Chapter 6

A Bayes Regularized Ordinary Differential Equation Model for the Inference of Gene Regulatory Networks

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ABSTRACT

Differential equation models provide a detailed, quantitative description of transcription regulatory networks. However, due to the large number of model parameters, they are usually applicable to small networks only, with at most a few dozen genes. Moreover, they are not well suited to deal with noisy data. In this chapter, we show how to circumvent these limitations by integrating an ordinary differential equation model into a stochastic framework. The resulting model is then embedded into a Bayesian learning approach. We integrate the-biologically motivated-expectation of sparse connectivity in the network into the inference process using a specifically defined prior distribution on model parameters. The approach is evaluated on simulated data and a dataset of the transcriptional network governing the yeast cell cycle.

INTRODUCTION

Developments in experimental technologies such as DNA microarrays and real-time PCR experiments render quantitative measurements of expression levels of a large number of genes feasible, and make the acquisition of time series concentration data possible. Such data can be used to reconstruct gene regulatory networks from the data, and to derive detailed quantitative models describing the dynamics of a system under consideration. These models can then be used to run simulations, to study the effect of particular interventions, and to analyze the dynamic behavior of the network under various conditions.

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Several different approaches have been developed in the last decade to infer regulatory networks from gene expression measurements. These approaches differ in the level of detail used to describe regulatory control mechanisms, and in the methods employed to estimate model parameters. The most frequent models used are correlation based models, models based on information theory, Boolean networks, Bayesian networks or, more generally, graphical models, and ordinary differential equations. Our focus in the following will be on the latter, and we will show how to integrate them into a probabilistic framework, which allows it to apply a Bayesian learning approach to parameter estimation.

Ordinary differential equations provide a quantitative time and state continuous description of a system's dynamic behavior. They are usually based on chemical reaction kinetics, and model parameters correspond directly to reaction rates, binding affinities and degradation rates. Therefore, they provide a very detailed and realistic description of a system under consideration. On the downside, the consequence of this detailed description in view of limited data is that the number of model parameters to be estimated usually far exceeds the number of measurements available. Parameter estimation then leads to underdetermined optimization problems. It is for this reason that in practice, network inference with (nonlinear) differential equation models is limited to networks of at most a few dozen components.

Another disadvantage of ordinary differential equation models is that they are not well suited to handle noisy data. However, experimental data are often prone to considerable noise. This further complicates the estimation of model parameters, since learning algorithms may simply tune to the noise in the data, instead of deriving true biological mechanisms.

In the following, we will describe an inference approach for gene regulatory networks from time series gene expression data which combines the detailed quantitative dynamics of differential equation models with a probabilistic modeling approach, thus taking noisy measurements into account. Parameters in this framework are estimated using Bayes' theorem. The problem with underdetermined models can then be addressed by integrating additional assumptions on model parameters through suitably chosen prior distributions. We discuss one particular prior distribution, which drives the inference to sparse networks. We then show that this enables the method to cope with datasets consisting of only few time points and a large number of model parameters. This makes the method particularly suitable for the task of quantitative modeling from typical real-world experimental datasets. We illustrate this claim both on simulated and real gene expression data from the transcriptional network governing the yeast cell cycle. Finally, we discuss relations between Bayes regularized differential equation models and other stochastic approaches from a more general point of view.

BACKGROUND

We will now derive the system of differential equations we use to model genetic regulatory networks. The underlying assumption is that these equations describe the true states of the biological system, which is hence a deterministic system. We will discuss this assumption and its consequences in more detail later.

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