Research project for a Master 2 internship in theoretical computer science

Boolean networks generalised updatings
Towards understanding biological clocks

Abstract

Since the end of the sixties, Boolean networks introduced by McCulloch and Pitts in [MP43] have become central mathematical models of genetic regulation networks [Kau69, Tho73], for which many theoretical and applied results have been obtained [GM90, MAB98]. However, one question that remains open concerns the influence of the way Boolean entities update their states (1 or 0, expressed or not) along time [AGMS09, Nou12, NS18]. Two standpoints have appeared to be the most studied, according to more or less reasonable biological arguments :

(i) block-sequential updates that consist in separating the entities in disjoint blocks so that update is parallel inside a block but sequential between blocks [Rob86] ;

(ii) asynchronous updates that consist in considering all the possible sequential updates [Tho81].

Biologically speaking, these two approaches do not succeed in reflecting the reality of biological clocks at the level of genetic regulations. In this project, we propose to study more complex updates to reach a better understanding of the richness and the intricacies of biological regulation and highlight them in real biological networks.

Keywords : Discrete dynamical systems theory and combinatorics, Boolean networks, updating modes, biological regulation networks.

Objectives

The very objectives are to consider a definition of updating modes complying with biological heterogeneities (e.g., authorizing repetitions and avoiding non-fair updates *i.e.*, updates enabling entities to change state infinitely more often than other), to characterise them from an enumerative combinatorics point of view and to discover kinds of networks robust/sensitive to them (creation/suppression of attractors, even fixed points). According to the background of the candidate, one objective could also consist in finding and developing new adapted tools to study their influence in real biological networks.

Proposed approach

The proposed approach is mainly theoretical and takes place at the frontier of discrete mathematics and theoretical computer science : it deals with dynamical system and graph theories, enumerative combinatorics, complexity and computability on Boolean networks, each of these domains used in analysing deeply and subtly the behaviours of biological networks. More precisely, on the basis of general periodic updating modes that can be viewed as finite sequences of finite subsets of entities (and sub-families of these that include for instance block-sequential and asynchronous updating modes), the first work will consist in finding explicit formulae of the number of such updating modes, and put it in relation with already proven results. The second part will be dedicated to the study of specific features that allow creating/removing fixed points (we know that creation is possible, we do not know anything about removal). A possible third part would be to tackle the adaptation of useful tools (like update graphs) to this framework.

Interdisciplinarity

Whilst essentially anchored in mathematics and computer science, this project is driven by strong biological motivations : first, studying the impact of updating modes is a way to reach a better understanding of the chromatin dynamics which gives rise to the genetic expression clock ; second, previous studies showed that classical updating modes are not powerful enough to model biological systems exhibiting some kinds of synchronizing behaviours, like Zeitgebers (i.e. timers), which has been shown to be possible with the update modes mentioned above (and notably highlighted in plant growth and physiology). Moreover, analysing robustness/sensitivity of the asymptotic dynamics (creation/removal of fixed points for instance) of biological networks can lead to an adaptable and plastic framework to do cell reprogramming and model the emergence of new (even potentially pathological) phenotypes.

Supplementary information

The candidate/student will integrate the CANA (calcul naturel / natural computation) team of the LIS (Laboratoire d'informatique et systèmes / Laboratory of Computer Science and Systems) and will work in strong collaboration with the MABIOS (Mathématiques et algorithmique pour la biologie des systèmes / Mathematics and algorithms for systems biology) team of the I2M (Institut de mathématiques de Marseille / Institute of Mathematics of Marseille).

Internship duration : From 5 to 6 months.
Internship location : LIS and I2M, Luminy, Marseille, France.
Supervision : Sylvain Sené (LIS) and Laurent Tichit (I2M).
Compensation : Legal internship compensation implemented at Aix-Marseille University.

Références

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