

Chapter 22

A Model for a Heterogeneous Genetic Network

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ABSTRACT

In this chapter, we propose a new model for gene regulatory networks (GRN). The model incorporates more biological detail than other approaches, and is based on an artificial genome from which several products like genes, mRNA, miRNA, noncoding RNA, and proteins are extracted and connected, giving rise to a heterogeneous directed graph. We study the dynamics of the networks thus obtained, along with their topology (using degree distributions). Some considerations are made about the biological meaning of the outcome of the simulations.

INTRODUCTION

The recent ability to sequence an organism's genome, in particular the human one, was a great breakthrough thought to be the key to new ways to diagnose, treat, and some day prevent the thousands of disorders that affect us. However, simply knowing the gene sequences is not enough and the challenge is currently in deciphering how genes determine the phenotypic traits of an organism and how the genome controls the development of organisms.

For a long time it was believed that the DNA in the genes was transcribed into RNA, which in turn was translated into proteins in a one-way process. This is called the molecular biology's central dogma. The central dogma explains the basic process of gene expression into proteins, but is unable to explain several essential phenomena such as cellular differentiation, where cells with the same genetic information to behave differently according to their function in the organism. The explanation to such unaccountable

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processes lies in complex networks of interactions, known as regulatory networks, between genes and many other molecules including proteins, the very products of gene expression.

Since these regulatory networks are highly non-linear and have several thousand variables it is paramount to find computational models for them, albeit the difficulty of the task (Voit, 2000). Various approaches more or less abstract and more or less general for modeling gene regulatory networks appeared in the last decades. On one end of a possible axis of classification there are highly detailed biochemical models, such as Reinitz's phage- λ model (Reinitz, 1990), with which predictions and simulations of small and well understood systems can be performed; on the other end there are abstract models, such as Stuart Kauffman's Random Boolean Networks (Kauffman, 1993), that are commonly used to study broad scale and gross properties of the networks. Towards this more abstract end of the range, considerations are usually made about the network's topologies and dynamics (Kauffman, 1993; Thomas, 2001; Liebovitch, 2006; Barabási, 1999; Reil, 1999; Kuo, 2004; and Banzhaf, 2003; to name just a few). Most of the models used in these studies often merge the several processes that occur in protein synthesis, or focus on regulation only at transcription level. Given that regulation occurs at any stage of protein synthesis including transcription, RNA processing, mRNA decay, translation and post-translation (Hartl, 2005); it should be interesting to observe how the dynamics and topologies might be different when intermediate steps and entities are considered.

In this chapter we consider existing classes of models and their relevance for the exploration of theories and hypothesis regarding the structural and dynamic properties of regulatory networks when additional layers of regulation are taken into account. A new model for gene regulation complying with this aim is described later on. In order to compare the networks obtained with this model with networks obtained from previous models, we study some of their statistical properties, including: topology (using degree distributions) and dynamic behaviors.

BACKGROUND

Several models for Gene Regulatory Networks have been proposed in recent years. Because the biological processes involved in gene regulation are so highly complicated, the majority of these makes the assumption that the control of gene expression resides only in the regulation of gene transcription. Moreover, this may also be due to the nature of the most widely available microarray data (Gear, 2004; D'haeseleer, 2000). This overview is not meant to be exhaustive and we only briefly mention some of the known models. For a more extensive review and in-depth descriptions see de Jong (2002), Hasty (2001), Goncalves (2007), D'haeseleer (2000) and Gear (2004). We can classify the models that will be discussed here according to the following aspects: variables such as product concentrations are discrete, continuous or mixed; time is discrete and the update of the variables is either synchronous or asynchronous (there are, however, cases where time is continuous); space is discrete, continuous or absent (see Figure 1).

One very influential discrete approach early adopted a complex systems view of the genome (Kauffman, 1993). In this approach Kauffman represented the regulatory system as a network of logical components connected at random, creating networks, which he coined as Random Boolean Networks (RBNs). These RBNs exhibited emergent properties, such as cyclic attractors, point attractors, robustness and homeostasis, that also occur in real biological systems. The abstract similarity between the RBNs and biological cells made the simplification of modelling time as discrete time steps and considering only

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