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• **Supplementary File** •

Aggregation Method to Reachability and Optimal Control of Large-Size Boolean Control Networks

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Appendix A Notations used in the body of this paper

- $\dot\cup$ denotes the disjoint union of sets.
- $\Delta_p := \{\delta_p^j := Col_j(I_p) : j = 1, \cdots, p\}$. For example, $\delta_3^1 := [1\ 0\ 0]^\top$, $\delta_3^2 := [0\ 1\ 0]^\top$, $\delta_3^3 := [0\ 0\ 1]^\top$, $\Delta_3 := \{\delta_3^j : j = 1, 2, 3\}$.
- $\mathcal{L}_{k\times h} := \Big\{[\delta_k^{i_1}\ \cdots\ \delta_k^{i_h}] := \delta_k[i_1\ \cdots\ i_h] : i_j \in \{1, \cdots, k\}, j = 1, \cdots, h\Big\}$.
- $N = \{x_1, x_2, \cdots, x_n\}$ denotes a set of n nodes, and $M = \{x_{i_1}, x_{i_2}, \cdots, x_{i_m}\} \subseteq N$, $1 \leqslant m < n$. Denote the state of node x_i by ς_i, where $\varsigma_i \in \Delta_2$, $i = 1, \cdots, n$. Then, the natural projection from N to M, denoted by $\sigma_{N,M} : \Delta_{2^n} \to \Delta_{2^m}$, is defined as $\sigma_{N,M}(\ltimes_{i=1}^n \varsigma_i) = \ltimes_{j=1}^m \varsigma_{i_j}$. In addition, for a nonempty ordered set $N' = \{a_1, \cdots, a_s\} \in \Delta_{2^n}^s$, $\sigma_{N,M}(N') := \{\sigma_{N,M}(a_1), \cdots, \sigma_{N,M}(a_s)\}$; for a set group $N'' = \{N_i' \in \Delta_{2^n}^{s_i} : N_i' \neq \emptyset, i = 1, \cdots, h\}$, $\sigma_{N,M}(N'') := \{\sigma_{N,M}(N_i') : i = 1, \cdots, h\}$.

Appendix B Proofs in the body of the letter

Appendix B.1 Proof of Corollary 1

When $Z_i = \emptyset$, this theorem becomes Theorem 3.3 in [1]. Thus, we only consider $Z_i \neq \emptyset$ in the following proof.

When $\kappa = 1$, by Definition 1, $\alpha_i^d = \delta_{2^{n_i}}^{\theta_i}$ is reachable from $\alpha_i^0 = \delta_{2^{n_i}}^{\lambda_i}$ at the first step, if and only if there exists $\beta_i(0) := \delta_{2^{m_i}}^{\mu} \in \Delta_{2^{m_i}}$ such that

$$\delta_{2^{n_i}}^{\theta_i} = F_i \delta_{2^{q_i}}^{\xi_i} \delta_{2^{m_i}}^{\mu} \delta_{2^{n_i}}^{\lambda_i}.$$

Noticing that $F_i \delta_{2^{q_i}}^{\xi_i} \delta_{2^{m_i}}^{\mu} = F_i \delta_{2^{m_i+q_i}}^{2^{m_i}(\xi_i-1)+\mu}$, that is, $\delta_{2^{n_i}}^{\theta_i} = F_i \delta_{2^{m_i+q_i}}^{2^{m_i}(\xi_i-1)+\mu} \delta_{2^{n_i}}^{\lambda_i}$, we have $[F_i \delta_{2^{m_i+q_i}}^{2^{m_i}(\xi_i-1)+\mu}]_{\theta_i,\lambda_i} = 1 > 0$. Then, it is easy to see that

$$\begin{aligned}
[R_i(1)]_{\theta_i,\lambda_i} &= [M_i(0)]_{\theta_i,\lambda_i} \\
&= \Big[\sum_{j=1}^{2^{m_i}} F_i \delta_{2^{m_i+q_i}}^{2^{m_i}(\xi_i-1)+j}\Big]_{\theta_i,\lambda_i} \\
&\geqslant [F_i \delta_{2^{m_i+q_i}}^{2^{m_i}(\xi_i-1)+\mu}]_{\theta_i,\lambda_i} > 0.
\end{aligned}$$

Hence, the conclusion is true for $\kappa = 1$.

Assuming the truth of the conclusion for $\kappa = s > 1$, we prove the truth of the conclusion for $\kappa = s+1$. When $\kappa = s+1$, we divide the proof into two steps. Firstly, there exists $\delta_{2^{n_i}}^{\zeta_i} \in \Delta_{2^{n_i}}$ such that $\delta_{2^{n_i}}^{\zeta_i}$ is reachable from $\delta_{2^{n_i}}^{\lambda_i}$ at the s-th step. Secondly, $\delta_{2^{n_i}}^{\theta_i}$ is reachable from $\delta_{2^{n_i}}^{\zeta_i}$ at the first step. Then, we have $[R_i(s)]_{\zeta_i,\lambda_i} > 0$ and $[M_i]_{\theta_i,\zeta_i} > 0$. Therefore,

$$\begin{aligned}
[R_i(s+1)]_{\theta_i,\lambda_i} &= [M_i^s M_i(0)]_{\theta_i,\lambda_i} \\
&= \sum_{j=1}^{2^{n_i}} [M_i]_{\theta_i,j} [M_i^{s-1} M_i(0)]_{j,\lambda_i} \\
&\geqslant [M_i]_{\theta_i,\zeta_i} [R_i(s)]_{\zeta_i,\lambda_i} > 0.
\end{aligned}$$

Therefore, the conclusion is true for $\kappa = s+1$.

By induction, the conclusion is true for any positive integer κ.

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Appendix B.2 Proof of Theorem 1

(Sufficiency) From condition (i) and 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, $i = 1, 2, \cdots, \rho$. Then, for any subnetwork Σ_i, $i \in \Phi_2$, one can obtain Ω_i.

By condition (ii) and Definition 2, there exists at least one κ-matchable control sequence, denoted by $\{w_i^{a_i,c_i} : i \in \Phi_2\}$, where $w_i^{a_i,c_i} \in \Omega_i$, $a_i \in \{1, \cdots, b_i\}$ and $c_i \in \{1, \cdots, |\Omega_i^{a_i}|\}$.

Then, for this κ-matchable control sequence, one can obtain a control sequence driving BCN (1) from x^0 to x^d at the κ-th step, denoted by $u = \{u(t) : t = 0, \cdots, \kappa-1\}$, where $u(t) = \ltimes_{j=1}^m u_j(t)$. In fact, if $u_j \in U_i$, then $\{u_j(t) : t = 0, \cdots, \kappa-1\}$ can be constructed as $\{u_j(t) : t = 0, \cdots, \kappa-1\} = \sigma_{Z_i \cup U_i, \{u_j\}}(w_i^{a_i,c_i})$. Therefore, under the control $u = \{u(t) : t = 0, \cdots, \kappa-1\}$, BCN (1) is reachable from x^0 to x^d at the κ-th step.

(Necessity) If BCN (1) is reachable from x^0 to x^d at the κ-th step, then there exists at least one control sequence $\{u(t) : t = 0, \cdots, \kappa-1\}$ satisfying $x(\kappa; x^0, u) = x^d$. Denote the corresponding state trajectory by $\{x(t) : t = 0, \cdots, \kappa\}$, where $x(0) = \delta_{2^n}^{\lambda}$, $x(\kappa) = \delta_{2^n}^{\theta}$. Obviously, subnetwork Σ_i, $i \in \Phi_1$ 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, and the state trajectory is $T_i^1 = \{\delta_{2^{n_i}}^{l_0^1} \to \delta_{2^{n_i}}^{l_1^1} \to \cdots \to \delta_{2^{n_i}}^{l_\kappa^1}\}$, where $\delta_{2^{n_i}}^{l_t^1} = \sigma_{X,X_i}(x(t))$, $t = 0, 1, \cdots, \kappa$. In addition, under the following control sequence, subnetwork Σ_i, $i \in \Phi_2$ 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:

$$w_i^{a_i,c_i} := \{\tilde{u}_i(t) : t = 0, \cdots, \kappa-1\}, \tag{B1}$$

where $\tilde{u}_i(t) = \gamma_i(t) \ltimes \beta_i(t)$, $\gamma_i(t) = \sigma_{X,Z_i}(x(t))$, and $\beta_i(t) = \sigma_{U,U_i}(u(t))$. Then, by Corollary 1, $[R_i(\kappa)]_{\theta_i,\lambda_i} > 0$, $\forall\, i = 1, 2, \cdots, \rho$. Therefore, condition (i) holds.

Denote the state trajectory corresponding to $w_i^{a_i,c_i}$ by $T_i^{a_i} = \{\delta_{2^{n_i}}^{l_0^{a_i}} \to \delta_{2^{n_i}}^{l_1^{a_i}} \to \cdots \to \delta_{2^{n_i}}^{l_\kappa^{a_i}}\}$. Then

$$\delta_{2^{n_i}}^{l_t^{a_i}} = \sigma_{X,X_i}(x(t)), \tag{B2}$$

$t = 0, 1, \cdots, \kappa$. Set $\tilde{T}_i^{a_i} := \{\delta_{2^{n_i}}^{l_0^{a_i}}, \delta_{2^{n_i}}^{l_1^{a_i}}, \cdots, \delta_{2^{n_i}}^{l_{\kappa-1}^{a_i}}\}$, $i = 1, 2, \cdots, \rho$, and for any $i \in \Phi_1$, $a_i = 1$. For any $i \in \{1, 2, \cdots, \rho\}$, $j \in \Phi_2$, $i \neq j$, denote $Y_i^j = \{y_{i_{j_r}} : j_r \in \{1, \cdots, p_i\}, r = 1, \cdots, p_i^j\}$, whose elements keep the order in Y_i. Then, for any $i \in \{1, 2, \cdots, \rho\}$, $j \in \Phi_2$, $i \neq j$, on one hand, by (B2), $\sigma_{X_i, Y_i^j}(\tilde{T}_i^{a_i}) = \{\ltimes_{r=1}^{p_i^j} y_{i_{j_r}}(t) : t = 0, \cdots, \kappa-1\}$; on the other hand, by (B1), $\sigma_{Z_j \cup U_j, Z_j^i}(w_j^{a_j,c_j}) = \{\ltimes_{r=1}^{p_i^j} y_{i_{j_r}}(t) : t = 0, \cdots, \kappa-1\}$. Therefore, $\sigma_{X_i, Y_i^j}(\tilde{T}_i^{a_i}) = \sigma_{Z_j \cup U_j, Z_j^i}(w_j^{a_j,c_j})$ holds for any $i \in \{1, 2, \cdots, \rho\}$, $j \in \Phi_2$, $i \neq j$. By Definition 2, $\{w_i^{a_i,c_i} : i \in \Phi_2\}$ is a κ-matchable control sequence, that is, $\mathcal{M} \neq \emptyset$, which implies that condition (ii) holds.

Appendix B.3 Proof of Proposition 2

On one hand, assume that large-size BCN (2) is reachable from $x^0 = \delta_{2^n}^{\lambda}$ to $x^d = \delta_{2^n}^{\theta}$ at the κ-th step. Then, at least one control sequence can be obtained, denoted by $\{u(t) : t = 0, \cdots, \kappa-1\}$, and the corresponding state trajectory is $\{x(t) : t = 0, \cdots, \kappa\}$, where $x(0) = x^0$, $x(\kappa) = x^d$. For any partition Ξ satisfying Assumption 1, assume that Ξ contains $\hat{\rho}$ subnetworks, denoted by $\hat{\Sigma}_i$, $i = 1, 2, \cdots, \hat{\rho}$. In addition, for each subnetwork $\hat{\Sigma}_i$, denote the parameters by $\hat{X}_i$, $\hat{U}_i$, $\hat{Z}_i$, $\hat{Y}_i$, $\hat{n}_i$, $\hat{m}_i$, $\hat{q}_i$, $\hat{p}_i$, $\hat{\alpha}_i^0 = \sigma_{X,\hat{X}_i}(x^0) = \delta_{2^{n_i}}^{\lambda_i}$, and $\hat{\alpha}_i^d = \sigma_{X,\hat{X}_i}(x^d) = \delta_{2^{n_i}}^{\theta_i}$. Denote $\hat{\Phi}_1 := \{i \in \{1, 2, \cdots, \hat{\rho}\} : \hat{Z}_i \cup \hat{U}_i = \emptyset\}$ and $\hat{\Phi}_2 := \{1, 2, \cdots, \hat{\rho}\} \setminus \hat{\Phi}_1$. Then, by virtue of the necessity part of Theorem 1, for each subnetwork $\hat{\Sigma}_i$, $i \in \hat{\Phi}_1$, it is obvious that $\hat{\Sigma}_i$ is reachable from $\hat{\alpha}_i^0 = \delta_{2^{n_i}}^{\lambda_i}$ to $\hat{\alpha}_i^d = \delta_{2^{n_i}}^{\theta_i}$ at the κ-th step; for each subnetwork $\hat{\Sigma}_i$, $i \in \hat{\Phi}_2$, one can obtain that $\hat{\Sigma}_i$ is reachable from $\hat{\alpha}_i^0 = \delta_{2^{n_i}}^{\lambda_i}$ to $\hat{\alpha}_i^d = \delta_{2^{n_i}}^{\theta_i}$ at the κ-th step under control sequence $\hat{w}_i^{a_i,c_i} := \{\tilde{u}_i(t) : t = 0, \cdots, \kappa-1\}$. Thus, by Corollary 1, one can conclude that condition (i) in Theorem 1 holds. In addition, one can verify that $\{\hat{w}_i^{a_i,c_i} : i \in \hat{\Phi}_2\}$ is a κ-matchable control sequence. Thus, condition (ii) in Theorem 1 holds.

On the other hand, given a partition Ξ (here, we assume that the parameters of Ξ is the same as the above Ξ) satisfying Assumption 1, and suppose that the condition (i) and condition (ii) of Theorem 1 are satisfied. Then, according to Definition 2, one can obtain a κ-matchable control sequence, denoted by $\{\hat{w}_i^{a_i,c_i} : i \in \hat{\Phi}_2\}$. In addition, based on the sufficiency part of Theorem 1, from the above κ-matchable control sequence, a control sequence $u = \{u(t) : t = 0, \cdots, \kappa-1\}$ driving BCN (2) from x^0 to x^d at the κ-th step can be obtained. Therefore, by resorting to the first part of this proof, it is easy to see that for any other partition Ξ' satisfying Assumption 1, the conditions in Theorem 1 are still satisfied.

Appendix C Algorithm of obtaining an acyclic aggregated graph which satisfies Assumption 1

Consider large-size BCN (1) and denote the network graph of (1) by $G = (N, E)$.

Algorithm C1 The algorithm of obtaining an acyclic aggregated graph which satisfies Assumption 1.

- Step 1: Obtain all strongly connected components of G, and consider each one as a super node;
- Step 2: If there exists at least one state node in every super node, then an acyclic aggregated graph which satisfies Assumption 1 is obtained and stop. Otherwise, arbitrarily choose a super node N_i contains no state node, and go to Step 3;
- Step 3: Choose another super node N_j satisfying the condition that there exists an edge from some $v_s \in N_i$ to some $v_t \in N_j$. Then, combine N_i and N_j to form a super node and go back to Step 2.

Appendix D Computational complexity analysis of Theorem 1

Given an aggregation of large-size BCN (2) which contains ρ subnetworks. For subnetwork Σ_i, $i = 1, 2, \cdots, \rho$, there exist at most $2^{\kappa(m_i+q_i)}$ control sequences which can drive Σ_i from α_i^0 to α_i^d at the κ-th step. Let $\zeta := \max_{i\in\{1,2,\cdots,\rho\}}\{m_i + q_i\}$. Then, in order to verify the reachability of BCN (2) via Theorem 1, one needs to handle matrices of sizes $2^{n_i} \times 2^{m_i+n_i}$, $i = 1, 2, \cdots, \rho$ and enumerate at most $2^{\rho\kappa\zeta}$ combinations of control sequences. Therefore, the time complexity of Theorem 1 is exponential in the number of nodes. However, the establishment Theorem 1 makes it possible to verify the reachability of large-size BCNs in the following two special cases: (i) Note that it is feasible to verify the reachability of each subnetwork. When there exists a subnetwork which is not reachable, the original large-size BCN is not reachable. (ii) When $|\Omega_i|$ is very small, say $|\Omega_i| \ll 2^{\zeta\kappa}$, it is possible to verify the κ-matchable condition. In the future, we devote to reducing the computational complexity of Theorem 1 for the application to general large-size BCNs.

Appendix E Examples

Appendix E.1 An example used to illustrate how Corollary 1 and Proposition 1 work

Consider the following BCN:

$$\begin{cases} x_1(t+1) = x_1(t)\bar{\vee}(x_2(t) \wedge x_3(t)), \\ x_2(t+1) = x_2(t)\bar{\vee}x_3(t), \\ x_3(t+1) = \neg x_3(t), \\ x_4(t+1) = x_5(t) \wedge u(t), \\ x_5(t+1) = x_4(t)\bar{\vee}u(t)\bar{\vee}x_2(t), \\ x_6(t+1) = x_8(t)\bar{\vee}x_5(t), \\ x_7(t+1) = x_6(t)\bar{\vee}x_3(t), \\ x_8(t+1) = x_7(t), \end{cases} \tag{E1}$$

where x_i, $i = 1, \cdots, 8$ and u denote states and control input, respectively. Fig. 1 shows an aggregation of BCN (E1). Denote the subnetwork corresponding to N_i by Σ_i, $i = 1, 2, 3$. Letting $x^0 = \delta_{256}^{25}, x^d = \delta_{256}^{163}$ and $\kappa = 3$, we consider the reachability of subnetworks Σ_1, Σ_2 and Σ_3, respectively.

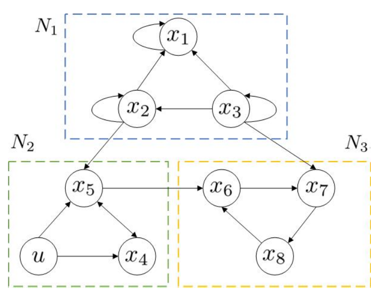

Fig. 1: Aggregation of BCN (E1).

For subnetwork Σ_1, the state trajectory from $\alpha_1^0 = \delta_8^1$ to $\alpha_1^d = \delta_8^6$ is $T_1^1 = \{\delta_8^1 \to \delta_8^8 \to \delta_8^7 \to \delta_8^6\}$.

Consider subnetwork Σ_2, we have $Z_2 = \{x_2\}$, $Y_2 = \{x_5\}$. Calculating F_2 and splitting F_2 into 4 equal blocks, we have $[M_2^2 M_2(0)]_{1,4} = 4 > 0$. By Corollary 1, subnetwork Σ_2 is reachable from α_2^0 to α_2^d at the third step. By calculation, all possible state trajectories of Σ_2 are $T_2^1 = \{\delta_4^4 \to \delta_4^3 \to \delta_4^1 \to \delta_4^1\}$, $T_2^2 = \{\delta_4^4 \to \delta_4^3 \to \delta_4^3 \to \delta_4^1\}$ and $T_2^3 = \{\delta_4^4 \to \delta_4^4 \to \delta_4^3 \to \delta_4^1\}$. In addition, by resorting to Proposition 1, the set of control sequences is

$$\Omega_2 = \Big\{\{\delta_4^1, \delta_4^3, \delta_4^1\}, \{\delta_4^1, \delta_4^2, \delta_4^3\}, \{\delta_4^2, \delta_4^2, \delta_4^3\}, \{\delta_4^2, \delta_4^3, \delta_4^3\}\Big\}.$$

Subnetwork Σ_3 is reachable from $\alpha_3^0 = \delta_8^1$ to $\alpha_3^d = \delta_8^3$ at the third step, and the corresponding state trajectories are $T_3^1 = \{\delta_8^1 \to \delta_8^3 \to \delta_8^6 \to \delta_8^3\}$, $T_3^2 = \{\delta_8^1 \to \delta_8^3 \to \delta_8^2 \to \delta_8^3\}$. In addition, the set of control sequences is $\Omega_3 = \Big\{\{\delta_4^2, \delta_4^3, \delta_4^3\}, \{\delta_4^2, \delta_4^4, \delta_4^1\}\Big\}$.

Appendix E.2 An example used to show how Theorem 1 works

Consider the BCN model of Pseudomonas aeruginosa QS system [2]. Given an aggregation shown in Fig. 2. Verify whether or not the Pseudomonas aeruginosa QS system is reachable from $x^0 = \delta_{16777216}^{6870173}$ to $x^d = \delta_{16777216}^{8706044}$ at the second step.

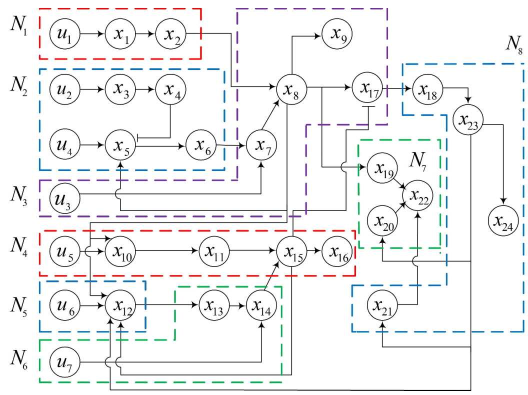

Fig. 2: Aggregation of Pseudomonas aeruginosa QS system.

Since $[M_1 M_1(0)]_{3,2} = 1 > 0$, subnetwork Σ_1 is reachable from δ_4^2 to δ_4^3 at the second step. The corresponding state trajectory and the set of control sequences are $T_1 = \{\delta_4^2 \to \delta_4^1 \to \delta_4^3\}$ and $\Omega_1 = \Big\{\{\delta_2^1, \delta_2^2\}\Big\}$, respectively. By calculation, subnetwork Σ_i is reachable from α_i^0 to α_i^d at the second step, $i = 2, 3, \cdots, 8$.

By Definition 2, one can obtain 64 different 2-matchable control sequences. Therefore, the Pseudomonas aeruginosa QS system is reachable from x^0 to x^d at the second step. By Remark 1, the set of control sequences is

$$U = \Big\{\{\delta_{128}^i, \delta_{128}^j\} : i = 5, \cdots, 8, 13, \cdots, 16, 21, \cdots, 24, 29, \cdots, 32; j = 72, 80\Big\}.$$

Appendix E.3 An example used to show the necessity of verifying κ-matchable condition

Consider the Boolean network model of colitis-associated colon cancer with 70 nodes and 153 edges [3]. The network graph of colitis-associated colon cancer network is shown in Fig. 3.

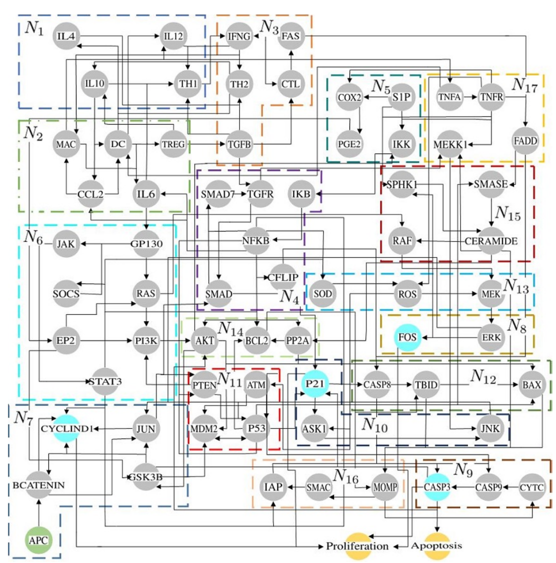

Fig. 3: Network graph of colitis-associated colon cancer network.

Colorectal cancer is one of the most common malignancies. It is shown that colorectal cancer is closely correlated with inflammation. The modeling and analysis of colitis-associated colon cancer network establish a framework for the study of inflammation-associated cancer [3]. Note that the existing results on colitis-associated colon cancer network are mainly based on experiments, and it is meaningful to develop a mathematical tool for the study of colitis-associated colon cancer network.

In the colitis-associated colon cancer network, "APC" denotes an input node, "Proliferation", "Apoptosis" denote two output nodes, and the remaining ones are state nodes. According to [3], the output dynamics of colitis-associated colon cancer network is

$$\begin{cases} \text{Proliferation}(t) = (\text{FOS}(t) \wedge \text{CYCLIND1}(t)) \wedge \neg(\text{P21}(t) \vee \text{CASP3}(t)), \\ \text{Apoptosis}(t) = \text{CASP3}(t), \end{cases} \tag{E2}$$

Given $X_0 = (1\ 0\ 1\ 1\ 0\ 1\ 0\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 1\ 0)$
and $X_d = (1\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 0\ \ 1\ 0\ 1\ 1\ 1\ 0\ 1\ 0\ 0\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 0\ 1\ \ 0\ 1\ 1\ 0\ 1\ 0\ 0\ 0\ 0\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 1$

1 1 0 1 1). According to (E2), it is easy to verify that state X_0 corresponds to "Proliferation" being "ON" and "Apoptosis" being "OFF", while state X_d corresponds to "Proliferation" being "OFF" and "Apoptosis" being "ON". In the following, we investigate the 3-step reachability of colitis-associated colon cancer network from state X_0 to state X_d based the aggregation method. For full names and Boolean logical rules of nodes in colitis-associated colon cancer network, please refer to [3].

Choose the aggregation shown in Fig. 3, where the whole BCN is partitioned into 17 small-size subnetworks (Table 1), denoted by Σ_i, $i = 1, 2, \cdots, 17$.

Table 1: Notations of each subnetwork in aggregation.

	X_i	$Z_i \cup U_i$
Σ_1	TH1, IL4, IL12, IL10	TREG, TH2, TGFB, MAC, IFNG, CTL
Σ_2	TREG, MAC, IL6, DC, CCL2	NFKB, TNFA, IL10, IFNG
Σ_3	FAS, TH2, TGFB, IFNG, CTL	TREG, TH1, IL4
Σ_4	CFLIP, IKB, NFKB, SMAD, SMAD7, TGFR	IKK, JUN, TGFB
Σ_5	COX2, IKK, PGE2, S1P	AKT, SPHK1, TNFR
Σ_6	EP2, GP130, JAK, PI3K, RAS, STAT3	PGE2, PTEN, IL6
Σ_7	BCATENIN, CYCLIND1, GSK3B, JUN	AKT, EP2, ERK, JNK, STAT3
Σ_8	ERK, FOS	MEK
Σ_9	CASP3, CASP9, CYTC	CASP8, IAP, MOMP, P21
Σ_{10}	ASK1, JNK, P21	CASP3, GSK3B, MEKK1, P53, ROS, SMAD
Σ_{11}	ATM, MDM2, P53, PTEN	AKT, GSK3B, JNK, JUN, NFKB, ROS
Σ_{12}	BAX, CASP8, TBID	AKT, BCL2, CFLIP, FADD, P21, P53, PP2A
Σ_{13}	MEK, ROS, SOD	NFKB, RAF, STAT3, TNFR
Σ_{14}	AKT, BCL2, PP2A	CASP3, CERAMIDE, NFKB, P53, PI3K, STAT3
Σ_{15}	CERAMIDE, RAF, SMASE, SPHK1	ERK, FADD, P53, RAS, TNFR
Σ_{16}	IAP, MOMP, SMAC	BAX, BCL2, CERAMIDE, NFKB, STAT3, TBID
Σ_{17}	FADD, MEKK1, TNFR, TNFA	CERAMIDE, FAS, TGFR, MAC

Firstly, we consider the reachability of subnetworks. Take subnetwork Σ_3 as an example. We have $\alpha_3^0 = \delta_{32}^1$, $\alpha_3^d = \delta_{32}^{18}$ and $\gamma_3(0) = \delta_8^1$. Since $[M_3^2 M_3(0)]_{18,1} = 2 > 0$, by Corollary 1, α_3^d is reachable from α_3^0 at the third step. Similar to subnetwork Σ_3, one can verify that subnetwork Σ_i is reachable from α_i^0 to α_i^d at the third step, $i \in \{1, 2, \cdots, 16\} \setminus \{3\}$.

Next, we check the 3-matchable condition. For subnetwork Σ_4 with $\alpha_4^0 = \delta_{32}^1$, $\alpha_4^d = \delta_{32}^{18}$ and $\gamma_4(0) = \delta_8^1$, there exists one state trajectory from α_4^0 to α_4^d at the third step as $T_4^1 = \{\delta_{64}^1 \to \delta_{64}^{30} \to \delta_{64}^{56} \to \delta_{64}^{21}\}$. In addition, the set of control sequences is

$$\Omega_4 = \Big\{\{\delta_8^1, \delta_8^1, \delta_8^1\}, \{\delta_8^1, \delta_8^2, \delta_8^1\}, \{\delta_8^1, \delta_8^3, \delta_8^1\}, \{\delta_8^1, \delta_8^4, \delta_8^1\}, \{\delta_8^1, \delta_8^1, \delta_8^3\}, \{\delta_8^1, \delta_8^2, \delta_8^3\}, \{\delta_8^1, \delta_8^3, \delta_8^3\}, \{\delta_8^1, \delta_8^4, \delta_8^3\}\Big\}.$$

Considering subnetwork Σ_3, there exists one state trajectory from α_3^0 to α_3^d at the third step, that is, $T_3^1 = \{\delta_{32}^1 \to \delta_{32}^{10} \to \delta_{32}^{32} \to \delta_{32}^{18}\}$. Then, we have $\tilde{T}_3^1 = \{\delta_{32}^1, \delta_{32}^{10}, \delta_{32}^{32}\}$.

It is easy to see from Table 1 that $Y_3^4 = Z_4^3 = \{\text{TGFB}\}$. By a simple calculation, for $\alpha_3(2) = \delta_{32}^{32}$, one can obtain that $\sigma_{X_3, Y_3^4}(\{\alpha_3(2)\}) = \{\delta_2^2\}$. However, for $\gamma_4(2) = \delta_8^1$ and $\gamma_4(2) = \delta_8^3$, it holds that $\sigma_{Z_4, Z_4^3}(\{\gamma_4(2)\}) = \{\delta_2^1\}$. Then, for each $w_4 \in \Omega_4$, we have $\sigma_{X_3, Y_3^4}(\tilde{T}_3^1) \neq \sigma_{Z_4, Z_4^3}(w_4)$. Therefore, according to Definition 2, the colitis-associated colon cancer network is not 3-matchable. Thus, the CACC network is not reachable from X_0 to X_d at the third step.

From this example, one can see that for a given aggregation, although all subnetworks are reachable, the whole large-size network maybe not reachable, which supports the necessity of verifying κ-matchable condition.

Appendix E.4 An example used to illustrate Remark 2

Recall the example in Appendix E.1. We check whether or not BCN (E1) is 3-matchable.

It is obvious that the aggregation given in Fig. 1 is an acyclic aggregation, and it holds that $Y_i^j = Z_j^i = \emptyset$, $i > j$, $i, j = 1, 2, 3$.

Since subnetwork Σ_1 has no input, according to the unique state trajectory from α_1^0 to α_1^d, that is, $T_1^1 = \{\delta_8^1 \to \delta_8^8 \to \delta_8^7 \to \delta_8^6\}$, we have $\sigma_{X_1, Y_1^2}(\tilde{T}_1^1) = \{\delta_2^1, \delta_2^2, \delta_2^2\}$, $\sigma_{X_1, Y_1^3}(\tilde{T}_1^1) = \{\delta_2^1, \delta_2^2, \delta_2^1\}$, where $\tilde{T}_1^1 = \{\delta_8^1, \delta_8^8, \delta_8^7\}$.

By enumerating control sequences in Ω_2, one can obtain that only control sequence $w_2^{3,2} = \{\delta_4^2, \delta_4^3, \delta_4^3\}$ satisfies $\sigma_{X_1, Y_1^2}(\tilde{T}_1^1) = \sigma_{Z_2 \cup U_2, Z_2^1}(w_2^{3,2})$. Then, the corresponding state trajectory is $T_2^3 = \{\delta_4^4 \to \delta_4^4 \to \delta_4^3 \to \delta_4^1\}$. In addition, similar to subnetwork Σ_2, there exists a unique control sequence $w_3^{2,1} = \{\delta_4^2, \delta_4^4, \delta_4^1\} \in \Omega_3$ satisfying $\sigma_{X_1, Y_1^3}(\tilde{T}_1^1) = \sigma_{Z_3 \cup U_3, Z_3^1}(w_3^{2,1})$.

Then, we just need to consider the matchability between subnetworks Σ_2 and Σ_3. Since $\sigma_{X_2, Y_2^3}(\tilde{T}_2^3) = \sigma_{Z_3 \cup U_3, Z_3^2}(w_3^{2,1})$, one can conclude that $\{w_2^{3,2}, w_3^{2,1}\}$ is a 3-matchable control sequence. Therefore, BCN (E1) is 3-matchable.

In order to check the 3-matchable condition of BCN (E1), according to Definition 2, one needs to verify whether or not (9) holds for any $i \in \{1, 2, 3\}$, $j \in \{2, 3\}$, $i \neq j$. However, in this example, by virtue of the acyclic aggregation, one just needs to verify the cases of $i = 1$, $j = 2$, $i = 1$, $j = 3$, and $i = 2$, $j = 3$. Thus, acyclic aggregation can reduce the number of times for matchability when verifying the κ-matchable condition.

Appendix E.5 An example used to show how Algorithm 1 works

Consider the following Boolean model for the lac operon in Escherichia coli [4]:

$$\begin{cases} x_1(t+1) = \neg x_7(t) \wedge x_3(t), \\ x_2(t+1) = x_1(t), \\ x_3(t+1) = \neg u_1(t), \\ x_4(t+1) = x_5(t) \wedge x_6(t), \\ x_5(t+1) = \neg u_1(t) \wedge x_2(t) \wedge u_2(t), \\ x_6(t+1) = x_1(t), \\ x_7(t+1) = \neg x_4(t) \wedge \neg x_8(t), \\ x_8(t+1) = x_4(t) \vee x_5(t) \vee x_9(t), \\ x_9(t+1) = \neg u_1(t) \wedge (x_5(t) \wedge u_2(t)). \end{cases} \tag{E3}$$

Fig. 4 shows an aggregation of BCN (E3). Denote the subnetwork corresponding to N_i by Σ_i, $i = 1, 2, 3$. Given $x^0 = \delta_{512}^{53}$, $\kappa = 2$ and $\mathbf{r} = (r_1, r_2, \cdots, r_{512})^\top \in \mathbb{R}^{512}$, where the element r_j, $j = 1, 2, \cdots, 512$ in $\mathbf{r}$ is given by the following function:

$$r_j = -j^2 + 9.8j - 14.$$

We solve this Mayer-type optimal control problem according to Algorithm 1.

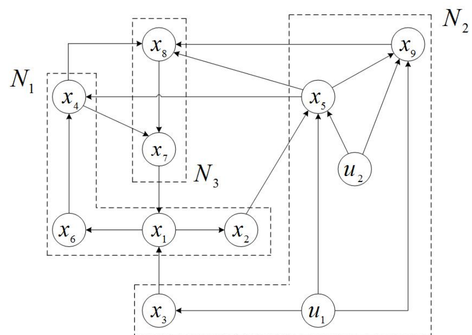

Fig. 4: Aggregation of Boolean model (E3) for the lac operon in Escherichia coli.

Firstly, by Algorithm 1, setting $i = 1$ and calculating x_1^d satisfying $\mathbf{r}^\top x_1^d = \max\{r_j : j = 1, 2, \cdots, 512\}$, we can obtain $x_1^d = \delta_{512}^5$, where the lac operon is "on".

Secondly, verify whether or not BCN (E3) is reachable from δ_{512}^{53} to δ_{512}^5 at the second step by Theorem 1. On one hand, by a simple calculation, we can obtain that $[M_i M_i(0)]_{\theta_i, \lambda_i} > 0$, $i = 1, 2, 3$. On the other hand, we can respectively find all the control sequences driving α_i^0 to α_i^d at the second step, $i = 1, 2, 3$ as $\Omega_1 = \left\{\{\delta_8^4, \delta_8^2\}\right\}$, $\Omega_2 = \left\{\{\delta_8^1, \delta_8^3\}, \{\delta_8^2, \delta_8^3\}, \{\delta_8^3, \delta_8^3\}, \{\delta_8^4, \delta_8^3\}\right\}$, and $\Omega_3 = \left\{\{\delta_8^7, \delta_8^1\}, \{\delta_8^7, \delta_8^2\}, \{\delta_8^7, \delta_8^3\}, \{\delta_8^7, \delta_8^4\}, \{\delta_8^7, \delta_8^5\}, \{\delta_8^7, \delta_8^6\}, \{\delta_8^7, \delta_8^7\}, \{\delta_8^7, \delta_8^8\}\right\}$. Then, it can be verified by Definition 2 that the control sequence $\left\{\{\delta_8^4, \delta_8^2\}, \{\delta_8^3, \delta_8^3\}, \{\delta_8^7, \delta_8^5\}\right\}$ is a 2-matchable control sequence, that is, BCN (E3) is 2-matchable. Therefore, condition (ii) of Theorem 1 holds. Therefore, BCN (E3) is reachable from x^0 to x_1^d at the second step. In addition, the control sequence u_1^* steering BCN (E3) from x^0 to x_1^d at the second step is $\{u(0), u(1)\} = \{\delta_4^3, \delta_4^3\}$.

By Theorem 2, the optimal control sequence is $\{u(0), u(1)\} = \{\delta_4^3, \delta_4^3\}$.

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