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Invertibility and nonsingularity of Boolean control networks☆

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ABSTRACT

Invertibility is an interesting and classical control-theoretic problem. However, there has been no result for the invertibility of Boolean control networks (BCNs) so far. We first adopt the theory of symbolic dynamics to characterize it. First, it is shown that a BCN generates a continuous mapping from the space of input trajectories to the space of output trajectories. Based on it, the concepts of nonsingularity and invertibility of BCNs are first defined as the injectivity and bijectivity of the mapping, respectively. Second, combined symbolic dynamics with the semi-tensor product (STP) of matrices, an equivalent test criterion for invertibility is given; easily computable algorithms to construct the inverse BCN for an invertible BCN are presented; and it is proved that invertibility remains invariant under coordinate transformations. Third, an equivalent test criterion for nonsingularity is given via defining a novel directed graph that is called weighted pair graph. Lastly, as an application of invertibility to systems biology, we prove that the BCN model proposed in Fauré et al. (2006) is not invertible, i.e., we prove that arbitrarily controlling mammalian cell cycles is unfeasible at the theoretical level.

1. Introduction

The Boolean network (BN), introduced first in Kauffman (1969), and then developed by Akutsu, Miyano, and Kuhara (2000) and Albert and Barabasi (2000), etc. is a simple and effective model to describe the behavior and relationships of cells, proteins, DNA and RNA in a biological system, named genetic regulatory networks (GRNs) (cf. Ideker, Galitski, & Hood, 2001, Kitano, 2002). Particularly in Ideker et al. (2001), exogenous perturbation and regulation to biological systems were described as "control", i.e., the concept of Boolean control networks (BCNs) came up. A BN/BCN is itself simple but reflects the local dynamical interactions of internal nodes (and external nodes). Hence recently, the dynamical properties of BNs/BCNs were widely investigated to understand the behavior of GRNs (cf. Akutsu, Hayashida, Ching, & Ng, 2007, Akutsu et al., 2000, Albert & Barabasi, 2000, Cheng, Qi, & Li, 2011).

Like the controllability and observability of BCNs (cf. Cheng & Qi, 2009, Fornasini & Valcher, 2013, Laschov, Margaliot, & Even, 2013, Zhang & Zhang, 2014, Zhao, Qi, & Cheng, 2010), invertibility is an interesting topic in the control-theoretic field. Moreover, in systems biology, the invertibility of BCNs is of extraordinary biological significance, as shown by taking a motivating example.

In Fauré, Naldi, Chaouiya, and Thieffry (2006), the dynamics of the core network regulating the mammalian cell cycle was formulated as a BCN model as shown in (1). The cell cycle involves a succession of molecular events leading to the reproduction of the genome of a cell (Synthesis phase) and its division into two daughter cells (Mitosis phase). The Synthesis and Mitosis phases are preceded by two gap phases, called G1 and G2 respectively, in which RNA and proteins are synthesized. Mammalian cell division is tightly controlled, for it must be coordinated with the overall growth of the organism, as well as answer specific needs, such as wound healing. This coordination is achieved through extra-cellular positive and negative signals whose balance decides whether a cell will divide or remain in a resting state (a fifth phase, G0). The positive signals or growth factors ultimately elicit the activation of protein CycD in the cell. Thus CycD is represented as the control input (Fauré et al., 2006).

The BCN model (1) consists of one input node, CycD, and nine state nodes (proteins), Rb, E2F, CycE, CycA, p27, Cdc20,

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Cdh1, UbcH10, CycB, which are represented as ten Boolean variables $u, x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9$, respectively, showing their activation and inactivation. Protein Cdc20 is responsible for the metaphase-to-anaphase transition: it activates separase through the destruction of its inhibitor securin; this activation elicits the cleavage of the cohesin complexes that maintain the cohesion between the sister chromatids, thus leading to their separation. Hence Cdc20 plays a central role in the division of cells (Fauré et al., 2006).

$$\begin{aligned}
x_1(t+1) &= (\bar{u}(t) \wedge \bar{x}_3(t) \wedge \bar{x}_4(t) \wedge \bar{x}_9(t)) \\
&\quad \vee (x_5(t) \wedge \bar{u}(t) \wedge \bar{x}_9(t)), \\
x_2(t+1) &= (\bar{x}_1(t) \wedge \bar{x}_4(t) \wedge \bar{x}_9(t)) \vee (x_5(t) \wedge \bar{x}_1(t) \wedge \bar{x}_9(t)), \\
x_3(t+1) &= x_2(t) \wedge \bar{x}_1(t), \\
x_4(t+1) &= (x_2(t) \wedge \bar{x}_1(t) \wedge \bar{x}_6(t) \wedge \overline{(x_7(t) \wedge x_8(t))}) \\
&\quad \vee (x_4(t) \wedge \bar{x}_1(t) \wedge \bar{x}_6(t) \wedge \overline{(x_7(t) \wedge x_8(t))}), \\
x_5(t+1) &= (\bar{u}(t) \wedge \bar{x}_3(t) \wedge \bar{x}_4(t) \wedge \bar{x}_9(t)) \\
&\quad \vee (x_5(t) \wedge \overline{(x_3(t) \wedge x_4(t))} \wedge \bar{u}(t) \wedge \bar{x}_9(t)), \\
x_6(t+1) &= x_9(t), \\
x_7(t+1) &= (\bar{x}_4(t) \wedge \bar{x}_9(t)) \vee x_6(t) \vee (x_5(t) \wedge \bar{x}_9(t)), \\
x_8(t+1) &= \bar{x}_7(t) \vee (x_7(t) \wedge x_8(t) \wedge (x_6(t) \vee x_4(t) \vee x_9(t))), \\
x_9(t+1) &= \bar{x}_6(t) \wedge \bar{x}_7(t),
\end{aligned} \tag{1}$$

where $\bar{\cdot}, \wedge, \vee$ denote logical operators: negation, conjunction and disjunction, respectively; t denotes time steps $0, 1, 2 \ldots$; u and x_i are Boolean variables, $i = 1, \ldots, 9$.

Then if at any time step, both activation and inactivation of Cdc20 can be achieved, one may control the division of cells. Since CycD is the control input of the BCN model, a natural idea is designing a CycD sequence to obtain any Cdc20 sequence. If this idea is reconsidered in a backward way, that is, determining the CycD sequence by using a Cdc20 sequence, and Cdc20 is regarded as the output node, then it becomes the invertibility problem in the control-theoretic field. Based on this idea, a natural problem arises:

Problem 1. Can one obtain any Cdc20 sequence by designing a CycD sequence?

In the sequel, we aim at answering this question.

Remark 1.1. Note that we formulate the control of the mammalian cell cycle as invertibility. Why not controllability? First, BCN (1) is not controllable (see Section 4). Second, controllability involves driving a state (nine proteins) to another state at some future time step, while it is powerless to obtain a target output sequence. While obtaining a target output sequence is just what we want.

The invertibility problem has been studied extensively for linear systems (cf. Brockett & Mesarovic, 1965, Morse & Wonham, 1971, Moylan, 1977, Sain & Massey, 1969, Silverman, 1969, etc.), nonlinear systems (cf. Hirschorn, 1979, Nijmeijer, 1982, Singh, 1982, etc.), and switched systems (cf. Tanwani & Liberzon, 2010, Vu & Liberzon, 2008, etc.). However, to the best of our knowledge, there has been no result on the invertibility problem of BCNs so far. The invertibility of linear/nonlinear systems are usually defined via the theories of frequency domain, linear spaces or differential geometry. For BCNs, the updating functions of nodes are essentially polynomials defined on linear spaces $(\mathcal{D}, \mathcal{D}^n)$ with module-2 addition and multiplication, where $\mathcal{D} = \{0, 1\}$. Since BCNs do not have frequency domain structure, $(\mathcal{D}, \mathcal{D}^n)$ is not locally Euclidean, and the updating functions are nonlinear, the concepts of invertibility of linear/nonlinear systems cannot be directly defined for BCNs. As a result, the approaches of dealing with the invertibility of linear/nonlinear systems cannot be directly used to deal with the invertibility of BCNs either.

Cellular automata are a type of symbolic dynamical systems, and have applications in computability theory, computational mathematics, physics, theoretical biology, cryptology, etc. A complete survey is referred to Kari (2005). Roughly speaking, a cellular automaton can be seen as a regular arrangement of countably infinitely many copies of a BCN. So the topological structure of cellular automata is much more complex than that of BCNs. Recently in Kari and Zhang (2013), an open problem on the chaos theory of cellular automata was solved. Since the configuration space of a 1-dimensional cellular automaton is topologically equivalent to the space of input trajectories of a BCN (details are seen in Section 2.2), we can attempt to use the theory of symbolic dynamics to characterize the invertibility of BCNs.

After trying the above idea, we find that the theory of symbolic dynamics is a suitable tool to deal with the invertibility of BCNs. By using the theory of symbolic dynamics, we obtain an equivalent test criterion for the invertibility of BCNs. Also by using the semi-tensor product (STP) of matrices, a natural generalization of the conventional matrix product, we give matrix representations for the obtained results.

Besides, to make a further theoretical attempt, we investigate a generalized invertibility which we call nonsingularity. Both invertibility and nonsingularity are in category of invertibility problems.

The rest of this paper is organized as follows: Section 2 introduces necessary preliminaries about STP, BCNs with their algebraic forms, and symbolic dynamics. Section 3 investigates the invertibility problem of BCNs. Section 4 shows that the foregoing BCN model of the core network regulating the mammalian cell cycle is not invertible. A brief conclusion ends this paper in Section 5.

2. Preliminaries

2.1. Boolean control networks and their algebraic forms based on the STP of matrices

Since the framework of STP is used in this paper, some notations about logic and STP are introduced.

- $\mathbb{R}$: the set of all real numbers
- $\mathbb{Z}$: the set of all integers
- $\mathbb{Z}_+$: the set of all positive integers
- $\mathbb{N}$: the set of all natural numbers
- $\mathbb{R}_{m\times n}$: the set of all $m \times n$ real matrices
- $[i, j]$: the set of consecutive integers $i, i+1, \ldots, j$
- I_n: the $n \times n$ identity matrix
- A^T: the transpose of a matrix A
- $\mathcal{D}$: the set $\{0, 1\}$
- δ_n^i: the ith column of the identity matrix I_n
- $\mathbf{1}_k$: $\sum_{i=1}^k \delta_k^i$
- Δ_n: the set $\{\delta_n^1, \ldots, \delta_n^n\}$ ($\Delta_2 := \Delta$)
- $\delta_n[i_1, \ldots, i_s]$: the logical matrix $[\delta_n^{i_1}, \ldots, \delta_n^{i_s}]$ $(i_1, \ldots, i_s \in \{1, 2, \ldots, n\})$
- $\mathcal{L}_{n\times s}$: the set of all $n \times s$ logical matrices, i.e., $\{\delta_n[i_1, \ldots, i_s] | i_1, \ldots, i_s \in \{1, 2, \ldots, n\}\}$
- $A > 0$: each entry of matrix A is positive
- $\mathrm{Row}_i(A)$ (resp. $\mathrm{Col}_i(A)$): the ith row (resp. column) of matrix A
- $A_1 \oplus A_2 \oplus \cdots \oplus A_n$: $\begin{bmatrix} A_1 & 0 & \cdots & 0 \\ 0 & A_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & A_n \end{bmatrix}$
- $\mathrm{diag}_n(A) = \oplus_{i=1}^n A$.

Definition 2.1 (*Cheng et al., 2011*). Let $A \in \mathbb{R}_{m\times n}$, $B \in \mathbb{R}_{p\times q}$, and $\alpha = \mathrm{lcm}(n, p)$ be the least common multiple of n and p. The STP of