Static Analysis of Boolean Networks based on Interaction Graphs: a Survey

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Motivation

Boolean Networks are interesting objects:

- High-level modelling of complex dynamical systems.
- Simple description of the evolution of the components:

$$f_1(x) = x_2 \vee x_3, \quad f_2(x) = x_1 \wedge \overline{x_3}, \quad \ldots$$

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Boolean Networks are interesting objects:

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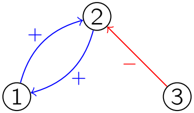
$$f_1(x) = x_2 \lor x_3, \quad f_2(x) = x_1 \land \overline{x_3}, \quad \ldots$$

But... exponential blow-up of the state space: model-checking is hard.

Overview

Interaction Graph (of f):

- Sums up the influences (either + or -) between components.
- Common abstraction (in biology, often the starting point).
- Computation of $G(f)$ is often fast.



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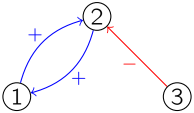

General idea: $G(f) \models P \Rightarrow f \models Q$

Pros

- P is generally very fast to check: compact proof of Q.
- There often exists a large amount of f' such that $G(f) = G(f')$.
- Help to understand some topological "patterns".

Outline

Boolean Network, Iteration Graphs

Boolean Network

- n components;
- collection of boolean functions $\langle f_1, \ldots, f_n \rangle$;
- $f_i : \mathbb{B}^n \to \mathbb{B}$ ($\mathbb{B} = \{0, 1\}$).

Example: $f_1(x) = x_3 \wedge (\overline{x_1} \vee x_2)$, $f_2(x) = x_3$, $f_3(x) = x_1 \vee x_2 \vee x_3$.

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Iteration Graphs

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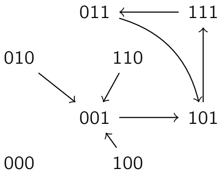

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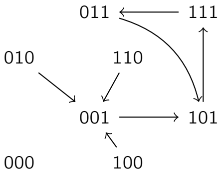
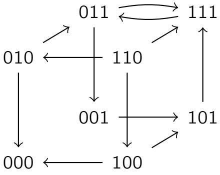


Asynchronous **IG**



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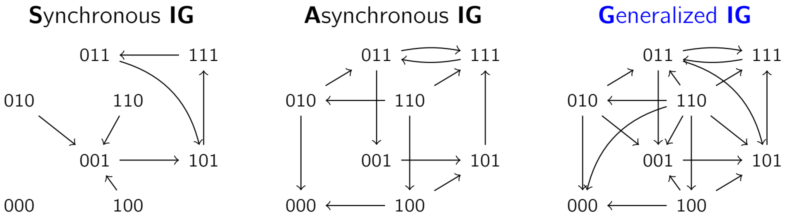

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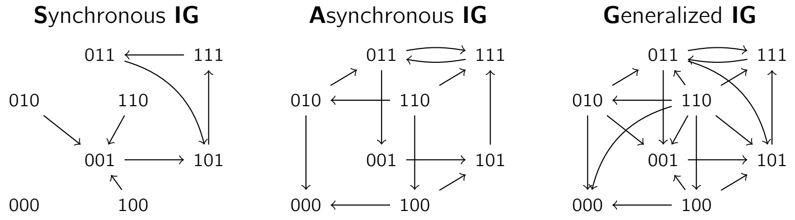


+ others (skipped).

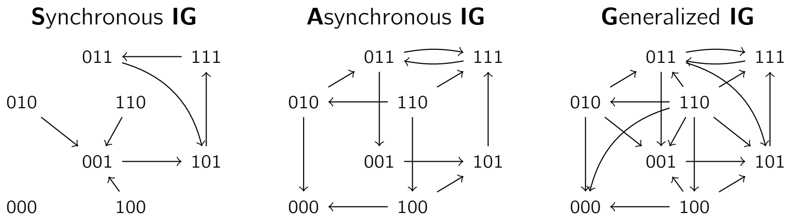
Attractors, Fixed points

Attractor

Given an **IG** Γ, $A \subseteq \mathbb{B}^n$ is an attractor iff $\forall x \to y \in \Gamma, x \in A \Rightarrow y \in A$, and A is minimal.

Fixed Point: attractor of length 1.

Examples



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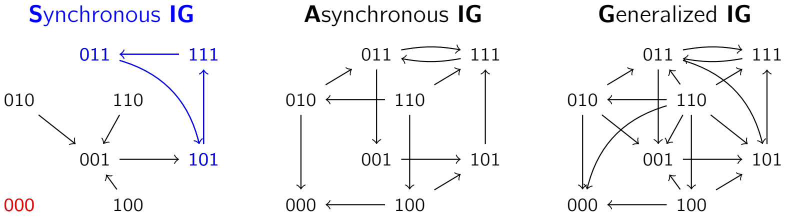

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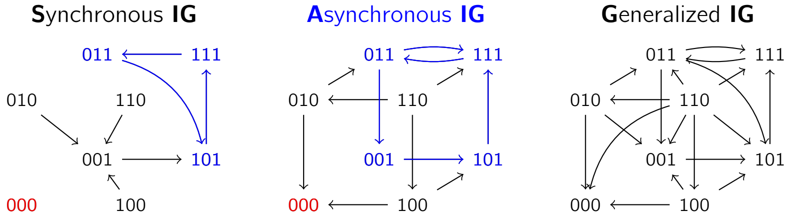

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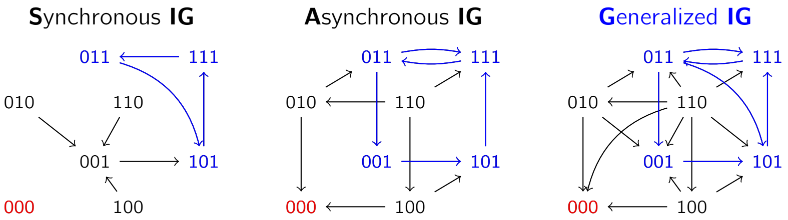

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Given a BN f, $G(f)$ is defined by:

- $j \xrightarrow{+} i \Leftrightarrow \exists x, x_j = 0, f_i(x) < f_i(\overline{x}^j)$;
- $j \xrightarrow{-} i \Leftrightarrow \exists x, x_j = 0, f_i(x) > f_i(\overline{x}^j)$.

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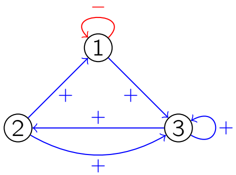


$1 \xrightarrow{-} 1 : f_1(001) > f_1(101)$;

$3 \xrightarrow{+} 2 : f_2(000) < f_2(001)$;

…

Outline

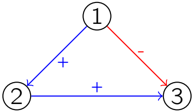
Absence of Cycles

Theorem (Robert, 1980)

If $G(f)$ has no cycle, then f has a unique fixed point x, and every path of **SIG**(f) *reaches this fixed point (in at most n steps).*

- Proved for **AIG**(f) [Robert, 1995].
- Proved for **GIG**(f) (and much more) [Bahi and Michel, 2000].

Idea: act as a delayed determinist affectation of components.



$f_1(x) = 1, \quad f_2(x) = x_1,$
$f_3(x) = \overline{x_1} \vee x_2$

Sample **SIG** path:
$000 \to 101 \to 110 \to 111$.

Absence of Positive Cycles

René Thomas' conjecture (1980): "*a necessary condition for a dynamical system to admit several stable states is the presence of a positive cycle in its interaction graph*".

Theorem (Remy, Ruet and Thieffry, 2008)

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Theorem (Aracena, Demongeot and Goles, 2004-2008)

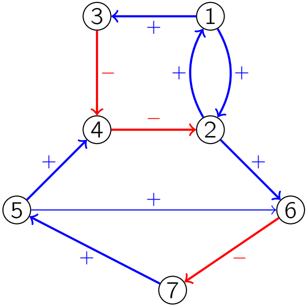
If $G(f)$ has a minimal in-degree at least one and has no positive cycle, then f has no fixed point.

Upper bound on fixed points

Theorem (Aracena, 2008; Richard, 2009)

Let I be a subset of $[n]$. If every positive cycle of $G(f)$ has a vertex in I, then **AIG**(f) *has at most $2^{|I|}$ attractors.*

Examples



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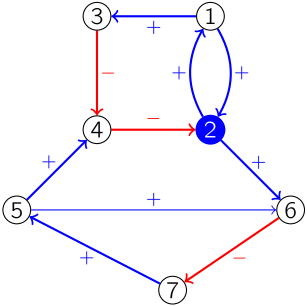

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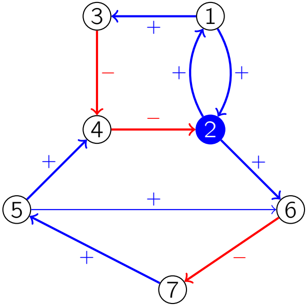

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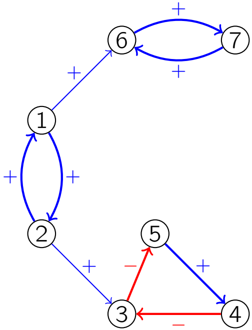

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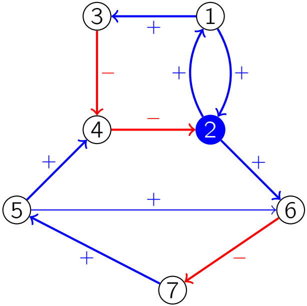

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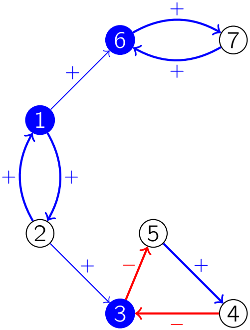

$\Rightarrow 2^3$ FP max

Absence of Negative Cycles

René Thomas' conjecture (1980) : "*a necessary condition for a dynamical system to produce sustained oscillations is the presence of a negative cycle in its interaction graph*".

Theorem (Richard, 2010)

If $G(f)$ has no negative cycle, then $\mathbf{AIG}(f)$ *has no cyclic attractor.*

$\Rightarrow$ if $G(f)$ has no negative cycle, then f has at least one fixed point (which can be computed in $O(n^2)$).

Topological Fixed Points

Topological Fixed Point: fixed-ness only depends on the graph topology.
$x \in \mathbb{B}^n$ is a TFP of f iff $\forall h : \mathbb{B}^n \to \mathbb{B}^n, G(f) = G(h) \Rightarrow h(x) = x$.

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Theorem (Paulevé and Richard, 2010)

$G(f)^\#$: $G(f)$ with simple arcs only; $p = \#$ connected components in $G(f)^\#$.

- *If the following three conditions hold, f has exactly 2^p TFP:*
  - *minimal in-degree of $G(f)^\#$ is ≥ 1;*
  - *$G(f)$ has no undirected negative cycle;*
  - *for every $i \in [n], \exists$ at most one j such that $j \xrightarrow{+} i$ and $j \xrightarrow{-} i$.*

(generalizes a theorem by Aracena, 2008)

Idea: if there is a positive (undirected) path from i to j, then $x_i = x_j$;
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- *If x is a TFP, then $\overline{x}$ is a TFP.*

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Topological Fixed Points
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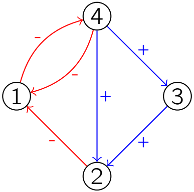
Example



- $x_1 = \overline{x_4} = \overline{x_2}$;
- $x_2 = x_3 = x_4$.

$\Rightarrow$ 0111 and 1000 are the only 2 TFPs.

Topological Fixed Points can be computed in $O(n + m)$; $m = \#$ arcs of $G(f)$.

Comparison of Iteration Graphs

Theorem (Noual 2011)

Assume that $G(f)$:

- *is simple,*
- *has no positive cycle of even length,*
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$x \to y \in \mathbf{GIG}(f) \Longrightarrow \mathbf{AIG}(f)$ *has a path from* x *to* y *of length* $|\Delta(x, y)|$.

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Hence, the number of attractors in $\mathbf{GIG}(f)$ *and* $\mathbf{SIG}(f)$ *is at least the number of attractors in* $\mathbf{AIG}(f)$.

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(continued...)

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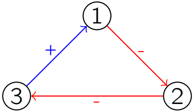

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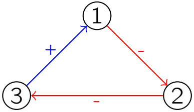

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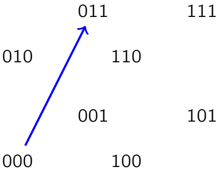

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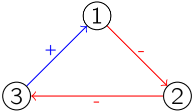

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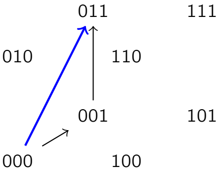

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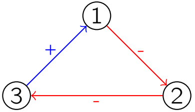

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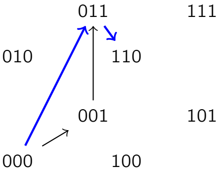

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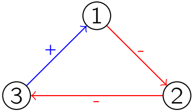

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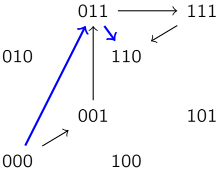

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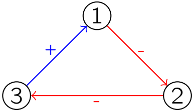

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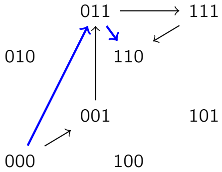
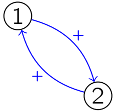
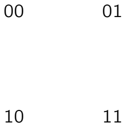




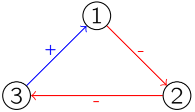
$$f_1(x) = x_2$$
$$f_2(x) = x_1$$



Comparison of Iteration Schemes

(continued...)

Examples



$$f_1(x) = x_3$$
$$f_2(x) = \overline{x_1}$$
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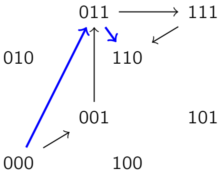

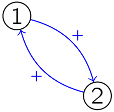

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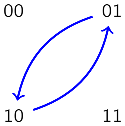
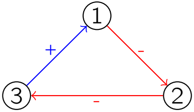


Comparison of Iteration Schemes

(continued...)

Examples



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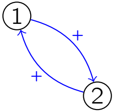

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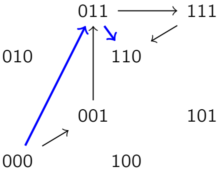

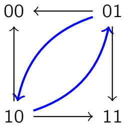

Network Reduction

Let $\tilde{f} : \mathbb{B}^{n-1} \to \mathbb{B}^{n-1}$ be defined from $f : \mathbb{B}^n \to \mathbb{B}^n$ ($n \to n \notin G(f)$) by:

$$\forall x \in \mathbb{B}^{n-1},\ \forall i \in [n-1], \qquad \tilde{f}_i(x) = f_i(\tilde{x}), \qquad \tilde{x} = (x, f_n(x,0)) \in \mathbb{B}^n.$$

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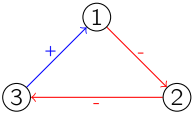
Theorem (Naldi, Remy, Thieffry, Chaouiya, 2009)

- $\tilde{f}(x) = x \Leftrightarrow f(\tilde{x}) = \tilde{x}$;
- $x \to^* y \in \textbf{AIG}(\tilde{f}) \Leftrightarrow \tilde{x} \to^* \tilde{y} \in \textbf{AIG}(f)$;
- *parity of paths in* $G(\tilde{f})$ *is the same as in* $G(f)$.

Network Reduction

(continued...)

Example



$y \in \mathbb{B}^3$
$f_1(y) = y_3$
$f_2(y) = \overline{y_1}$
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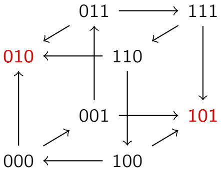
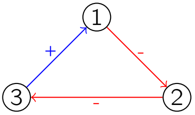


Network Reduction
(continued...)

Example



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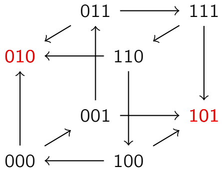
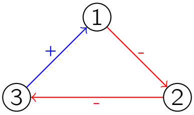


$x \in \mathbb{B}^2$
$\tilde{f}_1(x) = f_1(x, f_3(x, 0))$
$\tilde{f}_2(x) = \overline{x_1}$

Network Reduction

(continued...)

Example



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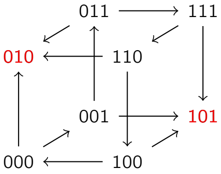

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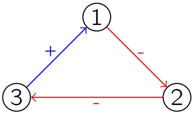
Network Reduction

(continued...)

Example



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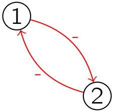

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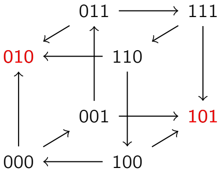

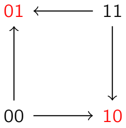

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- parity of paths in $G(\tilde{f})$ is the same as in $G(f)$.

Conclusion

- Cycles are necessary to obtain complex behaviours.
- Positive/negative cycles constrain the presence of fixed points/attractors.
- Conditions on cycles: comparison of **IG**s + network reduction.

Skipped: attractor lengths, more iteraction graphs comparisons, etc.

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Skipped: attractor lengths, more iteraction graphs comparisons, etc.

Extension to Discrete Networks:

- René Thomas' conjectures OK;
- Reduction OK;
- but not much...

Outlook

Going further with static analysis of BNs:

- Apply other kind of static analysis?
- More precise properties may need more precise abstractions.
- Analysis of quantitative features...

Related Work:

- [Naldi, Thieffry, Chaouiya, 2007]: decision diagrams to compute fixed points of BNs (and DNs).
- [Paulevé, Magnin, Roux, SASB'10]: abstract interpretation of reachability properties through the Process Hitting framework.
- (previous talk?)