Chapter XXXI
Discrete Networks as a Suitable Approach for the Analysis of Genetic Regulation

Elizabeth Santiago-Cortés
Universidad Nacional Autónoma de México, Mexico

Luis Mendoza
Universidad Nacional Autónoma de México, Mexico

ABSTRACT

Biological systems are composed of multiple interacting elements; in particular, genetic regulatory networks are formed by genes and their interactions mediated by transcription factors. The establishment of such networks is critical to guarantee the reliability of transcriptional performance in any organism. The study of genetic regulatory networks as dynamical systems is a helpful methodology to understand the transcriptional behavior of the genome. From a number of theoretical studies, it is known that networks present a complex dynamical behavior that includes stability, redundancy, homeostasis, and multistationarity. In this chapter we present some particular biological processes modeled as discrete networks to show that the theoretical properties of networks have a clear biological interpretation.

INTRODUCTION

Development of multicellular organisms requires the coordinated accomplishment of many molecular and cellular processes, like division and differentiation. Regulation of those processes must be very reliable, capable of resisting fluctuations of the internal and external environments. Without such homeostatic capacity, the viability of the organism would be compromised. For instance, unrestrained division of some cells may lead to the appearance of tumors, which may possibly cause death. Cellular processes

are finely controlled by a number of regulatory molecules, among them **transcription factors**. These are present inside cells at low quantities, and variations in their concentrations might alter cellular fate.

Modern high-throughput techniques have greatly increased the rate at which genomes are sequenced and genes are identified. Nonetheless, classic biochemical and physiological studies are necessary to identify the functions and molecular targets of the coded proteins. Of interest for this chapter are those genes that code for transcription factors. These proteins bind to cis-regulatory sequences of other genes, controlling or somehow modifying the **transcriptional rate** of their targets. If these targets code for other transcription factors, then and interdependence is created among genes forming a **genetic regulatory network** (Kauffman, 1991). The existence of regulatory networks have as a result the controlled and coordinated expression of a large group of genes. While these ideas are commonly accepted, biologists are not usually aware of the global properties of these networks. The reason is that they have some properties that are not evident or intuitive.

Modeling regulatory networks is very useful to understand how different gene expression patterns arise and are maintained. All cells in an organism have the same genes, and therefore the same global genetic regulatory network. Yet, each cell type differs from others in their particular molecular profile, *i.e.* in their **patterns of transcriptionally active genes** and the presence of other molecular markers. In addition, such genetic activation patterns are stable, in a normal situation cells do not differentiate continually from one type into another. This characteristics are due to the global properties of the underlying genetic regulatory networks (Kauffman, 1993; Thomas *et al*., 1995).

It is a common practice to graphically represent transcriptional regulatory interactions using **graphs**, since they are intuitive and easy to understand. However, the knowledge of the connectivity is not enough to determine the behavior of a regulatory network. For example, it is not possible to know how many **steady states** of genetic activation are allowed by a particular network, neither if those steady states are stable or not. To know these properties, it is necessary to incorporate the transcriptional rate of each gene as a function of its regulators. By doing this, a genetic regulatory network is translated into a **dynamical system**.

There is a large number of methodologies to analyze regulatory networks as dynamical systems (de Jong, 2002). Most modelers prefer to represent the dynamical system in the form of a set of ordinary differential equations that describe the transcriptional rate of genes. However, for most biological systems there is a lack of quantitative experimental information to fit the whole set of parameters in the system of equations. In contrast, there is a wealth of published experimental results that include *qualitative* information regarding the spatio-temporal activation of genes. Hence, some modelers have opted to model genetic regulatory networks as **discrete dynamical systems**.

It might appear at first sight that modeling using discrete variables is somehow inferior to the use of continuous variables, but it has been shown that continuous and discrete models share many qualitative dynamic features (Bagley and Glass, 1996; Glass, 1975; Glass and Kauffman, 1973; Muraille *et al*., 1996; Mendoza and Xenarios, 2006). In this chapter we present some properties of discrete networks, as well as some biological examples of regulatory genetic networks modeled as discrete state dynamical systems. These topics will show the reader that many important aspects of regulatory networks can be appropriately studied with the use of discrete dynamical systems.