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Stability and Structural Properties of Gene Regulation Networks with Coregulation Rules

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Abstract

Coregulation of the expression of groups of genes has been extensively demonstrated empirically in bacterial and eukaryotic systems. Such coregulation can arise through the use of shared regulatory motifs, which allow the coordinated expression of modules (and module groups) of functionally related genes across the genome. Coregulation can also arise through the physical association of multi-gene complexes through chromosomal looping, which are then transcribed together. We present a general formalism for modeling coregulation rules in the framework of Random Boolean Networks (RBN), and develop specific models for transcription factor networks with modular structure (including module groups, and multi-input modules (MIM) with autoregulation) and multi-gene complexes (including hierarchical differentiation between multi-gene complex members). We develop a mean-field approach to analyse the dynamical stability of large networks incorporating coregulation, and show that autoregulated MIM and hierarchical gene-complex models can achieve greater stability than networks without coregulation whose rules have matching activation frequency. We provide further analysis of the stability of small networks of both kinds through simulations. We also characterize several general properties of the transients and attractors in the hierarchical coregulation model, and show using simulations that the steady-state distribution factorizes hierarchically as a Bayesian network in a Markov Jump Process analogue of the RBN model.

Keywords: Random Boolean Networks, Mean-field Approximation, Network Motifs, Stochastic Gene Expression, Markov Jump Processes

1. Introduction

Empirical work has demonstrated that coregulation is a ubiquitous characteristic of transcription factor networks (which we shall refer to as gene regulation networks, or GRNs) in bacterial and eukaryotic systems. The operon model (Jacob and Monod (1961)) provides a simple example of the coregulation of a group of genes in bacteria. Extensive investigation of GRNs in the bacteria *Escherichia coli* and the yeast *Saccharomyces cerevisiae* has revealed a range of network motifs indicative of various types of coregulation between groups of operons or genes (Alon (2006, 2007); Milo et al. (2002); Shenn-Orr et al. (2002)). Further investigation of *Saccharomyces cerevisiae* has revealed that a large component of its GRN can be modeled as a collection of modules each with characteristic functional roles and regulatory motifs, and that these can be further organized into a collection of *module groups* which share common regulators and regulatory motifs in a combinatorial fashion (Pe'er et al. (2002); Segal et al. (2002, 2003)).

Further work in eukaryotic cells has revealed that coregulation of gene transcription can also occur through the physical association of multi-gene complexes which are transcribed together (Fanucchi et al. (2013); Li et al. (2012); Papantonis et al. (2012)). Such coregulation is dependent on the 3D chromatin conformation of the nucleus in a given cell, which may be stochastic (Fanucchi et al. (2013)). Further, results have shown that the multi-gene complexes formed can have a hierarchical structure, where the transcription of certain members in the complex is dependent on other members in the multi-gene complex being cotranscribed (Fanucchi et al. (2013); Li et al. (2012)). The functional relevance of such hierarchical coregulation is yet to be characterized.

In the following, we are interested in characterizing the properties of networks involving coregulation rules in a general sense. For this purpose, we draw on the framework of Random Boolean Networks (RBNs) (Kauffman (1969, 1993)). RBNs have provided a powerful framework in which the relationship between topological/rule-based constraints and dynamic (or emergent) properties of a network can be characterized through a combination of analytic and simulation-based methods. Examples of biologically inspired constraints include scale-free topology (Aldena (2003); Kauffman et al. (2004)) and *canalyzing* regulation rules (Kauffman et al. (2004)); while emergent dynamical properties include network stability/criticality (Derrida and Pomeau (1986); Kauffman et al. (2004)), attractor and transient structure (Kauffman (1993); Samuelsson and Troein (2003); Kauffman et al. (2004)), and evolvability (Torres-Sosa et al. (2012)). The application of mean-field methods from statistical physics has permitted analytic results to be obtained in a number of these cases (Aldena (2003); Derrida and Pomeau (1986); Kauffman et al. (2004)). Further, empirical studies have shown that RBNs can be used directly to understand the dynamical properties of actual biological sys-

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