Learning gene regulatory networks with delayed ODEs and continuous-time expression representation

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Regulation of gene expression is fundamental to the operation of a cell. Revealing the structure and dynamics of a gene regulatory network (GRN) from gene expression measurements is of great interest and represents a considerably challenging computational problem. In addition to the difficulties arising from stochasticity in the underlying biological phenomena and considerable measurement noise, many of the existing methods have fundamental limitations, such as difficulties to cope with non-uniform measurement intervals and delays. For example, methods such as Bayesian networks are based on the assumption of equally spaced measurements. On the other hand, ordinary differential equation (ODE) based methods with the first-order approximation of the derivative might have difficulties with long gaps between measurements. The current knowledge on biology suggests that the time delays are significant in gene regulation. In this work, we propose solutions for these problems and analyze their effectiveness.

Here we extend our previously published method [1] by incorporating delays into analysis and by replacing the first-order order approximation of the derivative with an analytic estimate from a continuous expression profile, obtained from a Gaussian process (GP) representation. Delays in gene expression modeling are naturally incorporated into the Bayesian framework. The aforementioned method is based on the use of Bayesian analysis with ODEs and non-parametric GP modeling for the transcriptional level regulation. The main differences between our method and the existing ODE based methods are non-parametric modeling of molecular kinetics and Bayesian analysis.

For the validation we use a recently published *in vivo* data set [2]. The validation is done based on the structure learning and predictive capabilities of the method. The obtained results demonstrate that our method provides more accurate network structure learning and it is able to predict the dynamics of the studied GRN. Our results also show that the model extensions mentioned above have a positive effect on the prediction and structure inference compared to the results of existing methods. In particular, our results demonstrate the important role of delays in gene regulation modeling.

In addition, we will shortly review our approach to the predictive signaling network modeling challenge (DREAM 4, Challenge 3) in the poster. Our approach to this challenge is quite similar to the method presented in this abstract.

[1] T. Äijö and H. Lähdesmäki. (2009) Learning gene regulatory networks from gene expression measurements using non-parametric molecular kinetics. *Bioinformatics*, in press.

[2] I. Cantone, et al. (2009) A yeast synthetic network for in vivo assessment of reverse-engineering and modeling approaches. *Cell*, 137(1), 172 – 181.