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Aggregation method to reachability and optimal control of large-size Boolean control networks

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Dear editor,

As an effective model of genetic regulatory networks, the Boolean network was introduced by Kauffman, and has since been extensively studied in systems biology. Boolean control networks (BCNs) are Boolean networks with control and output. Reachability is used to design control sequences that drive genes from unhealthy to healthy states, which is an important issue in the control of BCNs. Cheng et al. [1] proposed the semi-tensor product (STP) method, which was proved to be powerful in the investigation of BCNs [2–4]. Given the high computational complexity of the STP method in BCNs, several effective methods for studying large-size BCNs, such as the aggregation method, logical matrix factorization approach, and pinning control technique, have been established [5]. In particular, based on the aggregation method, Zhao et al. [6] established a necessary condition for the reachability of large-size BCNs, and pointed out that the establishment of efficient sufficient condition is challenging. As a result, developing a method for determining the reachability of large-size BCNs is important.

In this study, we explore the reachability of large-size BCNs. The concept of the κ-matchable condition is firstly established to deal with the reachability of large-size BCNs, and a criterion is proposed. The reachability results are applied to the Mayer-type optimal control problem, and an algorithm is developed to obtain all optimal solutions. The reachability analysis of a colitis-associated colon cancer network with 70 nodes and 153 edges (see Appendix E.3) demonstrates the application of key findings in large-size BCNs.

Preliminaries. A BCN can be described as follows:

$$x_i(t+1) = f_i(U(t), X(t)),\ i = 1, 2, \dots, n, \tag{1}$$

where $X(t) := (x_1(t), x_2(t), \dots, x_n(t)) \in \mathcal{D}^n$, $U(t) := (u_1(t), \dots, u_m(t)) \in \mathcal{D}^m$ are the states, control inputs of BCN (1) at time t.

Definition 1. Consider $X_0, X_d \in \mathcal{D}^n$. BCN (1) is said to be reachable from X_0 to X_d at the κ-th step, if there exists a control sequence $\{U(t) : t = 0, \dots, \kappa-1\} \subseteq \mathcal{D}^m$ such that $X(\kappa; X_0, U) = X_d$.

Identify 1 and 0 as δ_2^1 and δ_2^2, respectively. Setting $x(t) = \ltimes_{i=1}^n x_i(t)$, $u(t) = \ltimes_{j=1}^m u_j(t)$, one can obtain the following algebraic form of BCN (1):

$$x(t+1) = Fu(t)x(t), \tag{2}$$

where $F \in \mathcal{L}_{2^n \times 2^{m+n}}$. In this study, the default matrix product is the STP of matrices ($\ltimes$) [1].

Aggregation of BCNs. For BCN (1), let $N = \{x_i, u_j; i = 1, 2, \dots, n, j = 1, \dots, m\}$. Partition the nodes of BCN (1) into the following ρ blocks:

$$N = N_1 \dot\cup N_2 \dot\cup \cdots \dot\cup N_\rho, \tag{3}$$

where $N_i \subsetneqq N$ consists of state nodes $X_i = \{x_{i_j} : j = 1, \dots, n_i\}$ and control nodes $U_i = \{u_{i_j} : j = 1, \dots, m_i\}$. We call (3) an aggregation of BCN (1). According to [6], we can obtain the input nodes $Z_i = \{z_{i_j} : j = 1, \dots, q_i\}$ and output nodes $Y_i = \{y_{i_j} : j = 1, \dots, p_i\}$ for block N_i. Let Φ_1 denote the set of all integers $i \in \{1, 2, \dots, \rho\}$ satisfying $Z_i \cup U_i = \emptyset$, and let $\Phi_2 := \{1, 2, \dots, \rho\} \setminus \Phi_1$.

Assumption 1. X_i, $i = 1, 2, \dots, \rho$ are not empty, and each block in the aggregation is weakly connected.

Let Σ_i, $i = 1, 2, \dots, \rho$ denote the subnetwork corresponding to block N_i, the dynamics of which can be given as

$$x_{i_j}(t+1) = f_{i_j}(z_{i_k}(t), u_{i_l}(t), x_{i_h}(t); k = 1, \dots, q_i, \\ l = 1, \dots, m_i, h = 1, \dots, n_i),\ j = 1, \dots, n_i. \tag{4}$$

Then, the algebraic state space representation of Σ_i is

$$\alpha_i(t+1) = F_i \widetilde{u}_i(t) \alpha_i(t), \tag{5}$$

where $\alpha_i(t) = \ltimes_{j=1}^{n_i} x_{i_j}(t)$, $\widetilde{u}_i(t) = \gamma_i(t)\beta_i(t)$, $\gamma_i(t) = \ltimes_{j=1}^{q_i} z_{i_j}(t)$, $\beta_i(t) = \ltimes_{j=1}^{m_i} u_{i_j}(t)$ and $F_i \in \mathcal{L}_{2^{n_i} \times 2^{m_i+q_i+n_i}}$.

Reachability analysis. Consider the large-size BCN (1). Let $x^0 = \delta_{2^n}^\lambda$, $x^d = \delta_{2^n}^\theta$ and an aggregation consisting of ρ subnetworks Σ_i, $i = 1, 2, \dots, \rho$ be given. Let $\alpha_i^0 = \sigma_{X, X_i}(x^0) = \delta_{2^{n_i}}^{\lambda_i}$, $\alpha_i^d = \sigma_{X, X_i}(x^d) = \delta_{2^{n_i}}^{\theta_i}$. If $Z_i \neq \emptyset$, let

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$\gamma_i(0) = \sigma_{X,Z_i}(x^0) = \delta_{2^{q_i}}^{\xi_i}$. Let $M_i = \sum_{j=1}^{2^{m_i+q_i}} F_i \delta_{2^{m_i+q_i}}^j$ and

$$M_i(0) = \begin{cases} M_i, & q_i = 0, \\ \sum_{j=1}^{2^{m_i}} F_i \delta_{2^{m_i+q_i}}^{(\xi_i-1)2^{m_i}+j}, & q_i \neq 0. \end{cases} \quad (6)$$

Corollary 1. Subnetwork Σ_i is reachable from $\alpha_i^0 = \delta_{2^{n_i}}^{\lambda_i}$ to $\alpha_i^d = \delta_{2^{n_i}}^{\theta_i}$ at the κ-th step, iff $[R_i(\kappa)]_{\theta_i,\lambda_i} > 0$, where $R_i(\kappa) = M_i^{\kappa-1} M_i(0)$ (see Appendix B.1 for the proof).

Suppose that $i \in \Phi_1$ and the condition in Corollary 1 is satisfied. Then one can obtain the state trajectory from α_i^0 to α_i^d as $T_i^1 = \{\delta_{2^{n_i}}^{l_0^1} \to \delta_{2^{n_i}}^{l_1^1} \to \cdots \to \delta_{2^{n_i}}^{l_\kappa^1}\}$, where $l_0^1 := \lambda_i$, $l_\kappa^1 := \theta_i$ and $[F_i]_{l_{t+1}^1, l_t^1} = 1$, $t = 0, 1, \ldots, \kappa-1$.

Suppose that $i \in \Phi_2$ and the condition in Corollary 1 is satisfied. Let $\Gamma_k(\delta_{2^{n_i}}^{\theta_i})$ denote the k-th step reachable set of $\delta_{2^{n_i}}^{\theta_i}$. Based on the reachable sets, one can find all possible state trajectories T_i^a, $a = 1, \ldots, b_i$. Let $T_i^a = \{\delta_{2^{n_i}}^{l_0^a} \to \delta_{2^{n_i}}^{l_1^a} \to \cdots \to \delta_{2^{n_i}}^{l_\kappa^a}\}$, where $l_0^a := \lambda_i$ and $l_\kappa^a := \theta_i$. For each $t = 0, \ldots, \kappa-1$, one obtains all possible μ_t^a such that $[F_i \delta_{2^{m_i+q_i}}^{\mu_t^a}]_{l_{t+1}^a, l_t^a} = 1$, $\delta_{2^{n_i}}^{l_{t+1}^a} \in \Gamma_{\kappa-t-1}(\delta_{2^{n_i}}^{\theta_i})$. Let $\Lambda_i^a(t)$ denote the set of such μ_t^a. Then, the set of control sequences driving α_i^0 to α_i^d at the κ-th step corresponding to T_i^a is $\Omega_i^a = \{\{\delta_{2^{m_i+q_i}}^{\mu_0^a}, \delta_{2^{m_i+q_i}}^{\mu_1^a}, \ldots, \delta_{2^{m_i+q_i}}^{\mu_{\kappa-1}^a}\} : \mu_t^a \in \Lambda_i^a(t),\ t = 0, \ldots, \kappa-1\}$.

Proposition 1. For $i \in \Phi_2$, the set of control sequences driving α_i^0 to α_i^d at the κ-th step is

$$\Omega_i = \bigcup_{a=1}^{b_i} \Omega_i^a. \quad (7)$$

For each subnetwork Σ_i, $i \in \Phi_2$, give the following control sequence:

$$w_i^{a_i,c_i} \in \Omega_i,\ a_i \in \{1, \ldots, b_i\},\ c_i \in \{1, \ldots, |\Omega_i^{a_i}|\}. \quad (8)$$

Then, one can get the corresponding $T_i^{a_i}$. For $T_i^{a_i}$, let $\tilde{T}_i^{a_i} := \{\delta_{2^{n_i}}^{l_0^{a_i}}, \delta_{2^{n_i}}^{l_1^{a_i}}, \ldots, \delta_{2^{n_i}}^{l_{\kappa-1}^{a_i}}\}$ denote an ordered set. In addition, for each subnetwork Σ_i, $i \in \Phi_1$, set $\tilde{T}_i^{a_i} = \tilde{T}_i^1$. Let $Y_i^j := Y_i \cap Z_j$, $Z_j^i := Z_j \cap Y_i$. In fact, Y_i^j and Z_j^i represent the input nodes of block N_j that lie in N_i.

Definition 2. Consider x^0, x^d and (8). BCN (1) is said to be κ-matchable with regard to (8), if

$$\sigma_{X_i, Y_i^j}(\tilde{T}_i^{a_i}) = \sigma_{Z_j \cup U_j, Z_j^i}(w_j^{a_j,c_j}) \quad (9)$$

holds for any $i \in \{1, 2, \ldots, \rho\}$, $j \in \Phi_2$, $i \neq j$. In this case, we call $\{w_i^{a_i,c_i} : i \in \Phi_2\}$ a κ-matchable control sequence. Let $\mathcal{M}$ denote the set of κ-matchable control sequences. If $\mathcal{M} \neq \emptyset$, then BCN (1) is said to be κ-matchable. We claim that Eq. (9) naturally holds when $Y_i^j = Z_j^i = \emptyset$.

Theorem 1. Consider $x^0 = \delta_{2^n}^\lambda$, $x^d = \delta_{2^n}^\theta$ and an aggregation containing ρ subnetworks Σ_i, $i = 1, 2, \ldots, \rho$. For the subnetwork Σ_i, let $\alpha_i^0 = \sigma_{X,X_i}(x^0) = \delta_{2^{n_i}}^{\lambda_i}$, $\alpha_i^d = \sigma_{X,X_i}(x^d) = \delta_{2^{n_i}}^{\theta_i}$. Then, BCN (1) is reachable from x^0 to x^d at the κ-th step, iff (i) for any $i = 1, 2, \ldots, \rho$, it holds that $[R_i(\kappa)]_{\theta_i,\lambda_i} > 0$; (ii) BCN (1) is κ-matchable (see Appendix B.2 for the proof).

Remark 1. If $\{w_i^{a_i,c_i} : i \in \Phi_2\}$ is a κ-matchable control sequence, then a control sequence driving BCN (1) from x^0 to x^d at the κ-th step can be given as $u = \{u(t) : t = 0, \ldots, \kappa-1\}$, where $u(t) = \ltimes_{j=1}^m u_j(t)$. In fact, if $u_j \in U_i$, then $\{u_j(t) : t = 0, \ldots, \kappa-1\} = \sigma_{Z_i \cup U_i, \{u_j\}}(w_i^{a_i,c_i})$.

Remark 2. Acyclic aggregation can reduce the number of times for match ability when verifying the κ-matchable condition. In fact, given an acyclic aggregation and a combination of control sequences, when verifying (9), one only needs to consider the unidirectional match ability. The algorithm for obtaining an acyclic aggregated graph that meets Assumption 1 can be found in Appendix C.

Proposition 2. The choice of partition satisfying Assumption 1 does not affect the reachability analysis of large-size BCNs (See Appendix B.3 for the proof).

Mayer-type optimal control. Consider an initial state $x(0) = x^0 \in \Delta_{2^n}$, a final time $\kappa > 0$ and fix a vector $\boldsymbol{r} = (r_1, r_2, \ldots, r_{2^n})^{\mathrm{T}} \in \mathbb{R}^{2^n}$. For the convenience of expression, assume $r_{j_1} < r_{j_2} < \cdots < r_{j_{2^n}}$. Consider the cost-functional

$$C(u) = \boldsymbol{r}^{\mathrm{T}} x(\kappa; x^0, u). \quad (10)$$

The Mayer-type optimal control problem of BCN (1) can then be stated as follows: find all possible control sequences $u^* \in \Omega$ that maximize the cost-functional C.

Theorem 2. The Algorithm 1 generates optimal control sequences.

Algorithm 1 Discovering all solutions to the Mayer-type optimal control problem

1: Set $i = 1$ and calculate x_i^d satisfying $\boldsymbol{r}^{\mathrm{T}} x_i^d = r_{j_{2^n}}$;
2: Verify whether or not BCN (1) is reachable from x^0 to x_i^d at the κ-th step by Theorem 1. If yes, then we can find all control sequences u_i^* steering BCN (1) from x^0 to x_i^d at the κ-th step by Remark 1 and stop. Otherwise, set $i = i + 1$ and go to Step 3;
3: Calculate x_i^d satisfying $\boldsymbol{r}^{\mathrm{T}} x_i^d = r_{j_{2^n-i+1}}$ and go back to Step 2.

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Supporting information Appendixes A–E. The supporting information is available online at info.scichina.com and link.springer.com. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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