2011 50th IEEE Conference on Decision and Control and
European Control Conference (CDC-ECC)
Orlando, FL, USA, December 12-15, 2011

Probabilistic Control of Boolean Networks with Multiple Dynamics: Towards Control of Gene Regulatory Networks

Koichi Kobayashi and Kunihiko Hiraishi

Abstract— **A Boolean network is widely used as a model of gene regulatory networks. In control of gene regulatory networks using Boolean networks, we assume that the concentration level of a part of genes is arbitrarily determined as the control input. However, there are cases that no gene satisfying this assumption exists, and it is important to consider weak control. In this paper, a Boolean network with two types of the control inputs is proposed as a model of gene regulatory networks. The first control input is the control input satisfying the above assumption. The second control input is called here a weak control input, and dynamics i.e. Boolean functions are selected among the candidates of dynamics. For example, activation/inactivation of the whole network is controlled by the weak control input. In order to solve the optimal control problem, two approaches, i.e., an integer programming approach and a polynomial optimization approach are proposed.**

I. INTRODUCTION

During the last decade, there have been a lot of studies on modeling, analysis, and control of gene regulatory networks in the field of systems biology. Then it is appropriate to use a simple model, and various models such as Petri nets, Bayesian networks, Boolean networks, and hybrid systems have been developed so far. In control problems, Boolean networks and hybrid systems are frequently used [1], [2]. However, in the hybrid systems approach, a class of networks is limited to low-dimensional systems, because the computation time to solve the problem is too long.

In Boolean networks, dynamics such as interactions between genes are expressed by a set of Boolean functions [8]. Although there is a weakness that a Boolean network is too simple as a model of gene regulatory networks, this model can be applied to large-scale systems, and has been extensively studied. 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 [11]. Furthermore, a context-sensitive PBN (CS-PBN) in which the deciding time is randomly selected has been proposed as a general form of PBNs [7], [10]. For PBNs and CS-PBNs, the control methods have been developed so far [6], [7], [9], [10]. In these methods, the control input is given by the concentration level of a part of genes, that is, we assume that the concentration level of a part of genes can be arbitrarily determined. However, there exist cases such that this assumption is not satisfied, and it is suitable to suppose that weak control exists. As an example of the weak control methods, we point out that the whole network is activated/inactivated by an external stimulus. Also in CS-PBNs, activation/inactivation of the whole network is indirectly controlled by suitably selecting the probability of forcing a switch of Boolean functions [7], but finding the optimal probability is not easy. So a direct method is desirable from the practical viewpoint.

In this paper, first, a Boolean network with two types of the control inputs is proposed as a model of gene regulatory networks. The first control input is the control input satisfying the assumption that the binary value is arbitrarily determined. The second control input is called here a weak control input, and dynamics i.e. Boolean functions are selected among the candidates of dynamics. In addition, success/failure of switching of the binary value and Boolean functions is modeled as the probabilistic behavior. So Boolean networks with two types of the control inputs are modeled by PBNs.

Next, for Boolean networks with two types of the control inputs, solution methods of two optimal control problems is proposed. In existing solution methods 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. Transition probability matrices cannot be computed in MATLAB, even if the case of $n = 15$ (this size will be small-scale in gene regulatory networks). So the use of transition probability matrices is a crucial weakness, and is inconvenient for users. To overcome this technical issue, we propose two approaches, i.e., an integer programming approach and a polynomial optimization approach. The former approach is an extension of optimal control methods proposed in [9], and the low bound of some non-negative function is minimized. This problem is reduced to an integer linear programming problem. In the latter approach, the expected value of some non-negative function is minimized, and this problem is reduced to a polynomial optimization problem. In two approaches, given Boolean functions expressing dynamics are directly used, and implementation is easy. The proposed approaches provide us practical control methods of gene regulatory networks.

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. Let I_n, $0_{m\times n}$ denote the $n \times n$ identity matrix, the $m \times n$ zero matrix, respectively. For simplicity, we sometimes use the symbol 0 instead of $0_{m\times n}$, and the symbol I instead of I_n. For a matrix M, $\ln M$ denotes the matrix such that the (i,j)-th element is given as the natural logarithm of the (i,j)-th element in M.

K. Kobayashi and K. Hiraishi are with the School of Information Science, Japan Advanced Institute of Science and Technology, Ishikawa, Japan {k-kobaya,hira}@jaist.ac.jp

II. Boolean Networks with Two Types of the Control Inputs

First, Boolean networks (BNs) are explained.

Consider the following BN:

$$x(k+1) = f_a(x(k)) \tag{1}$$

where $x \in \{0,1\}^n$ is the state (e.g., the concentration of genes), $k = 0, 1, 2, \ldots$ is the discrete time. $f_a : \{0,1\}^n \to \{0,1\}^n$ is a given Boolean function with logical operators such as AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). Since the BN (1) is deterministic, $x(k+1)$ is uniquely determined for a given $x(k)$.

For the BN (1), consider two types of control inputs. First, as the standard control method, the control input is added to the BN (1) as follows:

$$x(k+1) = f(x(k), u(k)) \tag{2}$$

where $u \in \{0,1\}^m$ is the control input, i.e., the value of u (e.g., the concentration of genes) can be arbitrarily given, and $f : \{0,1\}^n \times \{0,1\}^m \to \{0,1\}^n$ is a given Boolean function. The i-th element of the state x and the i-th element of the control input u are denoted by x_i and u_i, respectively. Also in the BN (2), $x(k+1)$ is uniquely determined for given $x(k)$ and $u(k)$. Furthermore, in control of gene regulatory networks, it may be difficult to arbitrarily give the value of u by the effects of noises and disturbances, and there is a possibility that switching of the value is failed. Considering this fact, the control input is given as follows:

$$u(k) = \begin{cases} u(k) & \text{with the probability } q_1, \\ u(k-1) & \text{with the probability } 1 - q_1 \end{cases} \tag{3}$$

where $q_1 \in [0,1]$.

Next, as a weak control method, we consider to switch the Boolean function f itself by some external stimuli. Suppose that the candidates of f are given as f_i, $i = 1, 2, \ldots, l$. Then it will be difficult to select one Boolean function uniquely. So in this paper, we assume that one discrete probability distribution is selected among m_w discrete probability distributions. By $r_{i,j}$, denote the probability that the Boolean function f_j is selected in the i-th discrete probability distribution. Then

$$\sum_{j=1}^{l} r_{i,j} = 1, \quad i = 1, 2, \ldots, m_w$$

hold. m_w-dimensional binary variables $u^w \in \{0,1\}^{m_w}$ are assigned to m_w discrete probability distributions, and by u_i^w denote the i-th element of u^w. u^w corresponds to m_w kinds of external stimuli. Then the following equality constraint

$$\sum_{i=1}^{m_w} u_i^w(k) = 1 \tag{4}$$

is imposed. Considering the effects of noises and disturbances, u^w is given as follows:

$$u^w(k) = \begin{cases} u^w(k) & \text{with the probability } q_2, \\ u^w(k-1) & \text{with the probability } 1 - q_2 \end{cases} \tag{5}$$

where $q_2 \in [0,1]$.

Example 1: As a simple example, consider the following Boolean network of an apoptosis network [5]:

$$\begin{cases} x_1(k+1) = \neg x_2(k) \wedge u(k), \\ x_2(k+1) = \neg x_1(k) \wedge x_3(k), \\ x_3(k+1) = x_2(k) \vee u(k) \end{cases} \tag{6}$$

where the concentration level (high or low) of the inhibitor of apoptosis proteins (IAP) is denoted by x_1, the concentration level of the active caspase 3 (C3a) by x_2, and the concentration level of the active caspase 8 (C8a) by x_3. The concentration level of the tumor necrosis factor (TNF, a stimulus) is denoted by u, and is regarded as the control input.

Suppose that $l = 2$ and $m_w = 2$. Then as an example of the candidates of Boolean functions, we can consider

$$f_1 = \begin{bmatrix} \neg x_2(k) \wedge u(k) \\ \neg x_1(k) \wedge x_3(k) \\ x_2(k) \vee u(k) \end{bmatrix}, \quad r_{1,1} = 0.8, \quad r_{2,1} = 0.1, \tag{7}$$

$$f_2 = \begin{bmatrix} x_1(k) \\ x_2(k) \\ x_3(k) \end{bmatrix}, \quad r_{1,2} = 0.2, \quad r_{2,2} = 0.9. \tag{8}$$

We suppose that the Boolean function f_1 expresses the situation that time evolution is activated, and the Boolean function f_2 expresses the situation that time evolution is inactivated. In addition, two discrete probability distributions $\{r_{1,1}, r_{1,2}\}$ and $\{r_{2,1}, r_{2,2}\}$ are selected at each time by using u_1^h and u_2^h. For example, suppose that $\{r_{1,1}, r_{1,2}\}$ is selected at time 0. Then at time 1, either $\{r_{1,1}, r_{1,2}\}$ or $\{r_{2,1}, r_{2,2}\}$ is selected with the probability q_2. Otherwise, the distribution is not changed with the probability $1-q_2$, that is, this implies that switching is failed. ■

Since BNs with two types of the control inputs include the probabilistic behavior, these are generalized to probabilistic Boolean networks (PBNs). However, in the existing solution methods for optimal control of PBNs, it is necessary to compute state transition diagrams with 2^n nodes (n is the number of the state). Thus the existing method cannot be applied to large-scale systems, and is inconvenient for users. So a new solution method is required. In this paper, for BNs with two types of the control inputs, two approaches to optimal control are proposed. One of them is called an integer programming approach. The other is called a polynomial optimization approach. These methods provide us new solution methods, in which state transition diagrams are not computed.

Remark 1: By adding the candidates of Boolean functions, BNs with two types of the control inputs can be transformed into BNs with only the weak control input. That is, the control input u can be eliminated from (2) by fixing the value of u in (2). Then, noting (3), by using at most $2^{m+1}l$ candidates of Boolean functions, Boolean networks with only the weak control input can be derived. However, since this transformation is hard for users, we consider two types of the control inputs.

III. Integer Programming Approach

In this section, we propose an integer programming approach to optimal control of Boolean networks with two types of the control inputs. First, the problem considered in this section is given. Next, after some preparations, we propose a solution method.

A. Problem Formulation

First, the following two notations are defined. By $\pi_i(k)$, denote the probability that some Boolean function f_i is selected at time k. In addition, the probability that some sequence of Boolean functions $f_{i(k_1)}, f_{i(k_1+1)}, \ldots, f_{i(k_2)}$ is selected at time interval $[k_1, k_2]$ is denoted by

$$\pi(k_1, k_2) := \prod_{k=k_1}^{k_2} \pi_{i(k)}(k).$$

For simplicity of notation, $i(k_1), i(k_1+1), \ldots, i(k_2)$ are omitted in $\pi(k_1, k_2)$.

Next, for Boolean networks with two types of the control inputs, consider the following optimal control problem.

Problem 1: Suppose that for the Boolean network with two types of the control inputs, the initial state $x(0) = x_0$, the control inputs $u(-1)$, $u^w(-1)$, ρ satisfying $0 \leq \rho \leq 1$, and the control time N are given. Then for all combinations of Boolean functions satisfying the following constraint

$$\pi(0, N-1) \geq \rho, \tag{9}$$

find two control input sequences $u(0), u(1), \ldots, u(N-1)$ and $u^w(0), u^w(1), \ldots, u^w(N-1)$ minimizing the lower bound of the cost function

$$J = \sum_{i=0}^{N-1} \left\{ Qx(i) + R \begin{bmatrix} u(i) \\ u^w(i) \end{bmatrix} \right\} + Q_f x(N) \tag{10}$$

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

For simplicity of discussion, a linear function with respect to x and u is considered as a cost function, but a quadratic cost function may be used. In addition, using the offset vector $x_d \in \{0,1\}^n$, $x(i)$ may be replaced to $\hat{x}(i) := x(i) - x_d$. Then it is necessary that the cost function (10) is also replaced to $J = \sum_{i=0}^{N-1} \{Q|\hat{x}(i)| + Ru(i)\} + Q_f|\hat{x}(N)|$. Furthermore, in control of stochastic systems, the expected value of some non-negative function is frequently used as a cost function. In this section, we evaluate the control performance by using the lower bound.

If the constraint (9) is not included in Problem 1, then the behaviors is regarded as uncertain (nondeterministic) behaviors, and the best performance is derived in Problem 1. However, since combinations of Boolean functions selected with low probability are included, performance evaluation is not appropriate. So in order to exclude such combinations, we impose the constraint (9). See Section V-B for a method for deciding ρ. Similar problem formulations have been considered in optimal control of stochastic hybrid systems (see e.g. [3]).

We show an example for setting weighting vectors from the biological viewpoint.

Example 2: Consider the Boolean network expressing an apoptosis network in Example 1 again. For this system, we consider to find a control strategy such that a stimulus u is not applied as much as possible, and cell survival is achieved. $u = 0$ implies that a stimulus is not applied to the system, and $x_1 = 1$, $x_2 = 0$ express cell survival [5]. Then as one of appropriate cost functions, we can consider the following cost function

$$\begin{aligned} J = \sum_{i=0}^{N-1} \{10|x_1(i) - 1| + 10|x_2(i) - 0| + u(i)\} \\ +100|x_1(N) - 1| + 100|x_2(N) - 0|. \end{aligned}$$

By the coordinate transformation from x_1 to $x_1 - 1$, this cost function can be rewritten as the form of (10).

B. Proposed Solution Method

Consider reducing Problem 1 to an integer linear programming (ILP) problem.

First, to express success/failure of switching of the weak control input u^w, the following relation is introduced:

$$\delta^w(k) = \delta^s(k)u^w(k) + (1 - \delta^s(k))u^w(k-1) \tag{11}$$

where $\delta^w \in \{0,1\}^{m_w}$ and $\delta^s \in \{0,1\}^1$. $\delta^s = 1$ corresponds to success of switching, and $\delta^s = 0$ corresponds to failure of switching. From (11), we see that δ^w corresponds to the weak control input. Success/failure in the control input u can be expressed by adding the case of failure to the candidates of Boolean functions.

Next, by using the fact[1], the candidates of Boolean functions $f_i(x(k), u(k))$, $i = 1, 2, \ldots, l$ are transformed into a polynomial on the real number field. By $\hat{f}_i(x(k), u(k))$, denote the obtained polynomial. Then consider the following system using $\hat{f}_i(x(k), u(k))$:

$$x(k+1) = \sum_{i=1}^{l} \left\{ \delta_i(k) \hat{f}_i(x(k), u(k)) \right\} \tag{12}$$

where $\delta_1(k), \delta_2(k), \ldots, \delta_l(k)$ are binary variables satisfying

$$\sum_{i=1}^{l} \delta_i(k) = 1, \tag{13}$$

and $\delta(k) := [\ \delta_1(k) \quad \delta_2(k) \quad \cdots \quad \delta_l(k)\ ]^T$ is defined. δ is used to select the polynomial $\hat{f}_i$, and to express (9) as a linear form. Here, we define the following vector:

$$S_i := [\ r_{i,1} \quad r_{i,2} \quad \cdots \quad r_{i,l}\ ]. \tag{14}$$

[1]For two binary variables δ_1, δ_2, the following relations hold: (i) $\neg\delta_1$ is equivalent to $1 - \delta_1$, (ii) $\delta_1 \vee \delta_2$ is equivalent to $\delta_1 + \delta_2 - \delta_1\delta_2$, and (iii) $\delta_1 \wedge \delta_2$ is equivalent to $\delta_1\delta_2$.

Then by using the natural logarithm, $\pi(0, N-1)$ in (9) is expressed as

$$\begin{aligned}\ln \pi(0, N-1) &= \sum_{k=0}^{N-1} \left\{ \left(\sum_{i=1}^{m_w} \ln S_i \delta_i^w(k) \right) \delta(k) \right. \\ &\quad +(\ln q_2)\delta^s(k) \\ &\quad \left. +(\ln(1-q_2))(1-\delta^s(k)) \right\} \\ &=: \sum_{k=0}^{N-1} g(\delta^w(k), \delta^s(k), \delta(k)). \end{aligned} \tag{15}$$

In the case of $q_2 = 1$, from $\delta^s(k) = 1$ and $\ln 1 = 0$, we can derive

$$g(\delta^w(k), \delta^s(k), \delta(k)) = \left(\sum_{i=1}^{m_w} \ln S_i \delta_i^w(k) \right) \delta(k).$$

Then we obtain the following lemma.

Lemma 1: Problem 1 is equivalent to the following problem.

Problem A:

$$\begin{aligned} \text{find} \quad & u(k), u^w(k), \delta^w(k), \delta^s(k), \delta(k), \\ & k = 0, 1, \ldots, N-1 \\ \min \quad & \text{Cost function (10)} \\ \text{subject to} \quad & \text{System (12), } x(0) = x_0, \\ & \text{Inequality constraint:} \\ & \sum_{k=0}^{N-1} g(\delta^w(k), \delta^s(k), \delta(k)) \geq \ln \rho, \\ & \text{Equality constraint (4), (11), (13).} \end{aligned}$$

By using the result[2] in [4], the system (12), $g(\delta^w(k), \delta^s(k), \delta(k))$ and (11) can be equivalently expressed as the following linear form:

$$x(k+1) = Ax(k) + B_1\hat{\delta}(k) + B_2 z(k), \tag{16}$$

$$g(\delta^w(k), \delta^s(k), \delta(k)) = C_1\hat{\delta}(k) + C_2 z(k), \tag{17}$$

$$\delta^w(k) = Dz(k) + u^w(k-1), \tag{18}$$

$$Ex(k) + F_1\hat{\delta}(k) + F_2 z(k) \leq G \tag{19}$$

where (19) is the linear inequality obtained by applying the result in [4] to (12), $g(\delta^w(k), \delta^s(k), \delta(k))$ and (11). In addition, $\hat{\delta}(k) := [\ u(k)\ u^w(k)\ \delta^w(k)\ \delta^s(k)\ \delta(k)\ ]^T \in \{0,1\}^{m+m_w+m_w+1+l}$, and $z(k) \in \{0,1\}^p$ is an auxiliary binary variable. p is determined depending on the form of given Boolean functions.

By using (16), (17), (18) and (19), we obtain the following theorem straightforwardly.

Theorem 1: Problem A is equivalent to the ILP problem with $(m + 2m_w + l + p + 1)N$ decision variables. ■

Problem B can be solved by a suitable solver such as CPLEX [14].

[2]For binary variables $\delta_1, \delta_2, \ldots, \delta_n \in \{0,1\}$, the product $z = \delta_1\delta_2\cdots\delta_n$ is equivalent to a pair of $\sum_{i=1}^n \delta_i - z \leq n-1$ and $-\sum_{i=1}^n \delta_i + nz \leq 0$.

IV. Polynomial Optimization Approach

In this section, as the second approach, we propose a polynomial optimization approach. In this approach, we can give the expected value of some non-negative function as a cost function. First, the problem considered in this section is given. Next, we show a simple example, Finally, after preparations, we propose a solution method.

A. Problem Formulation

Consider the following optimal control problem.

Problem 2: Suppose that for the Boolean network with two types of the control inputs, the initial state $x(0) = x_0$, the control inputs $u(-1)$, $u^w(-1)$, and the control time N are given. Then find two control input sequences $u(0), u(1), \ldots, u(N-1)$ and $u^w(0), u^w(1), \ldots, u^w(N-1)$ minimizing the cost function

$$J = E\left[\sum_{i=0}^{N-1} \left\{ Qx(i) + R \begin{bmatrix} u(i) \\ u^w(i) \end{bmatrix} \right\} + Q_f x(N) \;\middle|\; x(0) = x_0 \right] \tag{20}$$

where $Q, Q_f \in \mathcal{R}^{1\times n}$, $R \in \mathcal{R}^{1\times(m+m_w)}$ are weighting vectors whose element is a non-negative real number, and $E[\cdot|\cdot]$ denotes a conditional expected value.

Hereafter, for simplicity of notation, the condition $x(0) = x_0$ in (20) is omitted.

B. Proposed Solution Method

First, from the standard result in probability theory, we obtain the following lemma immediately.

Lemma 2: Suppose that for n-dimensional binary random variable $x \in \{0,1\}^n$, the Boolean function $g(x)$, $g : \{0,1\}^n \to \{0,1\}^1$ is given, and the probability $P(x_i = 1)$ that the i-th element of x is equal to 1 is given. Define $\hat{x} := [\ P(x_1 = 1)\ \ P(x_2 = 1)\ \ \cdots\ \ P(x_n = 1)\ ]^T \in [0,1]^n$. Then the probability that $g(x)$ is equal to 1 is obtained by

$$P(g(x) = 1) = \hat{g}(\hat{x})$$

where $\hat{g}$ denotes the polynomial corresponding to g.

Note that from $g(x) \in \{0,1\}$, $E[g(x)] = P(g(x) = 1)$ holds. Using Lemma 2, consider to express the expected value of the state $E[x(k)]$. Some preparations are given. By $\hat{f}_i$, denote the polynomial corresponding to the candidate f_i of a Boolean function. By using S_i of (14), define

$$S(k) := \sum_{i=1}^{m_w} u_i^w(k) S_i \in [0,1]^{1\times l}.$$

Then the expected value of $S(k)$ is derived as

$$E[S(k)] = \sum_{i=1}^{m_w} E[u_i^w(k)] S_i.$$

In addition, the expected value of u is given as

$$E[u(k)] = q_1 u(k) + (1-q_1)u(k-1).$$

Then we obtain the following theorem.

Theorem 2: Suppose that for the Boolean network with two types of the control inputs, the initial state $x(0) = x_0$ is given. Then the expected value of the state, $E[x(k)]$ is expressed as the following polynomial system

$$E[x(k+1)] = \sum_{i=1}^{l} E[S^{(i)}(k)]\hat{f}_i(E[x(k)], E[u(k)]) \quad (21)$$

where $E[S^{(i)}(k)]$ denotes the i-th element of $E[S(k)]$.

Proof: First, consider the case of $k = 0$. Since each element of $E[u(0)]$ expresses the probability that each element of $u(0)$ is equal to 1, $\hat{f}_i(x_0, E[u(0)])$ implies the probability that each element of $\hat{f}_i(x_0, E[u(0)])$ is equal to 1. Then $E[x(1)]$ is derived as a weighted sum of $\hat{f}_i(x_0, E[u(0)])$, $i = 1, 2, \ldots, l$ using $E[S^{(i)}(k)]$, i.e.,

$$E[x(1)] = \sum_{i=1}^{l} E[S^{(i)}(0)]\hat{f}_i(x_0, E[u(0)]).$$

Next, consider the case of $k = 1$. Noting $P(x_i(1) = 1) = E[x_i(1)]$, from Lemma 2 we obtain

$$E[x(2)] = \sum_{i=1}^{l} E[S^{(i)}(1)]\hat{f}_i(E[x(1)], E[u(1)]).$$

By recursively repeating the above procedure, we obtain (21). ■

Sine $\hat{f}_j^{(i)}$ is a polynomial, the right-hand side of (21) is also a polynomial. Therefore, from Theorem 2, we see that the expected value $E[x(k)]$ of the state is expressed as a polynomial system.

Finally, consider reducing Problem 2 to a polynomial optimization problem. Then by using (21) in Theorem 2, we obtain the following result.

Theorem 3: Problem 2 is equivalent to the following polynomial optimization problem.

Problem C:

$$\begin{aligned} \text{find} \quad & E[x(k+1)] \in \mathcal{R}^n, \quad u(k) \in \mathcal{R}^m, \\ & u^w(k) \in \mathcal{R}^{m_w}, \quad k = 0, 1, \ldots, N-1 \\ \min \quad & \text{Cost function (20)} \\ \text{subject to} \quad & \text{System (21)}, \\ & u_i(k)(u_i(k)-1) = 0, \quad u_i^w(k)(u_i^w(k)-1) = 0. \end{aligned}$$

Since $E[x(k+1)] \in [0,1]^n$ is satisfied automatically from Theorem 2, we set $E[x(k+1)] \in \mathcal{R}^n$ in Problem C. In addition, by solving (21), $E[x(k+1)]$ can be eliminated from decision variables in Problem C. However, implementation makes easy by directly using (21). So $E[x(k+1)]$ is regarded as a decision variable.

The constraints $u_i(k)(u_i(k)-1) = 0$ and $u_i^w(k)(u_i^w(k)-1) = 0$ guarantee that $u(k)$ and $u^w(k)$ are binary variables. However, these constraints are non-convex, and the existence of these is one of the reason why the computation time to solve the problem is long. In a practical manner, instead of these non-convex constraints, it will be desirable to use the relaxed constraints $0 \le u_i(k) \le 1$ and $0 \le u_i^w(k) \le 1$.

V. Numerical Examples

A. WNT5A Network

Consider a gene regulatory network with the gene WNT5A, which is related to melanoma. The BN $x(k+1) = f_a(x(k))$ is given by $x_1(k+1) = \neg x_6(k)$, $x_2(k+1) = (\neg x_2(k) \wedge x_4(k) \wedge x_6(k)) \vee \{\neg x_2(k) \wedge (x_4(k) \vee x_6(k))\}$, $x_3(k+1) = \neg x_7(k)$, $x_4(k+1) = x_4(k)$, $x_5(k+1) = x_2(k) \vee \neg x_7(k)$, $x_6(k+1) = x_3(k) \vee x_4(k)$, and $x_7(k+1) = \neg x_2(k) \vee x_7(k)$, 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 [13] for further details.

In a WNT5A network, it important to inhibit the concentration level of the gene WNT5A [12]. We apply the proposed two approaches to control of a WNT5A network.

B. Integer Programming Approach

First, consider to apply the proposed integer programming approach. For simplicity, only the weak control input is considered. Then suppose that the number of the weak control inputs is two. If $u_1^w(k) = 1$, then $x(k+1) = f_a(x(k))$ with the probability 0.8 and $x_i(k+1) = x_i(k)$, $i = 1, 2, \ldots, 7$ with the probability 0.2 are selected. If $u_2^w(k) = 1$, then $x(k+1) = f_a(x(k))$ with the probability 0.1 and $x_i(k+1) = x_i(k)$, $i = 1, 2, \ldots, 7$ with the probability 0.9 are selected. The case of $u_1^w(k) = 1$ corresponds to the situation such that the behavior of a WNT5A network is activated. The case of $u_2^w(k) = 1$ corresponds to the situation such that the behavior of a WNT5A network is inactivated. From the above, $n = 7$, $m = 0$, $m_w = 2$, $l = 2$, and $r_{1,1} = 0.8$, $r_{1,2} = 0.2$, $r_{2,1} = 0.1$, $r_{2,2} = 0.9$. In addition, we set $q_2 = 1$. Since $\delta^s(k) = 1$ holds, $\delta^w(k) = u^w(k)$ is obtained from (11).

For this WNT5A network, consider solving Problem 1. Q, Q_f, R in Problem 1 is given as $Q = [\,1\ 0\ 0\ 0\ 0\ 0\ 0\,]$, $Q_f = [\,10\ 0\ 0\ 0\ 0\ 0\ 0\,]$, $R = [\,0\ 0\,]$, respectively. The initial state is given as $x_0 = [\,1\ 0\ 1\ 0\ 1\ 0\ 0\,]^T$. Then the number of decision variables in Problem B is $26N$. In this example, we set $N = 5$.

Next, we show the computation results. By $\underline{J}^*$, denote the optimal value of the lower bound of a given cost function in Problem 1. By $\overline{J}^*$, denote the upper bound of the cost function derived by using the optimal control input. First, consider the case of $\rho = 10^{-5}$. Then we can obtain $\underline{J}^* = 2$ and $\overline{J}^* = 15$. Since $u^w(k)$ is obtained as

$$u^w(0) = \begin{bmatrix} 0 \\ 1 \end{bmatrix}, \quad u^w(1) = \cdots = u^w(4) = \begin{bmatrix} 1 \\ 0 \end{bmatrix},$$

we see that the system is controlled by switching two discrete probability distributions. However, noting that $r_{2,1} = 0.1$ and $\rho = 10^{-5} (= (0.1)^5)$, all combinations of Boolean functions are considered, and the value of ρ is not appropriate. In

particular, $\overline{J}^* = 15$ implies $x_1(k) = 1$, $k = 0, 1, \ldots, 5$, and is the trivial upper bound.

Next, consider the case of $\rho = 0.1$. Then we can obtain $\underline{J}^* = 2$ and $\overline{J}^* = 5$. $u^w(k)$ is obtained as

$$u^w(0) = u^w(1) = u^w(4) = \begin{bmatrix} 1 \\ 0 \end{bmatrix},$$
$$u^w(2) = u^w(3) = \begin{bmatrix} 0 \\ 1 \end{bmatrix}.$$

Noting that the trivial value of $\overline{J}^*$ is 15, we see that in this case the effectiveness of control synthesis is clear.

Finally, we discuss the computation time to solve the problem. In this example, two kinds of ILP problems are solved. The computation times of these ILP problems were less than 20 [msec], where we used ILOG CPLEX 11.0 as an ILP solver on the computer with the Intel Core 2 Duo CPU 3.0GHz and the 4GB memory.

C. Polynomial Optimization Approach

Next, consider to apply the proposed polynomial optimization approach. For simplicity, the weak control input is not considered. In the BN model of a WNT5A network, the control input u is given by x_2 (the concentration level of the gene pirin), according to discussion on [6]. Then we obtain the following BN model:

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

In this example, suppose that one discrete probability distribution is given. The probabilistic behavior is given by

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

Then $l = 2^6 = 64$ holds, and one discrete probability distribution is determined. In addition, q_1 in (3) is given as $q_1 = 0.8$.

For this WNT5A network, consider solving Problem 2. Q, Q_f, R in Problem 1 is given as $Q = [\ 1\ \ 0\ \ 0\ \ 0\ \ 0\ \ 0\ ]$, $Q_f = [\ 10\ \ 0\ \ 0\ \ 0\ \ 0\ \ 0\ ]$, $R = 1$, respectively. The initial state and $u(-1)$ are given as $x_0 = [\ 1\ \ 1\ \ 0\ \ 1\ \ 0\ \ 0\ ]^T$ and $u(-1) = 1$, respectively. In this example, we set $N = 5$.

Next, we show the computation results. By solving Problem 2, 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

$$\begin{aligned}
E[x(1)] &= [\ 1\ \ 1\ \ 0\ \ 1\ \ 0.8\ \ 0\ ]^T, \\
E[x(2)] &= [\ 0.36\ \ 1\ \ 0\ \ 1\ \ 0.96\ \ 0\ ]^T, \\
E[x(3)] &= [\ 0.104\ \ 1\ \ 0\ \ 1\ \ 0.992\ \ 0.64\ ]^T, \\
E[x(4)] &= [\ 0.027\ \ 0.488\ \ 0\ \ 0.488\ \ 0.998\ \ 0.928\ ]^T, \\
E[x(5)] &= [\ 0.007\ \ 0.155\ \ 0\ \ 0.155\ \ 0.590\ \ 0.986\ ]^T.
\end{aligned}$$

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 2.86 [sec], where we used SparsePOP [15]. For large-scale networks, it will be necessary to consider an approximate solution method.

VI. Conclusion

In this paper, we have proposed a Boolean network with two types of the control inputs. This model can express several situations in control of gene regulatory networks. Furthermore, two approaches to optimal control have been proposed. In the polynomial optimization approach, the expected value of the state can be computed. The integer programming approach is suitable for control of large-scale gene regulatory networks. It is desirable to select one of the two approaches according to a given gene regulatory network.

One of the future works is to apply our approach to several biological systems. Also, it is important to consider to decrease the computation time for solving problems.

This work was supported by Grant-in-Aid for Young Scientists (B) 23760387 and Scientific Research (C) 21500009.

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