requirements

Candidates for this internship should have a strong motivation for interdisciplinary research at the interface between bioengineering, microfluidics, physics and developmental biology. Experience in live-microscopy or microfluidics with biological systems is a plus. Most importantly, the student should demonstrate a passion to see and study life in action. For details, please contact wolfgang.keil@curie.fr.

Environment

The Keil lab at Institut uses an interdisciplinary strategy to study transcriptional regulation, cell-fate patterning and morphogenesis in the model organism *C. elegans*. We are particularly interested in how developing system achieve robustness and precision in the face of environmental variability and molecular noise. To tackle this question, we develop and apply novel techniques for obtaining quantitative high-resolution dynamic gene expression data. We also develop theoretical approaches to conceptualise mechanisms of development and uncover general principles of developmental patterning. Check out https://curie.fr/equipe/keil for more information and feel free to contact us directly.

The Research Center at Institut Curie is a major player in the field of cancer research. It comprises a Hospital and a Research Center with over 1000 employees covering a wide range of nationalities. The Curie Institute Research Center aims to develop opened-ended science to progress in knowledge while exploiting arising possibilities to improve cancer care by stimulating synergies between research, training and innovation to support patients and serve our society.

Time frame

Start Date: January 2024
Duration: 6 months

Project references

Dynamics of Drosophila embryonic patterning network perturbed in space and time using microfluidics. Nature (2005) Lucchetta et al. https://doi.org/10.1038/nature03509

Desynchronizing Embryonic Cell Division Waves Reveals the Robustness of Xenopus laevis Development. Cell Reports (2017) Anderson et al.. https://doi.org/10.1016/j.celrep.2017.09.017

Team references

Circadian rhythm orthologs drive pulses of heterochronic miRNA transcription in *C. elegans*. Developmental Cell (2023); https://doi.org/10.1016/j.devcel.2023.08.006

An Epigenetic Priming Mechanism Mediated by Nutrient Sensing Regulates Transcriptional Output during C. elegans Development. Current Biology (2021) https://doi.org/10.1016/j.cub.2020.11.060

HLH-2/E2A Expression Links Stochastic and Deterministic Elements of a Cell Fate Decision during C. elegans Gonadogenesis. Current Biology (2019)
https://doi.org/10.1016/j.cub.2019.07.062

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https://doi.org/10.1016/j.devcel.2016.11.022