Chapter 18
Generalized Boolean Networks:
How Spatial and Temporal Choices Influence Their Dynamics

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ABSTRACT

Random Boolean Networks (RBN) have been introduced by Kauffman more than thirty years ago as a highly simplified model of genetic regulatory networks. This extremely simple and abstract model has been studied in detail and has been shown capable of extremely interesting dynamical behavior. First of all, as some parameters are varied such as the network's connectivity, or the probability of expressing a gene, the RBN can go through a phase transition, going from an ordered regime to a chaotic one. Kauffman's suggestion is that cell types correspond to attractors in the RBN phase space, and only those attractors that are short and stable under perturbations will be of biological interest. Thus, according to Kauffman, RBN lying at the edge between the ordered phase and the chaotic phase can be seen as abstract models of genetic regulatory networks. The original view of Kauffman, namely that these models may be useful for understanding real-life cell regulatory networks, is still valid, provided that the model is updated to take into account present knowledge about the topology of real gene regulatory networks, and the timing of events, without loosing its attractive simplicity. According to present data, many biological networks, including genetic regulatory networks, seem, in fact, to be of the scale-free type. From the point of view of the timing of events, standard RBN update their state synchronously. This assumption is open to discussion when dealing with biologically plausible networks. In particular, for genetic regulatory networks, this is certainly not the case: genes seem to be expressed in different parts of the network at different times, according to a strict sequence, which depends on the particular

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network under study. The expression of a gene depends on several transcription factors, the synthesis of which appear to be neither fully synchronous nor instantaneous. Therefore, we have recently proposed a new, more biologically plausible model. It assumes a scale-free topology of the networks and we define a suitable semi-synchronous dynamics that better captures the presence of an activation sequence of genes linked to the topological properties of the network. By simulating statistical ensembles of networks, we discuss the attractors of the dynamics, showing that they are compatible with theoretical biological network models. Moreover, the model demonstrates interesting scaling abilities as the size of the networks is increased.

INTRODUCTION TO RANDOM BOOLEAN NETWORKS

Gene regulatory networks are formed by genes, messenger RNA, and proteins. The interactions between these elements include transcription, translation, and transcriptional regulation (Albert, 2001). The processes are extremely complex and we are just beginning understanding them in detail. However, it is possible, and useful, to abstract many details of the particular kinetic equations in the cell and focus on the system-level properties of the whole network dynamics. This Complex Systems Biology approach, although not strictly applicable to any given particular case, may still provide interesting general insight.

Random Boolean Networks (RBNs) have been introduced by Kauffman more than thirty years ago (Kauffman, 1969) as a highly simplified model of genetic regulatory networks (GRNs). RBNs have been studied in detail by analysis and by computer simulations of statistical ensembles of networks and it has been shown to be capable of surprising dynamical behavior.

In the last decade, a host of new findings and the increased availability of biological data has changed our understanding of the structure and functioning of GRNs. In spite of this, we believe that the original view of Kauffman is still valid, provided that the model is updated to take into account the new knowledge about the topological structure and the timing of events of real gene regulatory networks without loosing its attractive simplicity. Following these guidelines, our aim in this work is to describe and test a new model that we call Generalized Boolean Networks (GBNs), which includes, at a high level of abstraction, structures and mechanisms that are hopefully closer to the observed data.

Adhering to the original Kauffman's view that attractors of the dynamics of RBNs are the important feature and that they roughly correspond to cell types, we will discuss the results of the systems ability to relax into stable cycles.

In Kauffman's RBNs (known as Classical RBNs) with N nodes, a node represents a gene and is modeled as an on-off device, meaning that a gene is expressed if it is on (1), and it is not otherwise (0). Each gene receives K randomly chosen inputs from other genes. From a simplistic point of view, the combined effect of proteins produced by genes g_1 to g_K attaching to a *mRNA* binding site, thus either promoting or repressing the activity of gene g, can be seen as a direct effect of a function $f(g_1,\ldots,g_K,g,t) \rightarrow g^{t+1}$. In this case, we allow g to be one of the arguments of the gene update function f, thus permitting self-regulation. If we assume all genes are Boolean nodes, we can define the activity of any gene at time $t+1$ as the result of a Boolean function of each of the gene's entries at time t.

Initially, one of the 2^{2^K} possible Boolean functions of K inputs is assigned at random to each gene. The network dynamics is discrete and synchronous: at each time step all nodes simultaneously examine