

ED STIC - Proposition de Sujets de Thèse pour la campagne d'Allocation de thèses 2017

Axe Sophi@Stic :

Titre du sujet :

Mention de thèse :

HDR Directeur de thèse inscrit à l'ED STIC :

Co-encadrant de thèse éventuel :

Nom :

Prénom :

Email :

Téléphone :

Email de contact pour ce sujet :

Laboratoire d'accueil :

Description du sujet :

The study of genetic regulatory networks has taken a qualitative leap through the use of modern genomic techniques that allow simultaneous measurement of the expression levels of all genes of an organism (DNA chips). In addition to high-throughput experimental methods, approaches in mathematics and computer science will be indispensable for analyzing the dynamics of genetic regulatory networks. BIOCORE team applies mathematical and computational methods from Control Theory and Dynamical Systems to the study of models of genetic networks and biological networks.

Biological networks play a major role in the regulation of living organisms and raise many regulation and control questions, such as stabilization towards a desired state. However, classical

control problems have to be revisited in a new light [2,4], as the control laws should satisfy biological constraints as well as be liable to experimental implementation. Synthetic biology experiments [1] have shown that it is possible to design and implement systems that exhibit a particular dynamical behavior, by assembling molecular components with the corresponding properties.

In addition, different mathematical formalisms may be used to model biological networks, for which different possible methods of analysis are available, each contributing with some new information. This project will focus on combining Boolean with piecewise affine models, to improve the characterization of the systems. These are useful modeling frameworks, based on a qualitative description of the systems that can be easily compared with the experimental data obtained from gene and protein expression [3]. One of the goals of the project is to develop methodologies for constructing piecewise affine and Boolean models from a given continuous model, to take advantage of the analytical tools available for the more abstract models [5].

This project will also address the problem of controlling the class of piecewise affine systems, under biologically appropriate restrictions. In general, the parameters of PWA systems represent synthesis and degradation rates of the molecular components of the biological network, and can be used as experimentally controlled “inputs” to the system. Possible control functions will be in the form of piecewise constant inputs to the system (constant in time intervals or in regions of space), and ranging in a qualitative scale. In a more advanced stage, control laws that depend on the variables of the system or dynamic feedback laws will also be explored. The control will be compared to a classical continuous one, and strategies will be studied to implement it with biological components.

The methods developed in this project will be applied to the genetic network that regulates growth in *E. coli*, with the goal of limiting growth rate under high nutrient availability (in collaboration with the biologists of the IBIS group, Grenoble). The aim is to implement the theoretical control in a biologically feasible form.

1. E. Andrianantoandro, S. Basu, D.K. Karig and R. Weiss. Synthetic biology: New engineering rules for an emerging discipline. *Molecular Systems Biology*, 2:2006.0028, 2006
2. E.D. Sontag. Some new directions in control theory inspired by systems biology. *IET Systems Biology*, 1:9-18, 2004
3. H. de Jong, J.L. Gouzé, C. Hernandez, M. Page, T. Sari and J. Geiselmann. Qualitative simulation of genetic regulatory networks using piecewise linear models. *Bull. Math. Biol.* 66:301-340, 2004
4. M. Chaves and J.-L. Gouzé. Exact control of genetic networks in a qualitative framework: the bistable switch example. *Automatica*, 47:1105-1112, 2011.
5. Wassim Abou-Jaoudé, Madalena Chaves, Jean-Luc Gouzé. Links between topology of the transition graph and limit cycles in a two-dimensional piecewise affine biological model. *Journal of Mathematical Biology*, Springer Verlag, 2014, 69 (6-7), pp.1461-1495.

Profile:

You are an ideal candidate for this position if you have a degree in applied mathematics (or similar) with a background in the analysis of dynamical systems, preferably familiar with control theory (and/or hybrid systems theory), you are enthusiastic for international and multidisciplinary work, and have a strong motivation to work on applications in biology and genomics.

Collaboration is planned with other INRIA teams as well as a biology laboratories.

see

<http://www-sop.inria.fr/members/Madalena.Chaves/>

<http://www-sop.inria.fr/members/Jean-Luc.Gouze/JLGouze-eng.html>

English version: