Construction Method of Probabilistic Boolean Networks Based on Imperfect Information

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Abstract: A probabilistic Boolean network (PBN) is well known as one of the mathematical models of gene regulatory networks. In a Boolean network, expression of a gene is approximated by a binary value, and its time evolution is expressed by Boolean functions. In a PBN, a Boolean function is probabilistically chosen from candidates of Boolean functions. One of the authors has proposed a method to construct a PBN from imperfect information. However, there is a weakness that the number of candidates of Boolean functions may be redundant. In this paper, this construction method is improved to efficiently utilize given information. To derive Boolean functions and those selection probabilities, the linear programming problem is solved. Here, we introduce the objective function to reduce the number of candidates. The proposed method is demonstrated by a numerical example.

Keywords: gene regulatory network; linear programming; matrix-based representation; probabilistic Boolean network

1. Introduction

One of the aims in systems biology is to develop a method for modeling, analysis, and control of gene regulatory networks. Control of gene regulatory networks is closely related to therapeutic interventions, and is important toward developing gene therapy technologies [1] in the future.

In the last decade, a Boolean network (BN) [2] and a probabilistic Boolean network (PBN) [3] have attracted much attention as mathematical models in control of gene regulatory networks. In a BN, dynamics such as interactions between genes are expressed by Boolean functions; that is, gene expression is expressed by a binary value (0 or 1). In a PBN, a Boolean function is randomly chosen at each time among candidates of Boolean functions. For a BN, controllability/reachability analysis [4–7] and optimal control [8–10] have been studied. Model reduction has also been studied in [11–13]. For a PBN, controllability/reachability analysis [14–17] and optimal control [18–22] have been studied (see also the survey paper [23]).

In this paper, we consider the problem of finding a PBN based on imperfect information such as the network structure, the sample mean, and the prescribed Boolean functions. For a BN, such a problem has been studied in [24,25]. For a PBN, such a problem has been studied in [26–28]. Comparing the method in [27] with other methods in [26,28], there is the advantage that the size of matrices manipulated in the procedure is smaller. Hence, we focus on the method in [27]. In this method, a linear programming (LP) problem with no objective function is solved. However, it is appropriate that the objective function is set based on imperfect information. In this paper, a new objective function, which can be set from the prescribed Boolean functions, is proposed. By a numerical example, the effectiveness of the proposed method is presented.

This paper is organized as follows. In Section 2, as a preparation, the outline of a PBN and its matrix-based representation is explained. In Section 3, the problem studied in this paper is formulated, and its solution method is derived. In Section 4, a numerical example is presented to show the effectiveness of the proposed method. In Section 5, we conclude this paper.

Notation: For the n-dimensional vector $x = [\begin{array}{cccc} x_1 & x_2 & \cdots & x_n \end{array}]^\top$ and the index set $\mathcal{I} = \{i_1, i_2, \ldots, i_m\} \subseteq \{1, 2, \ldots, n\}$, define $[x_i]_{i \in \mathcal{I}} := [\begin{array}{cccc} x_{i_1} & x_{i_2} & \cdots & x_{i_m} \end{array}]^\top$. For two matrices A and B, let $A \otimes B$ denote the Kronecker product of A and B. In addition, for q vectors $y_1, y_2, \ldots, y_q$ and the index set $\mathcal{J} = \{j_1, j_2, \ldots, j_p\} \subseteq \{1, 2, \ldots, q\}$, define $\bigotimes_{j \in \mathcal{J}} y_j := y_{j_1} \otimes y_{j_2} \otimes \cdots \otimes y_{j_p}$. For example, for q two-dimensional vectors $z_1, z_2, \ldots, z_q$ and $\mathcal{J} = \{1, 5\}$, we can obtain $\bigotimes_{j \in \mathcal{J}} z_j = z_1 \otimes z_5 = [\begin{array}{cccc} z_1^{(1)} z_5^{(1)} & z_1^{(1)} z_5^{(2)} & z_1^{(2)} z_5^{(1)} & z_1^{(2)} z_5^{(2)} \end{array}]^\top$, where $z_j^{(i)}$ is the i-th element of z_j. Finally, let $1_{m \times n}$ denote the $m \times n$ matrix whose elements are all one.

2. Preliminaries

As preliminaries, we explain a probabilistic Boolean network [3] and a matrix-based representation for a PBN [27].

2.1. Probabilistic Boolean Networks

First, we explain a (deterministic) Boolean network. A BN is defined by

$$
\begin{cases}
x_1(k+1) = f^{(1)}([x_j(k)]_{j \in \mathcal{N}^{(1)}}), \\
x_2(k+1) = f^{(2)}([x_j(k)]_{j \in \mathcal{N}^{(2)}}), \\
\vdots \\
x_n(k+1) = f^{(n)}([x_j(k)]_{j \in \mathcal{N}^{(n)}}),
\end{cases}
\tag{1}
$$

where $x := [\begin{array}{cccc} x_1 & x_2 & \cdots & x_n \end{array}]^\top \in \{0, 1\}^n$ is the state, and $k = 0, 1, 2, \ldots$ is the discrete time. The set $\mathcal{N}^{(i)} \subseteq \{1, 2, \ldots, n\}$ is a given index set, and the function $f_i : \{0, 1\}^{|\mathcal{N}^{(i)}|} \to \{0, 1\}^1$ is a given Boolean function consisting of logical operators such as AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). If $\mathcal{N}^{(i)} = \varnothing$ holds, then $x_i(k+1)$ is uniquely determined as 0 or 1.

Next, we explain a probabilistic Boolean network (see [3] for further details). In a PBN, the candidates of $f^{(i)}$ are given, and for each x_i, selecting one Boolean function is probabilistically independent at each time. Let

$$
f_l^{(i)} \left([x_j(k)]_{j \in \mathcal{N}_l^{(i)}} \right), \quad l = 1, 2, \ldots, q(i)
$$

denote the candidates of $f^{(i)}$. The probability that $f_l^{(i)}$ is selected is defined by

$$
c_l^{(i)} := \mathrm{Prob}\left(f^{(i)} = f_l^{(i)} \right).
$$

Then, the following relation

$$
\sum_{l=1}^{q(i)} c_l^{(i)} = 1
\tag{2}
$$

must be satisfied. Probabilistic distributions are derived from experimental results. Finally, $\mathcal{N}_i$, $i = 1, 2, \ldots, n$ are defined by

$$
\mathcal{N}_i := \bigcup_{l=1}^{q(i)} \mathcal{N}_l^{(i)}.
$$

2.2. Matrix-Based Representation for PBNs

In this subsection, we explain the outline of the matrix-based representation for PBNs [27]. Instead of this representation, we may use the matrix-based representation proposed in [5,6,14], where the semi-tensor product (STP) of matrices is used. In this paper, we do not need manipulation of matrices using the STP. Hence, we use a simple matrix-based representation based on truth tables.

First, we define the notation. Binary variables $x_i^0(k)$ and $x_i^1(k)$ are introduced. If $x_i(k) = 0$ holds, then $x_i^0(k) = 1$ holds, otherwise $x_i^0(k) = 0$ holds. If $x_i(k) = 1$ holds, then $x_i^1(k) = 1$ holds, otherwise $x_i^1(k) = 0$ holds. Then, the equality $x_i^0(k) + x_i^1(k) = 1$ is satisfied.

Using $x_i^0(k)$ and $x_i^1(k)$, consider transforming the BN (1) into a matrix-based representation. Define

$$\bar{x}_i(k) := \begin{bmatrix} x_i^0(k) \\ x_i^1(k) \end{bmatrix} \left(= \begin{bmatrix} 1 - x_i(k) \\ x_i(k) \end{bmatrix} \right).$$

Then, the matrix-based representation for $x_i(k+1)$ is given by

$$\bar{x}_i(k+1) = A^{(i)} \bigotimes_{j \in \mathcal{N}^{(i)}} \bar{x}_j(k), \tag{3}$$

where $A^{(i)} \in \{0,1\}^{2 \times 2^{|\mathcal{N}^{(i)}|}}$ and $\bigotimes_{j \in \mathcal{N}^{(i)}} \bar{x}_j(k) \in \{0,1\}^{2^{|\mathcal{N}^{(i)}|}}$. The matrix $A^{(i)}$ can be derived from the following procedure [24].

Procedure for deriving $A^{(i)}$ in (3):
Step 1: Derive a truth table for $x_i(k+1)$.
Step 2: Based on the obtained truth table, assign $x_i(k+1) = 0$ or $x_i(k+1) = 1$ for each element of $\bigotimes_{j \in \mathcal{N}^{(i)}} \bar{x}_j(k)$.
Step 3: Express the assignment obtained in Step 2 by a row vector. Denote the obtained row vector by $\overline{A}^{(i)} \in \{0,1\}^{1 \times 2^{|\mathcal{N}^{(i)}|}}$.
Step 4: Derive $A^{(i)}$ as

$$A^{(i)} = \begin{bmatrix} 1_{1 \times 2^{|\mathcal{N}_i|}} - \overline{A}^{(i)} \\ \overline{A}^{(i)} \end{bmatrix}.$$

Next, consider extending the matrix-based representation of BNs to that of PBNs. Noting that the probability distribution of each $\bar{x}_i$ is independent, $E[\bar{x}_i(k+1)]$ can be obtained as

$$E[\bar{x}_i(k+1)] = \left(\sum_{l=1}^{q(i)} c_l^{(i)} A_l^{(i)} \right) \bigotimes_{j \in \mathcal{N}_i} E[\bar{x}_j(k)], \tag{4}$$

where $A_l^{(i)} \in \{0,1\}^{2 \times 2^{|\mathcal{N}_i|}}$ and $\bigotimes_{j \in \mathcal{N}_i} \bar{x}_j(k) \in \{0,1\}^{2^{|\mathcal{N}_i|}}$. The matrix $A_l^{(i)}$ can be derived from the above procedure.

We present a simple example.

Example 1. *Consider the PBN with two states. Boolean functions and those selection probabilities are given as follows:*

$$f^{(1)} = \begin{cases} f_1^{(1)} = x_1(k) \wedge \neg x_2(k), & c_1^{(1)} = 0.8, \\ f_2^{(1)} = \neg x_1(k), & c_2^{(1)} = 0.2, \end{cases}$$

$$f^{(2)} = \begin{cases} f_1^{(2)} = x_1(k) \vee x_2(k), & c_1^{(2)} = 0.5, \\ f_2^{(2)} = x_1(k), & c_2^{(2)} = 0.3, \\ f_3^{(2)} = \neg x_2(k), & c_3^{(2)} = 0.2, \end{cases}$$

where $\mathcal{N}_1 = \mathcal{N}_2 = \{1, 2\}$, $q(1) = 2$, and $q(2) = 3$. Using the truth table, we derive the matrix-based representation for each Boolean function. As an example, consider the Boolean function $f_1^{(1)}$. From the truth table, we can obtain $f_1^{(1)} = 0$ if $(x_1, x_2) = (0, 0), (0, 1), (1, 1)$ and $f_1^{(1)} = 1$ if $(x_1, x_2) = (1, 0)$. Then, we can obtain the following matrix representation:

$$A_1^{(1)} = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}.$$

The second row in this matrix corresponds to the truth table. In a similar way, we can obtain other matrices as follows:

$$A_2^{(1)} = \begin{bmatrix} 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 0 \end{bmatrix}, \ A_1^{(2)} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 \end{bmatrix}, \ A_2^{(2)} = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}, \ A_3^{(2)} = \begin{bmatrix} 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 \end{bmatrix}.$$

Thus, we can obtain the matrix-based representation for the PBN as follows:

$$\begin{bmatrix} E[x_1^0(k+1)] \\ E[x_1^1(k+1)] \end{bmatrix} = \left(0.8 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix} + 0.2 \begin{bmatrix} 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 0 \end{bmatrix} \right) \begin{bmatrix} E[x_1^0(k)]E[x_2^0(k)] \\ E[x_1^0(k)]E[x_2^1(k)] \\ E[x_1^1(k)]E[x_2^0(k)] \\ E[x_1^1(k)]E[x_2^1(k)] \end{bmatrix},$$

$$\begin{bmatrix} E[x_2^0(k+1)] \\ E[x_2^1(k+1)] \end{bmatrix} = \left(0.5 \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 \end{bmatrix} + 0.3 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix} + 0.2 \begin{bmatrix} 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 \end{bmatrix} \right) \begin{bmatrix} E[x_1^0(k)]E[x_2^0(k)] \\ E[x_1^0(k)]E[x_2^1(k)] \\ E[x_1^1(k)]E[x_2^0(k)] \\ E[x_1^1(k)]E[x_2^1(k)] \end{bmatrix}.$$

3. Construction Problem and Its Solution Method

Using the matrix-based representation, the problem of finding a PBN is reduced to the problem of finding matrices. In this section, we formulate the construction problem of PBNs and propose its solution method.

First, let $s_{i,p}^{k+1}$, $s_{i,p}^k$, $p = 1, 2, \ldots, \bar{p}$ denote the sample mean of the states, which are measured multiple times at a certain time interval k and $k+1$ under a certain pattern p of the experiment, where $\bar{p}$ is the number of patterns. Each experiment can be characterized by the initial state. However, in an experiment of biological systems, there is the case where the initial state cannot be set precisely. In this paper, we suppose that the initial state for each pattern may be unknown. Next, we give the construction problem of a PBN as follows.

Problem 1. *For a PBN, suppose that the index set $\mathcal{N}_i$, $i = 1, 2, \ldots, n$ and the sample mean $s_{i,p}^{k+1}, s_{i,p}^k$, $i = 1, 2, \ldots, n$, $p = 1, 2, \ldots, \bar{p}$ are given. Then, find the probabilities $c_l^{(i)}$, $l = 1, 2, \ldots, q(i)$ and the Boolean functions $f_l^{(i)}$, $l = 1, 2, \ldots, q(i)$ satisfying $E[x_i(k+1)] = s_{i,p}^{k+1}$ and $E[x_i(k)] = s_{i,p}^k$ for the pair of $s_{i,p}^{k+1}$ and $s_{i,p}^k$.*

We remark here that in this problem, candidates of Boolean functions ($f_l^{(i)}$), those selection probabilities ($c_l^{(i)}$), and the number of candidates of Boolean functions ($q(i)$) are not given.

Problem 1 can be equivalently rewritten as the following problem using the matrix-based representation.

Problem 2. *For a PBN, suppose that the index set $\mathcal{N}_i$, $i = 1, 2, \ldots, n$ and the sample mean $s_{i,p}^{k+1}, s_{i,p}^k$, $i = 1, 2, \ldots, n$, $p = 1, 2, \ldots, \overline{p}$ are given. Then, find the probabilities $c_l^{(i)}$, $l = 1, 2, \ldots, q(i)$ and the matrices $\tilde{A}_l^{(i)}$, $l = 1, 2, \ldots, q(i)$ satisfying the following condition:*

$$\bar{s}_{i,p}^{k+1} = \sum_{l=1}^{q(i)} \left(c_l^{(i)} \tilde{A}_l^{(i)} \right) \left(\bigotimes_{j \in \mathcal{N}_i} \bar{s}_{i,p}^k \right), \tag{5}$$

where $\bar{s}_{i,p}^k := [\, 1 - s_{i,p}^k \quad s_{i,p}^k \,]^\top$.

It is difficult to directly reduce Problem 2 to a certain optimization problem. Here, we propose a solution method consisting of two steps. In the proposed method, first, the matrices including both the selection probabilities and the matrices expressing the Boolean functions are calculated by solving a linear programming (LP) problem. Next, the solution of Problem 2 is derived from the matrices obtained.

First, defining $\tilde{B}^{(i)} := \sum_{l=1}^{q(i)} c_l^{(i)} \tilde{A}_l^{(i)}$, (5) can be rewritten as

$$\bar{s}_{i,p}^{k+1} = \tilde{B}^{(i)} \left(\bigotimes_{j \in \mathcal{N}_i} \bar{s}_{i,p}^k \right), \tag{6}$$

where each element of $\tilde{B}^{(i)}$ must take on a real variable on $[0, 1]$. In addition, the sum of each column must be equal to 1.

Here, consider the following problem.

Problem 3. *For a PBN, suppose that the index set $\mathcal{N}_i$, $i = 1, 2, \ldots, n$ and the sample mean $s_{i,p}^{k+1}, s_{i,p}^k$, $i = 1, 2, \ldots, n$, $p = 1, 2, \ldots, \overline{p}$ are given. Then, find the matrices $\tilde{B}^{(i)}$, $i = 1, 2, \ldots, n$ satisfying (6).*

By a simple calculation, Problem 3 can be reduced to n LP problems with no objective function.

Using $\tilde{B}^{(i)}$ obtained by solving Problem 3, we can obtain the probabilities $c_l^{(i)}$, $l = 1, 2, \ldots, q(i)$, the matrices $\tilde{A}_l^{(i)}$, $l = 1, 2, \ldots, q(i)$, and $q(i)$. See e.g., [27] for the further details.

Now we consider the case where the candidate of Boolean functions is given by only one based on theoretical biology and past experiments. In this case, it is desirable that the probability that the Boolean function given in advance is chosen is higher than other selection probabilities. Here, we newly introduce the objective function for Problem 3.

The matrix $\tilde{B}^{(i)}$ is represented by

$$\tilde{B}^{(i)} = \begin{bmatrix} 1 - a_1^{(i)} & 1 - a_2^{(i)} & \cdots & 1 - a_{m^{(i)}}^{(i)} \\ a_1^{(i)} & a_2^{(i)} & \cdots & a_{m^{(i)}}^{(i)} \end{bmatrix},$$

where $m^{(i)} := 2^{|\mathcal{N}_i|}$ and a_q, $q = 1, 2, \ldots, m^{(i)}$ must satisfy $0 \le a_q^{(i)} \le 1$. Assume that the matrix-based representation of the Boolean function given in advance is given by

$$\tilde{B}_d^{(i)} = \begin{bmatrix} 1 - b_1^{(i)} & 1 - b_2^{(i)} & \cdots & 1 - b_{m^{(i)}}^{(i)} \\ b_1^{(i)} & b_2^{(i)} & \cdots & b_{m^{(i)}}^{(i)} \end{bmatrix},$$

where $b_q^{(i)}$, $q = 1, 2, \ldots, m^{(i)}$ are a given binary value.

Then, consider the following problem.

Problem 4. *For a PBN, suppose that the index set $\mathcal{N}_i$, $i = 1, 2, \ldots, n$ and the sample mean $s_{i,p}^{k+1}, s_{i,p'}^k$ $i = 1, 2, \ldots, n$, $p = 1, 2, \ldots, \overline{p}$ are given. Then, find the matrices $\tilde{B}^{(i)}$, $i = 1, 2, \ldots, n$ maximizing the following objective function $J^{(i)}$:*

$$J^{(i)} = J_1^{(i)} + J_2^{(i)} + \cdots + J_{m^{(i)}}^{(i)},$$

$$J_q^{(i)} = \begin{cases} 1 - a_q^{(i)} & \text{if } b_q^{(i)} = 0, \\ a_q^{(i)} & \text{if } b_q^{(i)} = 1 \end{cases}$$

subject to (6).

Problem 4 can also be reduced to n LP problems with the objective function. Hence, we can easily solve it. By solving Problem 4, it is expected that each element of $\tilde{B}^{(i)}$ obtained is close to that of $\tilde{B}_d^{(i)}$.

Remark 1. *In the existing methods in [26,28], the matrices of the size $2^n \times 2^n$ must be manipulated. On the other hand, in the method in [27] and the proposed method, the matrices of the size $2 \times 2^{|\mathcal{N}_i|}$ are manipulated. Hence, using the latter methods, a PBN can be derived by manipulating the matrices of the smaller size.*

4. Example

In this example, we consider the PBN with three states. Suppose that the index set for each i is given by $\mathcal{N}_1 = \{3\}$, $\mathcal{N}_2 = \{1, 3\}$, and $\mathcal{N}_3 = \{1, 2\}$, and the sample mean for each i is given by $s_1^{k+1} = s_1^k = 0.8$, $s_2^{k+1} = s_2^k = 0.4$, and $s_3^{k+1} = s_3^k = 0.7$ (i.e., $p = 1$). Suppose also that one of the candidates of Boolean functions is given by

$$\begin{cases} x_1(k+1) = \neg x_3(k), \\ x_2(k+1) = x_1(k) \wedge \neg x_3(k), \\ x_3(k+1) = x_1(k) \wedge \neg x_2(k). \end{cases}$$

We demonstrate the proposed method in the case of x_2. The matrix $\tilde{B}^{(2)}$ can be obtained as

$$\tilde{B}^{(2)} = \begin{bmatrix} 1 - a_1^{(2)} & 1 - a_2^{(2)} & 1 - a_3^{(2)} & 1 - a_4^{(2)} \\ a_1^{(2)} & a_2^{(2)} & a_3^{(2)} & a_4^{(2)} \end{bmatrix},$$

where $a_1^{(2)}$, $a_2^{(2)}$, $a_3^{(2)}$, and $a_4^{(2)}$ are decision variables. From the given Boolean function $x_2(k+1) = x_1(k) \wedge \neg x_3(k)$, the matrix $\tilde{B}_d^{(2)}$ can be obtained as

$$\tilde{B}_d^{(2)} = \begin{bmatrix} 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{bmatrix},$$

i.e., $b_1^{(2)} = b_2^{(2)} = b_4^{(2)} = 0$ and $b_4^{(2)} = 1$. Then, the objective function $J^{(2)}$ in the LP problem for x_2 is given by

$$J^{(2)} = (1 - a_1^{(2)}) + (1 - a_2^{(2)}) + a_3^{(2)} + (1 - a_4^{(2)}).$$

The constraint condition (5) is given by

$$\begin{bmatrix} 1 - 0.4 \\ 0.4 \end{bmatrix} = \begin{bmatrix} 1 - a_1^{(2)} & 1 - a_2^{(2)} & 1 - a_3^{(2)} & 1 - a_4^{(2)} \\ a_1^{(2)} & a_2^{(2)} & a_3^{(2)} & a_4^{(2)} \end{bmatrix} \begin{bmatrix} (1 - 0.8)(1 - 0.7) \\ (1 - 0.8)0.7 \\ 0.8(1 - 0.7) \\ 0.8 \cdot 0.7 \end{bmatrix}.$$

By solving the LP problem in which $J^{(2)}$ is maximized under the above constraint condition, we can obtain

$$\tilde{B}^{(2)} = \begin{bmatrix} 1 & 1 & 0 & 0.7143 \\ 0 & 0 & 1 & 0.2857 \end{bmatrix}.$$

This matrix can be decomposed as follows:

$$\tilde{B}^{(2)} = 0.7143 \begin{bmatrix} 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{bmatrix} + 0.2857 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}.$$

Hence, we can obtain two Boolean functions and those selection probabilities as follows:

$$f^{(2)} = \begin{cases} f_1^{(2)} = x_1(k) \wedge \neg x_3(k), & c_1^{(2)} = 0.7143, \\ f_2^{(2)} = \neg x_3(k), & c_2^{(2)} = 0.2857, \end{cases}$$

where $q(2) = 2$. In a similar way, we can obtain two Boolean functions and those selection probabilities for x_1 and x_3 as follows:

$$f^{(1)} = \begin{cases} f_1^{(1)} = \neg x_3(k), & c_1^{(1)} = 0.2857, \\ f_2^{(1)} = 1, & c_2^{(1)} = 0.7143, \end{cases}$$

$$f^{(3)} = \begin{cases} f_1^{(3)} = x_1(k) \wedge \neg x_2(k), & c_1^{(3)} = 0.5417, \\ f_2^{(3)} = \neg(x_1(k) \oplus x_2(k)), & c_2^{(3)} = 0.4583. \end{cases}$$

Thus, we can obtain the PBN.

In the case of Problem 3 (i.e., the case where there is no objective function in Problem 4), we can obtain the PBN as follows:

$$f^{(1)} = \begin{cases} f_1^{(1)} = \neg x_3(k), & c_1^{(1)} = 0.1379, \\ f_2^{(1)} = 1, & c_2^{(1)} = 0.8621, \end{cases}$$

$$f^{(2)} = \begin{cases} f_1^{(2)} = x_1(k) \wedge \neg x_3(k), & c_1^{(2)} = 0.4391, \\ f_2^{(2)} = \neg x_1(k) \vee x_3(k), & c_2^{(2)} = 0.3580, \\ f_3^{(2)} = \neg x_1(k), & c_3^{(2)} = 0.1065, \\ f_4^{(2)} = 1, & c_4^{(2)} = 0.0761, \\ f_5^{(2)} = \neg x_1(k) \wedge \neg x_3(k), & c_5^{(2)} = 0.0203, \end{cases}$$

$$f^{(3)} = \begin{cases} f_1^{(3)} = x_1(k) \wedge \neg x_2(k), & c_1^{(3)} = 0.4548, \\ f_2^{(3)} = \neg(x_1(k) \oplus x_2(k)), & c_2^{(3)} = 0.3167, \\ f_3^{(3)} = x_2(k), & c_3^{(3)} = 0.1154, \\ f_4^{(3)} = \neg x_1(k) \vee s_2(k), & c_4^{(3)} = 0.1108, \\ f_5^{(3)} = \neg x_1(k), & c_5^{(3)} = 0.0023. \end{cases}$$

From these results, we see that the probability that the Boolean function given in advance is chosen becomes higher by introducing the objective function. Thus, if a dominant Boolean function is known, then the proposed method is effective.

5. Conclusions

In this paper, we studied a construction method of PBNs based on the network structure and the sample mean. As an extension of the method in [27], we proposed a method for giving an appropriate objective function in the LP problem. Using it, the probability that the Boolean function given in

advance is chosen becomes higher. By a simple example, we demonstrated the effectiveness of the proposed method.

One of the future efforts is to develop a construction method using only the network structure. Applying the proposed method to large-scale gene regulatory networks is also important. To realize efficient computation, we will consider utilizing optPBN, a MATLAB-based toolbox [29].

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References

1. Santos-Rosa, H.; Caldas, C. Chromatin modifier enzymes, the histone code and cancer. *Eur. J. Cancer* **2005**, *41*, 2381–2402. [CrossRef] [PubMed]
2. Kauffman, S.A. Metabolic stability and epigenesis in randomly constructed genetic nets. *J. Theor. Biol.* **1969**, *22*, 437–467. [CrossRef]
3. Shmulevich, I.; Dougherty, E.R.; Kim, S.; Zhang, W. Probabilistic Boolean networks: A rule-based uncertainty model for gene regulatory networks. *Bioinformatics* **2002**, *18*, 261–274. [CrossRef] [PubMed]
4. Akutsu, T. *Algorithms for Analysis, Inference, and Control of Boolean Networks*; World Scientific Publishing: Singapore, 2018.
5. Cheng, D.; Qi, H. Controllability and observability of Boolean control network. *Automatica* **2009**, *45*, 1659–1667. [CrossRef]
6. Cheng, D.; Qi, H.; Li, Z. *Analysis and Control of Boolean Network: A Semi-tensor Product Approach*; Springer: Berlin/Heidelberg, Germany, 2011.
7. Kobayashi, K.; Imura, J.; Hiraishi, K. Polynomial-time algorithm for controllability test of a class of Boolean biological networks. *EURASIP J. Bioinform. Syst. Biol.* **2010**, *2010*, 210685. [CrossRef]
8. Kobayashi, K.; Hiraishi, K. Optimal control of Boolean biological networks modeled by Petri nets. *IEICE Trans. Fundam. Electron. Commun. Comput. Sci.* **2013**, *E96-A*, 532–539. [CrossRef]
9. Kobayashi, K.; Hiraishi, K. Optimal control of gene regulatory networks with effectiveness of multiple drugs: A Boolean network approach. *BioMed Res. Int.* **2013**, *2013*, 246761. [CrossRef]
10. Wu, Y.; Sun, X.-M.; Zhao, X.; Shen, T. Optimal control of Boolean control networks with average cost: A policy iteration approach. *Automatica* **2019**, *100*, 378–387. [CrossRef]
11. Kobayashi, K. Design of fixed points in Boolean networks using feedback vertex sets and model reduction. *Complexity* **2019**, *2019*, 9261793. [CrossRef]
12. Veliz-Cuba, A. Reduction of Boolean network models. *J. Theor. Biol.* **2011**, *289*, 167–172. [CrossRef]
13. Veliz-Cuba, A.; Aguilar, B.; Hinkelmann, F.; Laubenbacher, R. Steady state analysis of Boolean molecular network models via model reduction and computational algebra. *BMC Bioinform.* **2014**, *15*, 221. [CrossRef] [PubMed]
14. Li, F.; Sun, J. Controllability of probabilistic Boolean control networks. *Automatica* **2011**, *47*, 2765–2771. [CrossRef]
15. Kobayashi, K.; Hiraishi, K. Symbolic approach to verification and control of deterministic/probabilistic Boolean networks. *IET Syst. Biol.* **2012**, *6*, 215–222. [CrossRef] [PubMed]
16. Kobayashi, K.; Hiraishi, K. Verification and optimal control of context-sensitive probabilistic Boolean networks using model checking and polynomial optimization. *Sci. World J.* **2014**, *2014*, 968341. [CrossRef] [PubMed]
17. Toyoda, M.; Wu, Y. On optimal time-varying feedback controllability for probabilistic Boolean networks. *IEEE Trans. Neural Netw. Learn. Syst.* **2019**. [CrossRef] [PubMed]
18. Kobayashi, K.; Hiraishi, K. An integer programming approach to optimal control problems in context-sensitive probabilistic Boolean networks. *Automatica* **2011**, *47*, 1260–1264. [CrossRef]
19. Kobayashi, K.; Hiraishi, K. Optimal control of probabilistic Boolean networks using polynomial optimization. *IEICE Trans. Fundam. Electron. Commun. Comput. Sci.* **2012**, *E95-A*, 1512–1517. [CrossRef]

20. Kobayashi, K.; Hiraishi, K. Optimization-based approaches to control of probabilistic Boolean networks (Review Paper). *Algorithms* **2017**, *10*, 31. [CrossRef]

21. Shmulevich, I.; Dougherty, E.R. *Probabilistic Boolean Networks: The Modeling and Control of Gene Regulatory Networks*; Society for Industrial and Applied Mathematics: Philadelphia, PA, USA, 2010.

22. Wu, Y.; Shen, T. Policy iteration algorithm for optimal control of stochastic logical dynamical systems. *IEEE Trans. Neural Netw. Learn. Syst.* **2018**, *29*, 2031–2036. [CrossRef]

23. Trairatphisan, P.; Mizera, A.; Pang, J.; Tantar, A.A.; Schneider, J.; Sauter, T. Recent development and biomedical applications of probabilistic Boolean networks. *Cell Commun. Signal.* **2013**, *11*, 46. [CrossRef]

24. Kobayashi, K.; Hiraishi, K. ILP/SMT-based method for design of Boolean networks based on singleton attractors. *IEEE/ACM Trans. Comput. Biol. Bioinform.* **2014**, *11*, 1253–1259. [CrossRef] [PubMed]

25. Pal, R.; Ivanov, I.; Datta, A.; Bittner, M.L.; Dougherty, E.R. Generating Boolean networks with a prescribed attractor structure. *Bioinformatics* **2005**, *21*, 4021–4025. [CrossRef] [PubMed]

26. Ching, W.-K.; Chen, X.; Tsing, N.-K. Generating probabilistic Boolean networks from a prescribed transition probability matrix. *IET Syst. Biol.* **2009**, *3*, 453–464. [CrossRef] [PubMed]

27. Kobayashi, K.; Hiraishi, K. Design of probabilistic Boolean networks based on network structure and steady-state probabilities. *IEEE Trans. Neural Netw. Learn. Syst.* **2017**, *28*, 1966–1971. [CrossRef] [PubMed]

28. Zhang, S.-Q.; Ching, W.-K.; Chen, X.; Tsing, N.-K. Generating probabilistic Boolean networks from a prescribed stationary distribution. *Inf. Sci.* **2010**, *180*, 2560–2570. [CrossRef]

29. Trairatphisan, P.; Mizera, A.; Pang, J.; Tantar, A.A.; Sauter, T. optPBN: An optimisation Toolbox for Probabilistic Boolean Networks. *PLoS ONE* **2014**, *9*, 7. [CrossRef]