Enumeration and extension of non-equivalent deterministic update schedules in Boolean networks

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joint work with
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* Research stay August 2016–January 2017, funded by Labex project and Université de Nice

January 4th, 2017
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A genetic regulatory network consists of a set of genes, proteins, small molecules, and their mutual interactions.

(L. Mendoza and E. Alvarez, 1998)
Boolean networks

A finite set $V$ of $n$ elements and $n$ states variables $x_v \in \{0, 1\}$, $v \in V$
Boolean networks

Boolean Network

A finite set $V$ of $n$ element and $n$ states variables $x_v \in \{0, 1\}, \ v \in V$
Boolean Networks

A finite set $V$ of $n$ element and $n$ states variables $x_v \in \{0, 1\}$, $v \in V$

A global activation function $F = (f_v)_{v \in V} : \{0, 1\}^n \to \{0, 1\}^n$

- Composed by local activation functions $f_v : \{0, 1\}^n \to \{0, 1\}$

$f_1(x) = x_2 \land x_4$
$f_2(x) = x_1$
$f_3(x) = x_2 \lor x_3$
$f_4(x) = x_3 \land x_4$
Boolean Networks

- A finite set $V$ of $n$ elements and $n$ states variables $x_v \in \{0, 1\}$, $v \in V$
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  - Composed by local activation functions $f_v : \{0, 1\}^n \rightarrow \{0, 1\}$
- Schedule $s : V \rightarrow \{1, \ldots, n\}$

$s(2) = 1 \quad s(1) = 1$

$f_1(x) = x_2 \land x_4$
$f_2(x) = x_1$
$f_3(x) = x_2 \lor x_3$
$f_4(x) = x_3 \land x_4$
$s = \{1, 2, 3, 4\}$
Boolean networks

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- Schedule \( s : V \rightarrow \{1, \ldots, n\} \)

\[
egin{align*}
s(2) &= 2 & s(1) &= 1 \\
s(3) &= 3 & s(4) &= 4 \\
f_1(x) &= x_2 \land x_4 \\
f_2(x) &= x_1 \\
f_3(x) &= x_2 \lor x_3 \\
f_4(x) &= x_3 \land x_4 \\
s &= \{1\} \{2\} \{3\} \{4\}
\end{align*}
\]
Boolean networks

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A global activation function $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$

Composed by local activation functions $f_v : \{0, 1\}^n \rightarrow \{0, 1\}$

Schedule $s : V \rightarrow \{1, \ldots, n\}$

$F = \{f_v\}_{v \in V}$

$s(1) = 1$
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$s(3) = 3$
$s(4) = 4$

$f_1(x) = x_2 \land x_4$
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$s = \{1\} \{2\} \{3\} \{4\}$
Boolean networks

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$s(2) = 2$  
$s(1) = 1$

$s(3) = 3$  
$s(4) = 4$

$f_1(x) = x_2 \land x_4$
$f_2(x) = x_1$
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\[
s(1) = 1 \\
 s(2) = 2 \\
 s(3) = 3 \\
 s(4) = 4 \\
\]

\[
f_1(x) = x_2 \land x_4 \\
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$s = \{1\} \{2\} \{3\} \{4\}$
Boolean networks

A finite set $V$ of $n$ element and $n$ states variables $x_v \in \{0, 1\}$, $v \in V$

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Composed by local activation functions $f_v : \{0, 1\}^n \to \{0, 1\}$

Schedule $s : V \to \{1, \ldots, n\}$

$s(1) = 1$ $s(2) = 2$ $s(3) = 3$ $s(4) = 4$

$f_1(x) = x_2 \land x_4$
$f_2(x) = x_1$
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$f_4(x) = x_3 \land x_4$

$s = \{1\} \{2\} \{3\} \{4\}$
Boolean networks

A finite set \( V \) of \( n \) element and \( n \) states variables
\( x_v \in \{0, 1\}, \ v \in V \)

A global activation function
\( F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n \)

Composed by local activation functions
\( f_v : \{0, 1\}^n \rightarrow \{0, 1\} \)

Schedule \( s : V \rightarrow \{1, \ldots, n\} \)

\[
\begin{align*}
\text{s(2)} &= 2 & \text{s(1)} &= 2 \\
\text{s(3)} &= 1 & \text{s(4)} &= 1 \\
&
\end{align*}
\]

\[
\begin{align*}
&f_1(x) = x_2 \land x_4 \\
&f_2(x) = x_1 \\
&f_3(x) = x_2 \lor x_3 \\
&f_4(x) = x_3 \land x_4 \\
&s = \{3, 4\} \{1, 2\}
\end{align*}
\]
### Boolean Networks

- A finite set $V$ of $n$ elements and $n$ states variables $x_v \in \{0, 1\}$, $v \in V$
- A global activation function $F = (f_v)_{v \in V} : \{0, 1\}^n \to \{0, 1\}^n$
  - Composed by local activation functions $f_v : \{0, 1\}^n \to \{0, 1\}$
- Schedule $s : V \to \{1, \ldots, n\}$

**Example: (Update schedules in Boolean networks)**

- $s(2) = 2$, $s(1) = 2$
- $s(3) = 1$, $s(4) = 1$
- $f_1(x) = x_2 \land x_4$
- $f_2(x) = x_1$
- $f_3(x) = x_2 \lor x_3$
- $f_4(x) = x_3 \land x_4$
- $s = \{3, 4\} \{1, 2\}$
Boolean Networks

- A finite set $V$ of $n$ elements and $n$ state variables $x_v \in \{0, 1\}, \ v \in V$
- A global activation function $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$
  - Composed by local activation functions $f_v : \{0, 1\}^n \rightarrow \{0, 1\}$
- Schedule $s : V \rightarrow \{1, \ldots, n\}$

$$
\begin{align*}
\text{s(2)} &= 2 & \text{s(1)} &= 2 \\
\text{s(3)} &= 1 & \text{s(4)} &= 1
\end{align*}
$$

$$
\begin{align*}
f_1(x) &= x_2 \land x_4 \\
f_2(x) &= x_1 \\
f_3(x) &= x_2 \lor x_3 \\
f_4(x) &= x_3 \land x_4
\end{align*}
$$

$s = \{3, 4\} \ {\{1, 2\}}$
Dynamical behavior

The iteration of the Boolean network is given by:

$$x_{v}^{k+1} = f_{v}(x_{u}^{l_u} : u \in V), \quad l_u = \begin{cases} 
    k & \text{if } s(v) \leq s(u) \\
    k + 1 & \text{if } s(v) > s(u) 
\end{cases}$$
The iteration of the Boolean network is given by:

\[ x^{k+1}_v = f_v(x^l_u : u \in V), \quad l_u = \begin{cases} k & \text{if } s(v) \leq s(u) \\ k + 1 & \text{if } s(v) > s(u) \end{cases} \]

**Dynamical behavior**

**F**

\[ F^s : \{0, 1\}^n \to \{0, 1\}^n : \]

\[ f^s_v(x) = f_v(g^s_{v,u}(x) : u \in V), \quad g^s_{v,u}(x) = \begin{cases} x_u & \text{if } s(v) \leq s(u) \\ f^s_u(x) & \text{if } s(v) > s(u) \end{cases} \]
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \]

\[
\begin{align*}
  f_{s_1}^1(x) &= x_2 \land x_4 \\
  f_{s_1}^2(x) &= x_1 \\
  f_{s_1}^3(x) &= x_2 \lor x_3 \\
  f_{s_1}^4(x) &= x_3 \land x_4
\end{align*}
\]
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \]

\[ f_{s_1}^1(x) = x_2 \land x_4 \]
\[ f_{s_1}^2(x) = x_1 \]
\[ f_{s_1}^3(x) = x_2 \lor x_3 \]
\[ f_{s_1}^4(x) = x_3 \land x_4 \]
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \quad \text{and} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \]

\[ f_{s_1}^{s_1}(x) = x_2 \land x_4 \quad f_{s_2}^{s_2}(x) = x_2 \land x_4 \]
\[ f_{s_1}^{s_1}(x) = x_1 \]
\[ f_{s_1}^{s_1}(x) = x_2 \lor x_3 \]
\[ f_{s_1}^{s_1}(x) = x_3 \land x_4 \]
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \]

\[ f_{s_1}^1(x) = x_2 \land x_4 \]
\[ f_{s_1}^2(x) = x_1 \]
\[ f_{s_1}^3(x) = x_2 \lor x_3 \]
\[ f_{s_1}^4(x) = x_3 \land x_4 \]

\[ f_{s_2}^1(x) = x_2 \land x_4 \]
\[ f_{s_2}^2(x) = x_2 \land x_4 \]

Lilian Salinas (U. Concepción)
Update schedules in Boolean networks
Marseille 2017
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \]

\[ f_{s_1}^{S_1}(x) = x_2 \land x_4 \quad f_{s_2}^{S_2}(x) = x_2 \land x_4 \]
\[ f_{s_1}^{S_1}(x) = x_1 \quad f_{s_2}^{S_2}(x) = x_2 \land x_4 \]
\[ f_{s_1}^{S_1}(x) = x_2 \lor x_3 \quad f_{s_2}^{S_2}(x) = (x_2 \land x_4) \lor x_3 \]
\[ f_{s_1}^{S_1}(x) = x_3 \land x_4 \]
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \]

\[
\begin{align*}
  f_{s_1}^1(x) &= x_2 \land x_4 & f_{s_2}^1(x) &= x_2 \land x_4 \\
  f_{s_1}^2(x) &= x_1 & f_{s_2}^2(x) &= x_2 \land x_4 \\
  f_{s_1}^3(x) &= x_2 \lor x_3 & f_{s_2}^3(x) &= (x_2 \land x_4) \lor x_3 \\
  f_{s_1}^4(x) &= x_3 \land x_4 & f_{s_2}^4(x) &= ((x_2 \land x_4) \lor x_3) \land x_4
\end{align*}
\]
Boolean network

Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \quad s_3 = \{3, 4\} \{1, 2\} \]

\[
\begin{align*}
  f_{s_1}^1(x) &= x_2 \land x_4 \\
  f_{s_1}^2(x) &= x_1 \\
  f_{s_1}^3(x) &= x_2 \lor x_3 \\
  f_{s_1}^4(x) &= x_3 \land x_4 \\
  f_{s_2}^1(x) &= x_2 \land x_4 \\
  f_{s_2}^2(x) &= x_2 \land x_4 \\
  f_{s_2}^3(x) &= (x_2 \land x_4) \lor x_3 \\
  f_{s_2}^4(x) &= ((x_2 \land x_4) \lor x_3) \land x_4
\end{align*}
\]
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \]
\[ s_2 = \{1\} \{2\} \{3\} \{4\} \]
\[ s_3 = \{3, 4\} \{1, 2\} \]

\[ f_{s_1}^1(x) = x_2 \land x_4 \]
\[ f_{s_1}^2(x) = x_1 \]
\[ f_{s_1}^3(x) = x_2 \lor x_3 \]
\[ f_{s_1}^4(x) = x_3 \land x_4 \]
\[ f_{s_2}^1(x) = x_2 \land x_4 \]
\[ f_{s_2}^2(x) = x_2 \land x_4 \]
\[ f_{s_2}^3(x) = (x_2 \land x_4) \lor x_3 \]
\[ f_{s_2}^4(x) = ((x_2 \land x_4) \lor x_3) \land x_4 \]
\[ f_{s_3}^1(x) = x_2 \lor x_3 \]
\[ f_{s_3}^2(x) = x_2 \land x_4 \]
\[ f_{s_3}^3(x) = x_2 \lor x_3 \]
\[ f_{s_3}^4(x) = x_3 \land x_4 \]
Example of dynamical behavior

\[ s_1 = \{1, 2, 3, 4\} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \quad s_3 = \{3, 4\} \{1, 2\} \]

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\begin{align*}
  f_{s_1}^1(x) &= x_2 \land x_4 \\
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  f_{s_1}^4(x) &= x_3 \land x_4 \\
  f_{s_2}^1(x) &= x_2 \land x_4 \\
  f_{s_2}^2(x) &= x_2 \land x_4 \\
  f_{s_2}^3(x) &= (x_2 \land x_4) \lor x_3 \\
  f_{s_2}^4(x) &= ((x_2 \land x_4) \lor x_3) \land x_4 \\
  f_{s_3}^1(x) &= x_2 \land x_3 \land x_4 \\
  f_{s_3}^2(x) &= x_1 \\
  f_{s_3}^3(x) &= x_2 \lor x_3 \\
  f_{s_3}^4(x) &= x_3 \land x_4
\end{align*}
\]
\[ s_1 = \{1, 2, 3, 4\} \]
\[ s_2 = \{1\} \{2\} \{3\} \{4\} \]
\[ s_3 = \{3, 4\} \{1, 2\} \]

### State Transition Table

<table>
<thead>
<tr>
<th>State</th>
<th>( F^{s_1} )</th>
<th>( F^{s_2} )</th>
<th>( F^{s_3} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0000</td>
<td>0000</td>
<td>0000</td>
</tr>
<tr>
<td>1</td>
<td>0001</td>
<td>0000</td>
<td>0000</td>
</tr>
<tr>
<td>2</td>
<td>0010</td>
<td>0010</td>
<td>0010</td>
</tr>
<tr>
<td>3</td>
<td>0011</td>
<td>0011</td>
<td>0011</td>
</tr>
<tr>
<td>4</td>
<td>0100</td>
<td>0010</td>
<td>0010</td>
</tr>
<tr>
<td>5</td>
<td>0101</td>
<td>1010</td>
<td>0010</td>
</tr>
<tr>
<td>6</td>
<td>0110</td>
<td>0010</td>
<td>0010</td>
</tr>
<tr>
<td>7</td>
<td>0111</td>
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<td>1011</td>
</tr>
<tr>
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<td>0000</td>
<td>0100</td>
</tr>
<tr>
<td>9</td>
<td>1001</td>
<td>0100</td>
<td>0000</td>
</tr>
<tr>
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<td>0111</td>
</tr>
<tr>
<td>12</td>
<td>1100</td>
<td>0110</td>
<td>0110</td>
</tr>
<tr>
<td>13</td>
<td>1101</td>
<td>1110</td>
<td>0110</td>
</tr>
<tr>
<td>14</td>
<td>1110</td>
<td>0110</td>
<td>0110</td>
</tr>
<tr>
<td>15</td>
<td>1111</td>
<td>1111</td>
<td>1111</td>
</tr>
</tbody>
</table>
Dynamical problems related to schedule

- Does there exist two different update schedules $s_1, s_2$ such that the function $F$ updated with $s_1$ has the same dynamical behavior, that $F$ updated with $s_2$?
Dynamical problems related to schedule

- Does there exist two different update schedules $s_1, s_2$ such that the function $F$ updated with $s_1$ has the same dynamical behavior, that $F$ updated with $s_2$?

- Does there exist two update schedules $s_1, s_2$ such that the function $F$ updated with $s_1$ has the same attractors that $F$ updated with $s_2$?
Dynamical problems related to schedule

- Does there exist two different update schedules $s_1, s_2$ such that the function $F$ updated with $s_1$ has the same dynamical behavior, that $F$ updated with $s_2$?
- Does there exist two update schedules $s_1, s_2$ such that the function $F$ updated with $s_1$ has the same attractors that $F$ updated with $s_2$?
- Does there exist an update schedule $s$ such that the function $F$ updated with $s$ does not have limit cycles?
Dynamical problems related to schedule

- Does there exist two different update schedules \( s_1, s_2 \) such that the function \( F \) updated with \( s_1 \) has the same dynamical behavior, that \( F \) updated with \( s_2 \)?
- Does there exist two update schedules \( s_1, s_2 \) such that the function \( F \) updated with \( s_1 \) has the same attractors that \( F \) updated with \( s_2 \)?
- Does there exist an update schedule \( s \) such that the function \( F \) updated with \( s \) does not have limit cycles?
- Does there exist an update schedule \( s \) such that the function \( F \) updated with \( s \) has limit cycles?
Dynamical problems related to schedule

- Does there exist two different update schedules $s_1, s_2$ such that the function $F$ updated with $s_1$ has the same dynamical behavior, that $F$ updated with $s_2$?
- Does there exist two update schedules $s_1, s_2$ such that the function $F$ updated with $s_1$ has the same attractors that $F$ updated with $s_2$?
- Does there exist an update schedule $s$ such that the function $F$ updated with $s$ does not have limit cycles?
- Does there exist an update schedule $s$ such that the function $F$ updated with $s$ has limit cycles?
- Does there exist an update schedule $s$ such that given $x^1, \ldots, x^k, y^1, \ldots, y^k \in \{0, 1\}^n$, $F^s(x^i) = y^i$?
A labeled digraph is a graph $G$ with a label function $\text{lab}$, $(G, \text{lab})$ such that: $\text{lab} : A(G) \rightarrow \{\oplus, \ominus\}$

We say that a labeled digraph is an update digraph if there exists $s : V(G) \rightarrow \{1, \ldots, n\}$, an update function such that:

$$\forall (u, v) \in A(G), \text{lab}(u, v) = \oplus \iff s(u) \geq s(v)$$

\[ s_1 = \{1, 2, 3, 4\} \quad s_2 = \{1\} \{2\} \{3\} \{4\} \quad s_3 = \{3, 4\} \{1, 2\} \]
Why are we interested in update digraphs?

**Theorem (Aracena, Goles, Moreira, Salinas (2009))**

*Given two Boolean networks $N_1 = (F, s)$ and $N_2 = (F, s')$ which differ only in the update schedule. If the update digraphs associated to them are equal, then both networks have the same dynamical behavior.*
Why are we interested in update digraphs?

**Theorem (Aracena, Goles, Moreira, Salinas (2009))**

Given two Boolean networks $N_1 = (F, s)$ and $N_2 = (F, s')$ which differ only in the update schedule. If the update digraphs associated to them are equal, then both networks have the same dynamical behavior.

$s = \{2\} \{1\} \{3\} \{4\}$ and $s' = \{2\} \{3\} \{1\} \{4\}$

Of this way, we say that two update schedules are equivalent if and only if they have the same update digraph.
New questions

- Given a labeled digraph. Is it an update digraph?
New questions

- Given a labeled digraph. Is it an update digraph?
- If it is an update digraph. How do we find un update shedule with this update digraph?
New questions

- Given a labeled digraph. Is it an update digraph?
- If it is an update digraph. How do we find un update shedule with this update digraph?
- How many non-equivalent update schedules are there? How many elements does each have?
New questions

- Given a labeled digraph. Is it an update digraph?
- If it is an update digraph. How do we find un update shedule with this update digraph?
- How many non-equivalent update schedules are there? How many elements does each have?
- Given a certain dynamical property. Is there an equivalence class that holds it?
Given \((G, \text{lab})\) a labeled digraph, we define the reverse digraph as \((G_r, \text{lab}_r)\), where:

\[
V(G_r) = V(G)
\]

\[
A(G_r) = \{(u, v) / ((v, u) \in A(G) \land \text{lab}(v, u) = \ominus) \\
\lor ((u, v) \in A(G) \land \text{lab}(u, v) = \oplus)\}
\]

\[
\text{lab}_r(u, v) = \begin{cases} 
\ominus & \text{if } (v, u) \in A(G) \land \text{lab}(v, u) = \ominus \\
\oplus & \text{otherwise}
\end{cases}
\]
Reverse Path

A reverse path is a path in the reverse graph.

Labeled digraph

Reverse digraph

Update digraph

Labels and Update digraphs
Labels and Update digraphs

**Reverse Path**
A reverse path is a path in the reverse graph.

**Negative Reverse Path**
A negative reverse path is a path with an arc labeled $\ominus$ in the reverse graph.

Labeled digraph

Reverse digraph
Forbidden cycle

A forbidden cycle is a cycle with an arc labeled $\ominus$ in the reverse graph.

Theorem (Montalva (2012))

A labeled digraph is an update digraph if and only if there does not exist a forbidden cycle in its reverse digraph.
Is it an update digraph?

\[ G : \]

\[ G \oplus : \]

\[ G \ominus : \]

Forbidden cycle
Is it an update digraph?

$G : \quad G_{\oplus} :$

\[ \begin{array}{c}
\text{Forbidden cycle} \\
\text{Lilian Salinas (U. Concepción)} \\
\text{Update schedules in Boolean networks} \\
\text{Marseille 2017} \\
\end{array} \]
Is it an update digraph?

\[ G : \]

\[ G_\oplus : \]

Forbidden cycle

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Is it an update digraph?

\[ G : \]

\[ G_{\oplus} : \]

\[ G_{R} : \]
Is it an update digraph?

G :

G⊕ :

GR :

Forbidden cycle
How I find the update schedule of a label?

\[ G : \]

- How I find the update schedule of a label?
How I find the update schedule of a label?

\[ G : \]

\[ G_{\oplus} : \]

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How I find the update schedule of a label?

$G : \quad G_{\oplus} :$

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How I find the update schedule of a label?

$G$:

$G_{\oplus}$:

$G_R$:

$s = \{3, 4\} \setminus \{5\} \setminus \{1, 2\}$
How I find the update schedule of a label?

\[
g : \quad G \quad \quad \quad \quad G_{\oplus} : \quad \quad \quad \quad G_R : \quad \quad \quad \quad s = \{3, 4\} \{5\} \{1, 2\}
\]
Transition problem

Does there exist an update schedule \( s \) such that given \( x^1, \ldots, x^k, y^1, \ldots, y^k \in \{0, 1\}^n \), \( F^s(x^i) = y^i \)?
Transition problem

Does there exist an update schedule $s$ such that given $x^1, \ldots, x^k, y^1, \ldots, y^k \in \{0, 1\}^n$, $F^s(x^i) = y^i$?

Transition problem

Does there exist an update schedule $s$ such that given $x^1, \ldots, x^k, y^1, \ldots, y^k \in \{0, 1\}^n$, $F^s(x^i) = y^i$?

Limit cycle

<table>
<thead>
<tr>
<th>$v \in V(G')$</th>
<th>$v_1$</th>
<th>$v_2$</th>
<th>$v_3$</th>
<th>$v_4$</th>
<th>$v_5$</th>
<th>$v_6$</th>
<th>$v_7$</th>
<th>$v_8$</th>
<th>$v_9$</th>
<th>$v_{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x^0$</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$x^1$</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$x^2$</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$x^3$</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$x^4$</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$x^5$</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$x^6$</td>
<td>1</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>0</td>
</tr>
<tr>
<td>$x^7$</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

$f_{v_1}(x) = x_{v_1}$

$f_{v_2}(x) = (\neg x_{v_1} \land \neg x_{v_{10}}) \land ([\neg x_{v_4} \land \neg x_{v_5}] \lor x_{v_6})$

$f_{v_3}(x) = (\neg x_{v_2} \land \neg x_{v_5} \land \neg x_{v_{10}}) \lor (x_{v_6} \land \neg x_{v_2} \land \neg x_{v_{10}})$

$f_{v_4}(x) = x_{v_3} \land \neg x_{v_2}$

$f_{v_5}(x) = (\neg x_{v_2} \land \neg x_{v_7} \land (\neg (x_{v_8} \land x_{v_9})) \land (x_{v_3} \lor x_{v_5})$

$f_{v_6}(x) = (\neg x_{v_1} \land \neg x_{v_{10}}) \land ([\neg x_{v_4} \land \neg x_{v_5}] \lor [x_{v_6} \land \neg (x_{v_4} \land x_{v_5})])$

$f_{v_7}(x) = x_{v_{10}}$

$f_{v_8}(x) = (\neg x_{v_5} \land \neg x_{v_{10}}) \lor x_{v_7} \lor (x_{v_6} \land \neg x_{v_{10}})$

$f_{v_9}(x) = \neg x_{v_8} \lor (x_{v_8} \land x_{v_9} \land [x_{v_7} \lor x_{v_5} \lor x_{v_{10}}])$

$f_{v_{10}}(x) = \neg x_{v_7} \land \neg x_{v_8}$

Does there exist an update schedule $s$ such that given $x^1, \ldots, x^k, y^1, \ldots, y^k \in \{0, 1\}^n$, $F^s(x^i) = y^i$?

<table>
<thead>
<tr>
<th>Limit cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v \in V(G^f)$</td>
</tr>
<tr>
<td>$x^0$</td>
</tr>
<tr>
<td>$x^1$</td>
</tr>
<tr>
<td>$x^2$</td>
</tr>
<tr>
<td>$x^3$</td>
</tr>
<tr>
<td>$x^4$</td>
</tr>
<tr>
<td>$x^5$</td>
</tr>
<tr>
<td>$x^6$</td>
</tr>
<tr>
<td>$x^7$</td>
</tr>
</tbody>
</table>

$f_{v_1}(x) = x_v^1$
$f_{v_2}(x) = (\neg x_v^1 \land \neg x_v^{10}) \land ([\neg x_v^4 \land \neg x_v^5] \lor x_v^6)$
$f_{v_3}(x) = (\neg x_v^2 \land \neg x_v^5 \land \neg x_v^{10}) \lor (x_v^6 \land \neg x_v^2 \land \neg x_v^{10})$
$f_{v_4}(x) = x_v^3 \land \neg x_v^2$
$f_{v_5}(x) = (\neg x_v^2 \land \neg x_v^7 \land \neg (x_v^8 \land x_v^9)) \land (x_v^3 \lor x_v^5)$
$f_{v_6}(x) = (\neg x_v^1 \land \neg x_v^{10}) \land ([\neg x_v^4 \land \neg x_v^5] \lor [x_v^6 \land \neg (x_v^4 \land x_v^5)])$
$f_{v_7}(x) = x_v^{10}$
$f_{v_8}(x) = (\neg x_v^5 \land \neg x_v^{10}) \lor x_v^7 \lor (x_v^6 \land \neg x_v^{10})$
$f_{v_9}(x) = \neg x_v^8 \lor (x_v^8 \land x_v^9 \land [x_v^7 \lor x_v^5 \lor x_v^{10}])$
$f_{v_{10}}(x) = \neg x_v^7 \land \neg x_v^8$

Update Digraph Extension Problem

**UDE**

Given a labeled digraph \((G, \text{lab})\), find the set \(S(G, \text{lab})\) of all fully labeled extensions \(\text{lab}'\) of \(\text{lab}\) such that \((G, \text{lab}')\) is an update digraph.
**Problem**

Complexity

**CUDE**

Given \((G, lab)\) a labeled digraph, to determine the cardinality of the set \(S(G, lab)\).
Complexity

**Problem**

Given \((G, \text{lab})\) a labeled digraph, to determine the cardinality of the set \(S(G, \text{lab})\).

**Theorem**

*CUDE is \#P-complete*
**Acyclic orientation problem**

Given a graph to determine the number of acyclic orientations is $\#P$-complete.
Acyclic orientation problem

Given a graph to determine the number of acyclic orientations is #P-complete
Acyclic orientation problem

Given a graph to determine the number of acyclic orientations is \#P-complete
Acyclic orientation problem

Given a graph to determine the number of acyclic orientations is \( \#P \)-complete.
Theorem (Extension)

Given $G$ a digraph and $G'$ a subdigraph of $G$. If $(G', \text{lab}')$ is an update digraph, then there exists $\text{lab} : A(G) \rightarrow \{\oplus, \ominus\}$ such that $(G, \text{lab})$ is an update digraph and $\text{lab}|_{A(G')} = \text{lab}'$. 
Given a labeled digraph \((G, \text{lab})\) and an arc \((i, j)\) with \(\text{lab}(i, j) = \circ\):

- **If there exists a reverse path from \(i\) to \(j\), then the arc \((i, j)\) must be labeled** \(\oplus\).
- **If there exists a negative reverse path from \(j\) to \(i\), then the arc \((i, j)\) must be labeled** \(\ominus\).
Algorithm

Force

Proposition

Given a labeled digraph \((G, \text{lab})\) and an arc \((i, j)\) with \(\text{lab}(i, j) = \bigcirc\):

- If there exists a reverse path from \(i\) to \(j\), then the arc \((i, j)\) must be labeled \(\oplus\).
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Matrix \(M\)

\[
\begin{array}{c|ccccc}
V(G) & 1 & 2 & 3 & 4 & 5 \\
\hline
1 & \infty & 1 & \infty & -1 & \infty \\
2 & \infty & \infty & \infty & -1 & \infty \\
3 & -1 & -1 & \infty & -1 & \infty \\
4 & \infty & \infty & \infty & \infty & \infty \\
5 & \infty & \infty & \infty & \infty & \infty \\
\end{array}
\]
Algorithm

Force

Proposition

Given a labeled digraph \((G, \text{lab})\) and an arc \((i, j)\) with \(\text{lab}(i, j) = \bigcirc\):  

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- If there exists a negative reverse path from \(j\) to \(i\), then the arc \((i, j)\) must be labeled \(\ominus\)

Matrix \(M\)

<table>
<thead>
<tr>
<th>(V(G))</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\infty)</td>
<td>1</td>
<td>(\infty)</td>
<td>(-1)</td>
<td>(\infty)</td>
</tr>
<tr>
<td>2</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(-1)</td>
<td>(\infty)</td>
</tr>
<tr>
<td>3</td>
<td>(-1)</td>
<td>(-1)</td>
<td>(\infty)</td>
<td>(-1)</td>
<td>(\infty)</td>
</tr>
<tr>
<td>4</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(\infty)</td>
</tr>
<tr>
<td>5</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(\infty)</td>
<td>(\infty)</td>
</tr>
</tbody>
</table>
Algorithm

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Matrix \(M\)

\[
V(G) \quad | 
\begin{array}{ccccc}
1 & 2 & 3 & 4 & 5 \\
1 & \infty & 1 & \infty & -1 & \infty \\
2 & \infty & \infty & \infty & -1 & \infty \\
3 & -1 & -1 & \infty & -1 & \infty \\
4 & \infty & \infty & \infty & \infty & \infty \\
5 & \infty & \infty & \infty & \infty & \infty
\end{array}
\]
Algorithm

Force

Proposition

Given a labeled digraph \((G, \text{lab})\) and an arc \((i, j)\) with \(\text{lab}(i, j) = \bigcirc\):

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Matrix \(M\)

\[
\begin{array}{c|ccccc}
V(G) & 1 & 2 & 3 & 4 & 5 \\
\hline
1 & \infty & 1 & \infty & -1 & \infty \\
2 & \infty & \infty & \infty & \text{-1} & \infty \\
3 & \text{-1} & \text{-1} & \infty & \text{-1} & \infty \\
4 & \infty & \infty & \infty & \infty & \infty \\
5 & \infty & \infty & \infty & \infty & \infty \\
\end{array}
\]
Proposition

Given a labeled digraph \((G, lab)\) and an arc \((i, j)\) with \(lab(i, j) = ∘\):

- If there exists a reverse path from \(i\) to \(j\), then the arc \((i, j)\) must be labeled ⊕
- If there exists a negative reverse path from \(j\) to \(i\), then the arc \((i, j)\) must be labeled ⊖

Matrix \(M\)

<table>
<thead>
<tr>
<th>(V(G))</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>∞</td>
<td>1</td>
<td>∞</td>
<td>-1</td>
<td>∞</td>
</tr>
<tr>
<td>2</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
<td>-1</td>
<td>∞</td>
</tr>
<tr>
<td>3</td>
<td>-1</td>
<td>-1</td>
<td>∞</td>
<td>-1</td>
<td>∞</td>
</tr>
<tr>
<td>4</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
</tr>
<tr>
<td>5</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
</tr>
</tbody>
</table>
Proposition

Given a labeled digraph \((G, \text{lab})\) and an arc \((i, j)\) with \(\text{lab}(i, j) = \bigcirc\):

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Matrix \(M\)

\[
\begin{array}{c|ccccc}
V(G) & 1 & 2 & 3 & 4 & 5 \\
\hline
1 & \infty & 1 & \infty & -1 & \infty \\
2 & \infty & \infty & \infty & -1 & \infty \\
3 & -1 & -1 & \infty & -1 & \infty \\
4 & \infty & \infty & \infty & \infty & \infty \\
5 & \infty & \infty & \infty & \infty & \infty \\
\end{array}
\]
Example of SimpleLabel

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Marseille 2017

Marseille 2017
Example of SimpleLabel
Example of SimpleLabel

\[
lab(2, 1) = \oplus
\]

\[
lab(1, 2) = \oplus
\]

\[
lab(2, 1) = \ominus
\]

\[
lab(4, 1) = \ominus
\]
Example of SimpleLabel

\[ \text{lab}(2, 1) = \oplus \]

\[ \text{lab}(1, 2) = \ominus \]

\[ \text{lab}(4, 1) = \ominus \]
Example of SimpleLabel

\[
\text{lab}(2, 1) = \oplus \\
\text{lab}(1, 2) = \oplus\\n\{1, 2, 3, 4\}\\n\text{lab}(4, 1) = \ominus
\]
Example of SimpleLabel

\[
\text{lab}(2, 1) = \oplus
\]

\[
\text{lab}(1, 2) = \oplus
\]

\[
\text{lab}(1, 2) = \ominus
\]

\[
\text{lab}(1, 2) = \ominus
\]
Example of SimpleLabel

\[
\begin{align*}
\text{lab}(2, 1) &= \oplus \\
\text{lab}(1, 2) &= \oplus \\
\text{lab}(1, 2) &= \odot \\
\text{lab}(2, 1) &= \odot
\end{align*}
\]
**Example of SimpleLabel**

\[
\begin{align*}
\text{lab}(1, 2) &= \oplus \\
\text{lab}(2, 1) &= \ominus \\
\text{lab}(2, 1) &= \oplus \\
\end{align*}
\]
Example of SimpleLabel

Algorithm

Example of SimpleLabel

\[
\begin{align*}
\text{lab}(2, 1) &= \oplus \\
\text{lab}(1, 2) &= \oplus \\
\text{lab}(4, 1) &= \oplus
\end{align*}
\]
Example of SimpleLabel

\begin{align*}
\text{lab}(2, 1) &= \oplus \\
\text{lab}(1, 2) &= \ominus \\
\text{lab}(4, 1) &= \ominus \\
\text{lab}(4, 1) &= \ominus
\end{align*}

\begin{align*}
\{1, 2, 3, 4\} \\
\{1\} \{2, 3, 4\} \\
\{2, 3\} \{1, 4\} \\
\{2, 3, 4\} \{1\}
\end{align*}
Definition

Let \((G, lab)\) be an update digraph and \(\{G_1, \ldots, G_k\}\) its positive strongly connected components. We define its reduced labeled digraph by \(R(G, lab) = (G_{rd} = (V_{rd}, A_{rd}), lab_{rd})\), where:

- \(V_{rd} = \{v_1, \ldots, v_k\}\)
- \(A_{rd} = \{(v_i, v_j) | \exists (u, v) \in A(G) \cap (V(G_i) \times V(G_j))\}\)

\(lab_{rd}(v_i, v_j) = lab(u, v)\), if there exists \((u, v) \in (V(G_i) \times V(G_j)) \cap \text{Sup}(lab)\) and

\(lab_{rd}(v_i, v_j) = \bigcirc\) otherwise
Definition

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\(\text{lab}_{rd}(v_i, v_j) = \text{lab}(u, v)\), if there exists \((u, v) \in (V(G_i) \times V(G_j)) \cap \text{Sup}(\text{lab})\) and

\(\text{lab}_{rd}(v_i, v_j) = \bigcirc\) otherwise
Definition

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- \(V_{rd} = \{v_1, \ldots, v_k\}\)
- \(A_{rd} = \{(v_i, v_j) \mid \exists (u, v) \in A(G) \cap (V(G_i) \times V(G_j))\}\)

\(\text{lab}_{rd}(v_i, v_j) = \text{lab}(u, v)\), if there exists \((u, v) \in (V(G_i) \times V(G_j)) \cap \text{Sup}(\text{lab})\) and \(\text{lab}_{rd}(v_i, v_j) = \bigcirc\) otherwise.
### Strongly connected components

#### Divide by SCC

Let \((G, lab)\) an update digraph with SCC \(G_1, \ldots, G_k\) (ordered) over its reverse extended digraph, then:

\[
S(G, lab) = S\left(\widetilde{G_1}, lab|_{A(G_1)}\right) \circ_n \cdots \circ_n S\left(\widetilde{G_k}, lab|_{A(G_k)}\right)
\]
Algorithm: Divide and Conquer

Example: Division by SCC

\[
S(G[1, 2], \text{lab}) = \{\{1, 2\}\}
\]

\[
S(G[5], \text{lab}) = \{\{5\}\}
\]

\[
S(G[3, 4], \text{lab}) = \{\{3\}, \{4\}\}
\]

Then,

\[
S(G, \text{lab}) = S(G[1, 2], \text{lab}) \circ_n S(G[5], \text{lab}) \circ_n S(G[3, 4], \text{lab})
\]

\[
= \{\{1, 2\}\{5\}, \{2\} \{1\}{5}, \{1, 2\}\{3\}{4}, \{1\} \{2\}{5}\{3\}{4}\}
\]

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Example: Division by SCC

Algorithm

Divide and Conquer

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Example: Division by SCC

\[ S(G[1, 2], \text{lab}) = \{1, 2\}, \{2\} \{1\} \{5\} \]

\[ S(G[3, 4], \text{lab}) = \{3\} \{4\} \{1\} \{2\} \{5\} \]

Then, 

\[ S(G, \text{lab}) = S(G[1, 2], \text{lab}) \circ_n S(G[3, 4], \text{lab}) \circ_n S(G[5], \text{lab}) = \{\{1, 2\} \{5\}, \{2\} \{1\} \{5\}, \{3\} \{4\} \{1\} \{2\} \{5\}, \{1\} \{2\} \{5\} \{4\} \{3\}\} \]
Example: Division by SCC

Then,

$S(G[1, 2], lab) \bowtie S(G[5], lab) \bowtie S(G[3, 4], lab) = \{\{1, 2\}, \{5\}, \{2\}, \{1\}, \{5\}\}$

$\bowtie S(G, lab) = \{\{1, 2\}, \{5\}, \{3\}, \{4\}\}$
**Example: Division by SCC**

\[
S(G[1, 2], lab) = \{\{1, 2\}, \{2\}, \{1\}\}
\]

\[
S(G[5], lab) = \{\{5\}\}
\]

\[
S(G[3, 4], lab) = \{\{3\}, \{4\}, \{3\}\}
\]
Algorithm
Divide an Conquer

Example: Division by SCC

\[ S(G[1, 2], \text{lab}) = \{\{1, 2\}, \{2\} \{1\}\} \]
\[ S(G[5], \text{lab}) = \{\{5\}\} \]
\[ S(G[3, 4], \text{lab}) = \{\{3\} \{4\}, \{4\} \{3\}\} \]

Then,

\[ S(G, \text{lab}) = S(G[1, 2], \text{lab}) \circ_n S(G[5], \text{lab}) \circ_n S(G[3, 4], \text{lab}) \]
\[ = \{\{1, 2\} \{5\}, \{2\} \{1\} \{5\}\} \circ_n \{\{3\} \{4\}, \{4\} \{3\}\} \]
\[ = \{\{1, 2\} \{5\} \{3\} \{4\}, \{1\} \{2\} \{5\} \{3\} \{4\}, \{1, 2\} \{5\} \{4\} \{3\}, \{1\} \{2\} \{5\} \{4\} \{3\}\} \]
Bridges

Divide by Bridges

Let \((G, \text{lab})\) a connected digraph, \(G_U\) the underlying digraph of \(G\) and \(uv \in E(G_U)\) a bridge that divide \(G\) in \(G_1\) and \(G_2\), then

\[
S(G, \text{lab}) = S(G_1, \text{lab}|_{A(G_1)}) \circ \{u,v\} S(G_2, \text{lab}|_{A(G_2)})
\]
Example: Division by Bridges
Example: Division by Bridges
Example: Division by Bridges
Example: Division by Bridges

\[ S_1 \circ_{nrm,4} S_2 = \{\{1, 2, 3\}, \{3\}\{1, 2\}, \{3\}\{1\}\{2\}\} \circ_{nrm,4} \{\{6\}\{5\}\{4\}, \{6\}\{4\}\{5\}\}\]

\[
\begin{align*}
\{1, 2, 3\}\{6\}\{5\}\{4\} & \quad \{6\}\{5\}\{4\}\{1, 2, 3\} & \quad \{6\}\{5\}\{4, 1, 2, 3\} \\
\{3\}\{1, 2\}\{6\}\{5\}\{4\} & \quad \{6\}\{5\}\{4\}\{3\}\{1, 2\} & \quad \{3\}\{6\}\{5\}\{4, 1, 2\} \\
\{3\}\{1\}\{2\}\{6\}\{5\}\{4\} & \quad \{6\}\{5\}\{4\}\{3\}\{1\}\{2\} & \quad \{3\}\{1\}\{6\}\{5\}\{4, 2\} \\
\{1, 2, 3\}\{6\}\{4\}\{5\} & \quad \{6\}\{4\}\{5\}\{1, 2, 3\} & \quad \{6\}\{4, 1, 2, 3\}\{5\} \\
\{3\}\{1, 2\}\{6\}\{4\}\{5\} & \quad \{6\}\{4\}\{5\}\{3\}\{1, 2\} & \quad \{3\}\{6\}\{4, 1, 2\}\{5\} \\
\{3\}\{1\}\{2\}\{6\}\{4\}\{5\} & \quad \{6\}\{4\}\{5\}\{3\}\{1\}\{2\} & \quad \{3\}\{1\}\{6\}\{4, 2\}\{5\}
\end{align*}
\]
Example: UpdateLabel

```
Algorithm

Example

Example: UpdateLabel

```

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Update schedules in Boolean networks

Marseille 2017
Example: UpdateLabel

```
Example: UpdateLabel
```

```
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```
Example: UpdateLabel
Example: UpdateLabel
Example: UpdateLabel
Example: UpdateLabel
Example: UpdateLabel
Example: UpdateLabel
Example: UpdateLabel
Example: UpdateLabel
Example: UpdateLabel

Algorithm

Example
Example: UpdateLabel

Algorithm

Example

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Example: UpdateLabel
Example: UpdateLabel

Algorithm

Example

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Example: UpdateLabel

Algorithm

Example

Update schedules in Boolean networks

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Example: UpdateLabel

\[
\begin{align*}
&\oplus \quad \ominus \\
&\ominus \quad \oplus
\end{align*}
\]
Example: UpdateLabel
## Results

| Graph | Nodes | Arcs | $|S(G, \text{lab})|$ | SimpleLabel | Label |
|-------|-------|------|----------------|-------------|-------|
| $K_3$  | 3     | 6    | 13             | 0.02        | 0.02  |
| $K_5$  | 5     | 20   | 541            | 0.18        | 0.13  |
| $K_7$  | 7     | 42   | 47293          | 140.76      | 0.79  |
| $K_8$  | 8     | 56   | 545835         | > 22200.00  | 1.90  |
| $P_{10}$ | 10   | 18   | 19683          | 4.43        | 0.02  |
| $P_{12}$ | 12   | 22   | 177147         | 313.68      | 0.02  |
| $P_{50}$ | 50   | 98   | $3^{49}$       | –           | 0.09  |
| $P_{200}$ | 200  | 398  | $3^{199}$      | –           | 0.17  |
### Results for the network of mammalian cell cycle

<table>
<thead>
<tr>
<th>SimpleLabel</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>(sec)</td>
<td>(sec)</td>
</tr>
</tbody>
</table>

Number of update schedule: 466 712 5.230 2.966
Number of extensions: 1 440 0.016 0.033

Finally, only 216 non-equivalent update schedules have this cycle as an attractor.
 References


