# Principle for performing attractor transits with single control in Boolean networks

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(Received 15 May 2013; revised manuscript received 12 September 2013; published 4 December 2013)

We present an algebraic approach to reveal attractor transitions in Boolean networks under single control based on the recently developed matrix semitensor product theory. In this setting, the reachability of attractors is estimated by the state transition matrices. We then propose procedures that compute the shortest control sequence and the result of each step of input (control) exactly. The general derivation is exemplified by numerical simulations for two kinds of gene regulation networks, the protein-nucleic acid interactions network and the cAMP receptor of *Dictyostelium discoideum* network.

DOI: 10.1103/PhysRevE.88.062706 PACS number(s): 87.10.−e, 89.75.Fb, 89.75.Hc

## I. INTRODUCTION

Genetic regulatory networks (GRNs) that describe animal development have significant implications for studying the relationships and behaviors of all of the DNAs, RNAs, proteins, and cells in a biological system [1]. The GRNs require computational and formal methods to process massive amounts of data, and then to infer useful predictions about the states and behaviors of the system under known conditions [2]. For GRNs, the states that are revisited infinitely often in the long-time limit starting from a random initial condition constitute an attractor, which is a (or some) stable state of GRNs [3]. These attractors are treated as various cell fates, which are differentiation, proliferation, and apoptosis. The existence of GRNs show that the vast state of gene activities can be described by a small number of trajectories and attractor states. All those states that converge to the same attractor are called the basin of attraction of that attractor [4]. A particular property of an attractor is stationary and intrinsical robustness. Small perturbations of individual elements of the GRN will lead to transient states that will mostly return to the same attractor, for the convergence of the trajectories within a basin of attraction onto the attractor [5].

In several studies on GRNs such as genetic diseases and organogenesis, researchers realized that the state of GRN transits from one attractor to another one by control methods [6,7]. A method was adopted to present the comparative evaluation and concrete application of GRN inference to ovarian cancer for revealing potential drug targets [8]. Another approach was proposed to characterize the attractor transitions in the *Arabidopsis thaliana* floral organ [9]. It has been found that the repression of a single gene binding poly-pyrimidine-tract-binding protein was sufficient to induce transdifferentiation of fibroblasts into functional neurons [10]. The previous studies were mainly interested in intervening the GRNs system (with optimal cost) to help it transit to desirable attractors, and the goal of those studies was to make the system transit to the desirable attractors by single-control methods. However, most of the existing achievements in related fields were obtained by experiments. Due to the lack of necessary theoretical supports, it is hard to explain thoroughly diverse experimental findings in regulating different genes. Moreover, the actual impact on the control of some gene is uncertain [11]. In short, to prove the validity of the transformation of GRNs from one attractor to another by single control still remains an open crucial theoretical problem [12].

Here, we propose a promising method for attractor transitions with a single control in GRNs in this paper. In order to transform the whole network from one attractor to another, we present an algebraic approach, which is based on the model of Boolean network, to estimate the reachability of an attractor and to determine the appropriate control sequence. Additionally, unlike other existing multicontrol methods, our approach, on the basis of clear and strict evidences, mainly focuses on the shortest control sequence and the minimum controlled nodes.

## II. MODEL

The Boolean network (BN) has become a proper model in describing and analyzing the attractor transitions in GRNs in recent years. It represents a modeling tool which not only has been necessarily given our ignorance of many quantitative details, but also has been sufficient in providing a conceptual understanding of how a number of genes interact [13]. Since it can reflect basic dynamic characteristics of biological systems, BN has been widely used in *mammalian cell* [14], *Drosophila melanogaster* [15], and *Arabidopsis thaliana* [16].

A BN is composed of $n$ nodes, and each node has some inputs from adjacent nodes, and it can be described by

$$\begin{aligned} x_1(t+1) &= g_1(x_1(t),\ldots,x_n(t)),\\ x_2(t+1) &= g_2(x_1(t),\ldots,x_n(t)),\\ &\vdots\\ x_n(t+1) &= g_n(x_1(t),\ldots,x_n(t)), \end{aligned} \tag{1}$$

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where $g_i(i = 1,2,\ldots,n)$ is an $n$-ary logical function. $x_i(t)$ is the state of node $i$ at time $t$.

The logical dynamics described in Eq. (1) can be converted into an equivalent algebraic form of conventional linear iterative dynamics. Therefore, the algebraic approach with a semitensor product (STP) of matrices was proposed in Ref. [17] for analyzing the states of BN. In this paper, STP is denoted by "$\ltimes$." Assume there are two matrices $A \in \mathbb{R}^{m\times n}$ and $B \in \mathbb{R}^{p\times q}$, where $n$ is $k$ times as $p$. The STP of $A$ and $B$ is defined as $A \ltimes B = A(B \otimes E_k)$, where "$\otimes$" is the Kronecker product and $E_k$ is the identity matrix. The STP of matrices remains all the fundamental properties of the conventional matrix product [18].

With STP, a Boolean operation can be converted into a matrix product. Logical values "true" and "false" with two vectors are denoted as $\delta_2^1$ and $\delta_2^2$, where $\delta_n^r$ denotes the $r$th column of the identity matrix $E_n$. Some fundamental logical functions are identified as $M = [\delta_n^{i_1},\delta_n^{i_2},\ldots,\delta_n^{i_s}]$, which is also briefly expressed as $M = \delta_n[i_1,i_2,\ldots,i_s]$. In principle, we get the logic relationships: (1) negation: $M_n = \delta_2[2,1]$; (2) disjunction: $M_d = \delta_2[1,1,1,2]$; (3) conjunction: $M_c = \delta_2[1,2,2,2]$; (4) XOR: $M_p = \delta_2[2,1,1,2]$. The above matrices are called *structure matrices*.

According to STP, Eq. (1) can be converted into

$$x(t+1) = M_1x_1(t)M_2x_2(t)\ldots M_nx_n(t), \tag{2}$$

where $M_i,(i = 1,2,\ldots,n)$ is a structure matrix. Multiplying the right part of Eq. (2), we yield

$$x(t+1) = Lx(t), \tag{3}$$

where $L \in \Delta_{2^n\times 2^n}$ is called the *transition matrix*, and $x(t) = \ltimes_{i=1}^n x_i(t)$. Equation (1) is uniquely determined by the transition matrix $L$. It is important to emphasize that with Eq. (3), each column of $L$ represents a state of BN. Based on $L$, the state space is described as a directed graph. It is obviously that all of the state is moving toward the attractor. The set of state, which is all toward the same attractor, compose the basin of the attractor. Since every state must belong to a basin, the state space of Boolean network consists of all basins. In the rest of this paper, the number of columns in $L$ is given a symbol for this number called the state number.

A BN is a globally convergent system. An attractor, called a stable state of the system, includes two types: a fixed point or a cycle. The number of the fixed point is $N_1$ and the number of cycles with length $k$ is $N_k$. They are inductively determined by

$$\begin{aligned} N_1 &= \mathrm{Tr}(L), \\ N_k &= \frac{\mathrm{Tr}(L^k) - \sum_{i\in\mathscr{P}(k)} iN_i}{k}, \end{aligned} \tag{4}$$

where $\mathscr{P}(k)$ is the set of proper factors of $k$ [18]. The attractor of system (1) can be obtained by Eq. (4). We denote an attractor as

$$\{x_1 \to x_2 \to \cdots x_s \to x_1\},$$

where $x_i \in \mathcal{D}, i = 1,2,\ldots,s$ is the length of the attractor. $\mathcal{D} = \{e_1,e_2,\ldots,e_{2^n}\}$ is the state space of the system (1), where $e_j$ is a state number. According to $L$ and the attractor of system (1), the entirety of the basin of an attractor can be pictured in a map.

## III. ATTRACTOR TRANSITION

In this paper, we consider the case of a BN with a free control sequence, which is called the open-loop control [19]. This open-loop control could destroy the cycle structure of a GRN, and it is widely used in systems biology [20].

Here, we have an open-loop control model by adding the control $u(t)$ to node $x_1$:

$$\begin{aligned} x_1(t+1) &= g_1(x_1(t),\ldots,x_n(t),u(t)), \\ x_2(t+1) &= g_2(x_1(t),\ldots,x_n(t)), \\ &\vdots \\ x_n(t+1) &= g_n(x_1(t),\ldots,x_n(t)), \end{aligned} \tag{5}$$

where $u$ is the control (or input). According to Eq. (5), we get the following equation via Eq. (3):

$$x(t+1) = \tilde{L}x(t)u(t),$$

where $x \in \Delta_{2^n}, u \in \Delta_2, \tilde{L} \in \Delta_{2^n\times 2^{n+1}}$. The matrix $\tilde{L}$ is the linear representation of $L$ under the control $u(t)$. $\tilde{L}$ is called the *state transition matrix*.

Consider the system under control $u$ at the $k$th step. Then Eq. (5) is solved as

$$x(k) = \tilde{L}^k u(1)\ldots u(k-1), \tag{6}$$

where $\tilde{L}^k \in \Delta_{2^n\times 2^{n+k}}$ is the linear representation of system (5). By solving $\tilde{L}^k$, we get the results of an open-loop control.

The following result holds for Eq. (5).

*Theorem 1*. $x_d$ is reachable from $x_0$ at the $k$th step by the control $u$, if and only if

$$x_d \in Col\{\tilde{L}^k x_0\}, \tag{7}$$

where $Col\{A\}$ is a set of columns of matrix $A$.

We assume that there are two attractors in system (1), i.e., $A_1 = \{x_1,\ldots,x_i,\ldots,x_s\}$ and $A_2 = \{y_1,\ldots,y_j,\ldots,y_t\}$, where $(x_i,y_j) \in L$ is a stable state, $s$ is the number of states in $A_1$, and $t$ is that in $A_2$.

*Corollary 1*. $R_{A_1}$ is the reachable state set from $A_1$ at the $k$th step under control $u$, if and only if

$$R_{A_1} = Col\{\tilde{L}^k A_1\}. \tag{8}$$

*Definition 1*. Assume $R^*_{A_1}$ is the largest reachable set of $A_1$, if and only if

$$R^*_{A_1} = Col\big\{\cup_{i=1}^{\infty} \tilde{L}^i A_1\big\}. \tag{9}$$

*Theorem 2*. Assume that $k^*$ is the smallest $k > 0$ such that

$$Col\{\tilde{L}^{k+1}A_1\} \subset Col\{\tilde{L}^r A_1 | r = 1,2,\ldots,k\}.$$

Then the largest reachable set is

$$R^*_{A_1} = Col\{\cup_{i=1}^{k^*} \tilde{L}^i A_1\}. \tag{10}$$

*Proof. Part one*. By calculation, we obtain $\tilde{L}^k A_1 \in \mathscr{L}_{2^n\times 2^{l_1 k}}$. Since $\tilde{L} \in \mathscr{L}_{2^n\times 2^{n+1}}$, by the property of the semitensor product we yield

$$\tilde{L}^{k+1}A_1 = \tilde{L} \ltimes \tilde{L}^k A_1 = \tilde{L} \times [\tilde{L}^k A_1 \otimes E_2],$$

where "$\times$" is the conventional matrix product. Based on computation, we know that there are no new columns in this matrix $\tilde{L}^{k+t}, t \in [1,\infty)$.

*Part two*. We use the notation

$$Col\{\tilde{L}^k\} \otimes E_2 := \{X \otimes E_2 | X \in Col\{\tilde{L}^k\}\}.$$

If we assume $Col\{\tilde{L}^{(k+1)}A_1\} \subset Col\{\tilde{L}^r A_1 | r = 1,2,\ldots,k\}$, then

$$\begin{aligned} &Col\{\tilde{L}^{(k+2)}A_1\} \\ &= \{\tilde{L}\theta | \theta \in Col\{\tilde{L}^{k+1}A_1\} \otimes E_2\} \\ &\subset \{\tilde{L}\theta | \theta \in Col\{\tilde{L}^r A_1\} \otimes E_2, r = 1,2,\ldots,k\} \\ &= Col\{\tilde{L}^r A_1 | r = 2,3,\ldots,k+1\} \\ &\subset Col\{\tilde{L}^r A_1 \otimes E_2 | r = 1,2,\ldots,k\}. \end{aligned}$$

This inequality shows that after $k$ there are no more new columns. From *part one*, we know that there exists such a $k^*$.

Next, we will discuss the reachability from one attractor to another one in system (5).

*Definition 2*. The transition from $A_1$ to $A_2$ is reachable at the $k$th step, if and only if

$$\tilde{L}^k A_1 \cap A_2 \neq \phi, \tag{11}$$

where $\phi$ is the null set. To derive the reachability is to find the smallest $k$.

*Definition 3*. $k$ is the smallest step from $A_1$ to $A_2$, if and only if

$$\tilde{L}^{(k-1)}A_1 \cap A_2 = \phi, \quad \tilde{L}^k A_1 \cap A_2 \neq \phi. \tag{12}$$

In the following, we will discuss the case of unreachability.

*Definition 4*. $A_2$ is unreachable from $A_1$, if and only if

$$R^*_{A_1} \cap A_2 = \phi, \tag{13}$$

where $R^*_{A_1}$ is the largest reachable set of $A_1$.

Next, we will construct the shortest control sequence. From Eq. (12), we can obtain $k$, which is the smallest step from $A_1$ to $A_2$.

*Theorem 3*. Let $\{\tilde{L}^k A_1\} = [B_1,\ldots,B_i,\ldots,B_s]$, where $B_i = \tilde{L}^k x_i$. If there exists $i \in \{1,\ldots,s\}$ such that

$$A_2 \cap B_i \neq \phi, \tag{14}$$

then $x_i$ is called source state, and there must exist $j \in \{1,\ldots,t\}$, satisfying $A_2 \cap B_i = y_j$, here $y_j$ is called the destination state of $x_i$.

If $y_j$ is equal to the $d$th column of $B_i$, then the control sequence is

$$\delta^d_{2^k} = u(0)u(1)\cdots u(k-1), \tag{15}$$

where $u(i)$ $(i = 0,1,\ldots,k-1)$ is the control sequence.

*Proof*. Since $A_1 = \{x_1,\ldots,x_i,\ldots,x_s\}$, we have $\{\tilde{L}^k A_1\} = \{\tilde{L}^k x_1,\ldots,\tilde{L}^k x_i,\ldots,\tilde{L}^k x_s\}$; $B_i = \{\tilde{L}^k x_i\}$ is the reachable set of $x_i$ at $k$th step. $y_j = A_2 \cap B_i$ means that the transition from $x_i$ to $A_2$ is reachable based on the input at the $k$th step. Then $y_j$ is the destination state and $x_i$ is the source state.

Let $B_i = \{\overrightarrow{1},\ldots,\overrightarrow{d},\ldots,\overrightarrow{2^k}\}$, where $\overrightarrow{d}$ is the $d$th column of $B_i$. Since $\overrightarrow{d}$ represents a control sequence, $\delta^d_{2^k} = u(0)u(1)\ldots u(k-1)$.

This derivation proves the validity of our method. First we determine the largest reachable set of an attractor, second the smallest step between two attractors is calculated, third the destination state and the source state are obtained, and finally the control sequence can be achieved. Based on the control sequence and Eq. (7), we can solve the state of system in each step, and the path from the source state to the target state is also obtained.

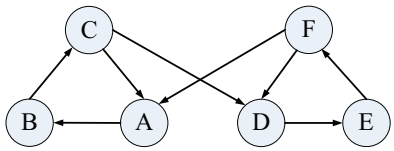


FIG. 1. (Color online) Model of gene regulation by protein-DNA interaction.

## IV. EXAMPLES

In order to illustrate our approach, two examples are given. The first example is an idealized protein-nucleic acid interaction involved in a gene regulation model, which describes the dynamic properties of a certain class of control mechanisms for a macromolecular synthesis in cells [21,22]. It is shown in Fig. 1.

The logic functions of this system are as follows:

$$\begin{aligned} A(t+1) &= C(t)F(t) + C(t) + F(t) + 1, \\ B(t+1) &= A(t), \\ C(t+1) &= B(t), \\ D(t+1) &= C(t)F(t) + C(t) + F(t) + 1, \\ E(t+1) &= D(t), \\ F(t+1) &= E(t), \end{aligned} \tag{16}$$

where $A \cdot B$ represents $A$ conjunction $B$, and $A + B$ represents the XOR operation between $A$ and $B$.

Different attractors of this system represent different levels of a metabolic species. Using Eqs. (2), (3), and (4), we yield that there are two attractors in the state space:

$$\begin{aligned} A_1 &= 101101 \to 010010 \to 101101, \\ A_2 &= 111111 \to 011011 \to 001001 \to 000000 \\ &\quad \to 100100 \to 111000 \to 111111 \end{aligned}$$

Next, the control $u(t)$ will be added on node $A$. The controlled system is expressed as

$$\begin{aligned} A(t+1) &= C(t)F(t) + C(t) + F(t) + 1 + u(t), \\ B(t+1) &= A(t), \\ C(t+1) &= B(t), \\ D(t+1) &= C(t)F(t) + C(t) + F(t) + 1, \\ E(t+1) &= D(t), \\ F(t+1) &= E(t). \end{aligned} \tag{17}$$

We change the state of the system from attractor $A_1$ to attractor $A_2$. By Eq. (12), the smallest step $k = 4$ is obtained. By Eq. (14), $y_j = \{001001\}$ is the destination state and $x_i = \{101101\}$ is the source state. The control sequence $u = (1,0,0,0)$ is obtained by Eq. (7). The path from the source state to the destination state is $101101 \xrightarrow{1} 110010 \xrightarrow{0} 111101 \xrightarrow{0} 011010 \xrightarrow{0} 001001$. Similarly, we get the control sequence from $A_2$ to $A_1$, i.e., $u = (1,0,0,0)$. The path is $011011 \xrightarrow{1} 101011 \xrightarrow{0} 010000 \xrightarrow{0} 101100 \xrightarrow{0} 010010$.

TABLE I. Results of control of system (16).

| Node | S-D attractor | Input | Control path |
|---|---|---|---|
| A | $A_1 \to A_2$ | 1000 | $101101 \xrightarrow{1} 110010 \xrightarrow{0} 111101 \xrightarrow{0} 011010 \xrightarrow{0} 001001$ |
| | $A_2 \to A_1$ | 1000 | $011011 \xrightarrow{1} 101001 \xrightarrow{0} 010000 \xrightarrow{0} 101100 \xrightarrow{0} 010010$ |
| B | $A_1 \to A_2$ | 100 | $010010 \xrightarrow{1} 111101 \xrightarrow{0} 011010 \xrightarrow{0} 001001$ |
| | $A_2 \to A_1$ | 100 | $001001 \xrightarrow{1} 010000 \xrightarrow{0} 101100 \xrightarrow{0} 010010$ |
| C | $A_1 \to A_2$ | 10 | $101101 \xrightarrow{1} 011010 \xrightarrow{0} 001001$ |
| | $A_2 \to A_1$ | 10 | $000000 \xrightarrow{1} 101100 \xrightarrow{0} 010010$ |
| D | $A_1 \to A_2$ | 1000 | $101101 \xrightarrow{1} 010110 \xrightarrow{0} 101111 \xrightarrow{0} 010011 \xrightarrow{0} 011011$ |
| | $A_2 \to A_1$ | 1000 | $011011 \xrightarrow{1} 001101 \xrightarrow{0} 000010 \xrightarrow{0} 100101 \xrightarrow{0} 010010$ |
| E | $A_1 \to A_2$ | 100 | $010010 \xrightarrow{1} 101111 \xrightarrow{0} 010011 \xrightarrow{0} 001001$ |
| | $A_2 \to A_1$ | 100 | $001001 \xrightarrow{1} 000010 \xrightarrow{0} 100101 \xrightarrow{0} 010010$ |
| F | $A_1 \to A_2$ | 10 | $101101 \xrightarrow{1} 010011 \xrightarrow{0} 001001$ |
| | $A_2 \to A_1$ | 10 | $000000 \xrightarrow{1} 100101 \xrightarrow{0} 010010$ |

Next, we will control node $B$, and then nodes $C, \ldots, F$. Table I shows the results of the control sequences.

In Table I, "Node" stands for the node which is controlled by $u(t)$. "S-D attractor" represents the source attractor and the destination attractor. "Input" represents the control sequences that we need. "Control Path" is the result of the input of each step, which includes the serial number of the source state, the input of each step, the serial number of the output state for each step, and the serial number of the destination state.

In Table I, it is obvious that the shortest control sequence from $A_1$ to $A_2$ is $u(t) = (1,0)$, and from $A_2$ to $A_1$ is $u(t) = (1,0)$. Therefore, nodes $C$ and $F$ are the optimal control nodes. Based on Table I, we find which genetic locus can affect fundamentally the representational value of a biochemical analysis, and the level of metabolism in this system will be changed in a specific way.

The second example is the cAMP receptor of *Dictyostelium discoideum*, which is a powerful system for genetic and functional analyses of a gene function. *D. discoideum* grows as separate, independent cells but interacts to form multicellular structures when challenged by adverse conditions. During aggregation, oscillatory waves of cAMP are generated from the center of the aggregating territory and are propagated toward neighboring cells. The responsiveness of cAMP is involved in the coordination of cell sorting and morphogenetic shape changes. The attractors of this model represent different types of cells [23,24]. The signaling pathways controlling aggregation are presented in Fig. 2.

The BN is a reasonable representation of the cAMP receptor of the *D. discoideum* system. Its logic functions are

$$\begin{aligned}
A(t+1) &= C(t) + 1,\\
B(t+1) &= A(t) + 1,\\
C(t+1) &= B(t)H(t) + H(t),\\
D(t+1) &= C(t),\\
E(t+1) &= D(t),\\
F(t+1) &= E(t) + 1,\\
G(t+1) &= D(t)E(t) + D(t) + E(t),\\
H(t+1) &= F(t)G(t) + G(t).
\end{aligned} \tag{18}$$

Based on Eqs. (2)–(4), we infer that the attractors of the system are

$$\begin{aligned}
A_1 &= 10000100 \to 10000100,\\
A_2 &= 11001110 \to 10000010 \to 10000101 \to 10100100\\
&\quad \to 00010100 \to 11001110,\\
A_3 &= 11001010 \to 10000011 \to 10100101 \to 00110100\\
&\quad \to 01011110 \to 11001010.
\end{aligned}$$

Next, we will take turns to control each node of this system to change the state of the system from one attractor to another one. The results of control are shown in Table II.

Table II shows that the shortest control sequence from $A_1$ to $A_2$ is $u(t) = (1)$, $A_1$ to $A_3$ is $u(t) = (1,1)$, $A_2$ to $A_1$ is $u(t) = (1)$, $A_2$ to $A_3$ is $u(t) = (1)$, $A_3$ to $A_1$ is $u(t) = (1)$, and $A_3$ to $A_2$ is $u(t) = (0)$. It has the best effciency based on the control of node C. The cAMP (inside the cell) and cAMP (outside the cell) play essential roles in controlling *D. discoideum* development according to Table II. Our simulation result in Table II verifies previous research results [23]. At the same time, we find the genetic locus selection criteria for attractor transit in theoretical basis.

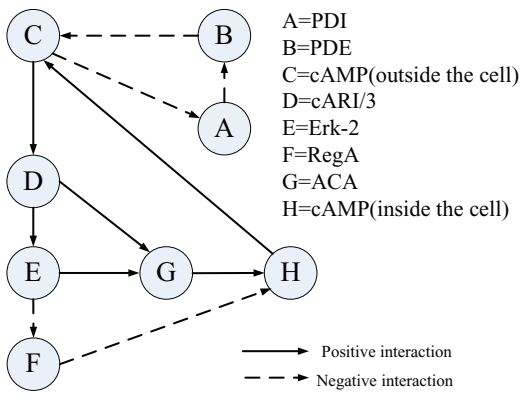


FIG. 2. (Color online) cAMP receptor of *D. discoideum* network.

TABLE II. Results of control of system (18).

| Node | S-D attractor | Input | Control path |
|---|---|---|---|
| A | $A_1 \to A_2$ | | Unreachable |
| | $A_1 \to A_3$ | | Unreachable |
| | $A_2 \to A_1$ | 100 | $11001110 \xrightarrow{1} 00000010 \xrightarrow{0} 11000101 \xrightarrow{0} 10000100$ |
| | $A_2 \to A_3$ | | Unreachable |
| | $A_3 \to A_1$ | 1100 | $01011110 \xrightarrow{1} 010011010 \xrightarrow{1} 01000011 \xrightarrow{0} 11000101 \xrightarrow{0} 10000100$ |
| | $A_3 \to A_2$ | 100 | $11001010 \xrightarrow{1} 00000011 \xrightarrow{0} 11100101 \xrightarrow{0} 00010100$ |
| | | 100 | $01011110 \xrightarrow{1} 01000000 \xrightarrow{0} 11000011 \xrightarrow{0} 10000101$ |
| B | $A_1 \to A_2$ | | Unreachable |
| | $A_1 \to A_3$ | | Unreachable |
| | $A_2 \to A_1$ | 10 | $10000010 \xrightarrow{1} 11000101 \xrightarrow{0} 10000100$ |
| | $A_2 \to A_3$ | | Unreachable |
| | $A_3 \to A_1$ | 110 | $11001010 \xrightarrow{1} 11000011 \xrightarrow{1} 11000101 \xrightarrow{0} 10000100$ |
| | $A_3 \to A_2$ | 10 | $11001010 \xrightarrow{1} 11000011 \xrightarrow{0} 10000101$ |
| | | 10 | $10000011 \xrightarrow{1} 11100101 \xrightarrow{0} 00010100$ |
| C | $A_1 \to A_2$ | 1 | $10000100 \xrightarrow{1} 10100100$ |
| | $A_1 \to A_3$ | 11 | $10000100 \xrightarrow{1} 10100100 \xrightarrow{1} 00110100$ |
| | $A_2 \to A_1$ | 1 | $10000101 \xrightarrow{1} 10000100$ |
| | $A_2 \to A_3$ | 1 | $10100100 \xrightarrow{1} 00110100$ |
| | $A_3 \to A_1$ | 1 | $10000011 \xrightarrow{1} 10000101$ |
| | $A_3 \to A_2$ | 0 | $10100101 \xrightarrow{0} 10000101$ |
| D | $A_1 \to A_2$ | 100 | $10000100 \xrightarrow{1} 10010100 \xrightarrow{0} 10001110 \xrightarrow{0} 10000010$ |
| | $A_1 \to A_3$ | 1100 | $10000100 \xrightarrow{1} 10010100 \xrightarrow{1} 10011110 \xrightarrow{0} 10001010 \xrightarrow{0} 10000011$ |
| | $A_2 \to A_1$ | 100 | $10100100 \xrightarrow{1} 00000100 \xrightarrow{0} 11000100 \xrightarrow{0} 100000100$ |
| | $A_2 \to A_3$ | 100 | $00010100 \xrightarrow{1} 11011110 \xrightarrow{0} 10001010 \xrightarrow{0} 10000011$ |
| | $A_3 \to A_1$ | 1100 | $10100101 \xrightarrow{1} 00100100 \xrightarrow{1} 01000100 \xrightarrow{0} 11000100 \xrightarrow{0} 10000100$ |
| | $A_3 \to A_2$ | 100 | $10100101 \xrightarrow{1} 00100100 \xrightarrow{0} 01010100 \xrightarrow{0} 11001110$ |
| | | 100 | $00110100 \xrightarrow{1} 01001100 \xrightarrow{0} 11000010 \xrightarrow{0} 10000101$ |
| E | $A_1 \to A_2$ | 100 | $10000100 \xrightarrow{1} 10001100 \xrightarrow{0} 10000010 \xrightarrow{0} 10000101$ |
| | $A_1 \to A_3$ | 110 | $10000100 \xrightarrow{1} 10001100 \xrightarrow{1} 10001010 \xrightarrow{0} 10000011$ |
| | $A_2 \to A_1$ | 10 | $000101000 \xrightarrow{1} 11000110 \xrightarrow{0} 10000100$ |
| | $A_2 \to A_3$ | 10 | $11001110 \xrightarrow{1} 10001010 \xrightarrow{0} 10000011$ |
| | | 10 | $10100100 \xrightarrow{1} 00011100 \xrightarrow{0} 11001010$ |
| | $A_3 \to A_1$ | 110 | $00110100 \xrightarrow{1} 01010110 \xrightarrow{1} 11000110 \xrightarrow{0} 10000100$ |
| | $A_3 \to A_2$ | 100 | $00110100 \xrightarrow{1} 01010110 \xrightarrow{0} 11001110$ |
| | | 10 | $01011110 \xrightarrow{1} 11000010 \xrightarrow{0} 10000101$ |
| F | $A_1 \to A_2$ | | Unreachable |
| | $A_1 \to A_3$ | | Unreachable |
| | $A_2 \to A_1$ | 10 | $11001110 \xrightarrow{1} 10000110 \xrightarrow{0} 10000100$ |
| | $A_2 \to A_3$ | 1 | $11001110 \xrightarrow{1} 11001010$ |
| | $A_3 \to A_1$ | 110 | $01011110 \xrightarrow{1} 11001110 \xrightarrow{1} 10000110 \xrightarrow{0} 10000100$ |
| | $A_3 \to A_2$ | 1 | $01011110 \xrightarrow{1} 11001110$ |
| G | $A_1 \to A_2$ | | Unreachable |
| | $A_1 \to A_3$ | | Unreachable |
| | $A_2 \to A_1$ | 10 | $11001110 \xrightarrow{1} 10000000 \xrightarrow{0} 10000100$ |
| | $A_2 \to A_3$ | | Unreachable |

TABLE II. (*Continued*.)

| Node | S-D attractor | Input | Control path |
|---|---|---|---|
| | $A_3 \to A_1$ | 110 | $01011110 \xrightarrow{1} 11001000 \xrightarrow{1} 10000000 \xrightarrow{0} 10000100$ |
| | $A_3 \to A_2$ | 10 | $11001010 \xrightarrow{1} 10000001 \xrightarrow{0} 10100100$ |
| | | 10 | $01011110 \xrightarrow{1} 11001000 \xrightarrow{0} 10000010$ |
| H | $A_1 \to A_2$ | 1 | $10000100 \xrightarrow{1} 10000101$ |
| | $A_1 \to A_3$ | 11 | $10000100 \xrightarrow{1} 10000101 \xrightarrow{1} 10100101$ |
| | $A_2 \to A_1$ | 1 | $10000010 \xrightarrow{1} 10000100$ |
| | $A_2 \to A_3$ | 1 | $10000101 \xrightarrow{1} 10100101$ |
| | $A_3 \to A_1$ | 11 | $11001010 \xrightarrow{1} 10000010 \xrightarrow{1} 10000100$ |
| | $A_3 \to A_2$ | 1 | $10000011 \xrightarrow{1} 10101000$ |

## V. CONCLUSION

In conclusion, we have considered the problem of attractor transformation in a BN, and have provided a general result which can realize the transformation among different attractors of a BN by single control. Here, we have demonstrated that the attractors of the protein-nucleic acid gene network and the *D. discoideum* gene network are robust. The robustness for different attractors are quite different. These robust dynamical properties are also seen in the common features of GRNs. Furthermore, some people suggested that not only the attractors of the biological system are robust, but also the pathways are robust [25]. In some case, biological systems have to be robust to function with external input. The more robust it is, the more evolvable, and more likely to be survived; robustness may provide us with a handle to understand the profound driving force of evolution.

Although the methods presented in this paper are limited by computational complexity such that they are only feasible for small BNs, they do provide complete solutions for some open problems and they are also relevant and interesting for the application of a new mathematical tool. Developing effective algorithms or approximate techniques for the present approach will be a challenging problem in future work.

## ACKNOWLEDGMENTS

This paper is supported by the National Natural Science Foundation of China (Grants No. 61170269, No. 61100204, and No. 61121061), the China Postdoctoral Science Foundation Funded Project (Grant No. 2013M540070), and the Beijing Higher Education Young Elite Teacher Project (Grant No. YETP0449).

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