Optimal Control of Asynchronous Boolean Networks Modeled Petri Nets

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Background

Systems biology is a new field in biology
that aims at system-level understanding of biological systems.

One of the significant topics is
modeling, analysis, and control of gene regulatory networks.

Gene Regulatory Networks

→ Ordinary/partial differential equations with high nonlinearity and high dimensionality

→ Various simpler models have been proposed.

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In the control problem,
Boolean networks and hybrid systems are used
as a model of gene regulatory networks.

Models of Gene Regulatory Networks

1. Hybrid systems:

Drawback: Plants are limited to only the low-dimensional systems.

e.g., [Azuma *et al.* 2008], [Belta *et al.* 2001]

2. Probabilistic/Deterministic Boolean networks (BNs) :

(1) The state is given by binary variables.

(2) The transition rules are given by Boolean functions. [Kauffman 1969]

Drawback: This model is too simple.

Advantage: This model can be applied to large-scale systems.

In this research, Boolean networks are used.

Existing Works in Control of Boolean Networks

Deterministic BNs: [Kauffman 1969]

1) Controllability analysis [Akutsu *et al*. 2007],
[Kobayashi, Imura, and Hiraishi 2009]

2) Use of a model checking tool [Langmead *et al*. 2009]

Probabilistic BNs (PBNs): [Shmulevich *et al*. 2002]

1) Optimal control [Datta *et al*. 2003], [Datta *et al*. 2004], [Pal *et al*. 2006]
[Kobayashi and Hiraishi 2011]
Automatica Special Issue on Systems Biology

2) Approximate algorithm [Akutsu *et al*. 2009]

3) Extension to context-sensitive PBNs [Pal *et al*. 2005]

Purpose of Our Research

1) It is important to consider the asynchronous behavior.
2) In probabilistic BNs, the asynchronous behavior is indirectly considered.

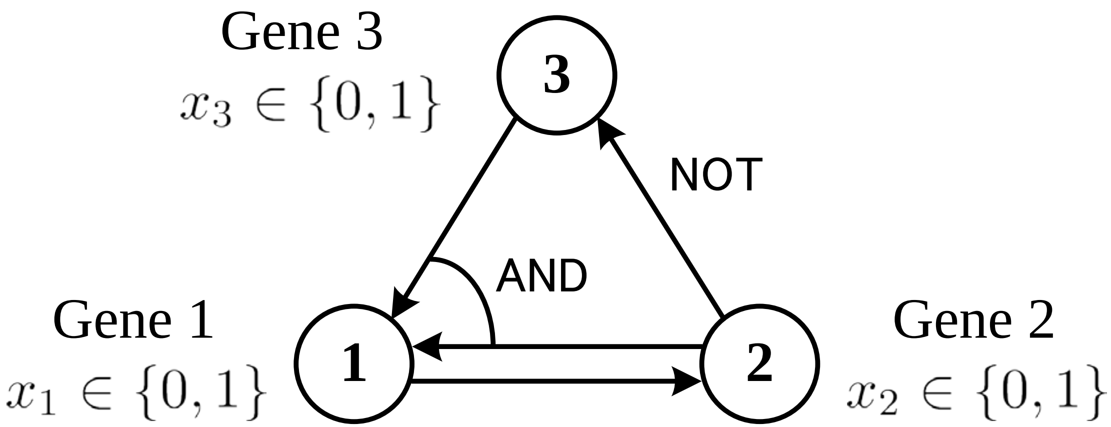
In this talk, as a direct approach, we propose

1) Petri net-based modeling, Extension of the result in [Chaouiya *et al*. ATPN2004]
2) Reduction of the optimal control problem to an integer programming problem.

Outline of This Presentation

1. Asynchronous Boolean Networks
2. Petri Net-Based Modeling
3. Optimal Control Problem
4. Numerical example

Example of Synchronous Boolean Networks



$$\begin{cases} x_1(k+1) = x_2(k) \wedge x_3(k) \\ x_2(k+1) = x_1(k) \\ x_3(k+1) = \neg x_2(k) \end{cases} \quad k = 0, 1, 2, \ldots$$

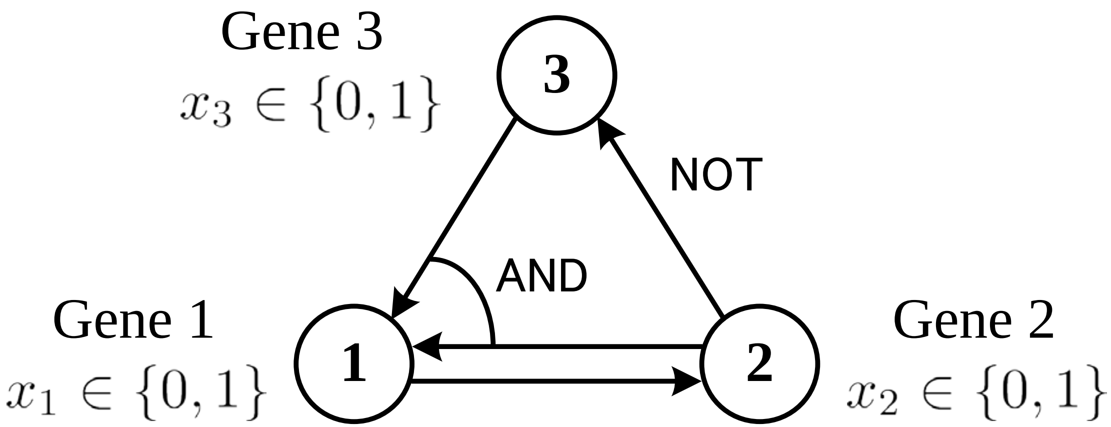
: discrete time

<u>Logical Operations</u>: $\wedge$: AND

$\vee$: OR

$\neg$: NOT

Example of Synchronous Boolean Networks



$$\begin{cases} x_1(k+1) = x_2(k) \wedge x_3(k) \\ x_2(k+1) = x_1(k) \\ x_3(k+1) = \neg x_2(k) \quad k = 0, 1, 2, \ldots \end{cases}$$

$$\begin{bmatrix} x_1(k) \\ x_2(k) \\ x_3(k) \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} \quad \rightarrow \quad \begin{bmatrix} x_1(k+1) \\ x_2(k+1) \\ x_3(k+1) \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix}$$

Existing Modeling of Asynchronous Boolean Networks

In [Tournier & Chaves 2009] and so on, ABNs are regarded as nondeterministic systems.

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

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

$$x(k+1) = \begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix} \qquad \begin{cases} x_1(k+1) = x_1(k) \\ x_2(k+1) = x_2(k) \\ x_3(k+1) = \neg x_2(k) \end{cases}$$

Given: $x(k) = \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix}$ $\qquad x(k+1) = \left\{ \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}, \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} \right\}$

All combinations are not considered.

Intuitive Method

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

⇓

1) 8 systems are derived.
2) By using 7 binary variables, the current system is selected among 8 systems.

For *n* genes, 2^n -1 binary variables are needed.

Multi-timescale dynamics can be represented.

[Faryabi *et al*. 2008]

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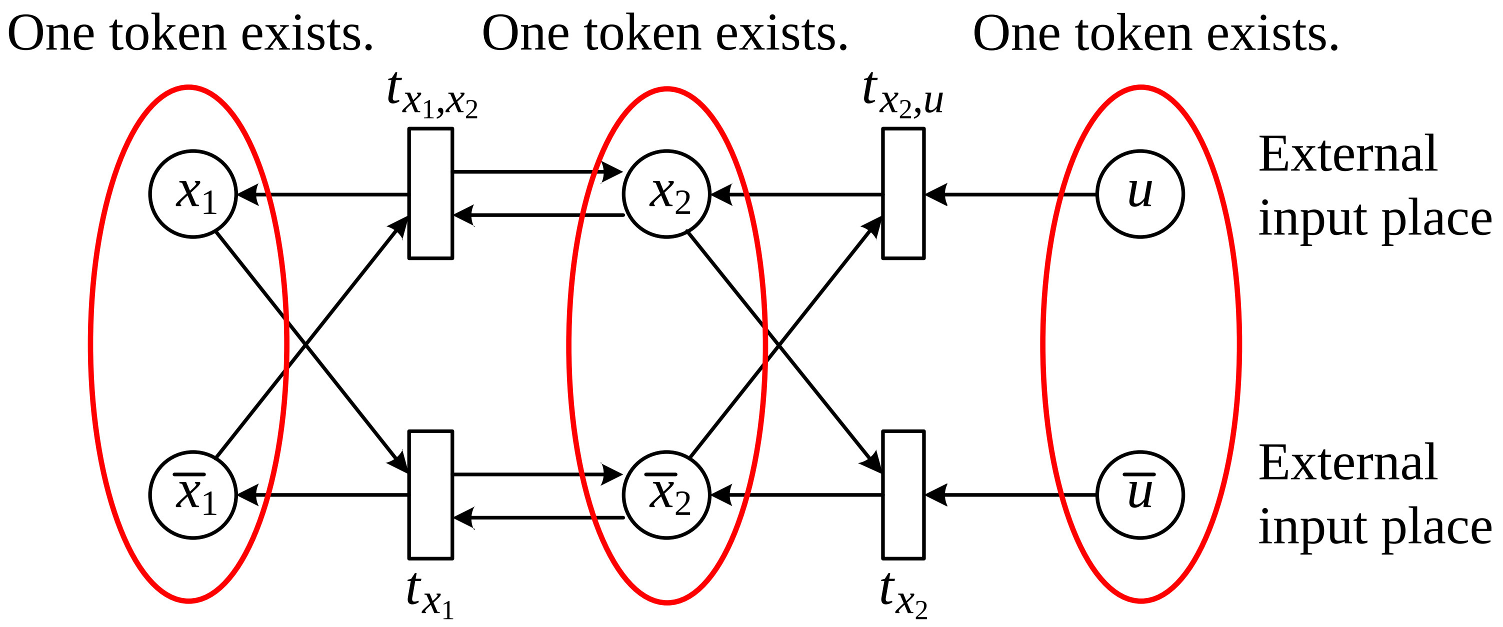
Simple Example

$$\begin{cases} x_1(k+1) = x_2(k), \\ x_2(k+1) = u(k) \end{cases}$$

State

Control input.
The value can be arbitrarily determined.

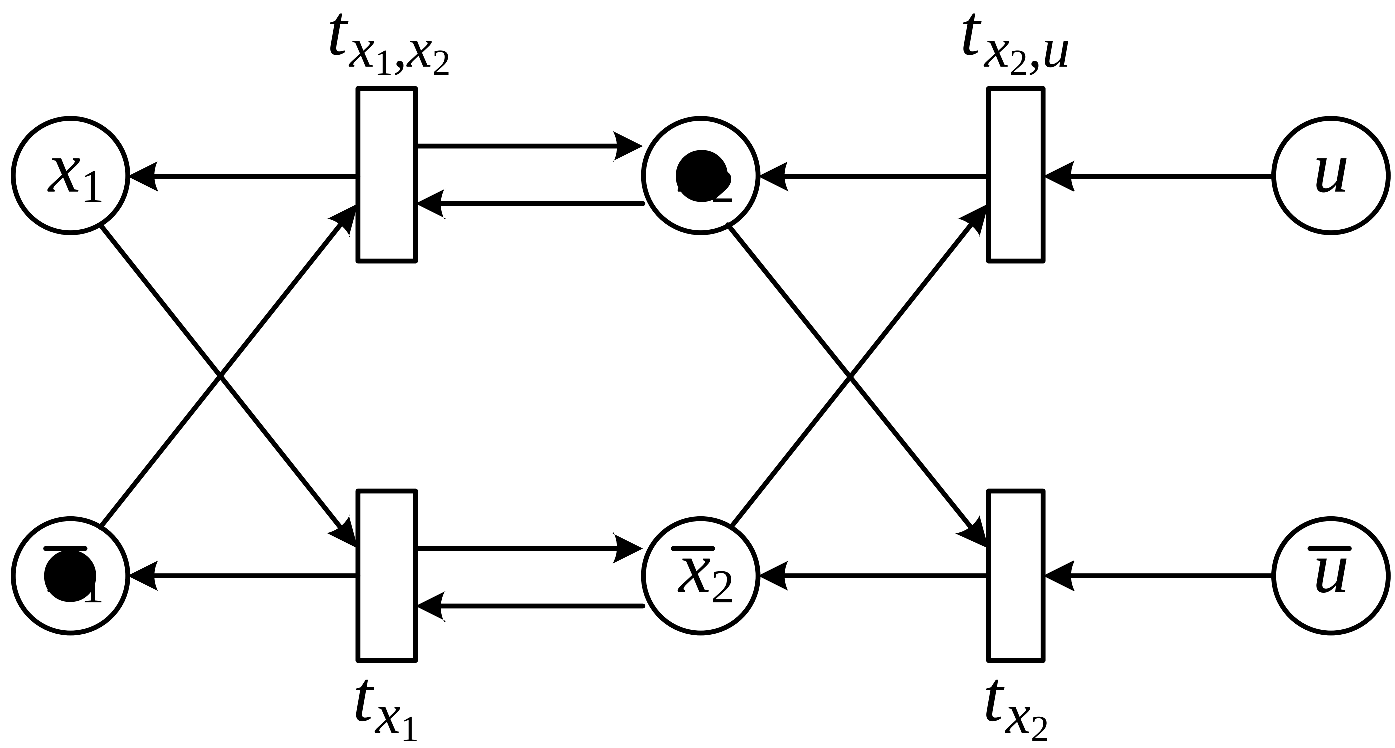


One token exists in the place $x_i \rightarrow x_i = 1$

One token exists in the place $\bar{x}_i \rightarrow x_i = 0$

Simple Example

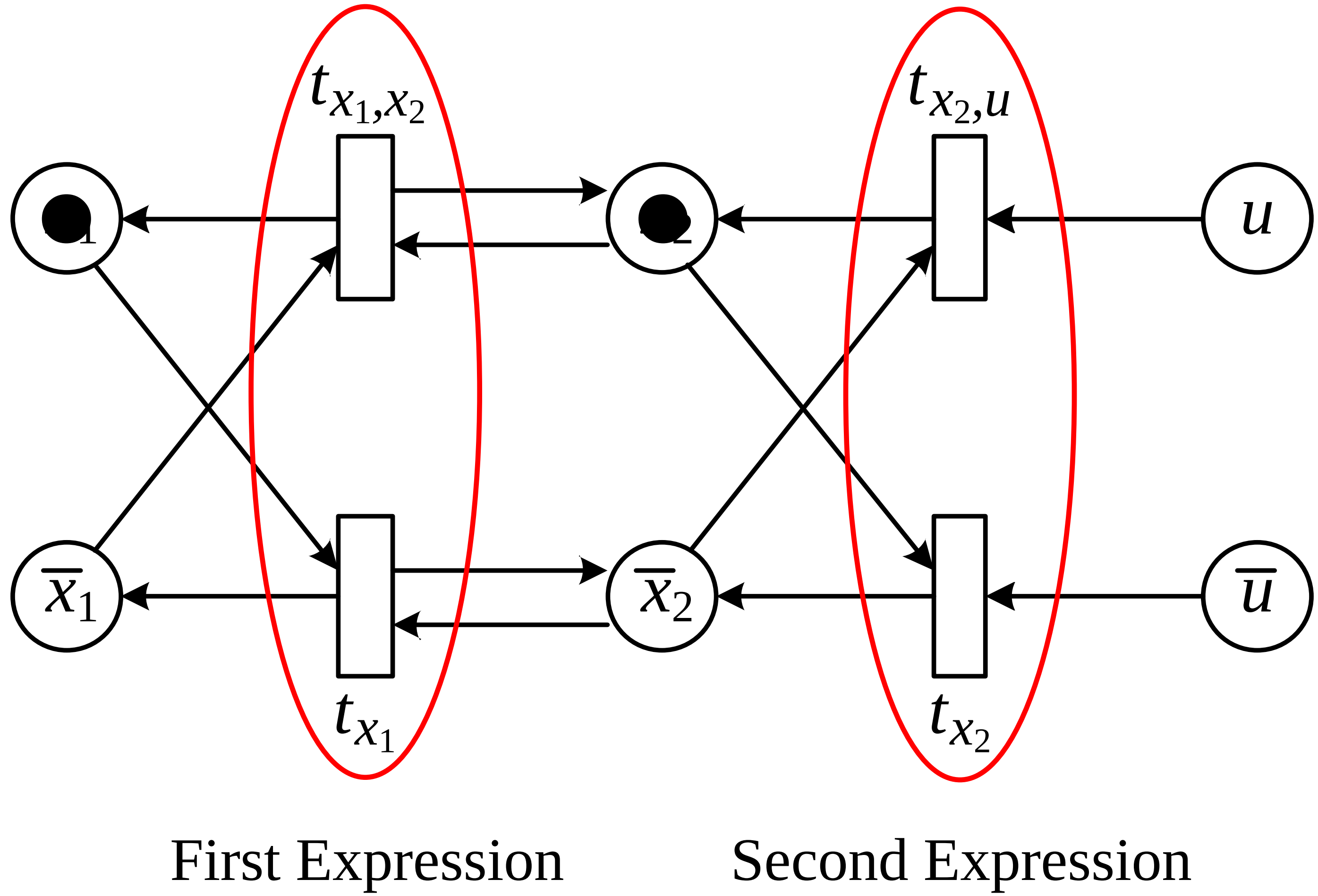
$$\begin{cases} x_1(k+1) = x_2(k), \\ x_2(k+1) = u(k) \end{cases} \qquad \begin{bmatrix} x_1(k) \\ x_2(k) \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$



The transition t_{x_1,x_2} may fire.

Simple Example

$$\begin{cases} x_1(k+1) = x_2(k), \\ x_2(k+1) = u(k) \end{cases} \qquad \begin{bmatrix} x_1(k+1) \\ x_2(k+1) \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \end{bmatrix}$$



Outline of The Proposed Modeling Method

$$x(k+1) = f(x(k), u(k)),\ \ x \in \{0,1\}^n,\ \ u \in \{0,1\}^m$$

State Control input

The proposed modeling method is an extension of the method in [Chaouiya *et al*. ATPN 2004] using the complementary-place transformation.

Places:

1) The number of places is 2(*n*+*m*)

   i.e., $x_1, \bar{x}_1, \ldots, x_n, \bar{x}_n, u_1, \bar{u}_1, \ldots, u_m, \bar{u}_m.$

2) A sum of tokens in $x_i(u_i), \bar{x}_i(\bar{u}_i)$ is 1.

Transitions:

1) The number of transitions depends on the number of arguments in each element of Boolean functions.

Simple Example

$$\mathcal{I}(1) = \{x_2, x_3\}, \ |\mathcal{I}(1)| = 2$$

4 combinations

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

2 combinations

2 combinations

$$\mathcal{I}(2) = \{x_1\}, \ |\mathcal{I}(2)| = 1$$

$$\mathcal{I}(3) = \{x_2\}, \ |\mathcal{I}(3)| = 1$$

8 transitions are needed.

Discussion on The Number of Transitions

Intuitive Method:

For n genes, 2^n -1 binary variables are needed.

→ The number of transitions is also given by 2^n -1.

Petri Net-Based Modeling:

The number of transitions is given by $\sum_{i=1}^{n} 2^{|\mathcal{I}(i)|}$.

In gene regulatory networks, $|\mathcal{I}(i)| \ll n$ holds.

Example: for $n = 10, \; |\mathcal{I}(i)| = 3$

$$2^n - 1 = 1023, \quad \sum_{i=1}^{n} 2^{|\mathcal{I}(i)|} = 80$$

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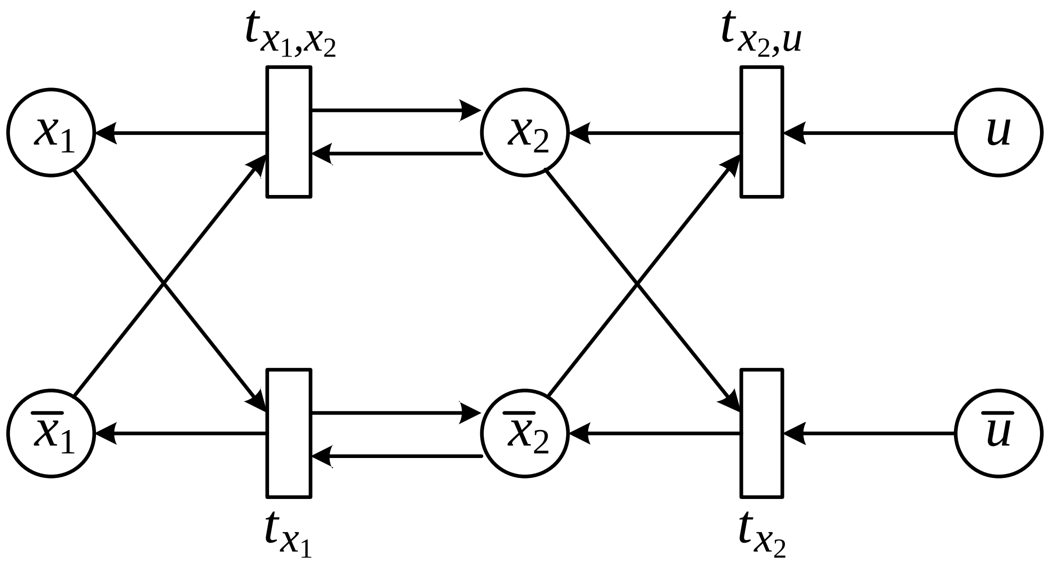
Transformation of Petri Nets



If the transition fires, then 1, otherwise 0.

If one token exists, then 1, otherwise 0.

$$x_1(k+1) = t_{x_1,x_2}(k)\bar{x}_1(k)x_2(k) + (1 - t_{x_1,x_2}(k))x_1(k)$$
$$-t_{x_1}(k)x_1(k)\bar{x}_2(k),$$

The dynamics on other states can expressed as a similar form.

Transformation of Petri Nets

If the transition fires, then 1, otherwise 0.

If one token exists, then 1, otherwise 0.

$$x_1(k+1) = t_{x_1,x_2}(k)\bar{x}_1(k)x_2(k) + (1 - t_{x_1,x_2}(k))x_1(k)$$
$$-t_{x_1}(k)x_1(k)\bar{x}_2(k),$$

$$z = \delta_1\delta_2\cdots\delta_n \;\Leftrightarrow\; \sum_{i=1}^{n}\delta_i - z \le n-1,\; -\sum_{i=1}^{n}\delta_i + nz \le 0$$

In addition, we impose $x_i(k) + \bar{x}_i(k) = 1,\; u_i(k) + \bar{u}(k) = 1.$

Linear Form: $\begin{cases} x(k+1) = Ax(k) + Bv(k) \\ Cx(k) + Dv(k) \le E \end{cases}$

$$x = [x_1 \;\bar{x}_1 \;\cdots\; x_n \;\bar{x}_n]^T \in \{0,1\}^{2n}$$

$$v = [u_1 \;\bar{u}_1 \;\cdots\; u_m \;\bar{u}_m \;\cdots]^T \in \{0,1\}^{2m+\alpha}$$

Optimal Control Problem

Linear Cost Function

find $v(k) \in \{0,1\}^{2m+\alpha},\ k = 0, 1, \ldots, N-1$

min $J = \sum_{k=0}^{N-1} \{Qx(k) + Ru(k)\} + Q_f x(N)$

subject to $\begin{cases} x(k+1) = Ax(k) + Bv(k) \\ Cx(k) + Dv(k) \leq E \end{cases}$

$$x = [x_1\ \bar{x}_1\ \cdots\ x_n\ \bar{x}_n]^T \in \{0,1\}^{2n}$$

$$v = [u_1\ \bar{u}_1\ \cdots\ u_m\ \bar{u}_m\ \cdots]^T \in \{0,1\}^{2m+\alpha}$$

This problem is equivalent to an integer linear programming problem.

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Gene Regulatory Network Related to Melanoma

[Xiao and Dougherty 2007]

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

x_1 : Expression of WNT5A

x_2 : Expression of S100P

x_3 : Expression of RET1

x_4 : Expression of MART1

x_5 : Expression of HADHB

x_6 : Expression of STC2

u : Expression of pirin

We obtain the Petri net with 14 places and 15 transitions.

Setting of Cost Function

$$x_i(k) + \bar{x}_i(k) = 1, \;\; u_i(k) + \bar{u}(k) = 1$$

It is desirable that

1) WNT5A (x_1) is inactive,
2) STC2 (x_6) and pirin (u) are active. (Technical reasons)

$$Q = Q_f = [10 \; 0 \; 0 \; \cdots \; 0 \; 0 \; 10]$$

To achieve $x_1 = 0, \;\; \bar{x}_1 = 1$

To achieve $x_6 = 1, \;\; \bar{x}_6 = 0$

$$R = [0 \; 1 \; 0 \; \cdots \; 0]$$

To achieve $u = 1, \;\; \bar{u} = 0$

$$N = 10$$

$$J = \sum_{k=0}^{N-1} \{Qx(k) + Ru(k)\} + Q_f x(N)$$

Constraints

1) 15 transitions are decomposed to 3 parts (A, B, C).
2) Each part has 5 transitions.

Transitions may fire at only corresponding time.

Time	0	1	2	3	4	5	6	7	8	9	10
	A	A	A	A	A	A	A	A	A	A	
		B		B		B		B		B	
						C				C	

We suppose multi-timescale dynamics.

Computation Results

Time	0	1	2	3	4	5	6	7	8	9	10
State 1	1	1	**0**	0	0	0	0	0	0	0	0
State 6	0	0	0	0	0	0	**1**	1	1	1	1
Input	1	1	1	1	1	**0**	1	1	1	1	

Time	0	1	2	3	4	5	6	7	8	9	10
	A	A	A	A	A	A	A	A	A	A	
		B		B		B		B		B	
						C				C	

One transition fires.

1) WNT5A (x_1) is inactive,
2) STC2 (x_6) and pirin (u) are active.

Computation Results

Time	0	1	2	3	4	5	6	7	8	9	10
State 1	1	1	**0**	0	0	0	0	0	0	0	0
State 6	0	0	0	0	0	0	**1**	1	1	1	1
Input	1	1	1	1	1	**0**	1	1	1	1	

Time	0	1	2	3	4	5	6	7	8	9	10
	A	A	A	A	A	A	A	A	A	A	
		B		B		B		B		B	
						C				C	

One transition fires.

The computation time: 30 [msec] (CPLEX 11.0)

420 binary variables

Conclusion

In this talk, we have proposed

1) Petri net-based modeling of asynchronous Boolean networks,

2) Reduction of the optimal control problem to an integer linear programming problem.

Future Works:

1) Application to large-scale biological systems

2) Development of computation time reduction techniques