Chapter 34
Methods for the Analysis of Intracellular Signal Transduction Systems

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ABSTRACT

This chapter introduces some practical methods for the analysis of intracellular signal transduction systems. If a biological system is described by a linear ordinary differential equation, various analytical tools are available to elucidate a control mechanism for the system in question. However, few systematic methods are available for nonlinear systems in which it is more capable of wide application for practical problems to describe a biological phenomenon by nonlinear modeling. Here, three effective methods for nonlinear systems analysis are demonstrated with a practical example involving a large-scale nonlinear model that includes signal transduction pathways, nucleocytoplasmic shuttling, and both transcriptional and translational control. Two methods of metabolic control analyses (MCA) are explained; the classical type can be applied to static conditions, and the alternative method can be used to analyze dynamic properties, such as peak, duration, and integral of time-course responses. Unlike MCA that cannot be experimentally verified because of technical limitations, the authors next explain an analytical method with a large perturbation. Finally, they introduce a parameter sensitivity analysis and explain that, by changing input characteristics, such as amplitude and frequency, some analysis of robustness can be achieved.

INTRODUCTION

Since the complete human genome sequence was identified in 2003, the life sciences have largely focused on analyzing the functions of molecules, gene regulatory networks and protein-protein interactions to enhance understanding of cellular systems. However, biological systems consist of many components, are complicated when viewed holistically and are difficult to fully understand. Systems biology is an emerging field of study that has recently attracted attention in the life sciences by providing and mathematical analyses to esti-

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mate/analyze a control structure and to predict the dynamic behavior of biological systems. Although the subjects of systems modeling range from molecules to an entire cell, the methodology commonly involves the extraction of key elements, simplification of complicated processes and mathematical description of dynamic features for a biological phenomenon of interest. There are many modeling and mathematical studies that are capable of explaining a mechanism underlying experimental data. An ideal model is constructed from fewer molecules, which simplifies network structure and ensures reasonable mathematical equations. A representative example is detailed in a study by McClean *et al.* (2007), wherein the authors addressed on the role of pheromone and osmotic signals in budding yeast and demonstrated that a model with mutual inhibition between two signal transduction pathways could explain characteristics of signal-specific downstream digital gene expression. It should be noted that the proposed model is described by an ordinary differential equation with just six state variables. Heinrich (2002) described the MAPK cascade with the few Michaelis-Menten equations and demonstrated a general principle of dynamic behavior, such that amplitude of MAPK response was regulated only by kinases in conditions of weak activation; however, MAPK phosphatases played no role in this process. Other examples include work in which the MAPK cascade in *Xenopus* oocytes was shown to be able to function as a switch that converts continuously varying extracellular stimuli into an on-off response that arises as a result of bistability from positive feedback within the system (Ferrell, 1998). Interestingly, positive feedback has been demonstrated in signal transduction pathways in many cell lines (Markevich, 2004; Santos, 2007; Nakakuki, 2008). An important conclusion of these studies is that such models provide a simple means to theoretically analyze the inherent properties of the system in question. As a result, extensive analysis methods in differential equation and control theories in addition to others could be applied for these studies.

However, it is difficult to theoretically analyze a large and complex model because they generally contain higher-dimensional and nonlinear ordinary differential equations that make modeling a challenging task (Kholodenko, 1999; Schoeberl, 2002; Hatakeyama 2003). There are two routes to overcome the intractability of model analysis. The first way is to linearize a constructed model for which we expect to utilize theoretical analysis tools for linear systems. Azuma and colleagues (2008) described a gene regulatory network of a quorum-sensing system in the pathogenic bacterium *Pseudomonas aeruginosa*. This regulatory network, which could be described by the law of mass action and a Michaelis-Menten-like equation, was approximated by a piecewise-affine system with eight regions; in addition, controllability analysis was performed in this study. Currently, there are two propositions in linearization approaches: first, a conversion from an original nonlinear system to the piecewise affine system is difficult because a biological system tends to be high-dimensional; secondly, even if we obtain the resultant piecewise affine system, a practical analytical method for systems divided into multiple dimensions is quite limited.

On the other hand, the second way is a numerical analytic approach that does not involve linearization. A typical method is sensitivity analysis, which contains practical tools such as metabolic control analysis (MCA) and parameter sensitivity analysis and is utilized in various studies (Nakakuki, 2010; Kholodenko, 1999; Hatakeyama, 2003). In this chapter, we explain how to apply these sensitive methods to a large-scale nonlinear biological model (Nakakuki, 2010), such as signal transduction, transcription and translation.

EXAMPLE MODEL

A MCF-7 human breast cancer cell proliferates or differentiates in response to epidermal growth factor (EGF) or heregulin (HRG). This responsivity is beneficial to the study of how intracellular