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Logical and symbolic analysis of robust biological dynamics

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Logical models provide insight about key control elements of biological networks. Based solely on the logical structure, we can determine state transition diagrams that give the allowed possible transitions in a coarse grained phase space. Attracting pathways and stable nodes in the state transition diagram correspond to robust attractors that would be found in several different types of dynamical systems that have the same logical structure. Attracting nodes in the state transition diagram correspond to stable steady states. Furthermore, the sequence of logical states appearing in biological networks with robust attracting pathways would be expected to appear also in Boolean networks, asynchronous switching networks, and differential equations having the same underlying structure. This provides a basis for investigating naturally occurring and synthetic systems, both to predict the dynamics if the structure is known, and to determine the structure if the transitions are known.

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Introduction

One of the defining characteristics of living organisms is a remarkable insensitivity of function and form to stochastic fluctuations both in the environment and in the organism itself. This robustness is a ubiquitous feature of dynamics of biological processes ranging from intrinsic oscillations and rhythms to the development of multicellular organisms.

The current explosion of information concerning biological processes on multiple size scales poses a challenge. Although there are many who are attempting to develop new computer methods and mathematical models that incorporate the most detailed anatomical and physiological data available, such approaches often do not lend insight into the origin of robustness. An alternative approach is to identify defining characteristics of biological processes and to develop theoretical insight using methods that relate the structure and interactions in biological networks to qualitative descriptions of the dynamics. Although the roots for such an approach were set long ago [1–4], the emergence of systems biology has witnessed the determination of network structures, interactions and dynamics in a large number of different systems [5,6,7••]. Synthetic biology has enabled the construction of networks that support switchlike behavior and oscillatory dynamics. In some cases, logical analysis can aid in the design of the networks by predicting their dynamics before their synthesis [8•].

Logical models are providing insight into the underlying structures of a variety of biological systems [9•,10••]. In this review, we first discuss the state transition diagram, which provides the link between the logical models and the dynamic features. Then we discuss the topological structure of networks describing biological systems. We then review work that combines logical analyses with concepts from nonlinear and symbolic dynamics to provide a bridge between the structure and function of complex biological networks.

The state transition diagram

In continuous mathematical models of biological networks, variables represent such features as concentrations of chemicals, currents through ion channels, or firing rates of neurons. Trajectories show the changes of these variables over time. However, symbolic representations provide a useful alternative description of dynamics. The two main symbolic descriptions being used are the rate of change [11,12••], and a coarse graining of state space, for example by indicating whether variables are above or below some threshold [2,13,14••]. Using symbolic dynamics, trajectories can be represented as directed graphs, called *state transition diagrams*, in which each vertex represents a symbolic state, and the edges are directed to show the allowed transitions. The repressilator synthetic network [15] is composed of a set of three genes that code for transcription factors, where each of the transcription factors inhibits the synthesis of the next in sequence, giving $x \dashv y \dashv z \dashv x$, where $\dashv$ represents an inhibitory interaction. The repressilator network can be represented by binary variables. The state 1 for a variable could correspond either to the variable having a positive derivative [12••] or to the variable being above a threshold [16,14••]. The state 0 may analogously designate a negative derivative or a variable being below a threshold. Viewed as a Boolean switching network, an

appropriate transfer truth table representation for this network is

$(xyz)_t$	$(xyz)_{t+1}$
(111)	(000)
(110)	(100)
(101)	(001)
(100)	(101)
(011)	(010)
(010)	(110)
(001)	(011)
(000)	(111)

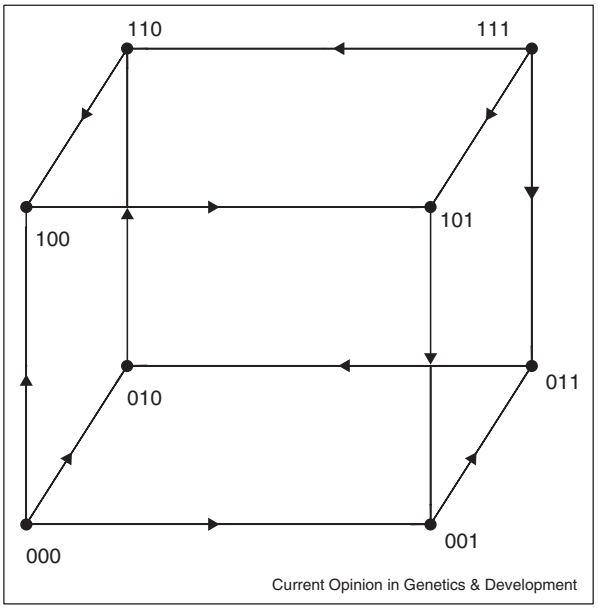
This switching circuit therefore displays two cycles $000 \rightarrow 111 \rightarrow 000 \rightarrow \ldots$, and $100 \rightarrow 101 \rightarrow 001 \rightarrow 011 \rightarrow 010 \rightarrow 110 \rightarrow 100 \rightarrow \ldots$. However, since the cycle $000 \rightarrow 111 \rightarrow 000 \rightarrow \ldots$ requires three elements to switch simultaneously, and in real systems modeled, for example, by differential equations or discrete systems with stochastic updating, there would only be the possibility for one element to switch in any time. Therefore, the logical network describing the repressilator circuit has the state transition diagram shown in Figure 1.

We propose that a large number of different biological systems contain an underlying logical structure which can be used to determine the state transition diagram by extending the methods used to determine Figure 1. Given the robustness of biological dynamics, the state transition diagrams will show an *attracting pathway*, in which all (or almost all) edges with one vertex on the pathway are directed toward it. Further, for systems that evolve robustly to a steady state, the state transition diagram will contain a stable node to which all neighboring states are directed. The presence of attracting pathways and stable nodes in logical state spaces provides the theoretical basis for explaining how gene networks robustly demonstrate oscillations or carry out computation [17,14••].

Topological structure of networks and interactions

One of the outstanding successes of modern biology has been the development of tools to determine on a mass scale the mutual interactions of key biological components including proteins, DNA, and RNA [18–22]. Various statistical and structural features of the resulting interaction graphs in biological systems can be compared with interactions graphs of social and man-made systems [23]. Although various characteristics (e.g. scale-free, small-world, power-law) have been ascribed to the global topological connectivity patterns in such networks, recent analyses question the validity of the original studies [24••]. Focus is shifting to the importance of *network motifs* defined as small subgraphs of a large network that occur with greater frequency than would occur simply by chance [6,25]. Network motifs indeed often correspond to functional modules [5,6,26••], such as positive and negative feedback loops and feedforward circuits, that are useful in self-regulation, differentiation, and signal transduction.

Figure 1



State transition diagram of the repressilator [15]. The attracting cycle corresponds to a stable oscillation in the experimental system and in mathematical models of the repressilator. The inconsistency between the figure and the truth table, as noted in the text, emphasizes an important shortcoming in synchronous updating.

In many instances, interactions can be determined to be activating or inhibiting. However, this characterization often lacks adequate specificity to make predictions about dynamics. For example, we may have two activating inputs for a given element of a network, but both may be needed for activation (AND function), or either alone (OR function) may be adequate. The dynamics could be very different in these two cases [16]. As another example, if a given element receives both activating and inhibiting inputs, the dynamics may differ depending on which was dominating when both were present. In early development in Drosophila, inhibitory inputs generally negate activating inputs when both are present [27,28••]. It is conceivable that a given input might be either activating or inhibiting depending on other factors such as the presence of other elements in the network. These examples show that it may be necessary to know more than the sign of the interaction.

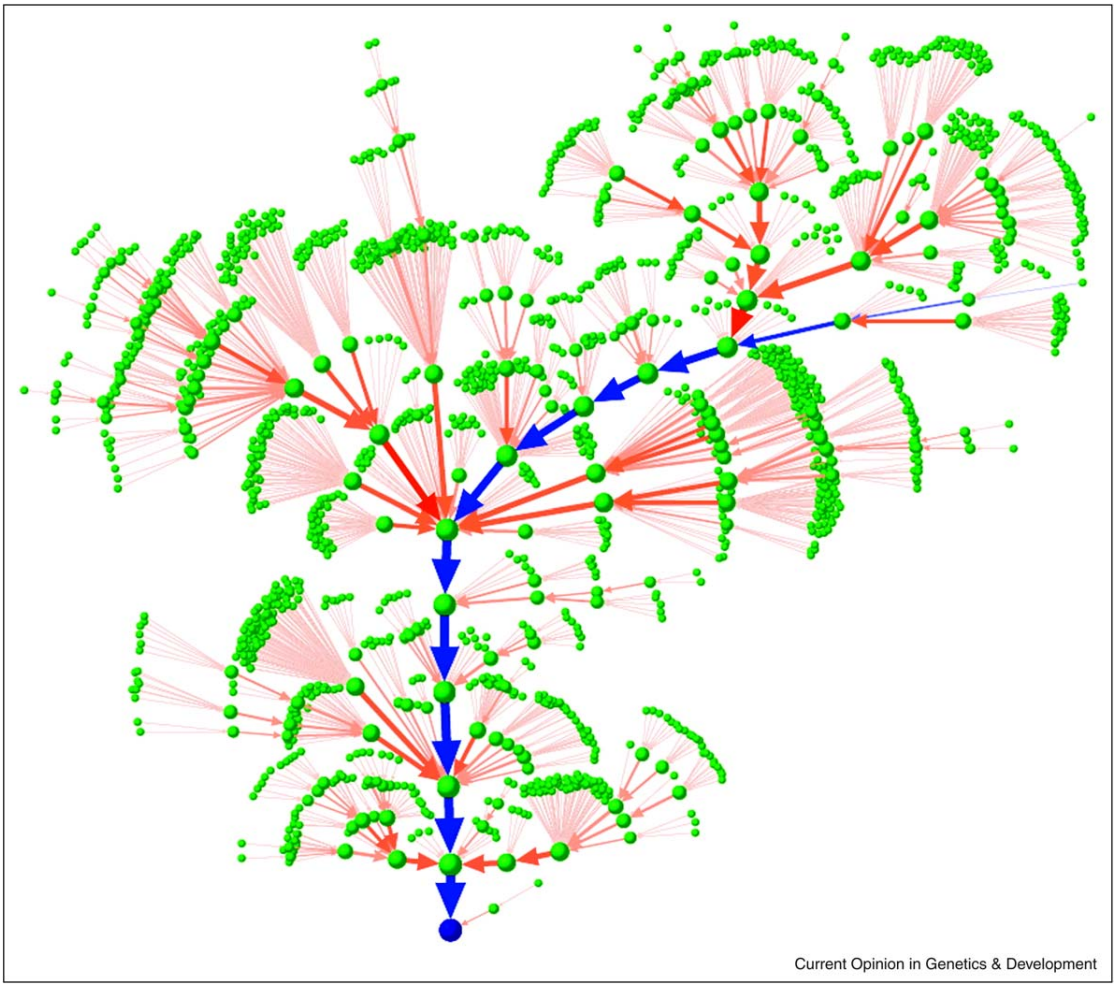
Logical models of biological networks

Logical models of biological processes are based on the assumption that key steps of biochemical control may often display control in which output variables change rapidly as input variables are varied. Proposed physiological bases for this ultrasensitivity include allosteric

changes in protein conformation, cooperative binding of transcription factors to DNA, and reaction cascades [7••,29,30•,31,32]. Such processes will only lead to sigmoidal dependence of output on input variables. However, state transition diagrams based on the logical structure can be often used to predict dynamics of continuous equations with sufficiently steep sigmoidal functions [33,16].

Many different types of model are subsumed under the rubric 'logical model' [34,10••]. In Boolean switching networks all variables update synchronously [1]. In one variant, the functions for each variable may not be fixed, but may be selected in a probabilistic fashion [35]. Since synchronous updating is not biologically realistic, various modifications have been tried. Thomas suggested incorporating time delays into the dynamical control [3]. Although the resulting class of Boolean delay equations may have extremely complex dynamics for some choices of delays and logic functions [36], such models have nevertheless been useful for modeling biological systems [37]. In alternative approaches for updating logical models of biological control, transitions are assigned to different synchronous priority classes [38], or asynchronous stochastic updating is assumed [39•,40–42]. Another approach embeds the logical structure in differential equations in which synchronous crossing of thresholds is rare [2,14••]. In this context the state transition is a directed hypercube, where each vertex is labeled by a Boolean vector as in Figure 1. Such state transition diagrams also show all the possible allowed transitions for logical networks with stochastic asynchronous updating. Consequently, based solely on the logical structure of the network, it is possible to predict symbolic sequences of transitions in various embodiments of the underlying logical structure. The wide range of logical models serves as a basis for simplified models of biological control of cell signaling networks [40,43,10••], cell cycle in yeast

Figure 2



The state transition diagram for a logical model of yeast. The vertices represent different logical states of gene activity. Reprinted with permission of the authors and publisher from [44]. Copyright (2004) National Academy of Sciences, U.S.A.

[26••,44–46,47••,48], cell death [42] and developmental systems in plants and animals [27,49–54].

The observation that the state transition diagram can be computed based on the logic alone provides a theoretical basis to investigate robustness based on the logical structure. Robust transition diagrams will be typified by attracting paths through the symbolic state space [44,47••,14••,48]. For example, Figure 2 shows the state transition diagram for the yeast cell cycle determined by Li *et al.* [44]. This is based on a simplified logical model of 11 genes in which each green vertex represents a different state of genes and the blue pathway represents the attracting cell cycle which will be expected to be robust to a wide range of parameters.

In systems with attracting paths, the dynamics in the Boolean systems with discrete time updating, stochastic updating, or differential equations would be expected to be analogous to each other.

Conclusions: extensions and open questions

Although the growing number of logical models of biological systems offers some optimism that the schemes described here may be broadly applicable, there are nevertheless a great many problems and directions that have not yet been adequately investigated.

Multivalued systems. In real systems the effective thresholds of a given component may not all be the same and it may be necessary to develop multivalued models [34,45]. Although the state transition diagram would no longer be a hypercube, the same basic ideas would apply.

Time delays. Many biological processes contain significant time delays [55•]. Although time delays have been used in mathematical models [3], the dynamics of Boolean delay equations can be quite complex [36]. Since in biological processes, a time delay may be associated with intermediate chemical compounds or transport from one compartment to another, one strategy to deal with time delays would be to expand the sets of variables. There is also a significant body of mathematical work dealing with the role of time delays in simple negative feedback systems [56] in which the delay may play a role of destabilizing a fixed point leading to a stable oscillation. These abstract mathematical results may be relevant to recent experimental studies of robust oscillations in *Escherichia coli* [55•].

Spatial structure. Logical models are proving useful in developmental biology [27,49–54]. However, there is still limited theoretical analysis on the integration of the state transition diagrams with dynamics in spatial systems, or whether attracting pathway here may correspond with the notion of canalization recently invoked by Reinitz and colleagues in their studies of development in Drosophila [28••]. This is a rich area for future development.

Reverse engineering. Symbolic methods provide a strategy to determine information about the structure of the dynamics based on the experimental observations of the state transitions. Using the methods described above, there is a one to one correspondence between a transition in a state transition diagram and an entry in the logic table. Thus, the state transition diagram offers a powerful method to determine the structure of gene networks based on observed dynamics [57,27,14••]. An alternative method of symbolic dynamics developed by Pigolotti *et al.*, provides information on signs of interactions based on changes in derivatives [12••].

Software for logical network analysis and simulation. Several software packages are now available to carry out simulations of genetic regulatory networks including *GNA: Genetic Network Analyzer* [58], GinSim [59]. We anticipate continued evolution and development of software facilitating investigation of dynamics of complex networks.

Physiological systems. A large literature deals with dynamics in physiological systems including cardiac and neural dynamics [60–63]. Although the heart and brain have incredible robustness in an individual and across species, the theoretical underpinnings of such robustness are still not well understood. Exploring the sensitivity of functional properties of ionic models to changes in parameters is an important area [64–67], and is sure to be a focus of future research.

The vast amount of data and apparent complexity of biological systems provide an overwhelming challenge to theory. One strategy is to try to incorporate as much data as possible to develop realistic models. Here we have provided a review of recent papers that point toward an alternative strategy — to use logical analysis and symbolic dynamics to help understand the robust dynamical features of biological systems.

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