Chapter 57
Optimal Intervention Methods for Markovian Gene Regulatory Networks

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ABSTRACT

A central problem in translational medicine is to provide a framework for deriving and studying effective intervention methods to elicit desired steady-state behavior for a gene regulatory network of interest with Markovian dynamics. Heretofore, two rather different external control approaches have been taken. The first optimizes a subjectively defined cost function while modeling treatment constraints; therefore, desirable shift of the steady-state mass is a by-product. The second approach, on the other hand, focuses solely on the steady-state behavior of the network and provides the maximal shift achievable. Although both approaches are optimal with respect to their objectives, the choice of which to use depends on the treatment goals.

INTRODUCTION

In order for a cancer treatment to be successful one must account for the patient's condition, the nature of the disease, its dynamics, the effect of antitumor drugs or radiation, the duration of effect and side effects. Each of these is a major field in the medical community, and a vast amount effort has been devoted to their characterization. Typically, the main objective of many treatment schemes is to find the right dose schedules while maximizing the benefit to toxicity ratio for a large portion of the patient population (Simon & Norton, 2006). To this end, treatments usually involve some kind of protocol and several drug candidates acting on various gene products with the aim of mitigating undesirable gene functions in cancer-related genetic pathways. Cancer therapies, for example chemotherapy, are usually administered in cycles, where each cycle begins by delivering a drug that kills cells which divide rapidly. The drug is effective for some period, on both normal and tumor cells, after which there is usually a rest period

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allowing the body to recover from the adverse effects of the drug (Brunton, Chabner, & Knollmann, 2010). To maximize the chance of eradicating a tumor, one should deliver the most effective drug at a sufficient dosage over as short a time as possible (Simon & Norton, 2006). However, since the toxicity of a drug could be intolerable to the patient, we desire a therapeutic method that acts very rapidly and with high efficiency so that a large percentage of tumor cells die or shift into a mode where they can no longer proliferate. The method should, at the same time, prolong patients' lives with reasonable quality during and after treatment.

The duration of effective response for a given set of drugs depends on many factors that may vary among a patient population or even in a population of cells within an individual. Achieving an acceptable success rate is tied to three key factors: (1) building accurate models for the underlying dynamical system governing the cancer and the drug response; (2) forcing cancerous cells to either initiate cell death or terminate differentiation as early as possible; and (3) choosing a suitable intervention strategy according to the states of the tumor and patient at the beginning of each therapeutic cycle (Yousefi, Datta, & Dougherty, 2013).

A gene regulatory network (GRN) refers to a class of models describing the multivariate functional relationships among a cohort of genes or their products. From a graphical perspective, genes are nodes in this network and edges describe regulatory relationships between genes. A GRN can be alternatively viewed as an input-output system, where the inputs are signals from signaling pathways or transcription factors, and the outputs are gene expression levels at a given time (Huang, Tienda-Luna, & Wang, 2009). A regulatory network should be able to predict the behavior of the collection of genes of interest under different conditions and perturbations (Dougherty & Shmulevich, 2012; Pe'er & Hacohen, 2011). These networks aim to model cellular control and how abnormal cell functions result from one or several breakdowns in the regulatory mechanisms, making them an important part of translational medicine (Dougherty, Pal, Qian, Bittner, & Datta, 2010).

Building a model for the underlying GRN is the first step toward designing optimal intervention. There has been a considerable amount of work on developing models and inference methods that provide accuracy, robustness, adaptivity and a system-level view, including Bayesian networks (Friedman, 2004), signed directed graphs (Kyoda, Baba, Onami, & Kitano, 2004), Petri nets (Chaouiya, Remy, & Thieffry, 2008; Matsuno, Doi, Nagasaki, & Miyano, 2000), differential equations (De Jong, 2002), stochastic differential equations (Chen, Wang, Tseng, Huang, & Kao, 2005; El Samad, Khammash, Petzold, & Gillespie, 2005), Boolean networks (Kauffman, 1969) and probabilistic Boolean networks (PBNs) (Shmulevich, Dougherty, Kim, & Zhang, 2002). Each modeling paradigm has its own strengths and weaknesses. For example, Bayesian networks are descriptive and require a large number of samples for inference. Boolean models are predictive, but they are very simplistic and come short when a more refined characterization of a regulatory process is needed. Although ordinary differential equations can capture quantitative molecular or physical details of the system, predictions are usually accurate only when the number of molecular species involved is large. When regulatory molecules are produced in small concentrations, fluctuations in the number of molecules have a significant impact on the process dynamics, and therefore a stochastic differential equation model is more appropriate (Cao & Samuels, 2009; Shmulevich & Aitchison, 2009).

Modeling GRNs via Markovian dynamical networks, such as PBNs, has received much attention recently because they are simple and can capture uncertainty, intrinsic or extrinsic, due to measurement noise in the data, latent variables or stochastic interactions among genes or gene products at different levels. Another feature of PBNs, which makes them attractive for studying intervention methods that affect