

Identification Procedure for Piecewise Affine Models of Genetic Regulatory Networks

Samuel Drulhe^{1,2,*}, Riccardo Porreca³,
Giancarlo Ferrari-Trecate^{3,4}, Hidde de Jong¹

1. Institut National de Recherche en Informatique et en Automatique,
Centre de recherche Rhône-Alpes, Grenoble, France
2. Université Joseph Fourier, Grenoble, France
3. Dipartimento di Informatica e Sistemistica, Università degli
Studi di Pavia, Pavia, Italy
4. Institut National de Recherche en Informatique et en Automatique,
Centre de recherche Rocquencourt, Paris, France

*E-mail: Samuel.Drulhe@inrialpes.fr

Extended Abstract

Recent advances of experimental techniques in biology have led to the production of enormous amounts of data on the dynamics of genetic regulatory networks. We present an approach for the identification of piecewise affine models [6] of genetic regulatory networks [2, 7] from experimental data. These models rely on the hypothesis that regulation happens at the level of the synthesis and the degradation of the gene expression products: kinetic parameters are considered as being constant until a regulating protein concentration crosses a switching threshold.

The method we present focuses on the problem of detecting switches among different modes of operation in gene expression data [9] and on the reconstruction of switching thresholds associated with regulatory interactions [4]. In particular, our method takes into account geometric constraints specific to piecewise affine models of genetic regulatory networks. Such a hybrid identification method is designed for output-error systems where the observations are noisy time-series measurements of concentration levels inside a cell.

The points are first clustered into modes on which the dynamical behavior is assumed to be fully described by a linear differential equation. From the resulting classification, a pattern recognition technique is used to reconstruct all combinations of switching thresholds that are consistent with measured data in piecewise affine models. For the different proposed solutions, it is then possible to provide an identified regulatory network and the dynamical parameters of each mode of operation.

We have systematically assessed our approach on synthetic data simulated from a model of the carbon starvation response in the bacterium *Escherichia coli* inspired from [10] with different Gaussian noise standard deviations and different sampling times. Our results show that the method, coupled with sufficiently precise time-series data which can be obtained from reporter gene experiments, enables a quantitative identification of piecewise affine models of genetic regulatory networks.

References

- [1] Edmund J. Crampin. System identification challenges from systems biology. In *Proc. 14th IFAC Symposium on System Identification, Newcastle, Australia*, pages 81–93, 2006.
- [2] Hidde de Jong. Modeling and simulation of genetic regulatory systems: a literature review. *J Comput Biol*, 9(1):67–103, 2002.
- [3] P. D’haeseleer, S. Liang, and R. Somogyi. Genetic network inference: From co-expression clustering to reverse engineering. *Bioinformatics - Oxford*, 16(8):707–726, 2000. ISSN 1367-4803.
- [4] Samuel Drulhe, Giancarlo Ferrari-Trecate, Hidde De Jong, and Alain Viari. Reconstruction of switching thresholds in piecewise-affine models of genetic regulatory networks. In João P. Hespanha and Ashish Tiwari, editors, *HSCC*, volume 3927 of *Lecture Notes in Computer Science*, pages 184–199. Springer, 2006. ISBN 3-540-33170-0.
- [5] Giancarlo Ferrari-Trecate, Marco Muselli, Diego Liberati, and Manfred Morari. A clustering technique for the identification of piecewise affine systems. *Automatica - Kidlington*, 39(2):205–218, 2003. ISSN 0005-1098.
- [6] L. Glass and S. A. Kauffman. The logical analysis of continuous, non-linear biochemical control networks. *J Theor Biol*, 39(1):103–29, 1973.
- [7] J. Hasty, D. McMillen, F. Isaacs, and J J Collins. Computational studies of gene regulatory networks: in numero molecular biology. *Nat. Rev. Genet.*, 2(4):268–79, 2001.
- [8] Theodore J. Perkins, Mike Hallett, and Leon Glass. Inferring models of gene expression dynamics. *J. Theor. Biol.*, 230(3):289–299, 2004.
- [9] Riccardo Porreca, Giancarlo Ferrari-Trecate, Daniela Chieppi, Lalo Magni, and Olivier Bernard. Switch detection in genetic regulatory networks. In Alberto Bemporad, Antonio Bicchi, and Giorgio C. Buttazzo, editors, *HSCC*, volume 4416 of *Lecture Notes in Computer Science*, pages 754–757. Springer, 2007. ISBN 978-3-540-71492-7.
- [10] Delphine Ropers, Hidde de Jong, Michel Page, Dominique Schneider, and Johannes Geiselmann. Qualitative simulation of the carbon starvation response in escherichia coli. *Biosystems*, 84(2):124–52, 2006.