Boolean Networks

Juri Kolčák

Brief History

"There is an urgent need for theories about the ways in which integrated genetic control systems might function."

– Stuart Kauffman (1969)

"The mere description of a situation as it is seen at a given state of research has often become heavy and tedious, requiring long sentences which are easily ambiguous or misleading. I have felt for some years an increasing necessity for a formalization of the concepts in the field."

– René Thomas (1973)

Boolean Abstraction

In the simplicity of the formalism, the modelled real system is necessarily abstracted.

Boolean network modelling constitutes a “top-down” abstraction, which allows us to generate hypotheses about the concrete system.

What kind of systems can be modelled by BNs

1. Made up of interacting entities.
2. Each entity is characterised by a variable quantity.
3. The events (and their mechanisms) are not directly observable, only their complete consequences.

“The base” model of complex interacting systems.

Definition - Syntax

$\mathbb{B} = \{0, 1\}$

A Boolean network of dimension $n \in \mathbb{N}$ is a function $f : \mathbb{B}^n \to \mathbb{B}^n$.

$x : \{1, \ldots, n\} \to \mathbb{B}$ is a configuration.

equivalently $x \in \mathbb{B}^n$

local function : $f_i : \mathbb{B}^n \to \mathbb{B}$

Influence Graph

Directed graph with signed edges.

$$G = (V, E)$$

$$E \subseteq V \times \{+, -\} \times V$$

In-neighbours of a node are known as **activators** or **inhibitors**.

i is an activator of j $\Leftrightarrow$ $(i, +, j) \in E$

i is an inhibitor of j $\Leftrightarrow$ $(i, -, j) \in E$

An influence graph is compatible with a Boolean network, if the edges "explain" the network.

difference

$\exists\, x, y \in \mathbb{B}^n$ with $\Delta(x,y) = \{i\} \land x_i = 0$ such that

$$\begin{cases} f_j(x) = 0 \land f_j(y) = 1 & \Rightarrow \quad (i, +, j) \in E \\ f_j(x) = 1 \land f_j(y) = 0 & \Rightarrow \quad (i, -, j) \in E \end{cases}$$

$f_1(x) = \neg x_3$

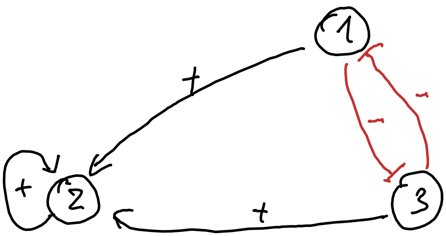
$f_2(x) = x_2 \land (x_1 \lor x_3)$

$f_3(x) = \neg x_1$

$x = (0, 0, 0)$

$y = (0, 0, 1)$

$j = 1$ $\qquad$ $i = 3$



$f_1(x) = \neg x_3$

$f_2(x) = x_2 \wedge (x_1 \vee x_3)$

$f_3(x) = \neg x_1$

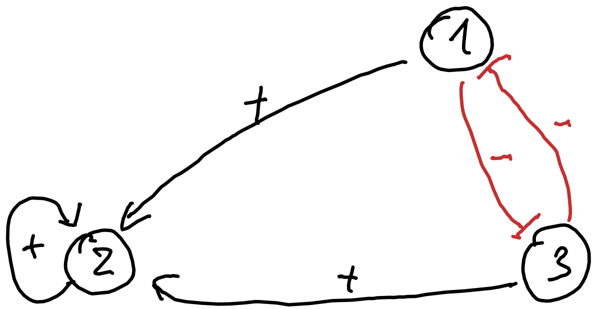
$g_1(x) = x_1 \wedge \neg x_2 \vee \neg x_3$

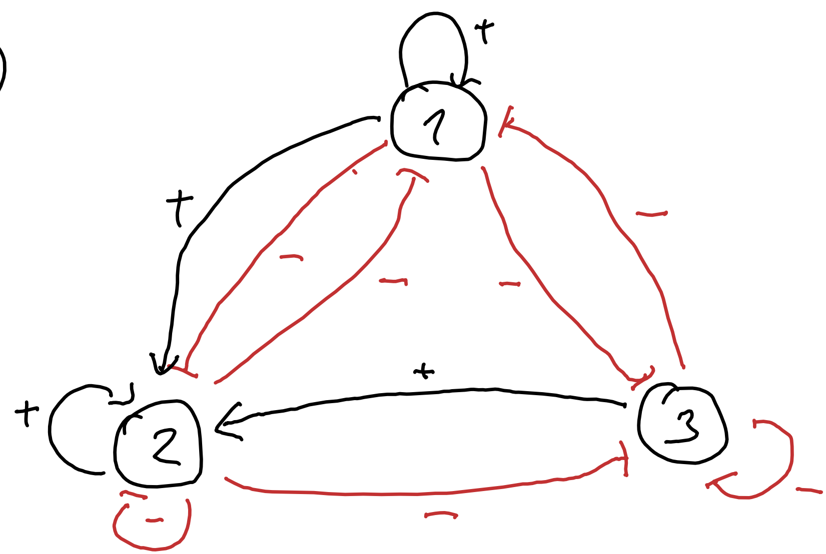
$g_2(x) = x_3 \wedge (x_1 \veebar x_2)$

$g_3(x) = \neg x_1 \vee \neg x_2 \vee \neg x_3$

$\veebar$ exclusive or (XOR)

$x \veebar y \approx (x \wedge \neg y) \vee (\neg x \wedge y)$





Discrete Regulatory Networks

Extension to a finite discrete domain
$\mathbb{M} = \{0, \ldots, k_1\} \times \cdots \times \{0, \ldots, k_n\}$, $k_1, \ldots, k_n \in \mathbb{N}$.

$f : \mathbb{M} \longrightarrow \mathbb{M}$

$x \in \mathbb{M}$

A special case are "Thomas networks", which retain the Boolean function.

D. Thieffry and R. Thomas. Dynamical behaviour of biological regulatory networks—ii. immunity control in bacteriophage lambda. *

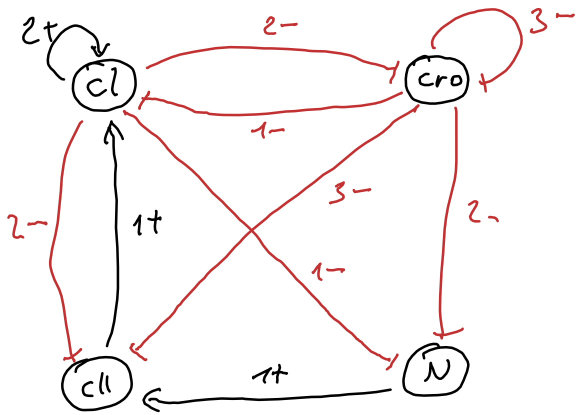
Bulletin of Mathematical Biology, 57(2):277–297, Mar 1995

$f : \mathbb{B}^n \longrightarrow \mathbb{B}^n$

$x \in \mathbb{M}$

edges have a threshold

step-wise updates



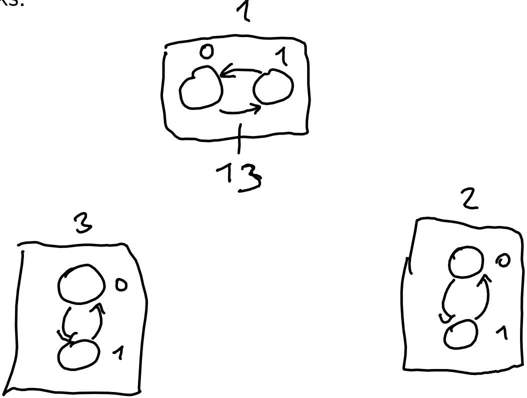
$\mathbb{M} = \{0,1,2\} \times \{0,1,2,3\} \times \mathbb{B} \times \mathbb{B}$

Automata Networks

Networks of communicating automata.

Cellular automata. von Neumann, 1966

Artificial neutral networks. McCulloch & Pitts, 1943



Dynamics

Updating function modifies configurations according to f.

$$\phi_i : \mathbb{B}^n \longrightarrow \mathbb{B}^n$$

$$\phi_i : x \longmapsto (x_1, \dots, x_{i-1}, f_i(x), x_{i+1}, \dots, x_n)$$

$$W \in \{1, \dots, n\}$$

$$\phi_W : x \longmapsto y \quad \text{such that}$$

$$\forall i \in \{1, \dots, n\} \quad y_i = \begin{cases} f_i(x) & \text{if } i \in W \\ x_i & \text{otherwise} \end{cases}$$

Transitions

An **elementary** transition exists for each application of an updating function.

$$x \xrightarrow{w}_f y \quad \Leftrightarrow \quad \phi_w(x) = y$$

A **non-elementary** transition exists for each predefined sequence of updating function applications.

$$x \xrightarrow{w_1,\dots,w_k}_f y \quad \Leftrightarrow \quad \phi_{w_k} \circ \dots \circ \phi_{w_1}(x) = y$$

A **trajectory** is a sequence of consecutive transitions.

$$x_0 \longrightarrow x_1 \longrightarrow \dots \longrightarrow x_k \quad \hat{=} \quad x_0 \longrightarrow^* x_k$$

An **updating mode** specifies a subset of elementary and non-elementary transitions.

$$(\mathbb{B}^n, \longrightarrow_{(f,\mu)}) \quad \mu\text{-updating mode}$$

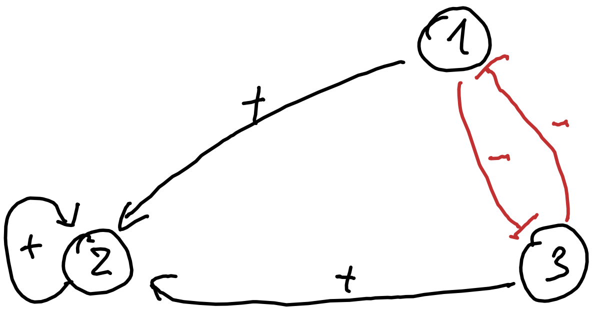
↳ subset of elementary and non-elementary transitions

$$f_1(x) = \neg x_3$$

$$f_2(x) = x_2 \wedge (x_1 \vee x_3)$$

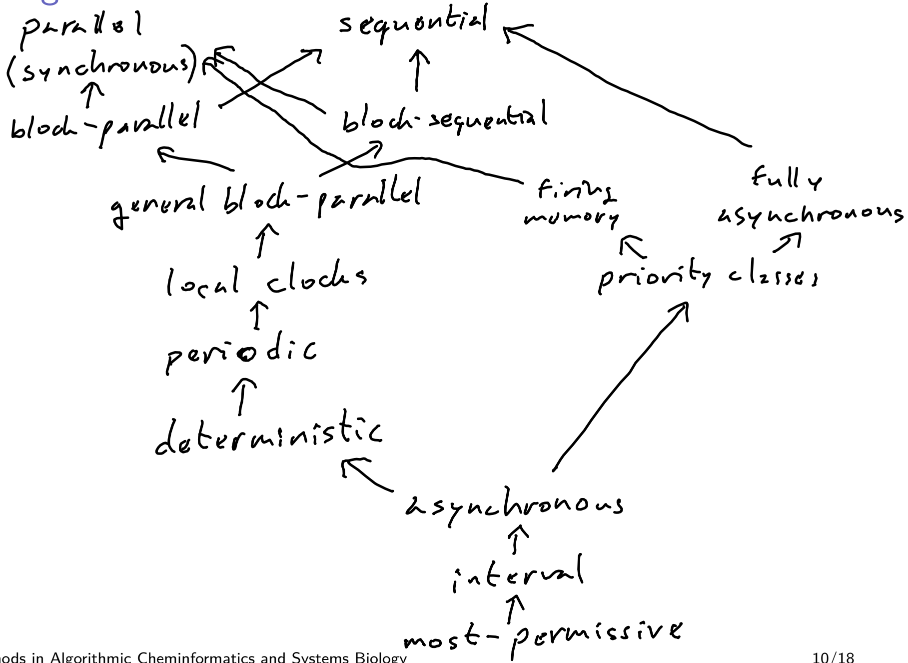
$$f_3(x) = \neg x_1$$

$$x \in \mathbb{B}^3$$

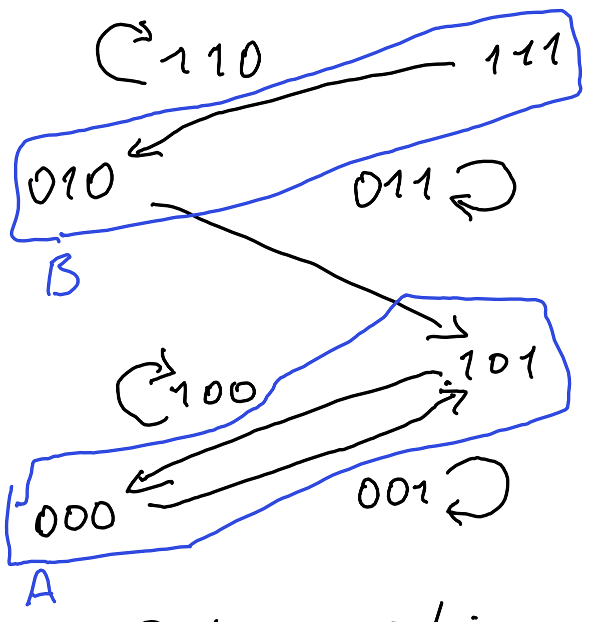


x	$f_1(x)$	$f_2(x)$	$f_3(x)$	ϕ_1	$\phi_{\{2,3\}}$	$\phi_{\{1,2,3\}}$
$(0,0,0)$	1	0	1	$(1,0,0)$	$(0,0,1)$	$(1,0,1)$
$(0,0,1)$	0	0	1	$(0,0,1)$	$(0,0,1)$	$(0,0,1)$
$(0,1,0)$	1	0	1	$(1,1,0)$	$(0,0,1)$	$(1,0,1)$

Updating Modes



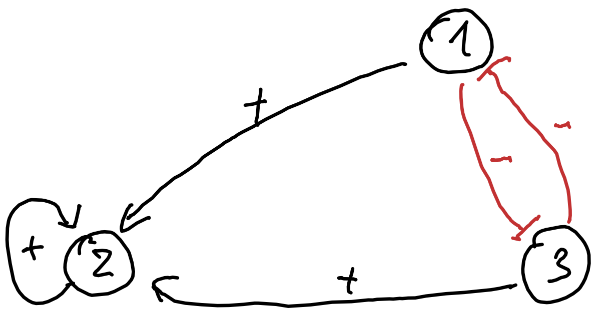
Synchronous μ_s only transitions $x \xrightarrow{W}_f y$ such that $W = \{1, \dots, n\}$



$f_1(x) = \neg x_3$

$f_2(x) = x_2 \wedge (x_1 \vee x_3)$

$f_3(x) = \neg x_1$



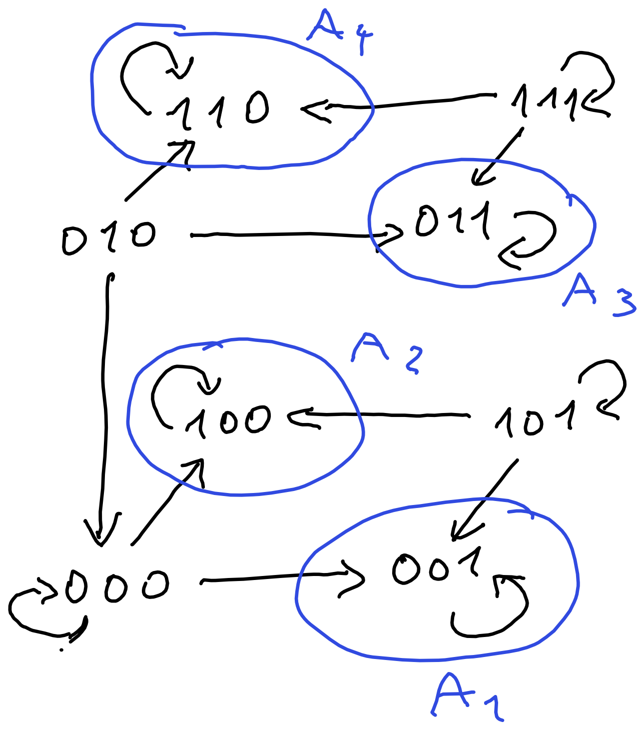
→ Deterministic

A → cyclic attractor (reachable bottom strongly connected component)

B → strong basin of attraction of A

" A is the only reachable attractor
(weak = A is reachable, but there are other reachable attractors.)

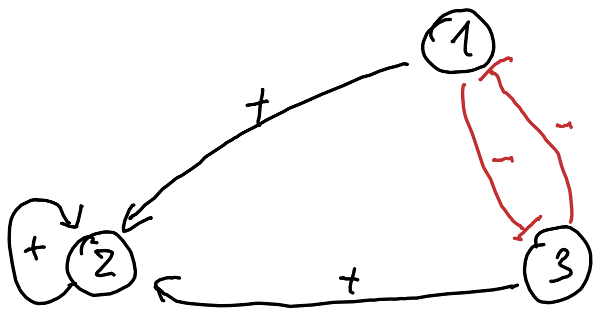
Fully asynchronous μ_f - only transitions $x \xrightarrow{W}_f y$ such that $W = \{i\}$ for $i \in \{1, \dots, n\}$



$f_1(x) = \neg x_3$

$f_2(x) = x_2 \wedge (x_1 \vee x_3)$

$f_3(x) = \neg x_1$



→ Non-deterministic

$A_1, \dots, A_4$ → attractors (simple)

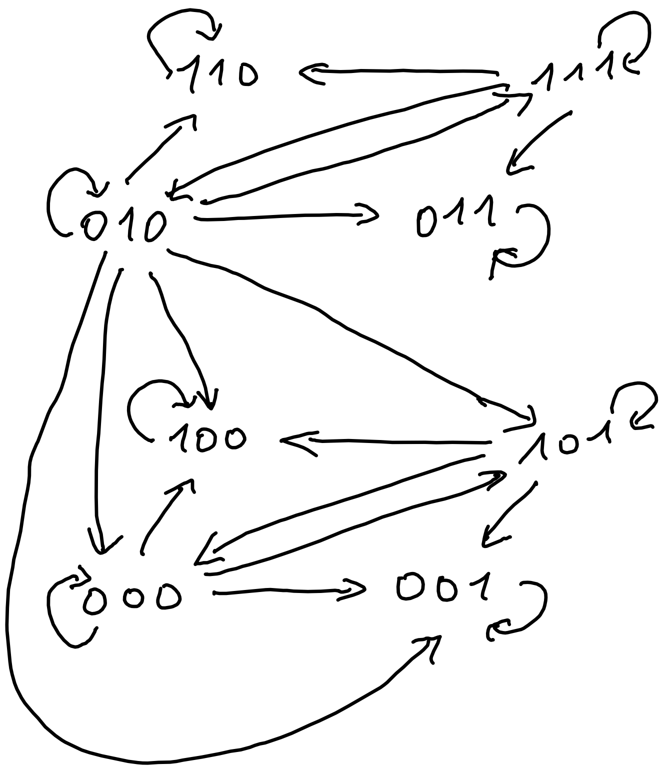
weak basins of attraction:

A_1 ... $\{101, 000, 010\}$ A_3 ... $\{111, 010\}$

A_2 ... $\{101, 000, 010\}$ A_4 ... $\{111, 010\}$

No strong basins!

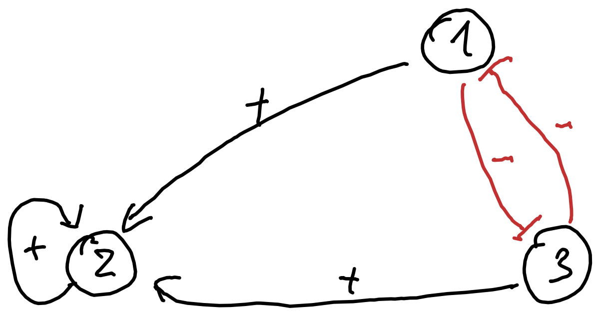
Asynchronous μ_a - all elementary transitions $x \xrightarrow{W}_f y$, $W \subseteq \{1, \dots, n\}$



$f_1(x) = \neg x_3$

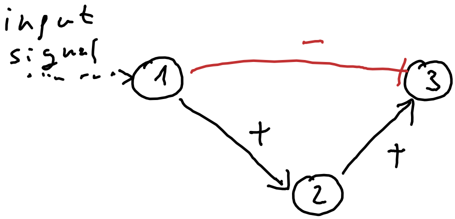
$f_2(x) = x_2 \wedge (x_1 \vee x_3)$

$f_3(x) = \neg x_1$



Incoherent Feed-Forward Loop of type 3 (I3-FFL)

S. Mangan and U. Alon. Structure and function of the feed-forward loop network motif. *Proceedings of the National Academy of Sciences*, 100(21):11980–11985, 2003

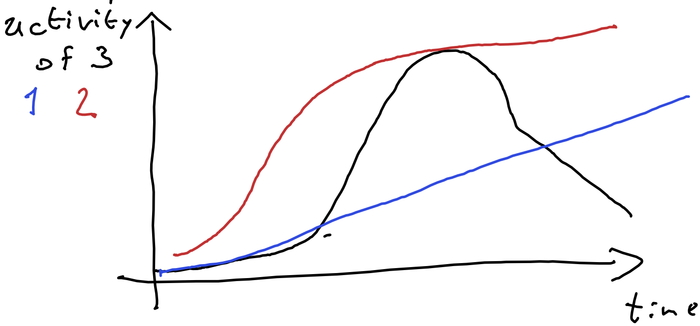


$$f_1(x) = 1$$
$$f_2(x) = x_1$$
$$f_3(x) = \neg x_1 \wedge x_2$$

asynchronous:

$$000 \longrightarrow 100 \longrightarrow 110 \circlearrowleft$$

qualitative measurements:



Most Permissive

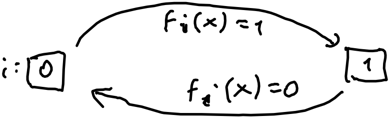
L. Paulevé, J. Kolčák, T. Chatain, and S. Haar. Reconciling qualitative, abstract, and scalable modeling of biological networks.

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

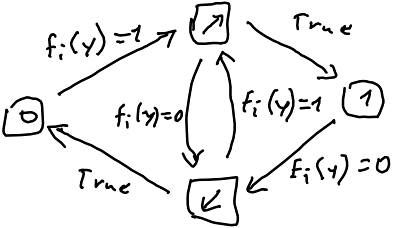
Succinctly defined using widening and narrowing operators on elementary set updates. A slightly more illustrative definition introduces pseudo-dynamical states.

$$x \in \{0, 1, \nearrow, \searrow\}^n$$

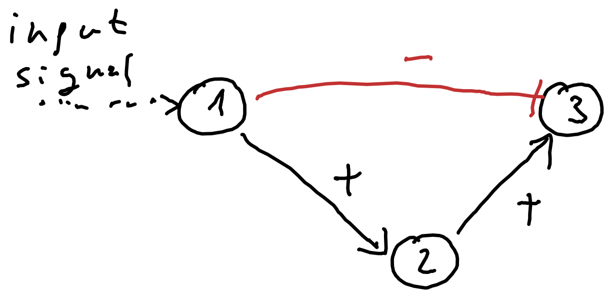
in elementary & non-elem.:



most-permissive:



$y \in \beta(x)$



$$f_1(x) = 1$$
$$f_2(x) = x_1$$
$$f_3(x) = \neg x_1 \wedge x_2$$

most permissive:

$$\begin{tikzcd} & & \vdots & & & \\ 000 \arrow[r] & \nearrow 00 \arrow[r] \arrow[d] & \nearrow\nearrow 0 \arrow[r] \arrow[d] & \nearrow\nearrow\nearrow \arrow[r] & \dots \arrow[r] & 111 \\ & 100 \arrow[r] & 1\nearrow 0 & & & \\ & & \vdots & & & \end{tikzcd}$$

$$\Phi^0(\{(0,0,0)\}) = \nabla(\{(0,0,0)\}) = \{(0,0,0)\}$$

$$\Phi(\{(0,0,0)\}) = \nabla(\{(0,0,0),(1,0,0)\}) = \{(0,0,0),(1,0,0)\}$$
$$\approx (*,0,0)$$

$$\Phi^2(\{(0,0,0)\}) = \nabla(\{(0,0,0),(1,0,0)\} \cup \{(1,1,0)\}) =$$
$$= \{(0,0,0),(1,0,0),(1,1,0),(0,1,0)\}$$
$$\approx (*,*,0)$$

$$\Phi^3(\{(0,0,0)\}) = \nabla(\{(0,0,0),(1,0,0),(1,1,0),(0,1,0)\} \cup$$
$$\cup \{(0,1,1)\}) = \mathbb{B}^3 \approx (*,*,*)$$
$$\shortparallel$$
$$\Phi^\omega(\{(0,0,0)\}) \qquad |\mathbb{B}^3| = 8$$

$$\Delta(\mathbb{B}^3) = \{(1,0,0),(1,1,0),(1,0,1),(1,1,1)\}$$

$$\Delta_W(\cancel{X}) = \{x \in X \mid \forall i \in W, \exists y \in X, x_i = f_i(y)\}$$

Refinements

Most permissive Boolean networks are guaranteed to capture any behaviour possible in any multivalued or continuous refinement.

Multivalued $F : \mathbb{M}^n \to \{-1, 0, 1\}^n$

$\forall x \in \mathbb{M}^n$ $\quad \mathbb{M} = \{0, \dots, k\}$ for $k \in \mathbb{N}$

$\forall i \in \{1, \dots, n\}$

$$F_i(x) > 0 \Rightarrow \exists y \in \beta(x), f_i(y) = 1$$

$$F_i(x) < 0 \Rightarrow \exists y \in \beta(x); f_i(y) = 0$$

$\forall y \in \beta(x_1, \dots, x_{i-1}, 0, x_{i+1}, \dots x_n), \quad y_i = 0$

$\forall y \in \beta(x_1, \dots, x_{i-1}, k, x_{i+1}, \dots, x_n), \quad y_i = 1$

continuous model F

$$\frac{\delta F_i(x)}{dt} > 0 \Rightarrow \exists y \in \beta(x), f_i(y) = 1$$

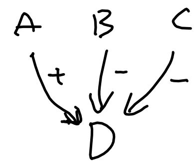
$$\frac{\delta F_i(x)}{dt} < 0 \Rightarrow \exists y \in \beta(x), f_i(y) = 0$$

Applications

- Reachability;
- Attractor analysis;
- Model inference;

↳ Literature/DB → information sufficient to construct the influence graph, but not the full BN

A	B	C	D
0	0	0	P_{000}
0	0	1	P_{001}
0	1	0	P_{010}
0	1	1	$P_{011} = 0$
1	0	0	$P_{100} = 1$
1	0	1	P_{101}
1	1	0	P_{110}
1	1	1	P_{111}



$P_{101} \geq P_{111}$

Complexity

Existence of a fixed point is NP-complete. $x = f(x)$

Reachability and attractor analysis are PSPACE-complete.

Reachability is P for locally monotone f (P^{NP} otherwise) with most permissive update mode.

Attractor analysis is co-NP for locally monotone f ($\text{co-NP}^{\text{co-NP}}$ otherwise) with most permissive update mode.

Fixed Point Stability

Fixed points are independent of the updating mode.

$$f(x) = x$$

Feedback Cycles

1980 (Robert)

If the influence graph is acyclic, every configuration of the system converges to the same attractor, a fixed point.

Thomas conjectures: 1981

1. Existence of a positive cycle in the influence graph is a necessary condition for the system having several fixed points.
2. Existence of a negative cycle in the influence graph is a necessary condition for the system having a limit cycle.

Let $C \subseteq E$ be a cycle in the influence graph

$$\mathrm{sign}(C) = \prod_{e \in C} \mathrm{sign}(e)$$

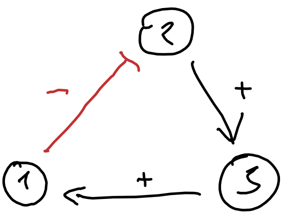
#2 fully asynchronous Richard 2010

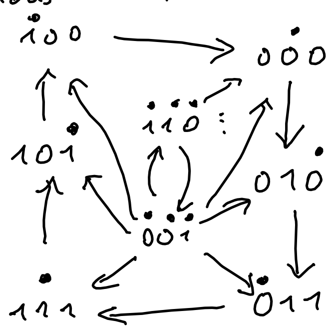
asynchronous Noual, Sené 2012

#1 synchronous Aracena et al. 2004, 2008

fully asynchronous Remy et al. 2008

asynchronous Noual 2012





Limit Properties

Aracena 2017

Let $\nu(G)$ be the maximum number of disjoint cycles in G (packing number).

Let $\tau^+(G)$ be the minimum number of vertices that meets every positive cycle of G (positive feedback vertex set).

$\nu(G) + 1 \leq$ maximum number of fixed points $\leq$

$\leq 2^{\tau^+(G)}$