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Research Article

Attractor Transformation by Impulsive Control in Boolean Control Network

Bo Gao,[1,2,3] Haipeng Peng,[2] Dawei Zhao,[2] Wenguang Zhang,[4] and Yixian Yang[1,2]

[1] *School of Computer and Information Technology, Beijing Jiaotong University, Beijing 100044, China*
[2] *Information Security Center, Beijing University of Posts and Telecommunications, P.O. Box 145, Beijing 100876, China*
[3] *School of Computer Information Management, Inner Mongolia University of Finance and Economics, Hohhot 010051, China*
[4] *College of Animal Science, Inner Mongolia Agricultural University, Hohhot 010018, China*

Correspondence should be addressed to Bo Gao; gaobonmghhht@gmail.com

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Boolean control networks have recently been attracting considerable interests as computational models for genetic regulatory networks. In this paper, we present an approach of impulsive control for attractor transitions in Boolean control networks based on the recent developed matrix semitensor product theory. The reachability of attractors is estimated, and the controller is also obtained. The general derivation proposed here is exemplified with a kind of gene model, which is the protein-nucleic acid interactions network, on numerical simulations.

1. Introduction

Gene regulatory networks (GRNs) have been offering plenty of holistic approaches to biological processes. They can explicitly represent the causality of developmental processes and exactly describe the state set of biological systems [1]. Waddington and Kacser proposed a metaphor that the developmental process of GRNs can be represented by a ball rolling down along a landscape with peaks and valleys, and the steady states, which were called attractors, were found at the bottom of the basins [2]. In cell model, there is a one-to-one relationship between the attractors and the observed phenotypes. This means that different cell types can be characterized by different attractors [3]. The states of a GRN will stay in an attractor, unless it is perturbed by an outside impact [4].

In several studies on GRNs such as genetic organogenesis and diseases, researchers have considered to make the states of GRN transit from one attractor to another one by using control methods [5–7]. It was found that repression of a single RNA binding polypyrimidine tract-binding protein was sufficient to induce transdifferentiation of fibroblasts into functional neurons in [8]. An approach was presented to evaluate drug targets of GRN inference to ovarian cancer in [9]. The previous studies mainly focused on intervening the system to help it transit to the desirable attractors by controlling a (or some) valid genetic locus. Since most of the existing achievements in related fields were obtained based on the experiments, the actual impact of control on the same GRN is uncertain [10]. In brief, to estimate the effectiveness of the controller for the transformation of GRNs from one attractor to another one, still remains an open crucial theoretical problem [11–15].

A Boolean network (BN) is often used as a model for gene regulation which treats genes as binary nodes that are either expressed or unexpressed [4]. In order to manipulate networks, the control of BNs is an important topic. A Boolean control network (BCN) can be considered as a BN with additional binary inputs. BCNs are attracting considerable interests as computational models for GRNs which use the exogenous inputs. BCN has been widely used in yeast cell-cycle [16], *Drosophila melanogaster* [17], and other kinds of cells.

In this paper, we propose a theoretical method to estimate the effects of a certain impulsive controller in a BCN and solve the appropriate controller by using semitensor product. Compared with the existing methods, based on the results of the experiments, our mathematics-based approach is more accurate and simpler.

The rest of this paper is organized as follows. Section 2 reviews STP and the model of BN. In Section 3, the reachability of an attractor is realized and the controller is also obtained. Section 4 gives our main results of an example. Section 5 is the conclusion.

2. Preliminaries

2.1. Semitensor Product. Semitensor product (STP) of matrices was firstly proposed by Cheng and Dong. It is the algebraic form and the coordinate transformation of BN and BCN. Based on STP, BNs and BCNs can be converted into equivalent algebraic form of some standard discrete-time system [18]. In this paper, STP is denoted by "$\ltimes$".

Definition 1. Assuming there are two matrices $A \in \mathbb{R}^{m\times n}$ and $B \in \mathbb{R}^{p\times q}$, the STP of A and B is $A \ltimes B = (A \otimes I_{\alpha/n})(B \otimes I_{\alpha/p})$, where α is the least common multiple of n and p, "$\otimes$" is the Kronecker product, and I_k is the identity matrix.

The STP of matrices makes all the fundamental properties of the conventional matrix product remain true [19]. With STP, Boolean operation can be converted into matrix product. These two logical values, "true" and "false," are expressed in vector forms as δ_2^1 and δ_2^2, where δ_n^r denotes the rth column of the identity matrix I_k. 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 $M = \delta_n[i_1, i_2, \ldots, i_s]$. And the logic relationships are

(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 the structure matrices.

2.2. Attractor. A BN, which is typically formulated as a directed graph, composed of n nodes, whose state indicates whether the gene is switched 1 (on) or 0 (off). The state of each node at time $t+1$ is determined by the state of its spatial neighbors at time t. The system can be described by

$$\begin{aligned} x_1(t+1) &= f_1(x_1(t), x_2(t), \ldots, x_n(t)), \\ x_2(t+1) &= f_2(x_1(t), x_2(t), \ldots, x_n(t)), \\ &\vdots \\ x_n(t+1) &= f_n(x_1(t), x_2(t), \ldots, x_n(t)), \end{aligned} \tag{1}$$

where f_i $(i = 1, 2, \ldots, n)$ is an n-ary logical function.

The BN is a globally convergence system. An attractor, called the stable state of system, is in the form of either a single state (fixed point) or a repeating set of states (cycle) [20]. Here, we consider how to find the attractors of (1). According to STP, we define

$$A(t) = \ltimes_{i=1}^{n} x_n(t). \tag{2}$$

Then

$$A(t+1) = \ltimes_{i=1}^{n} M_i A(t), \tag{3}$$

where M_i $(i = 1\cdots n)$ is the structure matrix. Using the properties of STP, (3) can be converted into an algebraic form as

$$A(t+1) = LA(t), \tag{4}$$

where $L \in \Delta_{2^n\times 2^n}$ is called the transition matrix. The state of (1) is uniquely determined by the transition matrix. Each column of L, which is called state number, represents a state of the BN. The attractor has the following definitions:

(1) a state $x(t) \in \Delta_{2^n}$ is called a fixed point if $Lx(t) = x(t)$;

(2) $\{x(t), Lx(t), \ldots, L^k x(t)\}$ is called a cycle with length k if $L^k x(t) = x(t)$ and the elements in the set $\{x(t), Lx(t), \ldots, K^{k-1}x(t)\}$ are distinct.

Theorem 2. *In system* (1), *the number of length s cycles, N_s, is inductively determined by*

$$\begin{aligned} N_1 &= Trace(L), \\ N_k &= \frac{\left(Trace\left(L^k\right) - \sum_{s\in\mathcal{P}(k)} sN_s\right)}{k}, \quad 2 \le k \le 2^n, \end{aligned} \tag{5}$$

where $\mathcal{P}(k)$ is the set of proper factors of k. According to (5), *one can find all the attractors in the state space of BN* (1) *[21].*

3. Main Results

In GRNs, much attention focuses on making the whole system transit from one attractor to another by control methods [22, 23]. Since the impulsive controller could destroy the cycle structure of the biological system, it is widely used in GRNs [24]. First, we will judge the reachability of an attractor.

Assume $\mathcal{A}_1 = \{x_h \mid h = 1\cdots l_1\}$ and $\mathcal{A}_2 = \{y_r \mid r = 1\cdots l_2\}$ are two attractors in system (1). l_1 and l_2 are the lengths of $\mathcal{A}_1$ and $\mathcal{A}_2$, respectively. We will determine the reachability from $\mathcal{A}_1$ to $\mathcal{A}_2$.

Here, we consider a BCN with m impulsive inputs at time t, and it is defined as

$$\begin{aligned} \tilde{x}_1(t+1) &= \tilde{f}_1(x_1(t), \ldots, x_n(t), u_1(t), \ldots, u_m(t)), \\ &\vdots \\ \tilde{x}_n(t+1) &= \tilde{f}_n(x_1(t), \ldots, x_n(t), u_1(t), \ldots, u_m(t)), \end{aligned} \tag{6}$$

where f_i $(i = 1, 2, \ldots, n)$ is an n-ary logical function and u_j $(j = 1\cdots m)$ is the impulsive input. u_j is described as

$$u_j(t) = \begin{cases} \text{input}, & t = t_k, \\ \text{no input}, & t \ne t_k, \end{cases} \tag{7}$$

where input is 0 or 1. When system (6) is at time $t = t_k$, according to STP, we define

$$\widetilde{A}(t) = \left(\ltimes_{i=1}^{n} x_i(t)\right) \ltimes \left(\ltimes_{j=1}^{m} u_j(t)\right), \tag{8}$$

then

$$\widetilde{A}(t+1) = \ltimes_{i=1}^{n} M_i \widetilde{A}(t), \tag{9}$$

where M_i $(i = 1 \cdots n)$ is the structure matrix. So (9) can be converted into an algebraic form as follows:

$$\widetilde{A}(t+1) = \widetilde{L}\widetilde{A}(t), \tag{10}$$

where $\widetilde{L} \in \Delta_{2^n \times 2^{n+m}}$ is called the state transition matrix of system (6).

Theorem 3. *Consider* (6). *The transformation from attractor $\mathscr{A}_1$ to attractor $\mathscr{A}_2$ is reachable with controllers $u_1(t) \cdots u_m(t)$ if and only if*

$$\widetilde{L}\mathscr{A}_1 \cap \mathscr{A}_2 \neq \phi, \tag{11}$$

where ϕ is the null set.

Proof. Since $\widetilde{L}$ is the linear representation of matrix L with the inputs $u_1(t) \cdots u_m(t)$, $\widetilde{L}\mathscr{A}_1$ is the reachable state set of $\mathscr{A}_1$. The intersection set of $\widetilde{L}\mathscr{A}_1$ and $\mathscr{A}_2$ is the destination states from $\mathscr{A}_1$ to $\mathscr{A}_2$ with controllers $u_1(t) \cdots u_m(t)$. □

Definition 4. Assume y_r is the destination state for the transition from $\mathscr{A}_1$ to $\mathscr{A}_2$ if and only if

$$y_r \in \widetilde{L}\mathscr{A}_1 \cap \mathscr{A}_2, \tag{12}$$

then x_h is the source state if and only if

$$y_r = \widetilde{L}x_h, \tag{13}$$

where $x_h \in \mathscr{A}_1$ and $y_r \in \mathscr{A}_2$.

Next, we will find the existence of the controller for attractor transition.

Theorem 5. *Consider system* (6). *Assume $\widetilde{L}x_h = \{e_k \mid k = 1 \cdots 2^m\}$; if $y_r = e_k$, we have $\delta_{2^m}^k$. The impulsive controllers are obtained by*

$$\delta_{2^m}^k = u_1(t) \ltimes u_2(t) \ltimes \cdots u_m(t), \tag{14}$$

where $u_j(t)$ $(j = 1 \cdots m)$ is the impulsive input at time t.

Proof. Since $\widetilde{L}x_h$ is the destination state from x_h with impulsive inputs $u_1(t) \cdots u_m(t)$, each e_k represents each state which is from x_h by inputs $u_1(t) \cdots u_m(t)$. Equation (14) is based on the properties of STP.

We can solve the input values for a deterministic target by using (14). □

4. Example

In order to illustrate our approach, an example is given in this section. It is an idealized protein-nucleic acid interaction involved in gene regulation model in cells [25]. The type of unit component which we will study is shown as follows:

$$\begin{aligned}
x_1(t+1) &= 1 + x_3(t) + x_6(t) + x_3(t)x_6(t), \\
x_2(t+1) &= x_1(t), \\
x_3(t+1) &= x_2(t), \\
x_4(t+1) &= 1 + x_3(t) + x_6(t) + x_3(t)x_6(t), \\
x_5(t+1) &= x_4(t), \\
x_6(t+1) &= x_5(t),
\end{aligned} \tag{15}$$

where $A \cdot B$ represents A Conjunction B and $A + B$ represents the XOR operation between A and B. Based on (2)–(4), the L matrix of system (15) is $L = \delta_{64}[37\ 37\ 38\ 38\ 39\ 39\ 40\ 40\ 37\ 1\ 38\ 2\ 39\ 3\ 40\ 4\ 45\ 45\ 46\ 46\ 47\ 47\ 48\ 48\ 45\ 9\ 46\ 10\ 47\ 11\ 48\ 12\ 53\ 53\ 54\ 54\ 55\ 55\ 56\ 56\ 53\ 17\ 54\ 18\ 55\ 19\ 56\ 20\ 61\ 61\ 62\ 62\ 63\ 63\ 64\ 64\ 61\ 25\ 62\ 26\ 63\ 27\ 64\ 28]$.

Using (5), we obtain that there are the following two attractors in the state space:

$$\begin{aligned}
\mathscr{A}_1 &= (19) \longrightarrow (46) \longrightarrow (19), \\
\mathscr{A}_2 &= (1) \longrightarrow (37) \longrightarrow (55) \longrightarrow (64) \longrightarrow (28) \\
&\quad \longrightarrow (10) \longrightarrow (1).
\end{aligned} \tag{16}$$

The attractors of this system represent different quantities of the generation of a metabolic species.

Next, assume the system is already in attractor $\mathscr{A}_1$; we want to transit the whole system from $\mathscr{A}_1$ to $\mathscr{A}_2$ with some impulsive controllers.

The BCN is expressed as

$$\begin{aligned}
x_1(t+1) &= 1 + x_3(t) + x_6(t) + x_3(t)x_6(t), \\
x_2(t+1) &= x_1(t) + u_1(t), \\
x_3(t+1) &= x_2(t), \\
x_4(t+1) &= 1 + x_3(t) + x_6(t) + x_3(t)x_6(t), \\
x_5(t+1) &= x_4(t) + u_2(t), \\
x_6(t+1) &= x_5(t),
\end{aligned} \tag{17}$$

where u_1, u_2 are controllers.

Step 1. Using (8)–(10), we obtain the matrix $\widetilde{L}$. Based on the computing of $\widetilde{L}$, we obtain $\widetilde{L}\mathscr{A}_1 = \delta_{64}[64\ 62\ 48\ 46\ 1\ 3\ 17\ 19]$. According to (11), the intersection of two sets is $\widetilde{L}\mathscr{A}_1 \cap \mathscr{A}_2 = \delta_{64}[64\ 1] \neq \phi$. So, the transformation from $\mathscr{A}_1$ to $\mathscr{A}_2$ is reachable, and $y_{r1} = \delta_{64}[64]$ and $y_{r2} = \delta_{64}[1]$ are the destination states.

Step 2. Since $\mathscr{A}_1$ is made up of two states, which are $\mathscr{A}_{11} = \delta_{64}[19]$ and $\mathscr{A}_{12} = \delta_{64}[46]$, we have

$$\begin{aligned}
\widetilde{L}\mathscr{A}_{11} &= \delta_{64}[64\ 62\ 48\ 46], \\
\widetilde{L}\mathscr{A}_{12} &= \delta_{64}[1\ 3\ 17\ 19],
\end{aligned} \tag{18}$$

then $\widetilde{L}\mathscr{A}_{11} \cap y_{r1} \neq \phi$ and $\widetilde{L}\mathscr{A}_{12} \cap y_{r2} \neq \phi$.

So $x_{h1} = \mathscr{A}_{11} = \delta_{64}[19]$ and $x_{h2} = \mathscr{A}_{12} = \delta_{64}[46]$ are source states.

Step 3. Letting $\widetilde{L}\mathscr{A}_{11} = \{e_k \mid k = 1, \ldots, 4\}$, $y_{r1} = e_1$, we have δ_4^1. Based on Theorem 5, the impulsive controllers are described as

$$u_1(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k, \end{cases} \qquad u_2(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k. \end{cases} \tag{19}$$

Similarly, we can obtain other impulsive controllers which are described as

$$u_1(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k, \end{cases} \qquad u_2(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k, \end{cases} \tag{20}$$

whose source state is $\mathscr{A}_{12} = \delta_{64}[46]$.

The conclusion of this example is that there are two kinds of controllers which can transform the state of system (17) from attractor $\mathscr{A}_1$ to attractor $\mathscr{A}_2$. They can be described as follows.

The First. The source state number is 19, the destination state number is 64, and the impulsive controllers are

$$u_1(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k, \end{cases} \qquad u_2(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k. \end{cases} \tag{21}$$

The Second. The source state number is 46, destination state number is 1, and the impulsive controllers are

$$u_1(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k, \end{cases} \qquad u_2(t) = \begin{cases} 1, & t = t_k, \\ \text{no input}, & t \neq t_k. \end{cases} \tag{22}$$

5. Conclusion

This paper explores the problem of attractor transformation by impulsive control in BCN. We propose an effective algorithm which allows us to realize the transformation among different attractors of the BCN. Although the protein-nucleic acid gene network has relatively simple structure compared with those exhibited by metazoans, the attractors transformation by impulsive control is impressively significant. Our findings open a new perspective in the attractor transformation by impulsive control which is of utmost importance in areas as diverse as drug target and gene regulation and so forth. Developing more effective algorithms or approximate techniques for the present approaches will be the future work.

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References

[1] E. Davidson and M. Levine, "Gene regulatory networks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 14, p. 4935, 2005.

[2] C. H. Waddington and H. Kacser, *The Strategy of Genes*, George Allen Unwin, Bristol, UK, 1957.

[3] S. Huang, "Regulation of cellular states in mammalian cells from a genomewide view," in *Gene Regulation and Metabolism*, pp. 181–220, MIT Press, Cambridge, Mass, USA, 2002.

[4] S. A. Kauffman, "Metabolic stability and epigenesis in randomly constructed genetic nets," *Journal of Theoretical Biology*, vol. 22, no. 3, pp. 437–467, 1969.

[5] F. H. Willeboordse and K. Kaneko, "Externally controlled attractor selection in a high-dimensional system," *Physical Review E*, vol. 72, no. 2, Article ID 026207, 2005.

[6] A. Sakata, K. Hukushima, and K. Kaneko, "Funnel landscape and mutational robustness as a result of evolution under thermal noise," *Physical Review Letters*, vol. 102, no. 14, Article ID 148101, 2009.

[7] C. Cattani, G. Pierro, and G. Altieri, "Entropy and multifractality for the myeloma multiple TET 2 gene," *Mathematical Problems in Engineering*, vol. 2012, Article ID 193761, 14 pages, 2012.

[8] Y. Xue, K. Ouyang, J. Huang et al., "Direct conversion of fibroblasts to neurons by reprogramming PTB-regulated MicroRNA circuits," *Cell*, vol. 152, pp. 82–96, 2013.

[9] P. B. Madhamshettiwar, S. R. Maetschke, M. J. Davis, A. Reverter, and M. A. Ragan, "Gene regulatory network inference: evaluation and application to ovarian cancer allows the prioritization of drug targets," *Genome Medicine*, vol. 4, no. 5, article 41, 2012.

[10] L. T. MacNeil and A. J. M. Walhout, "Gene regulatory networks and the role of robustness and stochasticity in the control of gene expression," *Genome Research*, vol. 21, no. 5, pp. 645–657, 2011.

[11] C. Toma, "Advanced signal processing and command synthesis for memory-limited complex systems," *Mathematical Problems in Engineering*, vol. 2012, Article ID 927821, 13 pages, 2012.

[12] E. G. Bakhoum and C. Toma, "Specific mathematical aspects of dynamics generated by coherence functions," *Mathematical Problems in Engineering*, vol. 2011, Article ID 436198, 10 pages, 2011.

[13] M. Li, "Approximating ideal filters by systems of fractional order," *Computational and Mathematical Methods in Medicine*, vol. 2012, Article ID 365054, 6 pages, 2012.

[14] M. Li and W. Zhao, "Visiting power laws in cyber-physical networking systems," *Mathematical Problems in Engineering*, vol. 2012, Article ID 302786, 13 pages, 2012.

[15] M. Li, S. C. Lim, and S. Chen, "Exact solution of impulse response to a class of fractional oscillators and its stability," *Mathematical Problems in Engineering*, vol. 2011, Article ID 657839, 9 pages, 2011.

[16] A. Fauré, A. Naldi, C. Chaouiya, and D. Thieffry, "Dynamical analysis of a generic Boolean model for the control of the mammalian cell cycle," *Bioinformatics*, vol. 22, no. 14, pp. e124–e131, 2006.

[17] R. Albert and H. G. Othmer, "The topology of the regulatory interactions predicts the expression pattern of the segment polarity genes in drosophila melanogaster," *Journal of Theoretical Biology*, vol. 223, no. 1, pp. 1–18, 2003.

[18] D. Cheng and Y. Dong, "Semi-tensor product of matrices and its some applications to physics," *Methods and Applications of Analysis*, vol. 10, no. 4, pp. 565–588, 2003.

[19] D. Cheng and H. Qi, "A linear representation of dynamics of Boolean networks," *IEEE Transactions on Automatic Control*, vol. 55, no. 10, pp. 2251–2258, 2010.

[20] L. Li, H. Peng, Y. Yang, and X. Wang, "On the chaotic synchronization of Lorenz systems with time-varying lags," *Chaos, Solitons and Fractals*, vol. 41, no. 2, pp. 783–794, 2009.

[21] D. Cheng and H. Qi, "Controllability and observability of Boolean control networks," *Automatica*, vol. 45, no. 7, pp. 1659–1667, 2009.

[22] L. Li, Y. Yang, H. Peng, and X. Wang, "An optimization method inspired by "chaotic" ant behavior," *International Journal of Bifurcation and Chaos in Applied Sciences and Engineering*, vol. 16, no. 8, pp. 2351–2364, 2006.

[23] H. Peng, L. Li, Y. Yang, and F. Sun, "Conditions of parameter identification from time series," *Physical Review E*, vol. 83, no. 3, Article ID 036202, 2011.

[24] C. Villarreal, P. Padilla-Longoria, and E. R. Alvarez-Buylla, "General theory of genotype to phenotype mapping: derivation of epigenetic landscapes for N-node complex gene regulatory networks," *Physical Review Letters*, vol. 109, no. 11, Article ID 118102, 5 pages, 2012.

[25] B. C. Goodwin, *Temporal Organization in Cells: A Dynamic Theory of Cellular Control Process*, chapter 4, Academic Press, New York, NY, USA, 1963.