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PAPER

Optimal Control of Probabilistic Boolean Networks Using Polynomial Optimization

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SUMMARY In this paper, the optimal control problem of a probabilistic Boolean network (PBN), which is one of the significant models in gene regulatory networks, is discussed. In the existing methods of optimal control for PBNs, it is necessary to compute state transition diagrams with 2^n nodes for a given PBN with n states. To avoid this computation, a polynomial optimization approach is proposed. In the proposed method, a PBN is transformed into a polynomial system, and the optimal control problem is reduced to a polynomial optimization problem. Since state transition diagrams are not computed, the proposed method is convenient for users.

key words: *optimal control, polynomial optimization, probabilistic Boolean networks, systems biology*

1. Introduction

In the field of systems biology, there have been a lot of studies on modeling, analysis, and control of biological networks such as gene regulatory networks and metabolic networks. In control of biological networks, the control input has the following significance. The value of the control input expresses whether a stimulus is given to a cell. Then the control input is designed to obtain the state trajectory that transits from the initial state to the desired one. So the control input can represent the current status of therapeutic interventions, which are realized by radiation, chemotherapy, and so on. In order to develop gene therapy technologies (see e.g., [17]) in future, control of biological networks is important. Furthermore, in recent years, the important result on control of biological networks has been obtained in [13]. That is, feedback control of synthetic biological circuits has been implemented, and the experimental result in which cellular behavior is regulated by control has been obtained. This result suggests that control methods of biological networks can be realized. From these facts, it is important to develop control methods of biological networks.

Biological networks are in general expressed by ordinary/partial differential equations with high nonlinearity and high dimensionality. In control problems, Boolean networks and hybrid systems are frequently used [1], [3], [4], [10], [12]. In the hybrid systems-based approach, a class of biological networks are limited to low-dimensional systems, because the computation time to solve the control problem is too long. In Boolean networks, dynamics such as interactions between genes are expressed by Boolean functions [9]. There is a criticism that a Boolean network is too simple as a model of biological networks (see e.g., [14]), but this model can be relatively applied to large-scale systems. In addition, since the behavior of gene regulatory networks is stochastic by the effects of noise, it is appropriate that a Boolean function is randomly decided at each time among the candidates of Boolean functions. From this viewpoint, a probabilistic Boolean network (PBN) has been proposed in [18]. In the existing solution methods [5]–[8], [15], [16] of optimal control of PBNs, state transition diagrams with 2^n nodes (i.e., $2^n \times 2^n$ transition probability matrices) must be computed for a PBN with n states. As a result, in order to compute state transition diagrams, several issues such as memory consumption must be considered in implementation, and it is desirable to directly use a given Boolean function. The authors have proposed in [11] a control method in which state transition diagrams are not computed, but in this method the expected value of the state cannot be evaluated.

In this paper, a new method using polynomial optimization is proposed. First, we propose a method to express the expected value of the state as a polynomial system, which can be directly derived from a given Boolean function. Next, by using the obtained polynomial system, the optimal control problem is reduced to a polynomial optimization problem. For large-scale PBNs, it is difficult at this stage to solve a polynomial optimization problem. However, by using a suitable solver such as SparsePOP [22], implementation is easy. In this sense, the proposed method provides us an easy-to-use method.

This paper is organized as follows. In Sect. 2, the outline of PBNs is explained. In Sect. 3, the optimal control problem studied here is formulated. In Sect. 4 and Sect. 5, a solution method is proposed. In Sect. 6, the effectiveness of the proposed method is shown by using an artificial example. In Sect. 7, the proposed method is applied to an example on control of a WNT5A network. In Sect. 8, we conclude this paper.

Notation: Let $\mathcal{R}$ denote the set of real numbers. Let $\{0, 1\}^n$ denote the set of n-dimensional vectors, which consists of elements 0 and 1. For a matrix/vector X, let X^T denote the transpose of X. For an event A, let $P(A)$ denote the probability that A occurs. For two events A, B, let $P(A|B)$ denote the conditional probability of A given B. For two events A, B, let $E(A|B)$ denote the conditional expected value of A given B.

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2. Probabilistic Boolean Networks

In this section, we introduce a probabilistic Boolean network (PBN).

Consider the following PBN

$$\begin{cases} x_1(k+1) = f^{(1)}(k, x(k), u(k)), \\ x_2(k+1) = f^{(2)}(k, x(k), u(k)), \\ \vdots \\ x_n(k+1) = f^{(n)}(k, x(k), u(k)) \end{cases} \tag{1}$$

where $x = [x_1\ x_2\ \cdots\ x_n]^T \in \{0,1\}^n$ is the state (e.g., the expression of genes), $u = [u_1\ u_2\ \cdots\ u_m]^T \in \{0,1\}^m$ is the control input (e.g., the expression of genes), i.e., the value of u can be arbitrarily given, $k = 0, 1, 2, \ldots$ is the discrete time. For a fixed $k \in \{0, 1, \ldots\}$, $f^{(i)} : \{0, 1, \ldots\} \times \{0,1\}^n \times \{0,1\}^m \to \{0,1\}^1$ is a given Boolean function consisting of logical operators such as AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). In deterministic Boolean networks, $x(k+1)$ is uniquely determined for given k, $x(k)$, and $u(k)$. In PBNs, candidates of $f^{(i)}(k, x(k), u(k))$ are given, and for each x_i, selecting one Boolean function is probabilistically independent at each time. Candidates of $f^{(i)}(k, x(k), u(k))$ is denoted by $f_j^{(i)}(x(k), u(k))$, $j = 1, 2, \ldots, l(i)$, and the probability that $f_j^{(i)}(x(k), u(k))$ is selected is denoted by

$$c_j^{(i)} = P\left(f^{(i)}(k, x(k), u(k)) = f_j^{(i)}(x(k), u(k))\right).$$

Then the following relation

$$\sum_{j=1}^{l(i)} c_j^{(i)} = 1 \tag{2}$$

must be satisfied.

Example 1: As a simple example, consider the PBN with three states and one control input, which is a modified version of the model discussed in [2]. A Boolean function is given as

$$f^{(1)} = \begin{cases} f_1^{(1)} = x_3(k) \wedge u(k), & c_1^{(1)} = 0.8, \\ f_2^{(1)} = \neg x_3(k), & c_2^{(1)} = 0.2, \end{cases}$$
$$f^{(2)} = f_1^{(2)} = x_1(k) \wedge \neg x_3(k), \quad c_1^{(2)} = 1.0,$$
$$f^{(3)} = \begin{cases} f_1^{(3)} = x_1(k) \wedge \neg x_2(k), & c_1^{(3)} = 0.7, \\ f_2^{(3)} = x_2(k) \wedge u(k), & c_2^{(3)} = 0.3 \end{cases}$$

where $l(1) = 2$, $l(2) = 1$ and $l(3) = 2$ hold, and we see that the relation (2) is satisfied. Next, consider the state trajectories. Then for $x(0) = [\,0\ \ 0\ \ 0\,]^T$ and $u(0) = 0$, we can obtain

$$P\left(x(1) = [\,0\ \ 0\ \ 0\,]^T \mid x(0) = [\,0\ \ 0\ \ 0\,]^T\right) = 0.8,$$
$$P\left(x(1) = [\,1\ \ 0\ \ 0\,]^T \mid x(0) = [\,0\ \ 0\ \ 0\,]^T\right) = 0.2.$$

In this example, the cardinality of the finite state set $\{0,1\}^3$ is given by $2^3 = 8$, and we can obtain the state transition diagram of Fig. 1 by computing the transition from each state under $u(0) = 0$. In Fig. 1, the number assigned to each node denotes x_1, x_2, x_3 (elements of the state), and the number assigned to each arc denotes the transition probability from some state to other state. Note here that for simplicity, the state transitions from only $x(k) = [\,0\ \ 0\ \ 0\,]^T$, $[\,0\ \ 0\ \ 1\,]^T$, $[\,0\ \ 1\ \ 0\,]^T$, $[\,1\ \ 1\ \ 0\,]^T$ are illustrated in Fig. 1. □

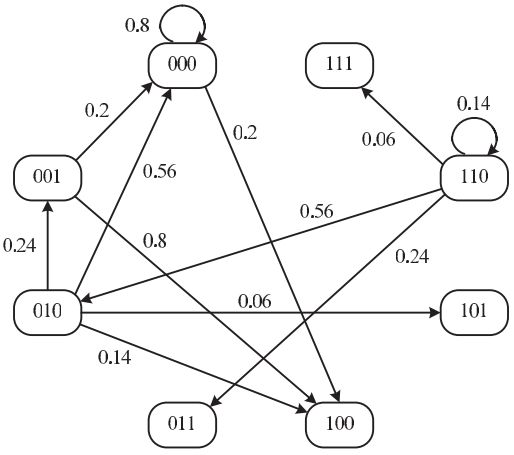

Fig. 1 State transition diagram under $u(0) = u_0$.

In the existing methods [5]–[8], [15], [16] for optimal control of PBNs, it is necessary to compute the state transition diagram such as Fig. 1, i.e., the transition probability matrix. The number of nodes in the state transition diagram is given by 2^n (n is the number of the state). From this, transition probability matrices with $2^n \times 2^n$ must be manipulated in a solution method of the optimal control problem. Then, in naive implementation using MATLAB, matrices with $2^{15} \times 2^{15}$ cannot be created due to memory consumption, where we used the standard computer on CPU: Intel Core i7 1.2 GHz, Memory: 4 GB, Windows 7 Professional 64 bit. Therefore, it is important to consider a solution method in which state transition diagrams are not computed. In addition, it is desirable to directly use a given Boolean function. In this paper, from this viewpoint, we propose a new method using polynomial optimization.

3. Problem Formulation

For the PBN (1), consider the following optimal control problem.

Problem 1: Suppose that for the PBN (1), the initial state $x(0) = x_0$ and the control time N are given. Then find a control input sequence $u(0), u(1), \ldots, u(N-1)$ minimizing the cost function

$$J = E\left[\sum_{k=0}^{N-1} \{Qx(k) + Ru(k)\} + Q_f x(N) \,\middle|\, x(0) = x_0\right] \tag{3}$$

where $Q, Q_f \in \mathcal{R}^{1\times n}$, $R \in \mathcal{R}^{1\times m}$ are weighting vectors whose element is a non-negative real number.

We consider that a linear cost function is appropriate from the following two reasons:

(i) For a binary variable $\delta \in \{0, 1\}$, the relation $\delta^2 = \delta$ holds. That is, in the cost function, the quadratic term such as $x_i^2(k)$ is not necessary.

(ii) In control of gene regulatory networks, the expression of a certain gene is frequently focused (see e.g., [6]). That is, in the cost function, the quadratic term such as $x_i(k)x_j(k)$, $i \neq j$ is not necessary. See Sect. 7 for the biological significance of this problem.

4. Transformation of PBNs into Polynomial Systems

Consider transforming PBNs into polynomial systems. First, the relation between Boolean functions and polynomials is given as a preparation. Next, a motivating example is shown. Finally, the result for a general PBN is derived.

4.1 Preparation

As a preparation, the following lemma [20] is introduced.

Lemma 1: Consider two binary variables δ_1 and δ_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 $\delta_1\delta_2$.
(iii) $\delta_1 \vee \delta_2$ is equivalent to $\delta_1 + \delta_2 - \delta_1\delta_2$. □

By Lemma 1, a given Boolean function can be transformed into a polynomial on the real number field. For example, $\delta_1 \vee \neg\delta_2$ is equivalently transformed into $\delta_1 + (1 - \delta_2) - \delta_1(1 - \delta_2) = 1 - \delta_2 + \delta_1\delta_2$.

4.2 Motivating Example

Using the PBN in Example 1, we explain the basic idea of the proposed method.

Suppose that for the PBN in Example 1, $x(0)$ and $u(0)$ are given as $x(0) = x_0 = [\ 0\ \ 0\ \ 0\ ]^T$ and $u(0) = 0$, respectively. Then from Fig. 1, we can obtain $E[x_1(1)|x(0) = x_0, u(0) = 0] = 0.8 \cdot 0 + 0.2 \cdot 1 = 0.2$. This result can also be obtained by using Lemma 1. By Lemma 1, $x_3(k) \wedge u(k)$ and $\neg x_3(k)$ are transformed into $x_3(k)u(k)$ and $1 - x_3(k)$, respectively. So we can obtain

$$\begin{aligned} E[x_1(1)|x(0) = x_0, u(0) = 0] &= 0.8(x_3(0)u(0)) \\ &\quad +0.2(1 - x_3(0)) \\ &= 0.2. \end{aligned}$$

In a similar way, $E[x_2(1)|x(0) = x_0, u(0) = 0]$ and $E[x_3(1)|x(0) = x_0, u(0) = 0]$ can be obtained as

$$\begin{aligned} E[x_2(1)|x(0) = x_0, u(0) = 0] &= x_1(0)(1 - x_3(0)) \\ &= 0, \end{aligned}$$

$$\begin{aligned} E[x_3(1)|x(0) = x_0, u(0) = 0] &= 0.7\{x_1(0)(1 - x_2(0))\} \\ &\quad +0.3(x_2(0)u(0)) \\ &= 0, \end{aligned}$$

respectively.

Next, suppose that $u(1)$ is given as $u(1) = 0$, and consider deriving $E[x(2)|x(0) = x_0, u(0) = u(1) = 0]$ (hereafter, the condition is omitted). Then, noting that a switch of a Boolean function is probabilistically independent for each state, we can obtain

$$\begin{aligned} E[x_1(2)] &= E[f^{(1)}(1, x(1), u(1))] \\ &= 0.8E[f_1^{(1)}(x(1), u(1))] \\ &\quad +0.2E[f_2^{(1)}(x(1), u(1))], \\ &= 0.8E[x_3(1)u(1)] + 0.2E[1 - x_3(1)] \\ &= 0.8E[x_3(1)]u(1) + 0.2 - 0.2E[x_3(1)] \\ &= 0.2, \\ E[x_2(2)] &= E[f^{(2)}(1, x(1), u(1))] \\ &= 1.0E[x_1(1)(1 - x_3(1))] \\ &= E[x_1(1)] - E[x_1(1)]E[x_3(1)] \\ &= 0.2, \\ E[x_3(2)] &= E[f^{(3)}(1, x(1), u(1))] \\ &= 0.7E[x_1(1) - x_1(1)x_2(1)] \\ &\quad +0.3E[x_2(1)u(1)] \\ &= 0.14. \end{aligned}$$

By recursively repeating, we can obtain $E[x(k)|*]$, $k \geq 3$. From this example, we see in an intuitively way that the expected value of the state can be expressed as a polynomial system.

4.3 General Case

For the general case, we can obtain the following theorem. Hereafter, for simplicity of notation, the condition in $E[x_i(k)|*]$ is omitted. In addition, by $\hat{f}^{(i)}$, denote the polynomial corresponding to the Boolean function $f^{(i)}$. By $\hat{f}_j^{(i)}$, denote the polynomial corresponding to the Boolean function $f_j^{(i)}$.

Theorem 1: Suppose that for the PBN (1), the initial state $x(0) = x_0$ is given. Then the expected value of the state, $E[x_i(k)]$ is expressed as the following polynomial system

$$\Sigma_i : \ E[x_i(k+1)] = \sum_{j=1}^{l(i)} c_j^{(i)} \hat{f}_j^{(i)}(E[x(k)], u(k)) \tag{4}$$

Proof : Note the following two points: (i) a switch of a Boolean function is probabilistically independent for each state, i.e., $E[x_ix_j] = E[x_i]E[x_j]$, $i \neq j$ holds, and (ii) each term of the polynomial $\hat{f}_j^{(i)}$ is given as the form of $ax_1^{e_1} \cdots x_n^{e_n} u_1^{e_{n+1}} \cdots u_m^{e_{n+m}}$, where a is an integer, and $e_i \in \{0, 1\}$, i,e, terms such as x_i^2 are not included in $\hat{f}_j^{(i)}$. From these points and $E[u(k)] = u(k)$, the system (4) is obtained

as follows:

$$\begin{aligned} E[x_i(k+1)] &= E[\hat{f}^{(i)}(k, x(k), u(k))] \\ &= \sum_{j=1}^{l(i)} c_j^{(i)} E[\hat{f}_j^{(i)}(x(k), u(k))] \\ &= \sum_{j=1}^{l(i)} c_j^{(i)} [\hat{f}_j^{(i)}(E[x(k)], u(k))] \end{aligned}$$

□

Since $\hat{f}_j^{(i)}(x(k), u(k))$ is a polynomial, the right-hand side of (4) is also a polynomial. Therefore, from Theorem 1, we see that the expected value $E[x(k)]$ of the state is expressed as a polynomial system.

5. Reduction to a Polynomial Optimization Problem

Consider reducing Problem 1 to a polynomial optimization problem. Then by using (4) in Theorem 1, we can obtain the following result.

Theorem 2: Problem 1 is equivalent to the following polynomial optimization problem:

Problem A:

$$\begin{aligned} \text{find} \quad & E[x(k+1)] \in \mathcal{R}^n, \ \ u(k) \in \mathcal{R}^m, \\ & k = 0, 1, \ldots, N-1, \\ \min \quad & \text{Cost function (3)}, \\ \text{subject to} \quad & \text{System } \Sigma_i,\ i = 1, 2, \ldots, n, \\ & x(0) = x_0, \\ & u_i(k)(u_i(k) - 1) = 0. \end{aligned}$$

Proof : Noting $E[u(k)] = u(k)$, this theorem is obtained immediately. □

Since from Theorem 1 and its proof, we see that $E[x(k+1)] \in [0,1]^n$ is satisfied automatically, we set $E[x(k+1)] \in \mathcal{R}^n$ in Problem A. In addition, by using a solution of the system Σ_i of (4), $E[x(k+1)]$ can be eliminated from decision variables in Problem A. However, implementation makes easy by directly using (4). So $E[x(k+1)]$ is regarded as a decision variable.

The constraint $u_i(k)(u_i(k) - 1) = 0$ guarantees that $u(k)$ is a binary variable. However, this constraint is non-convex, and its existence is one of the reason why the computation time to solve the problem is long. In a practical manner, instead of this non-convex constraint, it will be desirable to use the relaxed constraint $0 \le u_i(k) \le 1$.

6. Artificial Example

In order to evaluate the computation time for solving the problem, we consider one artificial example of a PBN with 15 states and 3 control inputs. We stress that the existing method cannot be applied to the optimal control problem of PBNs with such a size, because $2^{15} \times 2^{15}$ matrices cannot be created in MATLAB on the standard computer (see also the last paragraph of Sect. 2). See Appendix for further details of the considered PBN.

For the PBN in Appendix, consider solving the optimal control problem of Problem 1, where $Q = Q_f = [10\ 0\ 0\ 0\ 0\ 10\ 0\ 0\ 0\ 0\ 0\ 1\ 0\ 0\ 0\ 0]$ and $R = [1\ 1\ 1]$. For N, we consider four cases, i.e., $N = 2, 3, 4, 5$.

Next, we show the computation result. In the case of $N = 5$, the control input can be obtained as $u(0) = [1\ 1\ 1]^T$, $u(1) = u(2) = u(3) = u(4) = [1\ 1\ 0]^T$. We remark that the control input is not a constant vector. The computation time for solving the optimal control problem was as follows: $N = 2$: 0.6 [sec], $N = 3$: 19.6 [sec], $N = 4$: 218.8 [sec], $N = 5$: 333.4 [sec], where we used SparsePOP [22] on the standard computer on CPU: Intel Core i7 1.2 GHz, Memory: 4 GB, Windows 7 Professional 64 bit. We remark that the computation time depends on also a form of given Boolean functions. From this result, we see that the optimal control problem, which cannot be solved by the existing method, can be solved by the proposed method. In addition, we see that for a small N, the optimal control problem can be solved within practical time. For a large N and large-scale biological networks, it will be necessary to consider an approximate solution method.

7. Biological Example

Consider applying the proposed method to control of a WNT5A network. First, a WNT5A network is explained. Next, the computation result is shown.

7.1 WNT5A Network

Consider a gene regulatory network with the gene WNT5A, which is related to melanoma. A Boolean network model is given by

$$\begin{aligned} x_1(k+1) &= \neg x_6(k), \\ x_2(k+1) &= (\neg x_2(k) \wedge x_4(k) \wedge x_6(k)) \\ &\qquad \vee \{\neg x_2(k) \wedge (x_4(k) \vee x_6(k))\}, \\ x_3(k+1) &= \neg x_7(k), \\ x_4(k+1) &= x_4(k), \\ x_5(k+1) &= x_2(k) \vee \neg x_7(k), \\ x_6(k+1) &= x_3(k) \vee x_4(k), \\ x_7(k+1) &= \neg x_2(k) \vee x_7(k) \end{aligned}$$

where the concentration level (high or low) of the gene WNT5A is denoted by x_1, the concentration level of the gene pirin by x_2, the concentration level of the gene S100P by x_3, the concentration level of the gene RET1 by x_4, the concentration level of the gene MART1 by x_5, the concentration level of the gene HADHB by x_6, and the concentration level of the gene STC2 by x_7. See [21] for further details.

Next, suppose that the control input u is given by x_2

(the concentration level of the gene pirin), according to discussion on [6]. So by replacing x_2 and $x_3, x_4, \ldots, x_7$ with u and $x_2, x_3, \ldots, x_6$, respectively, we can obtain the following model

$$\begin{aligned}
x_1(k+1) &= f_d^{(1)}(x(k), u(k)) = \neg x_5(k),\\
x_2(k+1) &= f_d^{(2)}(x(k), u(k)) = \neg x_6(k),\\
x_3(k+1) &= f_d^{(3)}(x(k), u(k)) = x_3(k),\\
x_4(k+1) &= f_d^{(4)}(x(k), u(k)) = \neg x_6(k) \vee u(k),\\
x_5(k+1) &= f_d^{(5)}(x(k), u(k)) = x_2(k) \vee x_3(k),\\
x_6(k+1) &= f_d^{(6)}(x(k), u(k)) = x_6(k) \vee \neg u(k).
\end{aligned}$$

Furthermore, we add the probabilistic behavior as follows:

$$x_i(k+1) = \begin{cases} f_d^{(i)}(x(k), u(k)), \\ \qquad \text{with the probability } 0.8, \\ x_i(k), \quad \text{with the probability } 0.2, \end{cases}$$

where $l(i) = 2$ holds. Thus we can obtain the PBN model expressing a WNT5A network.

7.2 Computation Result

For the obtained PBN model, consider solving Problem A in Theorem 2. In a WNT5A network, it is important to inhibit the concentration level x_1 of the gene WNT5A [19]. From this fact, Q, Q_f, R in Problem A are given as

$$\begin{aligned}
Q &= [\,1\ 0\ 0\ 0\ 0\ 0\,],\ \ R = 1,\\
Q_f &= [\,10\ 0\ 0\ 0\ 0\ 0\,],
\end{aligned}$$

respectively. The initial state is given as $x_0 = [\,1\ 1\ 0\ 1\ 0\ 0\,]^T$. In addition, we set $N = 5$.

Next, we show the computation result. By solving Problem A, we obtain $u(0) = u(1) = 1, u(2) = u(3) = u(4) = 0$. The expected value of the state at each time is obtained as

$$\begin{aligned}
E[x(1)] &= [\,1\ 1\ 0\ 1\ 0.8\ 0\,]^T,\\
E[x(2)] &= [\,0.36\ 1\ 0\ 1\ 0.96\ 0\,]^T,\\
E[x(3)] &= [\,0.104\ 1\ 0\ 1\ 0.992\ 0.8\,]^T,\\
E[x(4)] &= [\,0.027\ 0.36\ 0\ 0.36\ 0.998\ 0.96\,]^T,\\
E[x(5)] &= [\,0.007\ 0.104\ 0\ 0.104\ 0.488\ 0.992\,]^T.
\end{aligned}$$

So we see that the concentration level x_1 of the gene WNT5A is inhibited with time.

Finally, we discuss the computation time to solve the problem. The computation time to solve this problem was 1.65 [sec]. So we see that for a PBN with such a size, the optimal control problem can be solved in practical time.

8. Conclusion

In this paper, we have proposed a new method for solving the optimal control problem of probabilistic Boolean networks. In the proposed method, a given Boolean function is directly used, and the optimal control problem is reduced to a polynomial optimization problem. The proposed method provides us an easy-to-use method for control theory of gene regulatory networks.

There are several open problems. For example, it is important to derive an efficient solution method for large-scale biological networks. In addition, application to several biological networks is also significant.

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Appendix: Details of the PBN in Sect. 6

In Sect. 6, we consider the following PBN with a cyclic structure and $l(i) = 2$, $i = 1, 2, \ldots, 15$:

$$f^{(1)} = \begin{cases} f_1^{(1)} = x_1(k) \wedge x_2(k) \wedge x_{15}(k), \\ f_2^{(1)} = \neg u_1(k), \end{cases}$$
$$f^{(2)} = \begin{cases} f_1^{(2)} = x_1(k) \wedge x_2(k) \wedge x_3(k), \\ f_2^{(2)} = x_2(k), \end{cases}$$
$$f^{(3)} = \begin{cases} f_1^{(3)} = x_2(k) \wedge x_3(k) \wedge x_4(k) \wedge u_3(k), \\ f_2^{(3)} = x_3(k), \end{cases}$$
$$f^{(4)} = \begin{cases} f_1^{(4)} = x_3(k) \wedge x_4(k) \wedge x_5(k), \\ f_2^{(4)} = x_4(k), \end{cases}$$
$$f^{(5)} = \begin{cases} f_1^{(5)} = x_4(k) \wedge x_5(k) \wedge x_6(k), \\ f_2^{(5)} = x_5(k), \end{cases}$$
$$f^{(6)} = \begin{cases} f_1^{(6)} = x_5(k) \wedge x_6(k) \wedge x_7(k), \\ f_2^{(6)} = \neg u_2(k), \end{cases}$$
$$f^{(7)} = \begin{cases} f_1^{(7)} = x_6(k) \wedge x_7(k) \wedge x_8(k), \\ f_2^{(7)} = x_7(k), \end{cases}$$
$$f^{(8)} = \begin{cases} f_1^{(8)} = x_7(k) \wedge x_8(k) \wedge x_9(k) \wedge u_1(k), \\ f_2^{(8)} = x_8(k), \end{cases}$$
$$f^{(9)} = \begin{cases} f_1^{(9)} = x_8(k) \wedge x_9(k) \wedge x_{10}(k), \\ f_2^{(9)} = x_9(k), \end{cases}$$
$$f^{(10)} = \begin{cases} f_1^{(10)} = x_9(k) \wedge x_{10}(k) \wedge x_{11}(k), \\ f_2^{(10)} = x_{10}(k), \end{cases}$$
$$f^{(11)} = \begin{cases} f_1^{(11)} = x_{10}(k) \wedge x_{11}(k) \wedge x_{12}(k), \\ f_2^{(11)} = \neg u_3(k), \end{cases}$$
$$f^{(12)} = \begin{cases} f_1^{(12)} = x_{11}(k) \wedge x_{12}(k) \wedge x_{13}(k), \\ f_2^{(12)} = x_{12}(k), \end{cases}$$
$$f^{(13)} = \begin{cases} f_1^{(13)} = x_{12}(k) \wedge x_{13}(k) \wedge x_{14}(k) \wedge u_2(k), \\ f_2^{(13)} = x_{13}(k), \end{cases}$$
$$f^{(14)} = \begin{cases} f_1^{(14)} = x_{13}(k) \wedge x_{14}(k) \wedge x_{15}(k), \\ f_2^{(14)} = x_{14}(k), \end{cases}$$
$$f^{(15)} = \begin{cases} f_1^{(15)} = x_1(k) \wedge x_{14}(k) \wedge x_{15}(k), \\ f_2^{(15)} = x_{15}(k). \end{cases}$$

In addition, $c_j^{(i)}$ is given as $c_j^{(i)} = 0.5$.

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