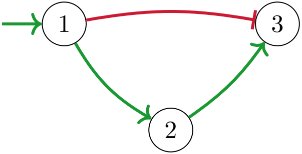
Most Permissive Semantics

Juri Kolčák

Friday 5th December, 2025

Incoherent Feed-Forward Loop 3



$$f_1(\mathbf{x}) = 1$$
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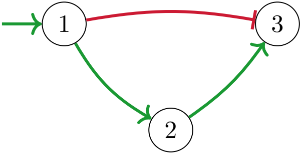

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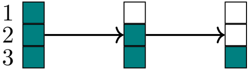

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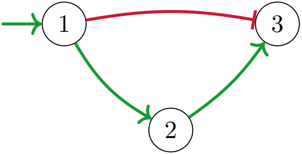

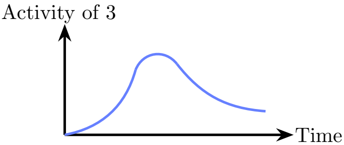

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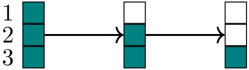
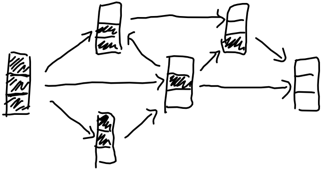
$f_1(x) = 1$

$f_2(x) = x_1$

$f_3(x) = \neg x_1 \lor x_2$





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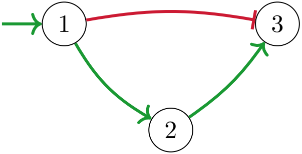

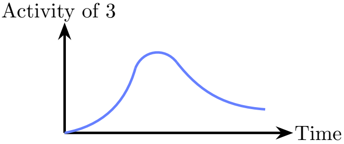

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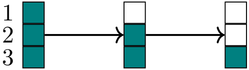
$1 \xrightarrow{+} 2$ and $2 \xrightarrow{+} 3$ are “fast acting”, have low **activation thresholds**.

$1 \xrightarrow{-} 3$ is “slow acting”, has a high **activation threshold**.



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Transient Values

TWO NEW VARIABLE VALUES:

- $\nearrow$ – "Variable **increasing** from 0 to 1";
- $\searrow$ – "Variable **decreasing** from 1 to 0";

Expanded state set, $\hat{S} = (\mathbb{B} \cup \{\nearrow, \searrow\})^n$.
The little roof denotes configurations with transient values, $\hat{\mathbf{x}} \in \hat{S}$.

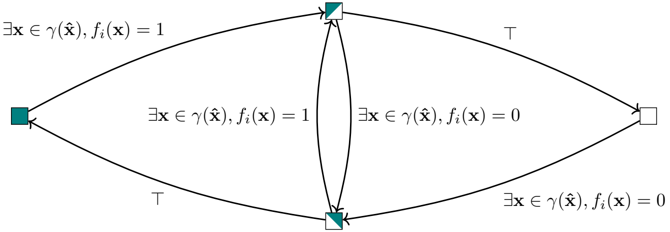
A variable that wants to increase (resp. decrease) value does not directly jump from 0 to 1 (resp. 1 to 0), but first changes to the increasing value, $\nearrow$ (resp. decreasing value, $\searrow$).

Transient values are used to denote that a variable may have crossed activation thresholds of some outgoing interactions, but possibly not all.

A variable in a transient value can thus be seen as either 0 or 1.

$$\gamma(\hat{\mathbf{x}}) \triangleq \{\mathbf{x} \in \mathbb{B} \mid \forall i \in \{1, \ldots, n\}, \hat{\mathbf{x}}_i \in \mathbb{B} \Rightarrow \mathbf{x}_i = \hat{\mathbf{x}}_i\}$$

Most Permissive Semantics



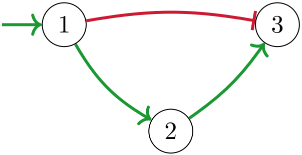
$$
\begin{aligned}
\forall \hat{\mathbf{x}} \neq \hat{\mathbf{y}} \in \hat{S}, \hat{\mathbf{x}} \xrightarrow{\hat{mp}} \hat{\mathbf{y}} \overset{\Delta}{\iff} & \exists i \in \{1, \dots, n\}, \Delta(\hat{\mathbf{x}}, \hat{\mathbf{y}}) = \{i\} \wedge \\
& [(\hat{\mathbf{x}}_i \neq 1 \wedge \hat{\mathbf{y}}_i = \nearrow \wedge \exists \mathbf{x} \in \gamma(\hat{\mathbf{x}}), f_i(\mathbf{x}) = 1) \vee \\
& (\hat{\mathbf{x}}_i \neq 0 \wedge \hat{\mathbf{y}}_i = \searrow \wedge \exists \mathbf{x} \in \gamma(\hat{\mathbf{x}}), f_i(\mathbf{x}) = 0) \vee \\
& (\hat{\mathbf{x}}_i = \nearrow \wedge \hat{\mathbf{y}}_i = 1) \vee \\
& (\hat{\mathbf{x}}_i = \searrow \wedge \hat{\mathbf{y}}_i = 0)]
\end{aligned}
$$

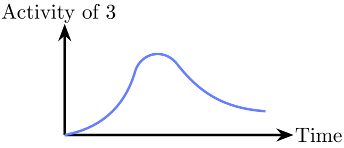
$$
\forall \mathbf{x} \neq \mathbf{y} \in \mathbb{B}^n, \mathbf{x} \xrightarrow{mp} \mathbf{y} \overset{\Delta}{\iff} \mathbf{x} \xrightarrow{\hat{mp}}{}^{*} \mathbf{y}
$$

L. Paulevé, J. Kolčák, T. Chatain, and S. Haar. Reconciling qualitative, abstract, and scalable modeling of biological networks.

Nature Communications, 11(1):4256, 08 2020

Incoherent Feed-Forward Loop 3 Revisited





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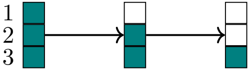

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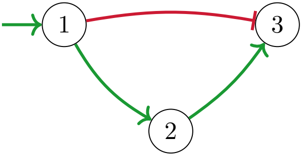

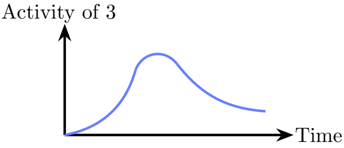

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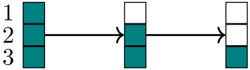
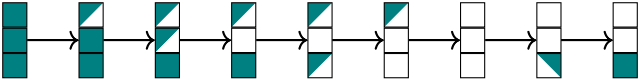
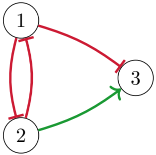




Most Permissive Semantics: Example



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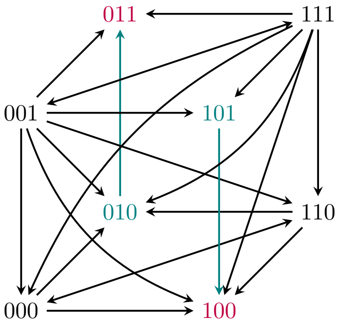
gen.



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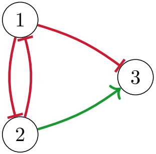

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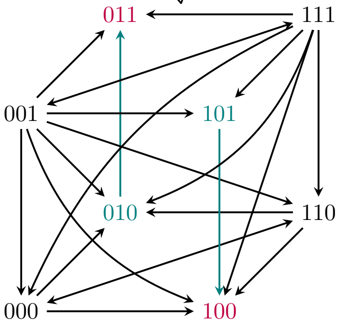
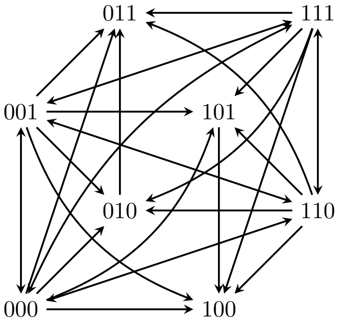


mp



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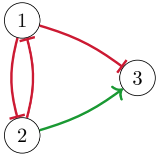

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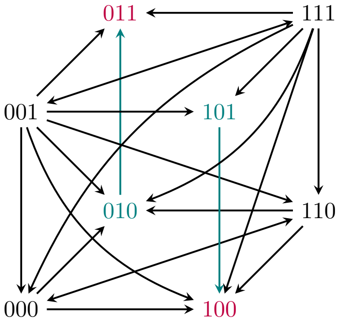
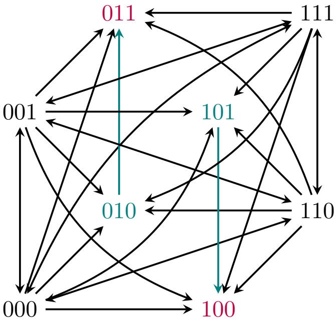




MP Semantics Properties

MONOTONICITY:

For any two MP configurations $\hat{\mathbf{x}}, \hat{\mathbf{y}} \in \hat{S}$, if for all variables $i \in \{1, \dots, n\}, \hat{\mathbf{y}}_i \in \mathbb{B} \to \hat{\mathbf{y}}_i = \hat{\mathbf{x}}_i$, then $\gamma(\hat{\mathbf{x}}) \subseteq \gamma(\hat{\mathbf{y}})$.

Let further $\hat{\mathbf{x}} \xrightarrow{\hat{mp}} \hat{\mathbf{x}}'$ be arbitrary such that $\hat{\mathbf{x}}'_j \in \{\nearrow, \searrow\}$ with $\{j\} = \Delta(\hat{\mathbf{x}}, \hat{\mathbf{x}}')$. Then either, $\hat{\mathbf{y}}_j = \hat{\mathbf{x}}'_j$, or there exists an MP configuration $\hat{\mathbf{y}}' \in \hat{S}$ such that $\hat{\mathbf{y}} \xrightarrow{\hat{mp}} \hat{\mathbf{y}}'$ with $\hat{\mathbf{x}}'_j = \hat{\mathbf{y}}'_j$.

“A variable update cannot be disabled by putting another variable into transient value.”

TRANSITIVITY:

For any $\mathbf{x}, \mathbf{y}, \mathbf{z} \in \mathbb{B}^n$, $\mathbf{x} \xrightarrow{mp} \mathbf{y}$ and $\mathbf{y} \xrightarrow{mp} \mathbf{z} \Rightarrow \mathbf{x} \xrightarrow{mp} \mathbf{z}$.

ATTRACTORS:

The attractors of an MPBN are exactly the minimal trap spaces.

$x \in \mathbb{B}^n$ $x \in A$ for some attractor A

Let $[x]_T$ be the smallest trap space containing x.

$A \neq [x]_T \Rightarrow \exists z \in [x]_T$ s.t. $x \overset{mp}{\not\rightarrow}{}^* z$

$\exists i \in \{1, \dots, n\}$ $z_i \neq x_i$

$z' \in [x]_T$ s.t. $z'_i = z_i$ and $x \xrightarrow{mp}{}^* z'$

such z' has to exist, otherwi fixing variable i to x_i would to a smaller trap space.

For every variable $i \in \{1, \dots, n\}$ free in $[x]_T$, we can reach a configuration z' with $z'_i \neq x_i$ From x

$x \xrightarrow{\hat{mp}}{}^* z'$ we can "stop before collapsing to Boolean values"

$\Rightarrow$ we reach $\hat{z}'$ such that $\gamma(\hat{z}') \supseteq \gamma(x)$

$\Rightarrow$ We can flip all free variables in sequence and reach $y \in [x]_T$ s.t. $y_i \neq x_i$ on all free variables

We can pick any subset $W \subseteq \{1, \dots, n\}$ of the free variables and reach $x^{\overline{W}}$, $x \xrightarrow{mp} x^{\overline{W}}$

$\exists W \subseteq \{1, \dots, n\}$ of free variable such that $z = x^{\overline{W}}$

"If we can cross the diagonal of hyper-cube, we can also walk along the sides"

Refinements

Let f be a Boolean network and g be a discrete multivalued network of the same dimension n, and let $\mathbb{M}$ be the state space of g ($\mathbb{M} = \{0, \dots, m_1\} \times \dots \times \{0, \dots, m_n\}$).

We define a function $\beta \colon \mathbb{M} \to 2^{\mathbb{B}^n}$ assigning to every multivalued configuration $\mathbf{x} \in \mathbb{M}$ a set of **possible binarisations** as follows:

$$\beta(\mathbf{x}) = \{\mathbf{y} \in \mathbb{B}^n \mid \forall i \in \{1, \dots, n\}, (\mathbf{x}_i = 0 \Rightarrow \mathbf{y}_i = 0) \wedge (\mathbf{x}_i = m_i \Rightarrow \mathbf{y}_i = 1)\}$$

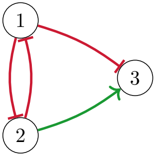
The multivalued network g is a **refinement** of the Boolean network f if and only if for every variable $i \in \{1, \dots, n\}$ and for every multivalued configuration $\mathbf{x} \in \mathbb{M}$, there exists a Boolean configuration $\mathbf{y} \in \beta(\mathbf{x})$ such that $g_i(\mathbf{x}) = f_i(\mathbf{y})$.

The same notion applies to ODE models, with the exception of not considering maxima in β and using derivatives in place of the local functions $g_1, \dots, g_n$.

Multivalued Refinement: Example

$m_1 = m_2 = 2$

$m_3 = 1$



$$f_1(\mathbf{x}) = \neg \mathbf{x}_2 \qquad g_1(\mathbf{x}) = \mathbf{x}_2 < 2$$
$$f_2(\mathbf{x}) = \neg \mathbf{x}_1 \qquad g_2(\mathbf{x}) = \mathbf{x}_1 < 2$$
$$f_3(\mathbf{x}) = \neg \mathbf{x}_1 \wedge \mathbf{x}_2 \qquad g_3(\mathbf{x}) = \mathbf{x}_1 < 2 \text{ and } \mathbf{x}_2 > 0$$

threshold of $1 \Rightarrow 2$

$\downarrow$

$g_2(x) = \neg \delta_1(x_1) \qquad \delta_1(x_1) = \begin{cases} 0 & \text{if } x_1 < \tau_{1,2} \\ 1 & \text{if } x_1 \geq \tau_{1,2} \end{cases}$

$$\beta(000) = \{000\} \qquad \beta(001) = \{001\}$$
$$\beta(100) = \{000, 100\} \qquad \beta(101) = \{001, 101\}$$
$$\beta(200) = \{100\} \qquad \beta(201) = \{101\}$$
$$\beta(010) = \{000, 010\} \qquad \beta(011) = \{001, 011\}$$
$$\beta(020) = \{010\} \qquad \beta(021) = \{011\}$$
$$\beta(110) = \{000, 100, 010, 110\} \qquad \beta(111) = \{001, 101, 011, 111\}$$
$$\beta(210) = \{100, 110\} \qquad \beta(211) = \{101, 111\}$$
$$\beta(120) = \{010, 110\} \qquad \beta(121) = \{011, 111\}$$
$$\beta(220) = \{110\} \qquad \beta(221) = \{111\}$$

The MPBN Abstraction is Complete

Let f be a Boolean network of dimension n and let g be a multivalued refinement of f with state space $\mathbb{M} = \{0, \dots, m_1\} \times \cdots \times \{1, \dots, m_n\}$.

For every multivalued configuration $\mathbf{x} \in \mathbb{M}$, let $\hat{\beta}(\mathbf{x}) = \Big\{\hat{\mathbf{x}} \in \hat{S} \mid \forall i \in \{1, \dots, n\}, (\hat{\mathbf{x}}_i = 0 \Leftrightarrow \mathbf{x}_i = 0) \wedge (\hat{\mathbf{x}}_i = 1 \Leftrightarrow \mathbf{x} = m_i)\Big\}$ be the set of all the corresponding most permissive configurations.

Then, the following theorem holds for any $\mathbf{x} \neq \mathbf{y} \in \mathbb{M}$:

$$\mathbf{x} \xrightarrow[g]{gen} \mathbf{y} \Rightarrow \forall \hat{\mathbf{x}} \in \hat{\beta}(\mathbf{x}), \exists \hat{\mathbf{y}} \in \hat{\beta}(\mathbf{y}), \hat{\mathbf{x}} \xrightarrow[f]{\hat{mp}}{}^{*} \hat{\mathbf{y}}$$

where for all $i \in \{1, \dots, n\}$:

$$\hat{\mathbf{y}}_i = \begin{cases} 0 & \text{if } \mathbf{y}_i = 0 \\ 1 & \text{if } \mathbf{y}_i = m_i \\ \nearrow & \text{if } \mathbf{y}_i > \mathbf{x}_i \text{ and } \mathbf{y}_i < m_i \\ \searrow & \text{if } \mathbf{y}_i < \mathbf{x}_i \text{ and } \mathbf{y}_i > 0 \\ \hat{\mathbf{x}}_i & \text{otherwise} \end{cases}$$

$\beta(x) = \gamma(\hat{x})$ meaning we can chose to evaluate our Boolean functions $f_i \dots$ on a configuration $z \in \gamma(\hat{x}) = \beta(x)$ such that $f_i(z) = g_i(\mathbf{x})$ for all i