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M2 thesis internship proposal

Deciphering the Cellular Code for Developmental Time

Start Date: January 2027
Duration: 6 months
Keywords: Waddington Landscape, cell-fate, dynamical systems, *C. elegans*, stem cells, live imaging
Location: Paris, 75005, France Institut Pierre-Gilles de Gennes (IPGG)
Follow-up PhD: yes, funding acquired

Project

During multicellular development, a large diversity of cell-types is generated from small pools of progenitor cells. To achieve **ordered** and **timely** generation of each cell-type, progenitor cells assess cues along two primary sources of information[1]: *space* and *time*. In the most classic example for the acquisition of *spatial* cell identities, cells interpret a position-dependent concentration of a diffusible morphogen to spatially pattern into various cell-types[2,3] (Fig. 1). **While quantitative and predictive descriptions of morphogen decoding for spatial identity have emerged over the past decades, similar "cellular rules" for *temporal* patterning (Fig. 1) have not been uncovered.**

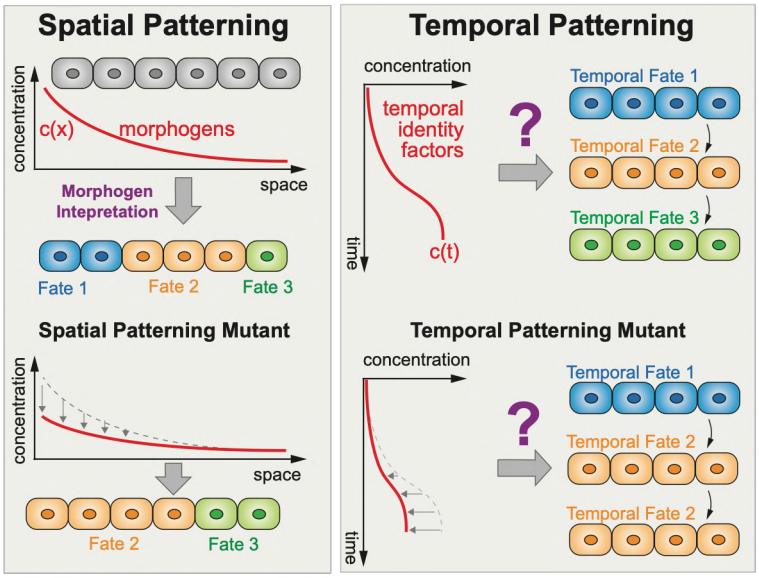


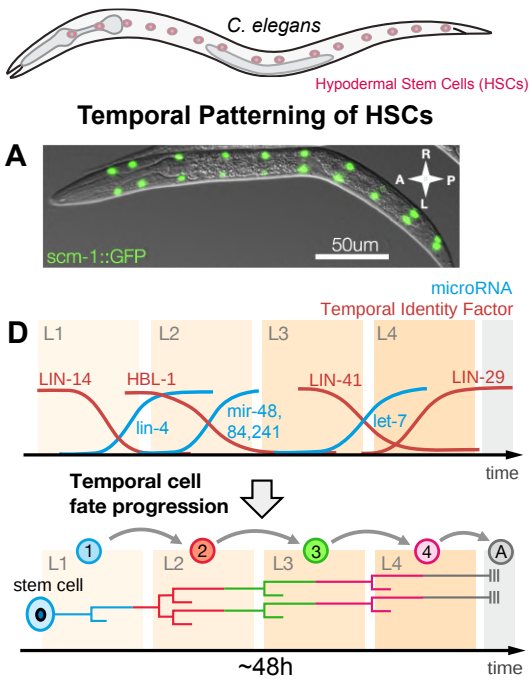
Figure 1: Spatial vs. temporal patterning to generate cell type diversity during development. In spatially patterning systems (left), cells interpret position-dependent morphogen concentrations to acquire cell-fates. In temporal patterning (right), cells execute a *sequence* of temporal cell fates in response to cell-intrinsic time-dependent concentrations of temporal identity factors (TIFs). The proposal aims to uncover principles by which cells interpret TIF dynamics to achieve timely and robust progression through temporal identities

Through live-imaging and mathematical modelling, the goal of this internship is to uncover **how cells interpret temporal cues** to generate **sequences of temporal identities** during development.

The key to **cracking the cellular code for developmental time** is measuring the *time-dependent* expression levels of temporal identity factors (TIFs) *together* with the resulting cell-fate sequences (Fig. 1). However, no *in-vivo* model system, be it the nervous system of fruit flies or the mammalian neo-cortex, has permitted such measurements up to now. In this project, we will use post-embryonic temporal patterning of hypodermal blast cells (HBCs) in the nematode *C. elegans* as a model system, which are uniquely qualified to overcome this current limitation of *in vivo* studies (Fig. 2).

In this system, stem cells express a series of transcription factors that are dynamically downregulated during development in a stepwise fashion to achieve a cell-fate progression (Fig.2). However, their expression has not been measured in live animals. This will be the our first task in this project. Next, we will measure cell-fate transformation in various temporal patterning mutants by counting stem cells numbers and computationally inferring the underlying cell-fate sequence.

Our team has previously shown that dynamical landscape models can quantitatively capture cell fate decisions during development (ref. 1). In collaboration with theoreticians from NCBS Bangalore and ENS, Paris, our final goal for this project will be to derive the first landscape models for temporal patterning



Schematics of the dynamics of the gene regulatory network during HBC temporal cell fate specification. (A) A C. elegans larva with HSCs labelled with GFP (green) (B) microRNAs (blue) accumulate in HBCs through transcriptional pulses (green) occurring once per larval stage. These miRNAs sequentially downregulate their targets which are the master temporal identity factors (TIFs) LIN-14, HBL-1, LIN-41, and LIN-29. (C) This leads to an invariant sequence of cell division patterns that characterizes each temporal fate, until blast cells terminally differentiate at the L4-to-adult transition. Cellular transitions between temporal fates 1, 2, 3 and 4 are evident by the execution of stereotypic cell-lineage patterns (color

This proposal will synthesize intuitive and predictive principles for cellular decision-making in the temporal domain, bound to generalize to other systems such as invertebrate or vertebrate nervous systems.

Requirements

Candidates for this interdiscplinary project should have a in biophysics or quantitative biology, as solid mathematical background and a strong interest pursuing in fundamental biological questions.

Prior experience with handling *C. elegans* or a background in model gene regulatory networks as dynamical systems is a plus.

Most importantly, candidates should be motivated to pursue interdisciplinary fundamental research and have a passion to see life in action. To apply, candidates should email us at wolfgang.keil@curie.fr. **The intership can be followd by a PhD thesis in the team for which funding has already been acquired.**

Environment

The Keil lab at Institut Curie 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 conceptualize 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.

Team references

(1) Quantitative guiding of developmental cell fate transitions using a dynamical landscape model. *PNAS* (2026) 10.1073/pnas.2521973123

(2) 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

(3) 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

(4) 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

(5) Long-Term High-Resolution Imaging of Developing *C. elegans* Larvae with Microfluidics. Developmental Cell (2017) https://doi.org/10.1016/j.devcel.2016.11.022