Mathematical Investigation of Non-Deterministic Switches in Cell Regulation

M2 Internship
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Context

Gene-regulatory networks control the establishment and maintenance of alternative gene expression states during development. Some target states require coordination, e.g. two copies of the same gene, but in *opposing* states, via a *'toggle switch'* (Garner et al. [4]); see e.g. [10, 2, 7, 8]. The 'choice' of which copy enters which state is not predetermined. Explaining, or predicting, these choices, or their possible failures, requires sound mathematical analysis; the results appear heavily dependent on the modeling approach chosen. Unlike technical systems whose design and construction is human-controlled, natural systems can hardly ever be described, observed or understood to the last detail, and with the quantitative precision required by continuous models, such as differential equations. Discrete models such as Boolean Networks or Petri nets, provide abstractions from an underlying, approximately continuous-valued, and often only partially known dynamics. This abstraction aims at over-approximating the set of reachable states, to allow for analyses of causal dependencies, and to provide predictions of (at least) all possible behaviours. Applied to the toggle switch context above, the discrete analysis predicts several alternative behaviours, that are sensitive to choices in the model of dynamics.

Objectives

In the context of the above or similar biological challenges, the study will focus on approaching the problem via continuous models (Chemical Reaction Networks, or CRNs [3]), discrete models (Boolean Networks and Petri nets [1]), and in-between ones, namely *Most Permissive Boolean Networks (MPBN) [9]* and *Continuous Petri Nets (CPN)* (see [5, 6]) that have recently emerged as computationally manageable models with largely improved state space coverage and explanatory power. The intern's mission will comprise:

- *Mastery of tools.* This includes understanding of the mathematical/computational models used, the associated analysis techniques, and the existing computer tools, such as those in the Colomoto environment.

– *Analysis of sensitivity.* Moving from one model to the other typically reveals different, sometimes surprising, features of the system evolution. The questions to be investigated include whether these shifts indicate e.g. existence of previously undetected stable or metastable subspaces, etc.

Keywords

Cell regulation, chemical reaction networks, Petri nets, Boolean networks

Candidate Profile

We are looking for a highly motivated student interested in interdisciplinary approaches, with one of two profiles:

– a background in computational biology and strong interest in system dynamics ;
– solid skills in formal computational or mathematical modelling, and a strong interest in biology.

References

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