Attractor Stability for biological networks in the Discrete-Continuous Spectrum

PhD Thesis
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Context

Attractors of network dynamics represent the long-term be- haviours of the modelled system. Their characterization is therefore crucial for understanding the response and differentiation capabilities of a dynamical system. *Biological* networks have an intrinsically complex dynamics that is hard analyse under the best circumstances. But in addition, 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. Therefore, instead of e.g. *chemical reaction networks (CRNs)* built using differential equations, one can use *discrete* models, such as Boolean Networks or Petri nets. These models provide an abstraction 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.

However, work in recent years has unearthed unsuspected limitations of discrete models (in fact, their failing to provide sufficient coverage of the studied system's state space). This leads us to making the boundary between discrete and continuous behaviour more permeable (rather than merely juxtaposing both, as in hybrid systems). A milestone here has been the introduction of *most permissive semantics* ([8]) for boolean networks (summarily abbreviated as *MPBNs*), which contains and extends all classical update modes, making heretofore undiscovered system states reachable and explorable. As an example of the implications, in cell regulatory networks this is tantamount to revealing possible cell phenotypes not previously predictable. These MPBNs remain a discrete model with a syntax enhanced by the addition of two new intermediate states per variable; in addition, they enjoy several nice structural properties and allow for computationally more efficient verifications.

Dually, we were able to show ([5]) how *continuous Petri nets (CPNs)* allow for precise abstract and symbolic semantics that show pathways and attractors in a discrete graph structure. Moreover, their linear dynamics permits to verify reachability and other properties in very efficient ways.

These two leads have recently merged in [6], with the proof that the boolean state reachability relations coincide for every MPBN and its canonical CPN translation.

Objectives

The thesis will aim at adapting concepts and methods from classical continuous stability theory as developped e.g. in [7], to Chemical Reaction Networks, or CRNs [4], to discrete models (Boolean Networks and Petri nets [3]), and in-between ones, namely *Most Permissive Boolean Networks (MPBN) [8]* 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. A benchmark comparison will be with the emerging theory of relative stability as a criterion for model selection, see [9], as well as with the works of Şafranek et al [2, 1]

Depending on the results obtained, techniques and concepts specific to the model class will then be developped. Possible extensions may also include *stochastic dynamics*, *robustness* under parameter perturbations, *abstract interpretation*, model selection, or process mining in metabolic or regulatory networks.

Work Context

The candidate will be working in the Musca team at INRIA Saclay, under the direction of Stefan HAAR. Musca is a joint team with CNRS and INRAE.

Candidate Profile

We are looking for a highly motivated student holding, or expecting, an M2 or equivalent, in computer science, mathematics or related fields, with good skills in formal computational or mathematical modelling. A strong interest in dynamical systems is required; a background in computational biology is helpful but not mandatory.

References

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