Optimal Control of Asynchronous Boolean Networks Modeled Petri Nets

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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.

In the control problem, Boolean networks and hybrid systems are used as a model 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]
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, \[\text{Extension of the result in [Chaouiya et al. ATPN2004]}\]

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

\[
\begin{align*}
    & x_1(k+1) = x_2(k) \land x_3(k) \\
    & x_2(k+1) = x_1(k) \\
    & x_3(k+1) = \neg x_2(k) \\
\end{align*}
\]

$k = 0, 1, 2, \ldots$

: discrete time

**Logical Operations:**

$\land$: AND

$\lor$: OR

$\neg$: NOT
Example of Synchronous Boolean Networks

Gene 1
\[ x_1 \in \{0, 1\} \]

Gene 2
\[ x_2 \in \{0, 1\} \]

Gene 3
\[ x_3 \in \{0, 1\} \]

\[
\begin{cases}
    x_1(k + 1) &= x_2(k) \land x_3(k) \\
    x_2(k + 1) &= x_1(k) \\
    x_3(k + 1) &= \neg x_2(k) & k = 0, 1, 2, \ldots
\end{cases}
\]

\[
\begin{bmatrix}
    x_1(k) \\
    x_2(k) \\
    x_3(k)
\end{bmatrix}
= \begin{bmatrix}
    1 \\
    0 \\
    1
\end{bmatrix}
\rightarrow
\begin{bmatrix}
    x_1(k + 1) \\
    x_2(k + 1) \\
    x_3(k + 1)
\end{bmatrix}
= \begin{bmatrix}
    0 \\
    1 \\
    1
\end{bmatrix}
\]
In [Tournier & Chaves 2009] and so on, ABNs are regarded as nondeterministic systems.

\[
\begin{align*}
    x_1(k+1) &= x_2(k) \land x_3(k) \\
    x_2(k+1) &= x_1(k) \\
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    x_1(k+1) &= x_1(k) \\
    x_2(k+1) &= x_2(k) \\
    x_3(k+1) &= \neg x_2(k)
\end{align*}
\]

Given: \( x(k) = \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} \) \quad \text{then} \quad x(k+1) = \begin{bmatrix} 0 & 1 & 1 \\ 0 & 1 & 1 \\ 1 & 0 & 1 \end{bmatrix}

All combinations are not considered.
Intuitive Method

\[
\begin{align*}
    x_1(k + 1) &= x_2(k) \land x_3(k) \\
    x_2(k + 1) &= x_1(k) \\
    x_3(k + 1) &= \neg x_2(k)
\end{align*}
\]

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]
1. Asynchronous Boolean Networks

2. Petri Net-Based Modeling

3. Optimal Control Problem

4. Numerical example
Simple Example

\[
\begin{align*}
    x_1(k + 1) &= x_2(k), \\
    x_2(k + 1) &= u(k)
\end{align*}
\]

State Control input.
The value can be arbitrarily determined.

One token exists.

One token exists.

One token exists.

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

One token exists in the place $\overline{x}_i \rightarrow \overline{x}_i = 0$
The transition $t_{x_1,x_2}$ may fire.
\[
\begin{cases}
x_1(k+1) = x_2(k), \\
x_2(k+1) = u(k)
\end{cases}
\]

\[
\begin{bmatrix}
x_1(k+1) \\
x_2(k+1)
\end{bmatrix} =
\begin{bmatrix}
1 \\
1
\end{bmatrix}
\]
Outline of The Proposed Modeling Method

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

State Control input

The proposed modeling method is an extension of the method in [Chaouiy 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

\[ \mathcal{I}(1) = \{x_2, x_3\}, \quad |\mathcal{I}(1)| = 2 \]

\[
\begin{align*}
  x_1(k + 1) &= x_2(k) \land x_3(k) \\
  x_2(k + 1) &= x_1(k) \\
  x_3(k + 1) &= \neg x_2(k)
\end{align*}
\]

\[ \mathcal{I}(2) = \{x_1\}, \quad |\mathcal{I}(2)| = 1 \]

\[ \mathcal{I}(3) = \{x_2\}, \quad |\mathcal{I}(3)| = 1 \]

4 combinations
2 combinations
2 combinations
8 transitions are needed.
Discussion on The Number of Transitions

**Intuitive Method:**

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

\[ \rightarrow \text{The number of transitions is also given by } 2^n - 1. \]

**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 \( n = 10 \), \( |\mathcal{I}(i)| = 3 \)

\[ 2^n - 1 = 1023, \quad \sum_{i=1}^{n} 2^{|\mathcal{I}(i)|} = 80 \]
Outline of This Presentation

1. Asynchronous Boolean Networks

2. Petri Net-Based Modeling

3. Optimal Control Problem

4. Numerical example
If the transition fires, then 1, otherwise 0.

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

\[ -t_{x_1}(k)x_1(k)\bar{x}_2(k), \]

If one token exists, then 1, otherwise 0.

The dynamics on other states can expressed as a similar form.
In addition, we impose  

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

If the transition fires, then 1, otherwise 0.

If one token exists, then 1, otherwise 0.

\[ z = \delta_1 \delta_2 \cdots \delta_n \iff \sum_{i=1}^{n} \delta_i - z \leq n-1, \quad -\sum_{i=1}^{n} \delta_i + n z \leq 0 \]

In addition, we impose  

\[ x_i(k) + \bar{x}_i(k) = 1, \quad u_i(k) + \bar{u}(k) = 1. \]

**Linear Form:**  

\[
\begin{align*}
\begin{cases}
x(k + 1) &= Ax(k) + Bv(k) \\
C x(k) + D v(k) &\leq E
\end{cases}
\end{align*}
\]

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

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

Linear Cost Function

\[
\begin{align*}
\text{find} & \quad v(k) \in \{0, 1\}^{2m+\alpha}, \quad k = 0, 1, \ldots, N - 1 \\
\text{min} & \quad J = \sum_{k=0}^{N-1} \{Qx(k) + Ru(k)\} + Q_f x(N) \\
\text{subject to} & \quad \begin{cases} \\
\quad x(k + 1) = Ax(k) + Bv(k) \\
\quad Cx(k) + Dv(k) \leq E \\
\end{cases}
\end{align*}
\]

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

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

This problem is equivalent to an integer linear programming problem.
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Gene Regulatory Network Related to Melanoma

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

\[
\begin{align*}
x_1(k + 1) &= \neg x_5(k), \\
x_2(k + 1) &= \neg x_6(k), \\
x_3(k + 1) &= x_3(k), \\
x_4(k + 1) &= \neg x_6(k) \lor u(k), \\
x_5(k + 1) &= x_2(k) \lor x_3(k), \\
x_6(k + 1) &= x_6(k) \lor \neg u(k)
\end{align*}
\]

\text{\textbf{\textit{x}}}_1 : \text{Expression of WNT5A} \\
\text{\textbf{\textit{x}}}_2 : \text{Expression of S100P} \\
\text{\textbf{\textit{x}}}_3 : \text{Expression of RET1} \\
\text{\textbf{\textit{x}}}_4 : \text{Expression of MART1} \\
\text{\textbf{\textit{x}}}_5 : \text{Expression of HADHB} \\
\text{\textbf{\textit{x}}}_6 : \text{Expression of STC2} \\
u : \text{Expression of pirin}

[Xiao and Dougherty 2007]
It is desirable that

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

$$Q = Q_f = \begin{bmatrix} 10 & 0 & 0 & \cdots & 0 & 0 & 10 \end{bmatrix}$$

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

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

$$R = \begin{bmatrix} 0 & 1 & 0 & \cdots & 0 \end{bmatrix}$$

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

$$N = 10 \quad J = \sum_{k=0}^{N-1} \{Qx(k) + Ru(k)\} + Q_f x(N)$$
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.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
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<td>B</td>
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<td>B</td>
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<tr>
<td>C</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

We suppose multi-timescale dynamics.
### Computation Results

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>State 1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>State 6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Input</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

One transition fires.

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

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

420 binary variables

### Table 1: Computation Results

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>State 1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>State 6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Input</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2: Transition Events

<table>
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<th>2</th>
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<th>5</th>
<th>6</th>
<th>7</th>
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</tr>
</thead>
<tbody>
<tr>
<td>A</td>
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</tr>
</tbody>
</table>

One transition fires.

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

420 binary variables
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