Sigmoidal transcriptional response of ERK-induced immediate-early genes

The proposed PhD project aims to understand how graded signalling inputs are transformed into a sigmoidal, switch-like transcriptional output in a multicellular context. During development, cells interpret fluctuating levels of signalling molecules to generate precise gene expression patterns with sharp boundaries. The mechanisms governing this process remain yet unclear and challenging to study, partly due to response heterogeneity that is inherent to many biological systems.

This project focuses on the FGF-ERK pathway in ascidian embryos, where a graded signal is converted into a sigmoidal transcriptional response of an immediate-early gene (IEG). The ascidian model offers a robust system for studying this process, as its invariant cellular configurations enable unambiguous identification of cells responding to FGF-ERK signalling. During early neural induction, all eight anterior ectoderm cells are exposed to FGF, but only two of them initiate neural specification by activating the IEG *Otx*. ERK activation levels scale with the contact surface between ectoderm and FGF-expressing mesendoderm cells, with neural precursors having the highest contact. The ERK-to-Otx input-output relationship follows a sigmoidal curve with a Hill coefficient of ~6.

The PhD student will explore the central working hypothesis that this sigmoidal response is driven by ETS-family transcriptional activator and repressor, Ets1/2 and ERF2, regulated by ERK in an inverse manner and competing for same DNA binding sites. The student will investigate cooperative binding, activator-repressor competition, multisite phosphorylation, nuclear transport, and stochastic signal dynamics as potential regulatory mechanisms. While these mechanisms have been studied individually, this project uniquely examines their combined effects.

This interdisciplinary project, conducted in collaboration with biologists and computational scientists, integrates quantitative imaging, molecular biology, and mathematical modeling. Given the evolutionary conservation of ERK cascades and their roles in development, homeostasis, and disease, the findings will have broad relevance to cell signalling, cancer biology, and developmental biology. (297 words)