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Efficient observability verification for large-scale Boolean control networks

Kuize Zhang[1,2] Karl Henrik Johansson[1]

1. ACCESS Linnaeus Center, School of Electrical Engineering and Computer Science
KTH Royal Institute of Technology, 10044 Stockholm, Sweden
E-mail: {kuzhan,kallej}@kth.se

2. College of Automation
Harbin Engineering University, 150001 Harbin, PR China
E-mail: zkz0017@163.com

Abstract: It is known that verifying observability of Boolean control networks (BCNs) is NP-hard in the number of nodes. In this paper, we use a node aggregation approach to overcome the computational complexity in verifying observability for networks with special structures. First, we define a class of network node aggregations with compatible observability. It is proven for this class of aggregations, the whole BCN being observable does not imply that all corresponding subnetworks are observable, and vice versa. Second, when the aggregations are acyclic, we prove that all corresponding subnetworks being observable implies that the overall BCN is observable, although the converse is not true. Third, we show that finding acyclic aggregations with small subnetworks can tremendously reduce the computational complexity in verifying observability. Finally, we use a BCN T-cell receptor kinetics model from the literature with 37 state nodes and 3 input nodes to illustrate the efficiency of these results. For this model, we derive the unique minimal set of 16 state nodes needed to be observed to make the overall BCN observable.

Key Words: Boolean control network, observability, node aggregation, graph theory

1 Introduction

Boolean networks (BNs), initiated by Kauffman [8] to model genetic regulatory networks in 1969, are a class of discrete-time discrete-space dynamical systems. In a BN, nodes can be in one of two discrete states "1" and "0", which represent the gene state "on" and "off", respectively. Every node updates its state according to a Boolean function of the network node states. When external regulation or perturbation is considered, BNs are naturally extended to Boolean control networks (BCNs) [6]. Although a BN or a BCN is a simplified model of a genetic regulatory network, they can be used to characterize many important phenomena of biological systems, e.g., cell cycles [4], cell apoptosis [14]. The study on BNs and BCNs has been paid wide attention [2, 16, 20].

The study on control-theoretic properties of BCNs dates back to 2007, when the problem of verifying controllability of a BCN was proved to be NP-hard in the number of nodes [1]. Since then, many basic properties of BCNs have been characterized, e.g., controllability [3, 21], observability [3, 5, 11, 15, 21], reconstructibility [5, 17]. Several of these findings are based on the semi-tensor product framework originally proposed in [3].

Observability is on using input sequences and the corresponding output sequences to determine the initial state. It is of fundamental use in state estimation, observer design, etc. A quantitative description of a complex dynamical system is normally based on its state information, but the practical use is inherently limited by the ability to estimate the system's state. The problem of how to use a subset of nodes (as output nodes) to observe the whole network's state has important applications in systems biology, and many other areas, since in practice experimental access is limited to only a subset of nodes [12].

Verifying observability of BCNs is NP-hard in the number of nodes [10], so computationally intractable. Existing verification algorithms [5, 15] run in exponential time in the number of nodes, so they cannot be used to deal with large-scale networks (with more than about 30 nodes) in a reasonable amount of time. It seems unlikely to exist fast algorithms for verifying observability of general BCNs, but an interesting direction is to focus on BCNs with special network structures. It is natural to develop a *node aggregation* method for which observability for the overall network follows from the verification of subnetworks. An aggregated graph of a BCN consists of super nodes and edges, where each super node corresponds to a collection of nodes of the original BCN. The node aggregation method has been widely used in pagerank algorithms [7], social networks [13], and also applied to controllability analysis of BCNs [19] and fixed-point computation of BNs [20]. It is NP-complete to verify existence of fixed points of BNs [18], so it is reasonable to use the node aggregation method for fixed-point computation of large BNs. The advantage of the node aggregation method has been illustrated by a BCN T-cell receptor kinetics model [9] in both [20] and [19], where the model has 37 state nodes and 3 input nodes,[1] i.e., it has 2^{37} states and 2^3 inputs. It is impossible to use the general methods given in [18, 21] to compute attractors or check controllability and stabilizability in a reasonable amount of time. However, using the node aggregation technique [19, 20], these two problems have been solved. In [20], an efficient way to look for attractors of BNs is proposed based on such a technique; particularly, for an acyclic node aggregation (i.e., when the aggregated graph is acyclic), all attractors of a BN are obtained by composing attractors of the corresponding subnetworks. Similar idea has been used to deal with controllabili-

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[1] In [20], in order to compute attractors, the 3 input nodes are assumed to be constant.

ty and stabilizability of BCNs [19]. It is proved in [19] that if a BCN is controllable (stabilizable) then all resulting subnetworks are controllable (stabilizable) for a node aggregation satisfying that each subnetwork has at least one state node. However, the converse is not true. It is partially because in order to verify controllability and stabilizability, external nodes (i.e., input nodes) of BCNs must be considered. In this paper, we show that for observability, neither of the bidirectional implications holds because not only input nodes but also output nodes must be considered, and observability is not dual to controllability for BCNs, which follows from the pairwise nonequivalence of four concepts of observability for BCNs [15]. Hence, the node aggregation method in [19] cannot be used to deal with observability.

The contributions of this paper are stated as follows.

1) We define a class of node aggregations for BCNs with compatible observability, prove that for such aggregations, the whole BCN being observable does not imply that all corresponding subnetworks are observable, and vice versa.
2) For acyclic node aggregations in this class, we prove that all corresponding subnetworks being observable imply that the overall BCN is also observable, although the converse is not true.
3) We show that finding such acyclic node aggregations with small subnetworks can tremendously reduce the computational complexity in verifying observability.
4) Finally, for a BCN T-cell receptor kinetics model with 37 state nodes and 3 input nodes [9], by finding suitable acyclic aggregations, we derive the unique minimal set of 16 state nodes needed to be observed to make the model observable.

The remainder of the paper is organized as below. In Section 2, basic concepts on BCNs, observability, and new node aggregations with compatible observability are introduced. In Section 3, observability results based on node aggregations are proved. In Section 4, the BCN T-cell receptor kinetics model is used to illustrate the efficiency of the main results given in Section 3. Section 5 is a short conclusion with further discussion.

2 Preliminaries

2.1 BCNs

Hereinafter, we denote $\mathcal{D} := \{0,1\}$; $[i,j] := \{i, i+1, \dots, j\}$ for integers $i \le j$; $C_i^j := \frac{i!}{j!(i-j)!}$ for positive integers $i \ge j$. 2^S stands for the power set of a set S, $\oplus$ and $\odot$ stand for the addition and multiplication modulo 2, respectively. A BCN is formulated as

$$\begin{aligned} x_1(t+1) &= f_1(x_1(t), \dots, x_n(t), u_1(t), \dots, u_m(t)), \\ &\vdots \\ x_n(t+1) &= f_n(x_1(t), \dots, x_n(t), u_1(t), \dots, u_m(t)), \\ y_1(t) &= h_1(x_1(t), \dots, x_n(t)), \\ &\vdots \\ y_q(t) &= h_n(x_1(t), \dots, x_n(t)), \end{aligned} \tag{1}$$

where $t = 0, 1, \dots$ denote discrete time steps; $x_i(t), u_j(t)$, and $y_k(t) \in \mathcal{D}$ denote values of state node x_i, input node u_j, and output node y_k at time step t, respectively, $i \in [1,n]$, $j \in [1,m]$, $k \in [1,q]$; $f_i : \mathcal{D}^{m+n} \to \mathcal{D}$ and $h_j : \mathcal{D}^n \to \mathcal{D}$ are Boolean functions, $i \in [1,n]$, $j \in [1,q]$.

Eqn. (1) is equivalently represented in the compact form

$$\begin{aligned} x(t+1) &= f(x(t), u(t)), \\ y(t) &= h(x(t)), \end{aligned} \tag{2}$$

where $t = 0, 1, \dots$; $x(t) \in \mathcal{D}^n$, $u(t) \in \mathcal{D}^m$, and $y(t) \in \mathcal{D}^q$ stand for the state, input, and output of the BCN at time step t; $f : \mathcal{D}^{n+m} \to \mathcal{D}^n$ and $h : \mathcal{D}^n \to \mathcal{D}^q$ are Boolean mappings.

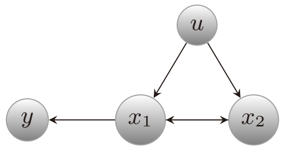

Fig. 1: Example of a network consisting of one input node u, two state nodes x_1, x_2, and one output node y.

Intuitively, a BCN performs dynamics over a network that is actually a directed graph consisting of input nodes, state nodes, and output nodes, where an input node has 0 indegree (i.e., the number of entering edges at the node), an output node has 0 outdegree (i.e., the number of leaving edges at the node), and state nodes may have both positive indegree and positive outdegree. In a network, each edge from node v_i to node v_j means that the value (1 or 0) of v_j at time step $t+1$ is affected by the value of v_i at time step t, each node v updates its value according to a Boolean function of values of nodes having a leaving edge that enters v. Note that over a network, there may exist different BCNs, e.g., the following two BCNs

$$\begin{aligned} x_1(t+1) &= x_2(t) \wedge u(t), \\ x_2(t+1) &= \neg x_1(t) \vee u(t), \\ y(t) &= x_1(t), \end{aligned} \tag{3}$$

where $t = 0, 1, \dots$; $x_1(t), x_2(t), u(t), y(t)$ are Boolean variables (1 or 0); $\wedge$, $\vee$, and $\neg$ denote AND, OR, and NOT, respectively,

$$\begin{aligned} x_1(t+1) &= x_2(t) \barwedge u(t), \\ x_2(t+1) &= \neg x_1(t) \wedge u(t), \\ y(t) &= x_1(t), \end{aligned} \tag{4}$$

where $t = 0, 1, \dots$; $x_1(t), x_2(t), u(t), y(t)$ are Boolean variables; $\barwedge$ denotes XOR, have the same network as shown in Fig. 1.

2.2 Observability

In [15], four types of observability are characterized for BCNs. In this paper, we are particularly interested in the linear type (also cf. [5]), as if a BCN satisfies this observability property, it is very easy to recover the initial state using input sequences and the corresponding output sequences.

Definition 2.1 *A BCN (2) is called observable if for all different initial states $x_0, x_0' \in \mathcal{D}^n$, for each input sequence $\{u_0, u_1, \dots\} \subset \mathcal{D}^m$, the corresponding output sequences $\{y_0, y_1, \dots\}$ and $\{y_0', y_1', \dots\}$ are different.*

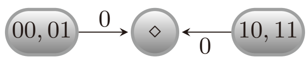

Fig. 2: Observability weighted pair graph of the BCN (3), where $\diamond$ denotes the subgraph generated by all diagonal vertices.

Fig. 3: Observability weighted pair graph of the BCN (4), where $\diamond$ denotes the subgraph generated by all diagonal vertices.

We use a graph-theoretic method proposed in [15] to verify this types of observability in what follows.

Definition 2.2 ([15]) *Consider a BCN (2). A weighted directed graph $\mathcal{G}_o = (\mathcal{V}, \mathcal{E}, \mathcal{W}, 2^{\mathcal{D}^m})$ is an observability weighted pair graph of the BCN (2) if the vertex set $\mathcal{V}$ equals $\{\{x, x'\} \in \mathcal{D}^n \times \mathcal{D}^n | h(x) = h(x')\}$, the edge set $\mathcal{E}$ equals $\{(\{x_1, x_1'\}, \{x_2, x_2'\}) \in \mathcal{V} \times \mathcal{V} |$there exists $u \in \mathcal{D}^m$ such that $f(x_1, u) = x_2$ and $f(x_1', u) = x_2'$, or, $f(x_1, u) = x_2'$ and $f(x_1', u) = x_2\} \subset \mathcal{V} \times \mathcal{V}$, and the weight function $\mathcal{W} : \mathcal{E} \to 2^{\mathcal{D}^m}$ assigns each edge $(\{x_1, x_1'\}, \{x_2, x_2'\}) \in \mathcal{E}$ a set $\{u \in \mathcal{D}^m | f(x_1, u) = x_2$ and $f(x_1', u) = x_2'$, or, $f(x_1, u) = x_2'$ and $f(x_1', u) = x_2\}$ of inputs. A vertex $\{x, x'\}$ is called diagonal if $x = x'$, and called non-diagonal otherwise.*

Proposition 2.3 ([15]) *A BCN (2) is not observable if and only if its observability weighted pair graph has a non-diagonal vertex v and a cycle C such that there is a path from v to a vertex of C.*

The computational cost of constructing the observability weighted pair graph of a BCN (2) is at most $(2^n + 2^n(2^n - 1)/2)2^m = 2^{n+m} + 2^{2n+m-1} - 2^{n+m-1}$. Hence the computational complexity of using Proposition 2.3 to check observability is $O(2^{2n+m-1})$. On the other hand, the size of the network of a BCN is at most $n + m + q + mn + n(n + q)$, which is significantly smaller than the size of the observability weighted pair graph, then is it possible to design an algorithm to check observability by using only the network? The answer is "No", because there exist two BCNs sharing the same network, one of which is observable, but the other of which is not observable (see BCNs (3) and (4)). Note that for a BCN (2), the subgraph $(\mathcal{V}_d, (\mathcal{V}_d \times \mathcal{V}_d) \cap \mathcal{E})$ generated by the set $\mathcal{V}_d$ of all diagonal vertices of its observability weighted pair graph contains a cycle; and for each diagonal vertex $v \in \mathcal{V}_d$, there is a path from v to some vertex of a cycle in the subgraph. Then the following corollary holds.

Corollary 2.4 *A BCN (2) is not observable if and only if in its observability weighted pair graph, either there is a path from a non-diagonal vertex to a diagonal vertex or there is a cycle consisting of only non-diagonal vertices.*

For example, BCNs (3) and (4) have the same network as shown in Fig. 1, (3) is not observable (see Fig. 2) by Corollary 2.4, but (4) is observable (see Fig. 3) by Proposition 2.3.

2.3 Node aggregations

For a BCN, let us denote the set of nodes of its network by $\mathcal{N} = \{x_1, \dots, x_n, u_1, \dots, u_m, y_1, \dots, y_q\}$, the set of state nodes by $\mathcal{X} = \{x_1, \dots, x_n\}$, the set of input nodes by $\mathcal{U} = \{u_1, \dots, u_m\}$, and the set of output nodes by $\mathcal{Y} = \{y_1, \dots, y_q\}$. The node aggregations adopted in this paper are represented as partitions of the set of nodes as follows:

$$\mathcal{N} = \mathcal{N}_1 \cup \dots \cup \mathcal{N}_s, \tag{5}$$

where each $\mathcal{N}_i$ is a nonempty proper subset of $\mathcal{N}$, and $\mathcal{N}_i \cap \mathcal{N}_j = \emptyset$ for all $i \neq j$, $i, j \in [1, s]$. Note that in a BCN (2), $\mathcal{U}$ can be empty, meaning that only a unique constant input sequence can be fed into the BCN. Hereinafter we assume that neither $\mathcal{X}$ nor $\mathcal{Y}$ can be empty. If $\mathcal{Y}$ is empty, then one cannot observe any information of states of the BCN. If $\mathcal{X}$ is empty, it is meaningless to observe the BCN. For a node aggregation (5), each part $\mathcal{N}_i$ is regarded as a super node, then the aggregation is regarded as a directed graph that is called an aggregated graph, where the edge set consists of edges of the network whose tails and heads belong to different super nodes. Also, each super node $\mathcal{N}_i$ is regarded as a subnetwork, denoted by Σ_i, called a *resulting subnetwork*. For each super node $\mathcal{N}_i$, its indegree (outdegree) is the sum of edges entering (leaving) $\mathcal{N}_i$ in the aggregated graph, $i \in [1, s]$. The purpose of aggregating network nodes of a BCN (2) is to verify observability of the BCN by verifying observability of its resulting subnetworks. So in order to reduce computational cost, the size of resulting subnetworks should be as small as possible.

In [19], controllability and stabilizability are considered, so the BCN (2) considered in [19] has an empty set of output nodes. Under the assumption that in a node aggregation (5), each super node $\mathcal{N}_i$ is weakly connected and contains at least one state node, it is proved that the BCN is controllable only if each subnetwork Σ_i is controllable, but the converse is not true. One directly sees that without the weak connectedness assumption, all results in [19] remain valid. For observability, since we must consider a nonempty set $\mathcal{Y}$ of output nodes, the node aggregations used in [19] cannot be used in this paper. We aggregate network nodes in different ways. Later on, for observability, we show somehow converse results compared to the controllability results given in [19].

In order to make each super node $\mathcal{N}_i$ be a BCN such that it is meaningful to verify its observability, we only consider a node aggregation (5) satisfying the following Assumption 1 in this paper. Assumption 1 is stronger than the previous assumption used in [19]. However, in order not to break the dynamics of the whole BCN, we must make this stronger assumption. Under Assumption 1, each resulting subnetwork Σ_i corresponding to each super node $\mathcal{N}_i$ is of the form (1), $i \in [1, s]$.

Assumption 1 *For each $i \in [1, s]$,*

1) *(making observing Σ_i meaningful) $\mathcal{N}_i \cap \mathcal{Y} \neq \emptyset$; if $\mathcal{N}_i \cap \mathcal{X} \neq \emptyset$, then in $\mathcal{N}_i$, for each state node $x \in \mathcal{N}_i \cap \mathcal{X}$, there is a path from x to an output node $y \in \mathcal{N}_i \cap \mathcal{Y}$ such that all parents of y in $\mathcal{X}$ belong to $\mathcal{N}_i$.*
2) *(making controlling Σ_i meaningful) If $\mathcal{N}_i$ has a positive indegree, then outside $\mathcal{N}_i$, all tails of all edges of the*

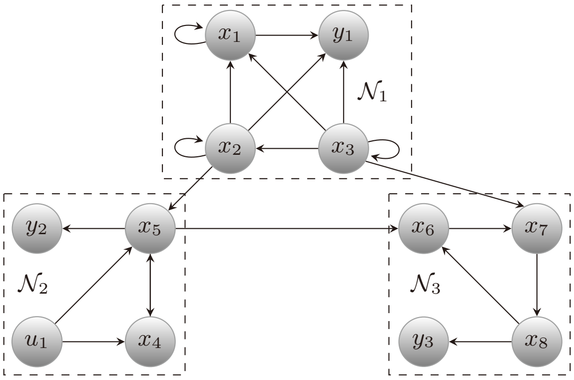

Fig. 4: Example of a node aggregation of a BCN with 8 state nodes, 1 input node, and 3 output nodes.

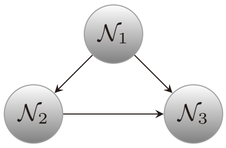

Fig. 5: Aggregated graph corresponding to Fig. 4.

network entering $\mathcal{N}_i$ are regarded as input nodes of Σ_i. (Note that all these tails are state nodes or input nodes of the network.)

Example 2.5 *Consider the following BCN corresponding to Fig. 4:*

$$\begin{aligned}
&\Sigma_1 : \begin{cases} x_1(t+1) = x_1(t) \oplus (x_2(t) \odot x_3(t)), \\ x_2(t+1) = x_2(t) \oplus x_3(t), \\ x_3(t+1) = x_3(t) \oplus 1, \\ y_1(t) = x_1(t) \odot (x_2(t) \oplus x_3(t)), \end{cases} \\
&\Sigma_2 : \begin{cases} x_4(t+1) = x_5(t) \odot u_1(t), \\ x_5(t+1) = x_4(t) \oplus u_1(t) \oplus x_2(t), \\ y_2(t) = x_5(t), \end{cases} \\
&\Sigma_3 : \begin{cases} x_6(t+1) = x_8(t) \oplus x_5(t), \\ x_7(t+1) = x_6(t) \oplus x_3(t), \\ x_8(t+1) = x_7(t), \\ y_3(t) = x_8(t), \end{cases}
\end{aligned} \tag{6}$$

where $t = 0, 1, \ldots$; $x_i(t), u_1(t), y_k(t) \in \mathcal{D}$, $i \in [1, 8]$, $k \in [1, 3]$.

In Fig. 4, all $\mathcal{N}_1, \mathcal{N}_2, \mathcal{N}_3$ contain output nodes; $\mathcal{N}_1$ and $\mathcal{N}_3$ contain no input node; $\mathcal{N}_1$ contains edges $x_1 \to y_1$, $x_2 \to y_1$, and $x_3 \to y_1$; $\mathcal{N}_2$ contains path $x_4 \to x_5 \to y_2$; $\mathcal{N}_3$ contains path $x_6 \to x_7 \to x_8 \to y_3$; x_2 is an input node of Σ_2; x_3 and x_5 are input nodes of Σ_3; subnetworks Σ_1, Σ_2, and Σ_3 in Eqn. (6) correspond to super nodes $\mathcal{N}_1, \mathcal{N}_2$, and $\mathcal{N}_3$, respectively. Hence this node aggregation satisfies Assumption 1. The corresponding aggregated graph is shown in Fig. 5.

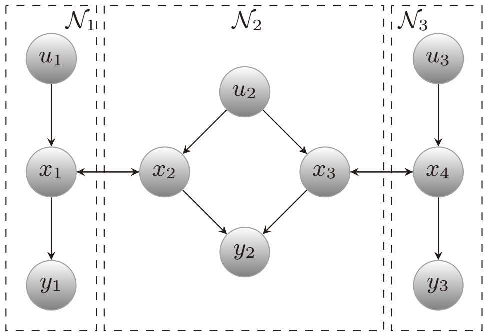

Fig. 6: Example of a node aggregation of a BCN with 4 state nodes, 3 input nodes, and 3 output nodes.

3 Observability analysis of large-scale BCNs

3.1 Observability analysis based on node aggregations

In this subsection, we show whether one can verify observability of a BCN (2) via verifying observability of its resulting subnetworks obtained by aggregating its network nodes under Assumption 1. First we investigate whether a BCN (2) being observable implies its resulting subnetworks also being observable. The BCN in the following Example 3.1 gives a negative answer.

Example 3.1 *Consider the following BCN corresponding to Fig. 6:*

$$\begin{aligned}
&\Sigma_1 : \begin{cases} x_1(t+1) = u_1(t) \oplus x_2(t), \\ y_1(t) = x_1(t), \end{cases} \\
&\Sigma_2 : \begin{cases} x_2(t+1) = u_2(t) \oplus x_1(t), \\ x_3(t+1) = u_2(t) \oplus x_4(t), \\ y_2(t) = x_2(t) \odot x_3(t), \end{cases} \\
&\Sigma_3 : \begin{cases} x_4(t+1) = u_3(t) \oplus x_3(t), \\ y_3(t) = x_4(t), \end{cases}
\end{aligned} \tag{7}$$

where $t = 0, 1, \ldots$; $x_i(t), u_j(t), y_k(t) \in \mathcal{D}$, $i \in [1, 4]$, $j, k \in [1, 3]$.

It is not difficult to see that the node aggregation in Fig. 6 satisfies Assumption 1, and subnetworks $\Sigma_1, \Sigma_2, \Sigma_3$ in Eqn. (7) correspond to super nodes $\mathcal{N}_1, \mathcal{N}_2, \mathcal{N}_3$ in Fig. 6, respectively. Σ_1 is observable, because $x_1(0) = y_1(0)$, and $y_1(0)$ can be observed. Symmetrically Σ_3 is also observable. In the observability weighted pair graph of Σ_2, we have an edge $\{00, 01\} \xrightarrow{000} \{00, 00\}$ from a non-diagonal vertex $\{00, 01\}$ to a diagonal vertex $\{00, 00\}$. Then by Corollary 2.4, Σ_2 is not observable. Now consider the whole BCN (7). We have $x_1(0) = y_1(0)$, $x_2(0) = x_1(1) \oplus u_1(0) = y_1(1) \oplus u_1(0)$, $x_3(0) = x_4(1) \oplus u_3(0) = y_3(1) \oplus u_3(0)$, $x_4(0) = y_3(0)$, $y_1(0), y_1(1), y_3(0), y_3(1)$ can be observed, $u_1(0)$ and $u_3(0)$ can be designed, hence (7) is observable.

The aggregated graph corresponding to Fig. 6 contains cycles $\mathcal{N}_1 \leftrightarrow \mathcal{N}_2$ and $\mathcal{N}_2 \leftrightarrow \mathcal{N}_3$. Then if a node aggregation of a BCN (2) contains no cycle and satisfies Assumption 1, is it true that a BCN (2) being observable implies its resulting subnetworks also being observable? The following Example 3.2 gives a negative answer again.

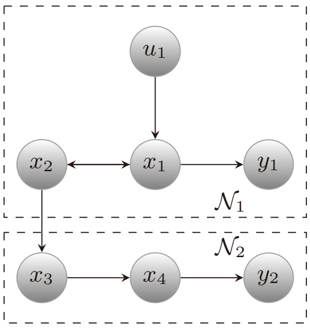

Fig. 7: Example of a node aggregation of a BCN with 4 state nodes, 1 input node, and 2 output nodes.

Example 3.2 *Consider the following BCN corresponding to Fig. 7:*

$$\Sigma_1 : \begin{cases} x_1(t+1) = x_2(t) \odot u_1(t), \\ x_2(t+1) = x_1(t), \\ y_1(t) = x_1(t), \end{cases}$$
$$\Sigma_2 : \begin{cases} x_3(t+1) = x_2(t), \\ x_4(t+1) = x_3(t), \\ y_2(t) = x_4(t), \end{cases} \tag{8}$$

where $t = 0, 1, \ldots$; $x_i(t), u_1(t), y_k(t) \in \mathcal{D}$, $i \in [1, 4]$, $k \in [1, 2]$.

The node aggregation shown in Fig. 7 satisfies Assumption 1, and the corresponding aggregated graph $\mathcal{N}_1 \to \mathcal{N}_2$ *contains no cycle. And subnetworks* Σ_1, Σ_2 *in Eqn. (8) correspond to super nodes* $\mathcal{N}_1, \mathcal{N}_2$ *in Fig. 7, respectively. In the observability weighted pair graph of* Σ_1*, we have an edge* $\{10, 11\} \xrightarrow{0} \{01, 01\}$ *from a non-diagonal vertex* $\{10, 11\}$ *to a diagonal vertex* $\{01, 01\}$*, then by Corollary 2.4,* Σ_1 *is not observable.* Σ_2 *is observable because* $x_4(0) = y_2(0)$, $x_3(0) = x_4(1) = y_2(1)$, $y_2(0)$ *and* $y_2(1)$ *can be observed. The whole BCN (8) is observable because* $x_1(0) = y_1(0)$, $x_2(0) = x_3(1) = x_4(2) = y_2(2)$, $x_3(0) = x_4(1) = y_2(1)$, $x_4(0) = y_2(0)$, $y_1(0), y_2(0), y_2(1)$, *and* $y_2(2)$ *can be observed.*

Next we discuss the opposite direction. That is, if a node aggregation satisfies Assumption 1, whether all resulting subnetworks being observable implies the whole BCN also being observable. Unfortunately, the answer is still negative. The following Example 3.3 shows such a node aggregation satisfying Assumption 1, containing a cycle and satisfying that, even if all resulting subnetworks are observable the overall BCN is not observable.

Example 3.3 *Consider the following BCN corresponding to Fig. 8.*

$$\Sigma_1 : \begin{cases} x_1(t+1) = u_1(t), \\ x_2(t+1) = x_1(t) \oplus x_4(t), \\ y_1(t) = x_2(t), \end{cases}$$
$$\Sigma_2 : \begin{cases} x_3(t+1) = x_1(t) \oplus x_4(t) \oplus 1, \\ x_4(t+1) = u_2(t), \\ y_2(t) = x_3(t), \end{cases} \tag{9}$$

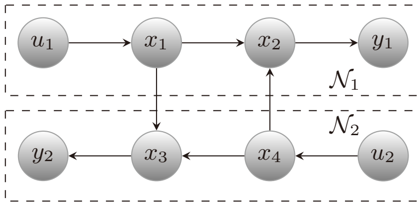

Fig. 8: Example of a node aggregation of a BCN with 4 state nodes, 2 input nodes, and 2 output nodes.

where $t = 0, 1, \ldots$; $x_i(t), u_j(t), y_k(t) \in \mathcal{D}$, $i \in [1, 4]$, $j, k \in [1, 2]$.

The node aggregation shown in Fig. 8 satisfies Assumption 1, and its aggregated graph is a cycle $\mathcal{N}_1 \leftrightarrow \mathcal{N}_2$*. For* Σ_1, $x_2(0) = y_1(0)$, $x_1(0) = x_2(1) \oplus x_4(0) = y_1(1) \oplus x_4(0)$*. Since* $y_1(0)$ *and* $y_1(1)$ *can be observed and* $x_4(0)$ *is designable,* Σ_1 *is observable. Similarly* Σ_2 *is also observable. Consider a non-diagonal vertex* $\{0110, 1111\}$ *of the observability weighted pair graph of (9), we have an edge* $\{0110, 1111\} \xrightarrow{u_1 u_2} \{u_1 01 u_2, u_1 01 u_2\}$*, where* $u_1, u_2 \in \mathcal{D}$*, and* $\{u_1 01 u_2, u_1 01 u_2\}$ *is a diagonal vertex of the observability weighted pair graph. Hence by Corollary 2.4, (9) is not observable.*

These two types of negative results show that observability possesses more complex properties than controllability does, as it is proved in [19] that if the whole BCN is controllable, then all resulting subnetworks are controllable under a weaker assumption than Assumption 1, where each super node contains at least one state node.

These negative results seem to presage that one cannot use the node aggregation method to verify observability. However, the situation finally becomes positive. Next we prove if a node aggregation satisfies Assumption 1 and contains no cycle, all resulting subnetworks being observable implies the whole BCN also being observable! These results are put into the following subsection.

3.2 Observability analysis based on acyclic node aggregations

A node aggregation (5) is called acyclic if its aggregated graph contains no cycle. For example, the node aggregation shown in Fig. 4 (its aggregated graph is depicted in Fig. 5) is acyclic.

Theorem 3.4 *Consider a BCN (2) that has an acyclic node aggregation (5) satisfying Assumption 1. If all resulting subnetworks are observable then the whole BCN is also observable.*

Proof First we show that for an acyclic node aggregation (5), there is a reordering (i.e., a bijective) $\tau : [1, s] \to [1, s]$ such that for each $i \in [1, s]$,

$$\mathcal{N}^i := \bigcup_{j=1}^{i} \mathcal{N}_{\tau(j)} \tag{10}$$

has zero indegree.

Since the node aggregation is acyclic, each subgraph of the aggregated graph $\mathcal{G}$ has a super node with indegree 0. Suppose on the contrary that a subgraph G of $\mathcal{G}$ has all super nodes with positive indegrees. Construct a new graph G' by reversing the directions of all edges of G. Then G' has a cycle, since G' has finitely many nodes, and each node has a positive outdegree. Then G and hence $\mathcal{G}$ have a cycle, which is a contradiction.

Choose $k_1 \in [1, s]$ such that $\mathcal{N}_{k_1}$ has zero indegree in $\mathcal{G}$, remove $\mathcal{N}_{k_1}$ and all edges leaving $\mathcal{N}_{k_1}$ from $\mathcal{G}$, and set $\tau(1) := k_1$. Then in the new $\mathcal{G}$, there is $k_2 \in [1, s] \setminus \{k_1\}$ such that $\mathcal{N}_{k_2}$ has zero indegree. Remove $\mathcal{N}_{k_2}$ and all edges leaving $\mathcal{N}_{k_2}$ from the new $\mathcal{G}$, and set $\tau(2) := k_2$. Repeat this procedure until $\mathcal{G}$ becomes empty, we obtain a bijective $\tau : [1, s] \to [1, s]$ such that (10) holds.

Second we show that if each subnetwork Σ_i corresponding to $\mathcal{N}_i$ is observable then the whole BCN is also observable. Suppose for a BCN (2) that each resulting subnetwork Σ_i is observable, $i \in [1, s]$. Then for each given input sequence $\{u_0, u_1, \dots\} \subset \mathcal{D}^m$, for all given different initial states $x_0, x_0' \in \mathcal{D}^n$, there is $k \in [1, s]$ such that the components of x_0, x_0' in $\mathcal{N}_{\tau(k)}$ are not equal, and the components of x_0, x_0' in $\mathcal{N}_{\tau(i)}$ are equal, $i \in [1, k-1]$. Note that

$$\begin{aligned}&\text{in the network, for all } i, j \in [1, s],\\ &\text{if there exist node } v \in \mathcal{N}_{\tau(i)} \text{ and node } v' \in \mathcal{N}_{\tau(j)}\\ &\text{such that } v \text{ affects } v' \text{ then } i \le j.\end{aligned} \tag{11}$$

Then since subnetworks $\Sigma_{\tau(k)}$ is observable, the output sequences of $\Sigma_{\tau(k)}$ corresponding to the components of x_0, x_0' and input sequence $\{u_0, u_1, \dots\}$ in $\mathcal{N}_{\tau(k)}$ are different. That is, the entire BCN is observable. □

In [19], a node aggregation (5) satisfying (10) is called cascading; and it is pointed out that each cascading node aggregation is acyclic, which can also be seen by (11). Hence a stronger result (Proposition 3.5) follows from this property in [19] and the proof of Theorem 3.4.

Proposition 3.5 *A node aggregation (5) is acyclic if and only if it is cascading.*

Example 3.6 *Recall Example 2.5. The node aggregation shown in Fig. 4 is acyclic and satisfies Assumption 1. Next we show that the resulting subnetworks $\Sigma_1, \Sigma_2, \Sigma_3$ in (6) are all observable. Then by Theorem 3.4, the whole BCN (6) is also observable.*

The observability weighted pair graph of Σ_1 has 8 diagonal vertices, and $1 + C_6^2 = 16$ non-diagonal vertices. The observability weighted pair graph of Σ_1 is shown in Fig. 9. In Fig. 9, there exists no path from a non-diagonal vertex to a diagonal vertex, and there exists no cycle in the subgraph generated by non-diagonal vertices. By Corollary 2.4, Σ_1 is observable.

For Σ_2, $x_5(0) = y_2(0)$, $x_4(0) = x_5(1) \oplus u_1(0) \oplus x_2(0) = y_2(1) \oplus u_1(0) \oplus x_2(0)$. $y_2(0)$ and $y_2(1)$ can be observed and $u_1(0)$ and $x_2(0)$ are designable, hence Σ_2 is observable.

For Σ_3, $x_8(0) = y_3(0)$, $x_7(0) = x_8(1) = y_3(1)$, $x_6(0) = x_7(1) \oplus x_3(0) = x_8(2) \oplus x_3(0) = y_3(2) \oplus x_3(0)$. $y_3(0), y_3(1)$, and $y_3(2)$ can be observed and $x_3(0)$ is designable, hence Σ_3 is also observable.

The whole BCN (6) has $2^8 = 256$ states, 2 inputs, and $2^3 = 8$ outputs. Its observability weighted pair graph has $(((1+C_6^2)*2+2^3)(2*2+2^2)((2C_4^2)*2+2^3)-2^8)/2 = 4992$ non-diagonal vertices, and $2^8 = 256$ diagonal vertices.

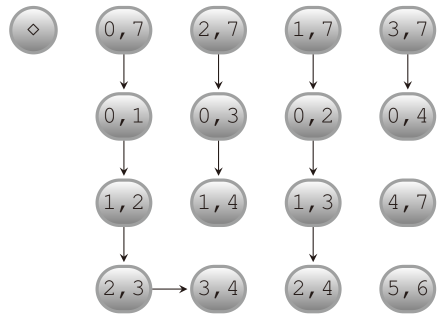

Fig. 9: Observability weighted pair graph of subnetwork Σ_1 in (6), where $\diamond$ denotes the subgraph generated by all diagonal vertices, numbers in circles are decimal representations for states of Σ_1, formally, $0 \sim 000$, $1 \sim 001$, $2 \sim 010$, $3 \sim 011$, $4 \sim 100$, $5 \sim 101$, $6 \sim 110$, $7 \sim 111$.

Hence it is much more complex to directly use Proposition 2.3 to check observability of (6) than using Theorem 3.4 and Proposition 2.3 to do it as above.

3.3 Complexity analysis

We analyze the computational complexity of using Theorem 3.4 and Proposition 2.3 to verify observability of the BCN (2). Following this way, we first find an acyclic node aggregation of (2) that satisfies Assumption 1, then check observability of all resulting subnetworks. If all resulting subnetworks are observable then the whole BCN is observable. Assume that we have obtained an acyclic node aggregation having k super nodes with almost the same size and satisfying Assumption 1. Then each super node approximately has $\frac{n}{k}$ state nodes and $\frac{m}{k}$ input nodes. The computational cost is approximately $k2^{\frac{2n+m}{k}-1}$ by Proposition 2.3. For large-scale BCNs, $2n+m$ is huge. When $k < l(2n+m)$ for some positive constant l, function $k2^{\frac{2n+m}{k}-1}$ is decreasing. Hence roughly speaking, the more super nodes a node aggregation has and the more close the sizes of these super nodes are, the more effective the node aggregation method is. It is hard to find such aggregations whose super nodes have approximately the same size, but we can find aggregations having sufficiently many super nodes. According to this rule, when aggregating nodes for a large-scale BCN, in order to reduce computational complexity as much as possible, one should make super nodes as small as possible.

4 Biological application

In this section, we apply our results given in Section 3 to study observability of the BCN T-cell receptor kinetics model [9].

4.1 Model

T-cells are a type of white blood cells known as lymphocytes. These white blood cells play a central role in adaptive immunity and enable the immune system to mount specific immune responses. T-cells have the ability to recognize potentially dangerous agents and subsequently initiate an immune reaction against them. They do so by using T-cell receptors to detect foreign antigens bound to major histocompatibility complex molecules, and then activate, through a signaling cascade, several transcription factors. These transcription factors, in turn, influence the cell's fate such as proliferation. For the details, we refer the reader to [9]. The BCN T-cell receptor kinetics model given in [9] is shown in Tab. 1, its network is shown in Fig. 10. In Fig. 10, there exist 3 input nodes and 37 state nodes. Hence the model has 2^3 inputs and 2^{37} states. In order to do a quantitative analysis for the T-cell model, it would be better to obtain the state information of the model first. Next we show the unique minimal set of state nodes needed to be observed to make the overall BCN observable. It is impossible to use a PC to deal with such a large BCN directly in a reasonable amount of time. We next use the node aggregation approach to deal with it.

4.2 Observability analysis based on acyclic node aggregations

In order to obtain the initial state of the BCN, one must choose some state nodes to observe, since there exists no output node in the network. The chosen state nodes and their corresponding output nodes are represented as the nodes with shadows and their shadows, respectively, in Fig. 10. *The main result obtained in this subsection is that we find the minimal set*

$$\{TCRbind, cCbl, PAGCsk, Rlk, TCRphos, SLP76, Itk, Grb2Sos, PLCg(bind), CRE, AP1, NFkB, NFAT, Fos, Jun, RasGRP1\} \tag{12}$$

of 16 *state nodes needed to be observed to make the BCN observable as follows.* That is to say, if all nodes in (12) are observed then the BCN is observable, and if any one of them cannot be observed then the BCN is not observable.

We partition the BCN T-cell network as in Fig. 10, where the aggregation satisfies Assumption 1, and the corresponding aggregated graph with nodes $\mathcal{N}_1, \dots, \mathcal{N}_5$ is acyclic. In order to prove that the network is observable when all states in Eqn. (12) are observed, by Theorem 3.4, we only need to prove that all corresponding subnetworks $\mathcal{N}_1, \dots, \mathcal{N}_5$ are observable. Since none of $\mathcal{N}_1, \dots, \mathcal{N}_5$ is large-scale, we can use Proposition 2.3 to verify that all of them are observable very quickly. We can also prove that if any one of these 16 state nodes shown in (12) is not observed, even though all the other state nodes are observed, then the whole BCN is not observable by direction observation. Here we do not show the details due to the page limitation.

On the other hand, a weaker type of observability (i.e., [15, Def. 5], not equivalent to the one studied in this paper) of BCNs is characterized in [11] by using an algebraic method, and it is proved that for the BCN T-cell receptor kinetics model, the unique minimal set of nodes needed to be observed to make the whole BCN observable is

$$\{TCRbind, Rlk, TCRphos, SLP76, Itk, Grb2Sos, PLCg(bind), CRE, AP1, NFkB, NFAT, Fos, Jun, RasGRP1\}, \tag{13}$$

which is a proper subset of (12). The method for verifying observability adopted in [11] is using the concept of observability to compute two algebraic varieties (actually their unique reduced Gröbner bases), and then compare these bases. Although this method is very fast for sparse Boolean

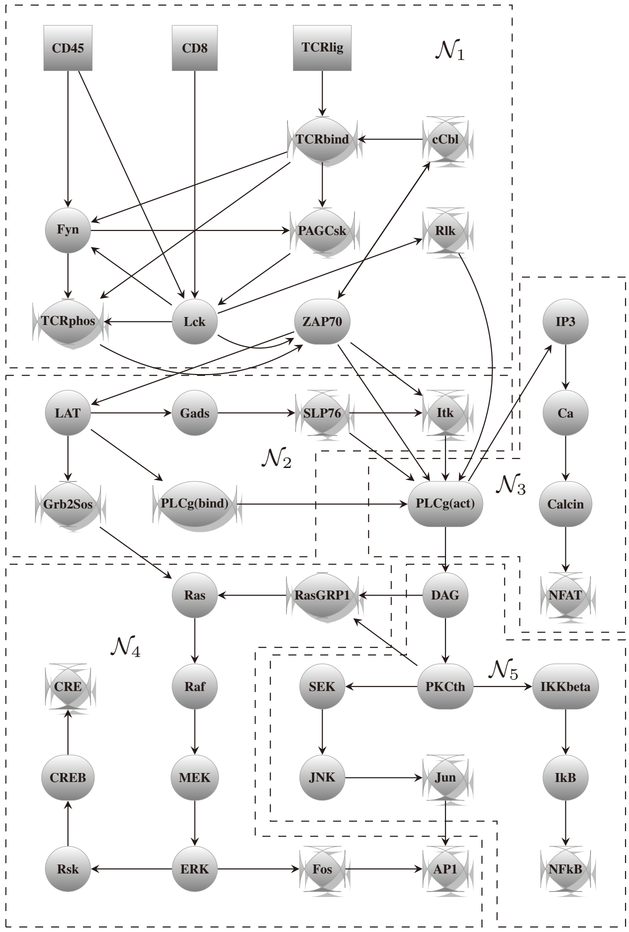

Fig. 10: Network of the T-cell receptor kinetics model (cf. [9]), where rectangles denote input nodes, the other nodes denote state nodes, particularly the nodes with shadows are chosen to be observed. The node aggregation shown in this figure is acyclic.

control networks, it does not apply to the observability studied in this paper to the best of our knowledge.

5 Conclusion

In this paper, we used a node aggregation method to reduce the computational complexity of verifying observability of large-scale BCNs with special structures. We first defined a special class of node aggregations of BCNs with compatible observability, then we showed that for acyclic node aggregations in this special class, the resulting subnetworks being observable implies the whole BCN being observable, and acyclic node aggregations are equivalent to cascading node aggregations frequently used in the literature. Finding such node aggregations having sufficiently many subnetworks can tremendously reduce the computational complexity in verifying observability. Hence key point is to find an effective method to look for such node aggregations.

It was proved in [20] that the node aggregation consisting of strongly connected components is the finest acyclic node aggregation. However, this node aggregation may not be compatible with observability, since observability may be meaningless for some strongly connected components. Hence how to find acyclic node aggregations compatible

Nodes	Boolean rule	Nodes	Boolean rule	Nodes	Boolean rule
CD8	Input	Gads	LAT	PKCth	DAG
CD45	Input	Grb2Sos	LAT	PLCg(act)	(Itk∧PLCg(bind)∧SLP76∧ZAP70) ∨(PLCg(bind)∧Rlk∧SLP76∧ZAP70)
TCRlig	Input	IKKbeta	PKCth	PAGCsk	Fyn∨(¬TCRbind)
AP1	Fos∧Jun	IP3	PLCg(act)	PLCg(bind)	LAT
Ca	IP3	Itk	SLP76∧ZAP70	Raf	Ras
Calcin	Ca	IkB	¬IKKbeta	Ras	Grb2Sos∨ RasGRP1
cCbl	ZAP70	JNK	SEK	RasGRP1	DAG∧PKCth
CRE	CREB	Jun	JNK	Rlk	Lck
CREB	Rsk	LAT	ZAP70	Rsk	ERK
DAG	PLCg(act)	Lck	(¬PAGCsk)∧CD8∧CD45	SEK	PKCth
ERK	MEK	MEK	Raf	SLP76	Gads
Fos	ERK	NFAT	Calcin	TCRbind	(¬cCbl)∧TCRlig
Fyn	(Lck∧CD45) ∨(TCRbind∧CD45)	NFkB	¬IkB	TCRphos	Fyn∨(Lck∧TCRbind)
				ZAP70	(¬cCbl)∧Lck∧TCRphos

Table 1: Updating rules for the nodes of the T-cell receptor kinetics model [9].

with observability is still a challenging problem. In addition, since the node aggregation consisting of strongly connected components is the finest acyclic node aggregation, we can first find it, then furthermore aggregate some strongly connected components to make the new aggregation compatible with observability. This is left for further study.

The main contribution of this paper is showing that one can use the acyclic node aggregation method to deal with observability of large-scale BCNs, which may motive the study on observability of large-scale BCNs based on different types of node aggregations.

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