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# Control of Singleton Attractors in Boolean Networks Based on Model Reduction

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**Abstract**—In this paper, a control method of singleton attractors (fixed points) in Boolean networks (BNs) is proposed based on model reduction. In the model reduction method utilized, singleton attractors in the original BN and those in the reduced BN are one-to-one correspondence. Hence, the reduced BN can be utilized in control of singleton attractors. First, a BN and its model reduction method are explained. Next, the control problem of singleton attractors is formulated. Finally, this problem is reduced to an integer linear programming problem.

## 1. Introduction

Developing control methods of gene regulatory networks is one of the important problems in systems biology. In control of gene regulatory networks, a Boolean network (BN) [10] is widely used as a mathematical model (see, e.g., [1, 2, 5, 12, 13]). In a BN, gene expression is modeled by a binary value (0 or 1), and interactions between genes are modeled by a set of Boolean functions. This model is too simple, but is useful in the first step of developing control theory.

Several control methods of BNs have been proposed so far. In this paper, we focus on control of singleton attractors (fixed points). Singleton attractors in Boolean networks (BNs) represent cell types or states of cells [11], and are important to decide characteristics of cells. Many results on analysis and control of singleton attractors have been obtained so far (see, e.g., [2, 6, 8, 15, 16, 17, 20]).

In this paper, the problem of controlling singleton attractors by external stimuli is studied based on model reduction. To the best of our knowledge, model reduction methods have not been utilized in the control problem. In the model reduction method utilized (see, e.g., [14, 19]), singleton attractors in the original BN and those in the reduced BN are one-to-one correspondence. This property is useful in control of singleton attractors. First, a BN and its model reduction method are explained. Next, the control problem of singleton attractors is formulated. Finally, this problem is reduced to an integer linear programming (ILP) problem. Using model reduction, the dimension of decision variables in the ILP problem can decrease.

**Notation:** For the finite set $A$, let $|A|$ denote the number of elements in $A$. For the numbers $x_1, x_2, \ldots, x_n$ and the index set $\mathcal{I} = \{i_1, i_2, \ldots, i_m\} \subseteq \{1, 2, \ldots, n\}$, define $[x_i]_{i\in\mathcal{I}} := [x_{i_1}\ x_{i_2}\ \cdots\ x_{i_m}]^\top$.

## 2. Boolean Networks

Consider the following BN:

$$\begin{cases} x_1(k+1) = f_1([x_j(k)]_{j\in\mathcal{P}_1}, [\neg x_j(k)]_{j\in\mathcal{N}_1}), \\ x_2(k+1) = f_2([x_j(k)]_{j\in\mathcal{P}_2}, [\neg x_j(k)]_{j\in\mathcal{N}_2}), \\ \vdots \\ x_n(k+1) = f_n([x_j(k)]_{j\in\mathcal{P}_n}, [\neg x_j(k)]_{j\in\mathcal{N}_n}), \end{cases} \tag{1}$$

where $x_i \in \{0, 1\}$, $i \in \{1, 2, \ldots, n\}$ is the state (e.g., the expression of genes), and $k \in \{0, 1, 2, \ldots\}$ is the discrete time. The set $\mathcal{P}_i \subseteq \{1, 2, \ldots, n\}$ is a given index set of nodes that affecting the state $x_i$ positively. The set $\mathcal{N}_i \subseteq \{1, 2, \ldots, n\} \setminus \mathcal{P}_i$ is a given index set of nodes that affecting the state $x_i$ negatively. The function $f_i : \{0, 1\}^{|\mathcal{P}_i|} \times \{0, 1\}^{|\mathcal{N}_i|} \to \{0, 1\}^1$ is a given Boolean function satisfying the following assumptions: i) $f_i$ is minimal (i.e., redundant terms such as $x_i \vee \neg x_i (= 1)$ are not included), ii) logical operators in $f_i$ are composed of AND ($\wedge$) and OR ($\vee$), and iii) $f_i$ is identical 0 or 1 if $\mathcal{P}_i = \mathcal{N}_i = \emptyset$ holds.

Next, some definitions are given. A singleton attractor and a cyclic attractor are defined as follows.

**Definition 1** *The state $x(k)$ is called a singleton attractor if $x(k + 1) = x(k)$ holds.*

**Definition 2** *The set of states $\{x(k), x(k+1), \ldots, x(k+p-1)\}$ ($p \geq 2$) is called a cyclic attractor if $x(k + i) \neq x(k)$, $i = 1, 2, \ldots, p-1$ and $x(k + p) = x(k)$ hold.*

An interaction graph obtained from a given BN is defined as follows (see, e.g., [15]).

**Definition 3** *An interaction graph of BNs is defined by a signed directed graph $G = (\mathcal{V}, \mathcal{E}, L)$, where $\mathcal{V} = \{1, 2, \ldots, n\}$ is the set of vertices corresponding to $x_i$, $i \in \{1, 2, \ldots, n\}$, $\mathcal{E} = \{(j, i) \in \{1, 2, \ldots, n\} \times \{1, 2, \ldots, n\} \mid j \in \mathcal{P}_i \cup \mathcal{P}_i\}$ is the set of arcs, $L : \mathcal{E} \to \{+, -\}$ is the labeling function such that $L(j, i) = +$ if $j \in \mathcal{P}_i$ while $L(j, i) = -$ if $j \in \mathcal{N}_i$.*

For a given interaction graph, a feedback vertex set is defined as follows (see, e.g., [7, 9]).

**Definition 4** *A set of vertices of an interaction graph is called a feedback vertex set if removal of vertices results an acyclic graph. In particular, a feedback vertex set is called a minimum feedback vertex set if the number of its elements is minimum.*

We remark here that in the above definition, the sign (+ or −) in an interaction graph is ignored. The computational complexity of finding a minimum feedback vertex set is NP-complete [9], but an approximate algorithm of finding it has been developed (see, e.g., [7]).

Finally, in this paper, input vertices and output vertices for a given interaction graph are newly defined as follows.

**Definition 5** *A vertex of a given interaction graph is called an input vertex if it corresponds to the Boolean function* $f_i$ *satisfying either* $x_i(k+1) = x_i(k)$ *(i.e.,* $\mathcal{P}_i = \{i\}$*) or* $x_i(k+1) = 0(1)$ *(i.e.,* $\mathcal{P}_i = \emptyset$*). In both cases,* $\mathcal{N}_i = \emptyset$ *holds.*

In other words, the state corresponding to the input vertex is not influenced from other states. An input vertex corresponds to an external stimulus.

**Definition 6** *A vertex of a given interaction graph is called an output vertex if it corresponds to the Boolean function* $f_i$ *satisfying* $\mathcal{P}_j \cap \{i\} = \emptyset$, $\mathcal{N}_j \cap \{i\} = \emptyset$, $j \neq i$.

In other words, the state corresponding to the output vertex does not influence other states.

We present a simple example.

**Example 1** *Consider the following simplified BN of an apoptosis network:*

$$\begin{cases} x_1(k+1) = x_1(k), \\ x_2(k+1) = x_1(k) \wedge \neg x_3(k), \\ x_3(k+1) = \neg x_2(k) \wedge x_4(k), \\ x_4(k+1) = x_1(k) \vee x_3(k), \end{cases} \tag{2}$$

*where* $x_1$ *is the concentration level (high or low) of the tumor necrosis factor (TNF, a stimulus),* $x_2$ *is the concentration level of the inhibitor of apoptosis proteins (IAP),* $x_3$ *is the concentration level of the active caspase 3 (C3a), and* $x_4$ *is the concentration level of the active caspase 8 (C8a). This model is described in [4], and is a simplified version of an apoptosis network model in [18]. In this model,* $x_3(k) = 0$ *implies cell survival, and* $x_2(k) = 0, x_3(k) = 1$ *imply cell death [4]. In this BN, the following relations hold:* $\mathcal{P}_1 = \{1\}$, $\mathcal{N}_1 = \emptyset$, $\mathcal{P}_2 = \{1\}$, $\mathcal{N}_2 = \{3\}$, $\mathcal{P}_3 = \{4\}$, $\mathcal{N}_3 = \{2\}$, $\mathcal{P}_4 = \{1, 3\}$, *and* $\mathcal{N}_3 = \emptyset$.

*First, the state transition diagram can be obtained as Fig. 1, where each node corresponds to the concrete value of the state. From this figure, we see that there exist four singleton attractors (*$[0\ 0\ 0\ 0]^\top$, $[0\ 0\ 1\ 1]^\top$, $[1\ 0\ 1\ 1]^\top$, *and* $[1\ 1\ 0\ 1]^\top$*) and two cyclic attractors (*$\{[0\ 0\ 0\ 1]^\top, [0\ 0\ 1\ 0]^\top\}$ *and* $\{[1\ 0\ 0\ 1]^\top, [1\ 1\ 1\ 1]^\top\}$*).*

*Next, the interaction graph can be obtained as Fig. 2. From this graph, we see that an interaction graph of a given BN can model interactions between genes.*

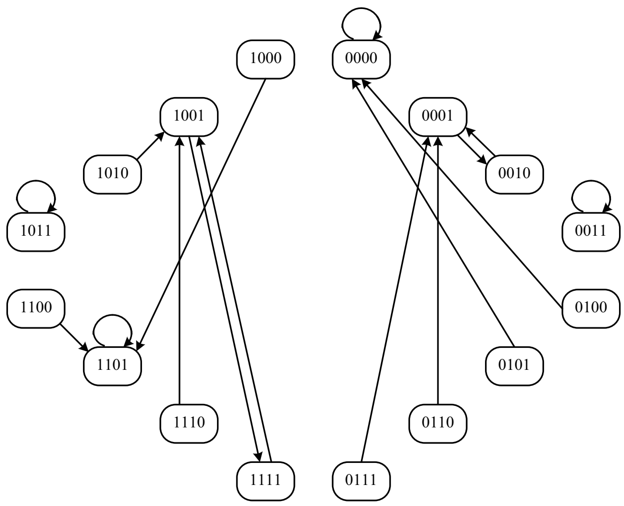


Figure 1: State transition diagram.

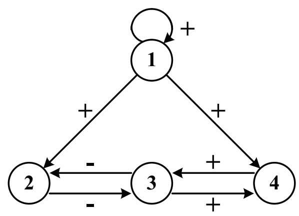


Figure 2: Interaction graph.

*Finally, the minimum vertex set for interaction graph in Fig. 2 is given by* $\{1, 3\}$. *The input vertex is given by node* 1. *In this interaction graph, there exist no output vertex.*

## 3. Model Reduction of Boolean Networks

In this section, a model reduction method for BNs is explained. Model reduction of BNs has been studied so far (see, e.g., [14, 19]). Based on these results, we introduce a sophisticated procedure of model reduction.

The procedure of model reduction introduced in this paper is given as follows.

**Procedure of model reduction of BNs:**

**Step 1:** For a given interaction graph, find a minimum feedback vertex set and a set of output vertices. Let $\mathcal{W}$ denote the union of these sets.

**Step 2:** Replace $x_j(k+1) = f_j(\cdot)$, $j \in \{1, 2, \ldots, n\} \setminus \mathcal{W}$ with $x_j(k) = f_j(\cdot)$.

**Step 3:** Using $x_j(k) = f_j(\cdot)$, $j \in \{1, 2, \ldots, n\} \setminus \mathcal{W}$, eliminate $x_j(k)$ from $f_i(\cdot)$, $i \in \mathcal{W}$.

**Step 4:** Eliminate $x_j(k)$ from $f_j(\cdot)$, $j \in \{1, 2, \ldots, n\} \setminus \mathcal{W}$.

**Step 5:** Simplify the Boolean functions obtained.

We explain this procedure using a simple example.

**Example 2** *Consider the BN in Example 1 again. In Step 1, we can obtain $\mathcal{W} = \{1, 3\}$. In Step 2, we can obtain $x_2(k) = x_1(k) \wedge \neg x_3(k)$ and $x_4(k) = x_1(k) \vee x_3(k)$. In Step 3, we can obtain*

$$\begin{cases} x_1(k+1) = x_1(k), \\ x_3(k+1) = \neg(x_1(k) \wedge \neg x_3(k)) \wedge (x_1(k) \vee x_3(k)). \end{cases}$$

*In Step 4, $x_2(k)$ and $x_4(k)$ must be eliminated from $f_2$ and $f_4$. However, these states are not included in $f_2$ and $f_4$. Finally, in Step 5, we can obtain*

$$\begin{cases} x_1(k+1) = x_1(k), \\ x_3(k+1) = x_3(k). \end{cases} \tag{3}$$

Hereafter, the reduced model obtained by the above procedure is denoted by

$$\begin{cases} x_i(k+1) = \hat{f}_i([x_j(k)]_{j \in \hat{\mathcal{P}}_i}, [\neg x_j(k)]_{j \in \hat{\mathcal{N}}_i}), \ \ i \in \mathcal{W}, \\ x_i(k) = \hat{f}_i([x_j(k)]_{j \in \hat{\mathcal{P}}_i}, [\neg x_j(k)]_{j \in \hat{\mathcal{N}}_i}), \ \ i \notin \mathcal{W}, \end{cases} \tag{4}$$

We remark here that the algebraic constraints $x_i(k) = \hat{f}_i(\cdots)$, $i \notin \mathcal{W}$ are included. This constraints are used in the control problem of singleton attractors.

For the reduced model obtained, the following theorem has been obtained [19].

**Theorem 1** *The set of singleton attractors for the BN (1) and the set of singleton attractors for the reduced BN (4) are one-to-one correspondence.*

We present a simple example.

**Example 3** *Consider the BN in Example 1 again. From Fig. 1, we see that there exist four singleton attractors. On the other hand, the reduced model for (2) is given by (3). From (3), we see that there exist four singleton attractors ($[0\ 0]^\top$, $[0\ 1]^\top$, $[1\ 0]^\top$, and $[1\ 1]^\top$). Thus, we see that singleton attractors for (2) and singleton attractors for (3) are one-to-one correspondence.*

We remark here that the algebraic constraints in (4) are required for computing singleton attractors in the original BN from the reduced BN.

## 4. Problem Formulation

Using the reduced BN, consider the control problem of singleton attractors. Hereafter, the following assumption is made for input vertices.

**Assumption 1** *There exists no input vertex such that the Boolean function is given by $x_i(k+1) = 0(1)$. In addition, for the state corresponding to the input vertex, its initial state can be arbitrary controlled.*

In other words, initial states corresponding to input vertices are regarded as a control input. Then, we consider the following problem.

**Problem 1** *Consider the reduced BN (4). Suppose that for states corresponding to vertices except for input vertices, desired singleton attractors $\alpha_1, \alpha_2, \ldots, \alpha_d \in \{0, 1\}^{n-m}$ are given, where $m$ is the number of input vertices. Find initial values of the states corresponding to the input vertices such that the reduced BN has desired fixed points.*

Singleton attractors represent cell types or states of cells [11]. Hence, the above problem is important to characterize the property of cells. Since in this problem, we focus on only singleton attractors, we can use the reduced BN (4).

## 5. Reduction to an Integer Linear Programming Problem

We consider rewriting Problem 1 as an integer linear programming (ILP) problem. First, as a preparation, the following lemma [21] is introduced.

**Lemma 1** *Consider two binary variables $\delta_1$ and $\delta_2$. Then, the following relations hold: (i) $\neg\delta_1$ is equivalent to $1 - \delta_1$, (ii) $\delta_1 \wedge \delta_2$ is equivalent to $\delta_1\delta_2$, and (iii) $\delta_1 \vee \delta_2$ is equivalent to $\delta_1 + \delta_2 - \delta_1\delta_2$.*

Using this lemma, (4) can be equivalently rewritten as a polynomial system with binary variables.

Furthermore, the following lemma [3] is also introduced.

**Lemma 2** *Suppose that binary variables $\delta_j \in \{0, 1\}$, $j \in \mathcal{J}$ are given, where $\mathcal{J}$ is some index set. Then $z = \prod_{j \in \mathcal{J}} \delta_j$ is equivalent to two linear inequalities $\sum_{j \in \mathcal{J}} \delta_j - z \le |\mathcal{J}| - 1$ and $-\sum_{j \in \mathcal{J}} \delta_j + |\mathcal{J}|z \le 0$, where $|\mathcal{J}|$ is the cardinality of $\mathcal{J}$.*

Using Lemma 1 and Lemma 2, the reduced BN (4) can be equivalently rewritten as the following pair of a linear state equation and a linear inequality:

$$\begin{cases} x_i(k+1) = A_i^1 \hat{x}(k) + B_i^{11} u(k) + B_i^{12} z(k), \ \ i \in \mathcal{W}, \\ x_i(k) = A_i^2 \hat{x}(k) + B_i^{21} u(k) + B_i^{22} z(k), \ \ i \notin \mathcal{W}, \\ C\hat{x}(k) + D_1 u(k) + D_2 z(k) \le E, \end{cases} \tag{5}$$

where $\hat{x}(k) \in \{0, 1\}^{|\mathcal{W}|-m}$ is the vector consisting of states corresponding to elements in $\mathcal{W}$ in which input vertices are excluded, and $u(k) \in \{0, 1\}^m$ consists of states corresponding to input vertices. Constant matrices/vectors such as $A_1^1$, $B_i^{11}$, $B_i^{12}$ can be obtained from the above lemmas. The vector $z(k) \in \{0, 1\}^p$ is the auxiliary binary variable, and the dimension $p$ can be determined from Boolean functions. Since the Boolean functions are simplified using the model reduction method in the previous section, the dimension $p$ of $z(k)$ in (5) is smaller than that in the original BN.

We present a simple example.

**Example 4** *Consider the reduced BN obtained in Example 2. In this case, the added variable is only $z_1(k)(= x_1(k)x_3(k))$ (i.e., $p = 1$). On the other hand, in the case of using the original BN (2), the added variables are $z_1(k)(= x_1(k)x_3(k))$ and $z_2(k)(= x_2(k)x_4(k))$ (i.e., $p = 2$). Thus, the dimension $p$ can decrease using the reduced BN. For large-scale BNs, the reduced BN is more effective.*

Using (5), Problem 1 can be rewritten as an ILP problem, where the number of binary variables is $m + p$.

## 6. Conclusion

In this paper, we studied a control method of singleton attractors based on the model reduction method. This problem was reduced to an ILP problem. One of the future effort is to develop an efficient computation method of model reduction.

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