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Dynamics and control at feedback vertex sets. II: A faithful monitor to determine the diversity of molecular activities in regulatory networks ☆

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HIGHLIGHTS

- A new theory to connect structure of a regulatory network and its dynamics.
- Dynamics of whole system can be identified by a subset of variables in the system.
- The subset is determined as a "feedback vertex set" of the network graph.
- The theory combines two mathematical concepts from different fields
- We analyze complex regulatory networks in biology as applications of our theory.

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ABSTRACT

Modern biology provides many networks describing regulations between many species of molecules. It is widely believed that the dynamics of molecular activities based on such regulatory networks are the origin of biological functions. However, we currently have a limited understanding of the relationship between the structure of a regulatory network and its dynamics. In this study we develop a new theory to provide an important aspect of dynamics from information of regulatory linkages alone. We show that the "feedback vertex set" (FVS) of a regulatory network is a set of "determining nodes" of the dynamics. The theory is powerful to study real biological systems in practice. It assures that (i) any long-term dynamical behavior of the whole system, such as steady states, periodic oscillations or quasi-periodic oscillations, can be identified by measurements of a subset of molecules in the network, and that (ii) the subset is determined from the regulatory linkage alone. For example, dynamical attractors possibly generated by a signal transduction network with 113 molecules can be identified by measurement of the activity of only 5 molecules, if the information on the network structure is correct. Our theory therefore provides a rational criterion to select key molecules to control a system. We also demonstrate that controlling the dynamics of the FVS is sufficient to switch the dynamics of the whole system from one attractor to others, distinct from the original.

1. Introduction

By the success of modern biology, we have many examples of large networks which describe regulations between a large number of species of molecules, such as genes, proteins or ions (e.g. Davidson et al., 2002; Oda et al., 2005). It is widely believed that the dynamics of molecular activities based on such regulatory networks are the origin of biological functions. For example, circadian rhythms observed in many species are produced by periodic oscillation of gene activities. The differences in characteristics of cells are produced by differences in gene expression patterns generated in the developmental process. Diversities of differentiated cells are considered to be caused by the diversity of steady states of gene expressions (Davidson et al., 2002). One of the major objectives in modern biology is to understand biological functions in terms of the dynamics of the activity of bio-molecules, based on experimentally determined regulatory networks.

However, a variety of obstacles still impede attempts to study the dynamics of biological systems based on the knowledge of regulatory

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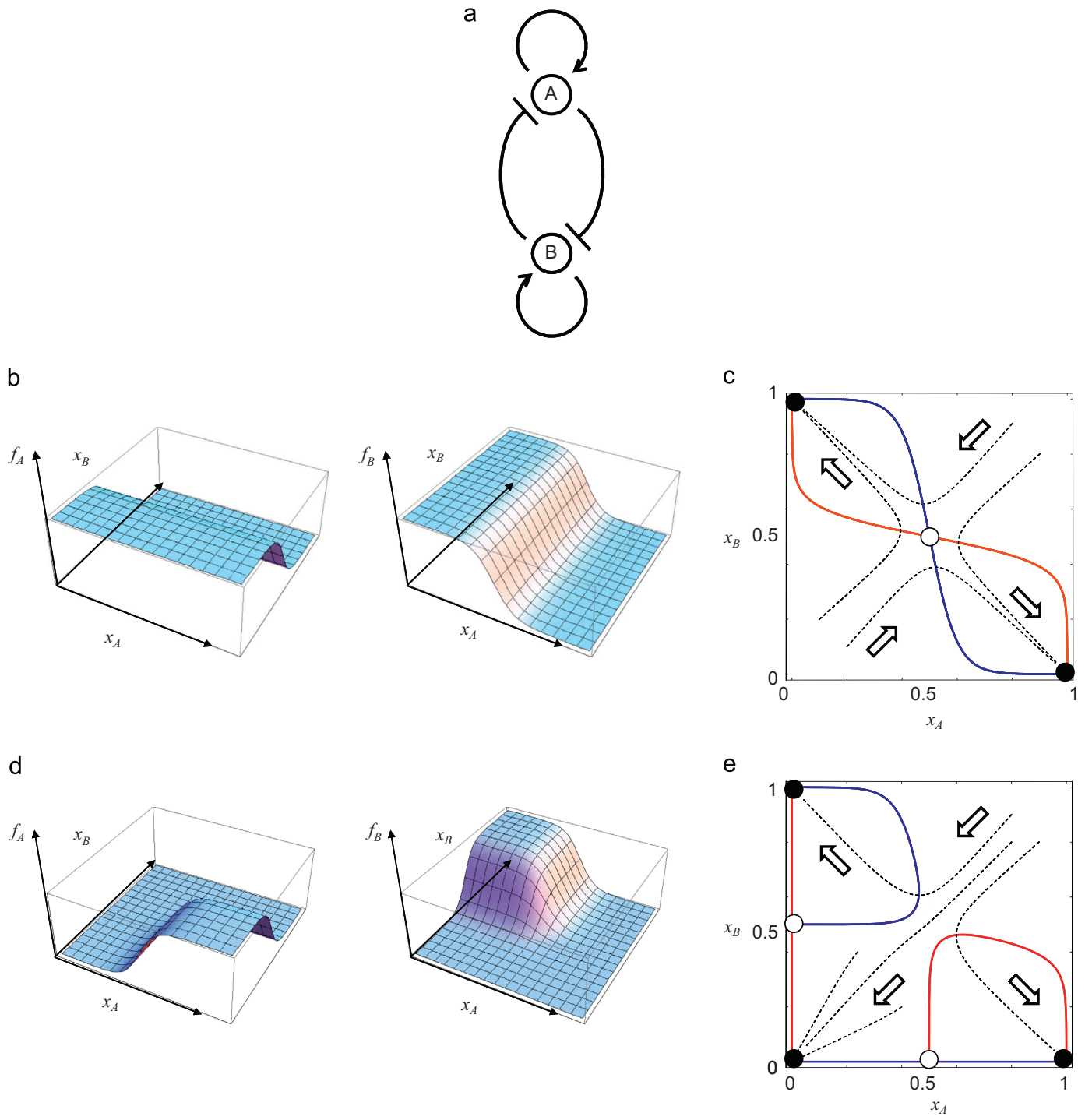

Fig. 1. An example of a two-vertex regulatory network and possible dynamical behaviors depending on regulatory functions. (a) Schematic representation of a regulatory network with two vertices. The directed edges show inhibitory regulatory interactions between nodes. (b, d) Examples of regulatory functions in which the genes are controlled by two different transcription factors. (b) $f_A=\{1+\exp[20(x_B-0.5)]\}^{-1}$, $f_B=\{1+\exp[20(x_A-0.5)]\}^{-1}$, $d_k(x_k)=x_k$, (d) $f_A=\{1+\exp[-20(x_A-0.5)]\}^{-1}\{1+\exp[20(x_B-0.5)]\}^{-1}$, $f_B=\{1+\exp[-20(x_B-0.5)]\}^{-1}\{1+\exp[20(x_A-0.5)]\}^{-1}$, $d_k(x_k)=x_k$, (c) and (e) shows dynamical trajectories and null-clines on two-dimensional state space using regulatory functions (b) and (d), respectively. Red and blue curves are null-clines of dynamics of x_A and x_B, respectively. Open and solid circle is unstable and stable stationary point, respectively. Broken curves are trajectories from different initial state.

networks systematically. One of the difficulties is the observation of dynamic processes. It is still difficult to observe the dynamics of the activity of bio-molecules with sufficient time resolution. Most of the data obtained by present experimental methods are snapshots of molecular activities rather than time tracks. The second problem is the reliability of the regulatory network itself. At present the regulatory networks are possibly incomplete in many studies of biological systems because of the complexity and working cost of experimental procedures to identify regulatory edges. The problem is fundamental because we can never exclude the possibility that unknown species of molecules or unknown regulations may take an important role in the focal phenomena.

The third and largest problem is that the information on the regulatory network alone is not sufficient to determine the