Efficient observability verification for special large-scale Boolean control networks with applications to Boolean biological systems

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Content

Boolean control networks

Boolean control networks (BCNs), Boolean networks with external regulation or perturbation included[a][b][c][d]

[a] T. Ideker, T. Galitski, and L. Hood (2001). "A new approach to decoding life: Systems biology". In: *Annual Review of Genomics and Human Genetics* 2.1, pp. 343–372.

[b] D. Cheng, H. Qi, and Z. Li (2011). *Analysis and Control of Boolean Networks: A Semi-tensor Product Approach*. Springer-Verlag London.

[c] T. Akutsu (2018). *Algorithms for Analysis, Inference, and Control of Boolean Networks*. World Scientific.

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

where $t = 0, 1, \ldots$; $x(t) \in \mathcal{D}^n, u(t) \in \mathcal{D}^m, y(t) \in \mathcal{D}^q$ denote the state, input, and output at time t, respectively; $f : \mathcal{D}^{n+m} \to \mathcal{D}^n$, $h : \mathcal{D}^n \to \mathcal{D}^q$ are logical functions.

Example 1 (A simple BCN)

$$\begin{aligned} A(t+1) &= B(t) \wedge u(t), \\ B(t+1) &= \neg A(t), \\ y(t) &= A(t), \end{aligned}$$

where $t = 0, 1, \ldots;\ A(t), B(t), u(t) \in \mathcal{D}$.

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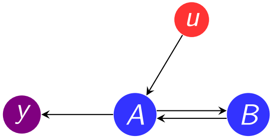

Figure 1: Dependency graph.

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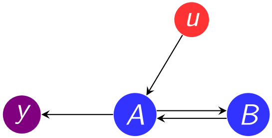

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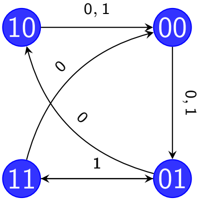

Figure 2: State-transition graph.

Observability: $(\mathcal{U}, \mathcal{Y}) \implies \mathcal{X}_0$

Observability describes whether one can use an input sequence and the corresponding output sequence to determine the initial state, a fundamental property in the computer science community[a] and the control science community[b].

[a] E.F. Moore (1956). "Gedanken-experiments on sequential machines". In: *Automata Studies, Annals of Math. Studies* 34, pp. 129–153.

[b] R.E. Kalman (1963). "Mathematical description of linear dynamical systems". In: *Journal of the Society for Industrial and Applied Mathematics Series A Control* 1.12, pp. 152–192.

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Provide bases for state estimation, observer design, controller synthesis, etc.

Four definitions of observability: Def. 1

Definition 1

A BCN (1) is called strongly multiple-experiment observable if for every initial state x_0, there exists a finite input sequence that determines x_0, i.e., x_0 can be determined by some input sequence depending on x_0 and the corresponding output sequence.

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A sufficient condition[a] (sufficient and necessary for controllable BCNs, "Automatica" 2008–2010 Best Paper)

[a] D. Cheng and H. Qi (2009). "Controllability and observability of Boolean control networks". In: *Automatica* 45.7, pp. 1659–1667.

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A sufficient and necessary condition[a]

[a] K. Zhang and L. Zhang (2014). "Observability of Boolean control networks: A unified approach based on the theories of finite automata and formal languages". In: *Proceedings of the 33rd Chinese Control Conference*, pp. 6854–6861.

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Definition 2 (Moore)

A BCN (1) is called multiple-experiment observable if for every two different initial states, there exists a finite input sequence that distinguishes them.

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[b] R. Li, M. Yang, and T. Chu (2015). "Controllability and observability of Boolean networks arising from biology". In: *Chaos: An Interdisciplinary Journal of Nonlinear Science* 25.2, p. 023104.

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A BCN (1) is called arbitrary-experiment observable if for every two different initial states, every sufficiently long input sequence can distinguish them.

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[b] K. Zhang and L. Zhang (2016). "Observability of Boolean control networks: A unified approach based on finite automata". In: *IEEE Transactions on Automatic Control* 61.9, pp. 2733–2738.

Example 2

$$x_1(t+1) = x_2(t)\bar{\nabla}u(t),$$
$$x_2(t+1) = x_1(t) \wedge u(t),$$
$$y(t) = x_1(t),$$

where $t = 0, 1, \ldots,$ $x_1(t), x_2(t), u(t), y(t) \in \{0, 1\}$.

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\end{aligned}
$$

where $t = 0, 1, \ldots,$ $x_1(t), x_2(t), u(t), y(t) \in \{0, 1\}$.
It is observable w.r.t. Def. 4, because $x_1(0) = y(0)$, $x_2(0) = x_1(1) \bar{\nabla} u(0)$, $x_1(1) = y(1)$.

Pairwise nonequivalence of different definitions of observability (by counterexamples)[a], showing that observability is not dual to controllability in BCNs.

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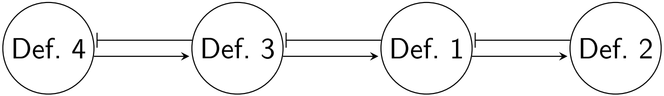

Figure 3: Sharp arrows mean "implies" and blunt arrows mean "does not imply".

Table 1: Complexity upper bounds for verifying observability in BCNs, where "S" means "sufficient condition", the same color represents equivalent methods.

	Def. 1	Def. 2	Def. 3	Def. 4
(Cheng and Qi, 2009)	S (STP)			
(Zhao, Qi, and Cheng, 2010)		S (STP)		
(Fornasini and Valcher, 2013)				$O(2^{4n+m})$
(Li, Yang, and Chu, 2014)			$O(2^{2^{2n}+m})$	
(Zhang and Zhang, 2014) (Zhang and Zhang, 2016) (weighted pair graph (WPG), $O(2^{2n+m})$)	$O(2^{n+2^{2n}+m})$	$O(2^{4n+m})$	$O(2^{2^{2n}+m})$	$O(2^{2n+m})$
(Li, Yang, and Chu, 2015) (computational algebra, very fast in sparse BCNs)		$O(2^{2^{2n}+m})$		
(Cheng et al., 2016) observability matrix (adjacency matrix of WPG)		$O(2^{2n+m})$		
(Zhu et al., 2018) observability graph (i.e., WPG)		$O(2^{2n+m})$		
(Cheng, Li, and He, 2018) set controllability		$O(2^{6n+m})$		
(Guo, 2018) parallel extension		$O(2^{6n+m})$	$O(2^{n2^{2n+1}+m})$	$O(2^{n2^{2n+1}+m})$

Extended to labeled nondeterministic finite-transition systems

observability in the arbitrary-experiment case (extended Def. 4) $\Longrightarrow$
observability in the simple-experiment case (extended Def. 3) $\Longrightarrow$
observability in the multiple-experiment case (extended Def. 2)[a]

[a] K. Zhang, T. Liu, and D. Cheng (2018). "Observability of finite labeled transition systems". In: *IEEE Transactions on Automatic Control* 63.6, pp. 1501–1512.

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Extended to probabilistic Boolean networks

finite-time observability with probability 1[a,b] (a special case of observability in the arbitrary-experiment case) $\Longrightarrow$ asymptotic observability in distribution[a] $\Longrightarrow$ finite-time observability in probability[c]

[a] R. Zhou, Y. Guo, and W. Gui (2019). "Set reachability and observability of probabilistic Boolean networks". In: *Automatica* 106, pp. 230–241.

[b] E. Fornasini and M.E. Valcher (2020). "Observability and reconstructibility of probabilistic Boolean networks". In: *IEEE Control Systems Letters* 4.2, pp. 319–324.

[c] J. Zhao and Z. Liu (2015). "Observability of probabilistic Boolean networks". In: *2015 34th Chinese Control Conference (CCC)*, pp. 183–186.

Definition 5 (weighted pair graph[a] (called observability graph[b] later))

[a] K. Zhang and L. Zhang (2016). "Observability of Boolean control networks: A unified approach based on finite automata". In: *IEEE Transactions on Automatic Control* 61.9, pp. 2733–2738.

[b] K. Zhang and K.H. Johansson (2020). "Efficient verification of observability and reconstructibility for large Boolean control networks with special structures". In: *IEEE Transactions on Automatic Control* 65.12, pp. 5144–5158.

Consider a BCN (1)*. A weighted directed graph* $\mathcal{G}_o = (\mathcal{V}, \mathcal{E}, \mathcal{W})$ *is called its observability graph if* $\mathcal{V} = \{\{x, x'\} \in \mathcal{D}_N \times \mathcal{D}_N | h(x) = h(x')\}$, $\mathcal{E} = \{(\{x_1, x_1'\}, \{x_2, x_2'\}) \in \mathcal{V} \times \mathcal{V} | (\exists u \in \mathcal{D}_M)[(f(x_1, u) = x_2 \wedge f(x_1', u) = x_2') \vee (f(x_1, u) = x_2' \wedge f(x_1', u) = x_2)]\}$, $\mathcal{W}((\{x_1, x_1'\}, \{x_2, x_2'\})) = \{u \in \mathcal{D}_M | (f(x_1, u) = x_2 \wedge f(x_1', u) = x_2') \vee (f(x_1, u) = x_2' \wedge f(x_1', u) = x_2)\}$.

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Proposition 1 ((Zhang and Zhang, 2016))

A BCN (1) *does not satisfy Def. 4 if and only if its observability graph has a non-diagonal vertex* v *(i.e.,* $\{x, x'\}$ *with* $x \neq x'$*) and a cycle* C *such that there is a path from* v *to some vertex of* C*.*

Example 3

Consider the following BCN

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\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{2}
$$

where $t = 0, 1, \dots;\ x_1(t), x_2(t), u(t), y(t) \in \mathcal{D}$. The BCN does not satisfy Def. 4 by its observability graph as follows and Prop. 1.

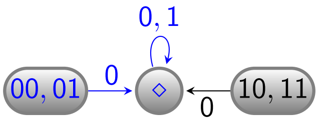

Figure 4: Observability graph of BCN (2), where $\diamond$ denotes the diagonal subgraph.

Content

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Towards large-scale BCNs

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- It is NP-hard to verify observability of BCNs in the number of nodes[a].

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- Many biological networks are large-scale and not all nodes can be directly measured[b], hence the problem of how to use a subset of nodes to observe the whole network's state is important.
- A node-aggregation method to efficiently verifying observability of two important classes of large-scale BCNs[c].

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Applications outside of BCNs

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[b] H. Ishii, R. Tempo, and E.W. Bai (2012). "A web aggregation approach for distributed randomized PageRank algorithms". In: *IEEE Transactions on Automatic Control* 57.11, pp. 2703–2717.

Applications in BCNs

fixed-point computation[a] and controllability verification[b] of a T-cell receptor kinetics BCN model with 37 state nodes (i.e., 2^{37} states) and 3 input nodes[c].

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Advantages and disadvantages

- Advantages: significantly reduce computational complexity when subnetworks are sufficiently small under several assumptions

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- Disadvantages:
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[c] S. Klamt et al. (2006). "A methodology for the structural and functional analysis of signaling and regulatory networks". In: *BMC Bioinformatics* 7:56, pp. 1–26.

Advantages and disadvantages

- Advantages: significantly reduce computational complexity when subnetworks are sufficiently small under several assumptions
- Disadvantages:
  - applicable to relatively sparse networks
  - equivalent conditions cannot be obtained

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- A node aggregation is a partition $\mathcal{N} = \mathcal{N}_1 \cup \cdots \cup \mathcal{N}_s$, i.e., $\mathcal{N}_1, \ldots, \mathcal{N}_s$ are nonempty, $\bigcup_{i=1}^{s} \mathcal{N}_i = \mathcal{N}$, $\mathcal{N}_k \neq \mathcal{N}_l$ for all $k \neq l$.

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- Consider the dependency graph $G = (\mathcal{N}, E)$ of a BCN, where $E \subset \mathcal{N} \times \mathcal{N}$, a node aggregation of G is regarded as a directed graph

$$G_A = (\mathcal{N}_A, E_A),$$

where the node set is $\mathcal{N}_A = \{\mathcal{N}_1, \dots, \mathcal{N}_s\}$; for all different $i, j \in [1, s]$, $(\mathcal{N}_i, \mathcal{N}_j) \in E_A$ if and only if there is an edge $(n_1, n_2) \in E$ for some $n_1 \in \mathcal{N}_i$ and $n_2 \in \mathcal{N}_j$.

Assumption 1

Consider a node aggregation G_A of the dependency graph $G = (\mathcal{N}, E)$ of a BCN. Let G_i be the subgraph of G generated by $\mathcal{N}_i$, $i \in [1, s]$. For each $i \in [1, s]$, $\mathcal{N}_i \cap \mathcal{Y} \neq \emptyset$; for each state node $x \in \mathcal{N}_i \cap \mathcal{X}$, there is a path from x to some output node $y \in \mathcal{N}_i \cap \mathcal{Y}$ in G_i such that all immediate predecessors of y belong to $\mathcal{N}_i$.

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Assum. 1 guarantees that observability is well defined for all subnetworks.

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Remark 1

From now on, observability always means Def. 4 (Kalman) unless otherwise specified.

Selected main results proved in[a]

[a] K. Zhang and K.H. Johansson (2020). "Efficient verification of observability and reconstructibility for large Boolean control networks with special structures". In: *IEEE Transactions on Automatic Control* 65.12, pp. 5144–5158.

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Theorem 1

For acyclic node aggregations satisfying Assum. 1, all subnetworks being observable implies the whole BCN being observable.

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Theorem 3 (by counterexamples)

For cyclic node aggregations satisfying Assum. 1, the whole BCN being observable does not imply all subnetworks being observable, or vice versa.

Example 4

Consider the BCN (left, with subnetworks $\mathfrak{B}_1, \mathfrak{B}_2, \mathfrak{B}_3$) and one of its node aggregations (right). The node aggregation satisfies Assum. 1.

$$
\mathfrak{B}_1 : \begin{cases} x_1(t+1) = x_1(t)\bar{\vee}(x_2(t) \wedge x_3(t)), \\ x_2(t+1) = x_2(t)\bar{\vee}x_3(t), \\ x_3(t+1) = \neg x_3(t), \\ y_1(t) = x_1(t) \wedge (x_2(t)\bar{\vee}x_3(t)), \end{cases}
$$

$$
\mathfrak{B}_2 : \begin{cases} x_4(t+1) = x_5(t) \wedge u_1(t), \\ x_5(t+1) = x_4(t)\bar{\vee}u_1(t)\bar{\vee}x_2(t), \\ y_2(t) = x_5(t), \end{cases} \qquad (3)
$$

$$
\mathfrak{B}_3 : \begin{cases} x_6(t+1) = x_8(t)\bar{\vee}x_5(t), \\ x_7(t+1) = x_6(t)\bar{\vee}x_3(t), \\ x_8(t+1) = x_7(t), \\ y_3(t) = x_8(t). \end{cases}
$$

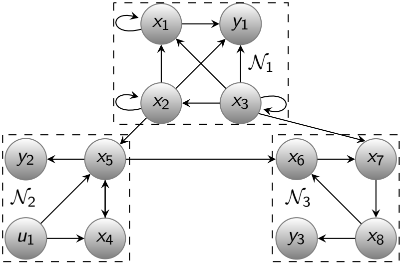


Figure 5: A node aggregation of (3).

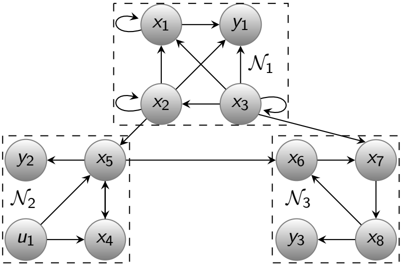
Example 4

Consider the BCN (left, with subnetworks $\mathfrak{B}_1, \mathfrak{B}_2, \mathfrak{B}_3$) and one of its node aggregations (right). The node aggregation satisfies Assum. 1. $\mathfrak{B}_2$ is observable: $x_5(0) = y_2(0)$, $x_4(0) = x_5(1) \bar{\vee} u_1(0) \bar{\vee} x_2(0)$, $x_5(1) = y_2(1)$.

$$\mathfrak{B}_1 : \begin{cases} x_1(t+1) = x_1(t) \bar{\vee} (x_2(t) \wedge x_3(t)), \\ x_2(t+1) = x_2(t) \bar{\vee} x_3(t), \\ x_3(t+1) = \neg x_3(t), \\ y_1(t) = x_1(t) \wedge (x_2(t) \bar{\vee} x_3(t)), \end{cases}$$

$$\mathfrak{B}_2 : \begin{cases} x_4(t+1) = x_5(t) \wedge u_1(t), \\ x_5(t+1) = x_4(t) \bar{\vee} u_1(t) \bar{\vee} x_2(t), \\ y_2(t) = x_5(t), \end{cases} \qquad (3)$$

$$\mathfrak{B}_3 : \begin{cases} x_6(t+1) = x_8(t) \bar{\vee} x_5(t), \\ x_7(t+1) = x_6(t) \bar{\vee} x_3(t), \\ x_8(t+1) = x_7(t), \\ y_3(t) = x_8(t). \end{cases}$$



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$$\mathfrak{B}_1 : \begin{cases} x_1(t+1) = x_1(t)\bar{\nabla}(x_2(t) \wedge x_3(t)), \\ x_2(t+1) = x_2(t)\bar{\nabla} x_3(t), \\ x_3(t+1) = \neg x_3(t), \\ y_1(t) = x_1(t) \wedge (x_2(t)\bar{\nabla} x_3(t)), \end{cases}$$
$$\mathfrak{B}_2 : \begin{cases} x_4(t+1) = x_5(t) \wedge u_1(t), \\ x_5(t+1) = x_4(t)\bar{\nabla} u_1(t)\bar{\nabla} x_2(t), \\ y_2(t) = x_5(t), \end{cases} \qquad (3)$$
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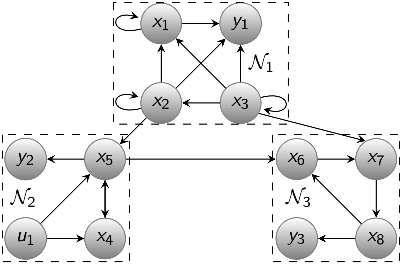


Figure 5: A node aggregation of (3).

Example 5

Recall BCN (3). By the observability graph of $\mathfrak{B}_1$ shown in Fig. 6, by Prop. 1, $\mathfrak{B}_1$ is observable.

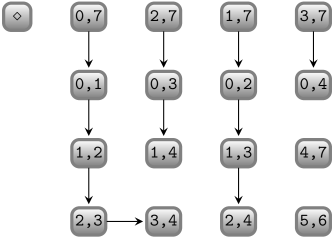
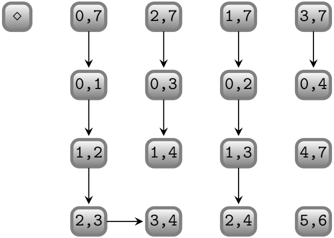


Figure 6: Observability graph of subnetwork $\mathfrak{B}_1$ of (3), numbers in circles are decimal representations for states of $\mathfrak{B}_1$.

Example 5

Recall BCN (3). By the observability graph of $\mathfrak{B}_1$ shown in Fig. 6, by Prop. 1, $\mathfrak{B}_1$ is observable. We have shown that subnetworks $\mathfrak{B}_2, \mathfrak{B}_3$ are both observable.



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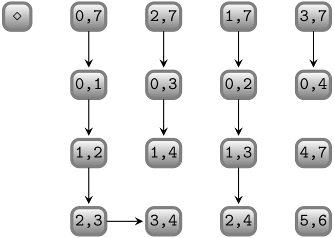

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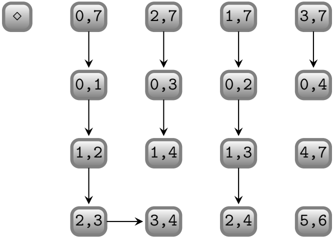
The observability graph of (3) has more than 5000 vertices.



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Content

To observability analysis of a T-cell receptor kinetics BCN model (with 37 state nodes (i.e., 2^{37} states) and 3 input nodes, proposed in[a]

[a] S. Klamt et al. (2006). "A methodology for the structural and functional analysis of signaling and regulatory networks". In: *BMC Bioinformatics* 7:56, pp. 1–26.

Nodes	Boolean rule	Nodes	Boolean rule	Nodes	Boolean rule
CD8	Input	Gads	LAT	PKCth	DAG
CD45	Input	Grb2Sos	LAT	PLCg(act)	PLCg(bind)∧SLP76∧ZAP70 ∧(Itk∨Rlk)
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

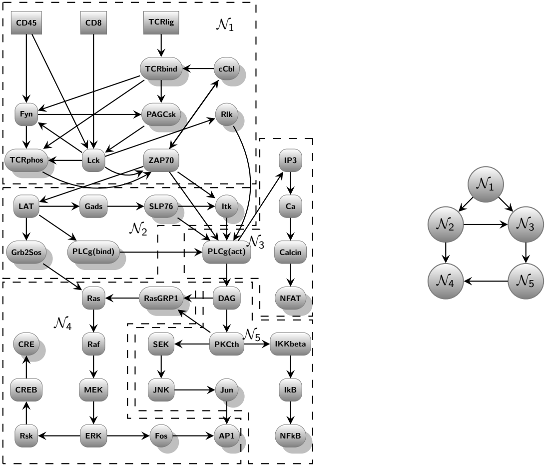

Figure 7: An acyclic node aggregation of the T-cell receptor kinetics network satisfying Assum. 1, where rectangles denote input nodes, other nodes denote state nodes, shadows denotes output nodes.

Results

We obtain the following unique minimal set[a]

$$\{TCRbind, cCbl, PAGCsk, Rlk, TCRphos, SLP76, Itk, Grb2Sos, PLCg(bind), CRE, AP1, NFkB, NFAT, Fos, Jun, RasGRP1\} \quad (4)$$

of 16 state nodes needed to be directly measured in order to make the whole T-cell network observable.

[a] K. Zhang and K.H. Johansson (2020). "Efficient verification of observability and reconstructibility for large Boolean control networks with special structures". In: *IEEE Transactions on Automatic Control* 65.12, pp. 5144–5158.

Comparison

The unique minimal set[a]

$$\{TCRbind, Rlk, TCRphos, SLP76,\\ Itk, Grb2Sos, PLCg(bind), CRE, AP1, NFkB,\\ NFAT, Fos, Jun, RasGRP1\} \tag{5}$$

of 14 state nodes needed to be directly measured in order to make the whole T-cell network satisfy Def. 2 (based on methods in computational algebra), where (5) is a proper subset of (4).

[a] R. Li, M. Yang, and T. Chu (2015). "Controllability and observability of Boolean networks arising from biology". In: *Chaos: An Interdisciplinary Journal of Nonlinear Science* 25.2, p. 023104.

Further reading

Further reading

- A second node-aggregation method[a] in which (1) subnetworks are labeled nondeterministic finite-transition systems[b] (not necessarily BCNs), (2) aggregations are not necessarily acyclic, (3) not all partition cells contain output nodes.

[a] K. Zhang and K.H. Johansson (2020). "Efficient verification of observability and reconstructibility for large Boolean control networks with special structures". In: *IEEE Transactions on Automatic Control* 65.12, pp. 5144–5158.

[b] K. Zhang, T. Liu, and D. Cheng (2018). "Observability of finite labeled transition systems". In: *IEEE Transactions on Automatic Control* 63.6, pp. 1501–1512.

Further reading

- A second node-aggregation method[a] in which (1) subnetworks are labeled nondeterministic finite-transition systems[b] (not necessarily BCNs), (2) aggregations are not necessarily acyclic, (3) not all partition cells contain output nodes.
- Compensate for the drawback of the first node-aggregation method when a BCN has only a small number of output nodes.

[a] K. Zhang and K.H. Johansson (2020). "Efficient verification of observability and reconstructibility for large Boolean control networks with special structures". In: *IEEE Transactions on Automatic Control* 65.12, pp. 5144–5158.

[b] K. Zhang, T. Liu, and D. Cheng (2018). "Observability of finite labeled transition systems". In: *IEEE Transactions on Automatic Control* 63.6, pp. 1501–1512.

Content

Done

Done

- Gave two classes of node aggregations to efficiently verify observability of large-scale BCNs with special structures.

Done

- Gave two classes of node aggregations to efficiently verify observability of large-scale BCNs with special structures.
- Applied the obtained theoretical results to observability analysis of a T-cell receptor kinetics BCN model.

Thank You for your attention!

References I

Akutsu, T. (2018). *Algorithms for Analysis, Inference, and Control of Boolean Networks*. World Scientific.

Chang, K.-C. and R. Fung (1989). "Node aggregation for distributed inference in Bayesian networks". In: *Proceedings of the 11th International Joint Conference on Artificial Intelligence - Volume 1*, pp. 265–270.

Cheng, D., C. Li, and F. He (2018). "Observability of Boolean networks via set controllability approach". In: *Systems & Control Letters* 115, pp. 22–25.

Cheng, D. and H. Qi (2009). "Controllability and observability of Boolean control networks". In: *Automatica* 45.7, pp. 1659–1667.

Cheng, D., H. Qi, and Z. Li (2011). *Analysis and Control of Boolean Networks: A Semi-tensor Product Approach*. Springer-Verlag London.

Cheng, D. and Y. Zhao (2011). "Identification of Boolean control networks". In: *Automatica* 47.4, pp. 702–710.

Cheng, D., H. Qi, T. Liu, and Y. Wang (2016). "A note on observability of Boolean control networks". In: *Systems & Control Letters* 87, pp. 76–82.

Fornasini, E. and M.E. Valcher (2013). "Observability, reconstructibility and state observers of Boolean control networks". In: *IEEE Transactions on Automatic Control* 58.6, pp. 1390–1401.

References II

Fornasini, E. and M.E. Valcher (2020). "Observability and reconstructibility of probabilistic Boolean networks". In: *IEEE Control Systems Letters* 4.2, pp. 319–324.

Guo, Y. (2018). "Observability of Boolean control networks using parallel extension and set reachability". In: *IEEE Transactions on Neural Networks and Learning Systems* 29.12, pp. 6402–6408.

Ideker, T., T. Galitski, and L. Hood (2001). "A new approach to decoding life: Systems biology". In: *Annual Review of Genomics and Human Genetics* 2.1, pp. 343–372.

Ishii, H., R. Tempo, and E.W. Bai (2012). "A web aggregation approach for distributed randomized PageRank algorithms". In: *IEEE Transactions on Automatic Control* 57.11, pp. 2703–2717.

Kalman, R.E. (1963). "Mathematical description of linear dynamical systems". In: *Journal of the Society for Industrial and Applied Mathematics Series A Control* 1.12, pp. 152–192.

Klamt, S., J. Saez-Rodriguez, J. A. Lindquist, L. Simeoni, and E. D. Gilles (2006). "A methodology for the structural and functional analysis of signaling and regulatory networks". In: *BMC Bioinformatics* 7:56, pp. 1–26.

Laschov, D., M. Margaliot, and G. Even (2013). "Observability of Boolean networks: A graph-theoretic approach". In: *Automatica* 49.8, pp. 2351–2362.

Li, R., M. Yang, and T. Chu (2014). "Observability conditions of Boolean control networks". In: *International Journal of Robust and Nonlinear Control* 24.17, pp. 2711–2723.

References III

Li, R., M. Yang, and T. Chu (2015). "Controllability and observability of Boolean networks arising from biology". In: *Chaos: An Interdisciplinary Journal of Nonlinear Science* 25.2, p. 023104.

Liu, Y.-Y., J.-J. Slotine, and A.-L. Barabási (2013). "Observability of complex systems". In: *Proceedings of the National Academy of Sciences* 110.7, pp. 2460–2465.

Moore, E.F. (1956). "Gedanken-experiments on sequential machines". In: *Automata Studies, Annals of Math. Studies* 34, pp. 129–153.

Zhang, K. and K.H. Johansson (2020). "Efficient verification of observability and reconstructibility for large Boolean control networks with special structures". In: *IEEE Transactions on Automatic Control* 65.12, pp. 5144–5158.

Zhang, K., T. Liu, and D. Cheng (2018). "Observability of finite labeled transition systems". In: *IEEE Transactions on Automatic Control* 63.6, pp. 1501–1512.

Zhang, K. and L. Zhang (2014). "Observability of Boolean control networks: A unified approach based on the theories of finite automata and formal languages". In: *Proceedings of the 33rd Chinese Control Conference*, pp. 6854–6861.

— (2016). "Observability of Boolean control networks: A unified approach based on finite automata". In: *IEEE Transactions on Automatic Control* 61.9, pp. 2733–2738.

Zhang, K., L. Zhang, and L. Xie (2020). *Discrete-Time and Discrete-Space Dynamical Systems*. Communications and Control Engineering. Springer International Publishing.

References IV

Zhao, J. and Z. Liu (2015). "Observability of probabilistic Boolean networks". In: *2015 34th Chinese Control Conference (CCC)*, pp. 183–186.

Zhao, Y., B.K. Ghosh, and D. Cheng (2016). "Control of large-scale Boolean networks via network aggregation". In: *IEEE Transactions on Neural Networks and Learning Systems* 27.7, pp. 1527–1536.

Zhao, Y., J. Kim, and M. Filippone (2013). "Aggregation algorithm towards large-scale Boolean network analysis". In: *IEEE Transactions on Automatic Control* 58 (8), pp. 1976–1985.

Zhao, Y., H. Qi, and D. Cheng (2010). "Input-state incidence matrix of Boolean control networks and its applications". In: *Systems & Control Letters* 59.12, pp. 767–774.

Zhou, R., Y. Guo, and W. Gui (2019). "Set reachability and observability of probabilistic Boolean networks". In: *Automatica* 106, pp. 230–241.

Zhu, Q., Y. Liu, J. Lu, and J. Cao (2018). "Observability of Boolean control networks". In: *Science China Information Sciences* 61.9, p. 092201.