Ecole Doctorale STIC

Sciences & Technologies de l'Information et de la Communication

ED STIC - Proposition de Sujets de Thèse

pour la campagne d'Allocation de thèses 2015

Axe Sophi@Stic : BioSanté|

Titre du sujet : Analysis and Control of models of biological regulatory systems Application: growth control in E. coli

Mention de thèse : ATSI

HDR Directeur de thèse inscrit à l'ED STIC : Jean-luc Gouzé

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Laboratoire d'accueil : INRIA

Description du sujet :

Biological networks play a major the role in the regulation of living organisms and raise many control questions, such as stabilization towards a desired state. However, classical control problems have to be revisited in a new light [7,8], 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.

This project will address the problem of controlling the class of piecewise affine systems, under biologically appropriate restrictions. Piecewise affine (PWA) systems constitute an intuitive theoretical framework for the study of genetic regulatory networks, as they are based on a qualitative description of the systems that can be easily compared with the experimental data obtained from gene and protein expression [5]. 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 current project will focus on studying control problems for small circuits (motifs such as simple positive and negative loops, feedforward loops) and then investigate the insertion of each motif and its control method into a larger network. Control problems can be related to generating invariant regions, stabilization to a given steady state, or generating periodic solutions. The methods developed in this project will be applied to the genetic network that regulates growth in E. Coli [6,9], with the goal of limiting growth rate under high nutrient availability. The aim is to implement the theoretical control in a biologically feasible form. Moreover, a larger model of growth, built by biologists, will be studied, identified, and simplified.

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. G. Batt, B. Yordanov, R. Weiss and C. Belta. Robustness analysis and tuning of synthetic gene networks. Bioinformatics, 23(18):2415:2422, 2007
3. C. Belta and L.C.G.J.M. Habets, Controlling a class of nonlinear systems on rectangles, IEEE Transactions on Automatic Control, vol. 51, no. 11, pp. 1749-1759, 2006
4. E. Farcot and J.-L. Gouze. A mathematical framework for the control of piecewise affine models of gene networks. Automatica, 44(9):2326-2332, 2008
5. H. de Jong, J.L. Gouze, 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
6. D. Ropers, H. de Jong, M. Page, D. Schneider, J. Geiselmann (2006), Qualitative simulation of the carbon starvation response in Escherichia coli. BioSystems, 84(2):124-152.
7. E.D. Sontag. Some new directions in control theory inspired by systems biology. IET Systems Biology, 1:9-18, 2004
8. E.D. Sontag. Mathematical Control Theory (2nd ed.). Springer, 1998
9. Carta, A., Chaves, M., Gouzé, J.-L. (2012). A Simple Model to Control Growth Rate of Synthetic E. coli during the Exponential Phase: Model Analysis and Parameter Estimation. Computational Methods in Systems Biology, Lecture Notes in Computer Science, Gilbert, D. and Heiner M. editors, pp 107-126, Springer Berlin Heidelberg, http://dx.doi.org/10.1007/978-3-642-33636-2_8

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Webpage of JL Gouze, http://www-sop.inria.fr/members/Jean-Luc.Gouze/JLGouze-eng.html
Webpage of Biocore, http://team.inria.fr/biocore

Requirements:
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 biology laboratories.

English version:

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