Non-expansive Boolean networks

Adrien Richard

Laboratoire I3S, CNRS & Université de Nice-Sophia Antipolis

joint work with

Enrico Formenti

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A **boolean network (BN)** is a function

$$\begin{aligned} f : \{0,1\}^n &\to \{0,1\}^n \\ x = (x_1, \ldots, x_n) &\mapsto f(x) = (f_1(x), \ldots, f_n(x)) \end{aligned}$$

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The **synchronous graph** of f is the digraph on $\{0,1\}^n$ with arc set

$$\{\ x \to f(x)\ :\ x \in \{0,1\}^n\ \}.$$

- A limit cycle (or synchronous attractor) is a cycle in this graph.
- A synchronous periodic point is a point that belongs to a limit cycle.
- The fixed points of f are the limit cycles of length one.

Example

$$\begin{cases} f_1(x) & = x_2 \vee x_3 \\ f_2(x) & = \overline{x_1} \wedge \overline{x_3} \\ f_3(x) & = \overline{x_3} \wedge (x_1 \vee x_2) \end{cases}$$

x	$f(x)$
000	000
001	110
010	101
011	110
100	001
101	100
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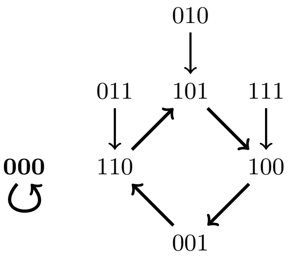
111	100

Synchronous graph



2 limits cycles
5 synchronous periodic points

The **asynchronous graph** of f is the digraph on $\{0,1\}^n$ with arc-set

$$\{\ x \to \overline{x}^i\ :\ x \in \{0,1\}^n,\ \forall i \in [n],\ f_i(x) \neq x_i\ \}.$$

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- An asynchronous attractor is a **terminal strong component**.
- An asynchronous periodic point is a point in an asyn attractor.
- The fixed points of f are the asynchronous attractors of size one.
- An asynchronous attractor of size at least two is cyclic.

Example

$$\begin{cases} f_1(x) &= x_2 \vee x_3 \\ f_2(x) &= \overline{x_1} \wedge \overline{x_3} \\ f_3(x) &= \overline{x_3} \wedge (x_1 \vee x_2) \end{cases}$$

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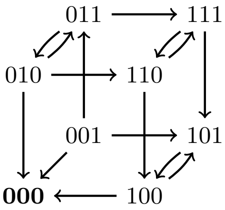

1 asynchronous attractor

1 asynchronous periodic point

The **interaction graph** of f is the **signed digraph** $\boldsymbol{G(f)}$ defined by:

- the vertex set is $\{1, \ldots, n\}$
- there is a positive arc $\boldsymbol{j \to i}$ is there exists $x \in \{0,1\}^n$ such that

$$f_i(x_1, \ldots, x_{j-1}, \mathbf{0}, x_{j+1}, \ldots, x_n) = \mathbf{0}$$
$$f_i(x_1, \ldots, x_{j-1}, \mathbf{1}, x_{j+1}, \ldots, x_n) = \mathbf{1}$$

- there is a negative arc $\boldsymbol{j \to i}$ is there exists $x \in \{0,1\}^n$ such that

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Example

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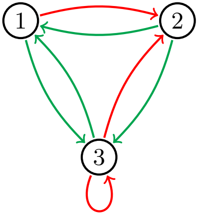
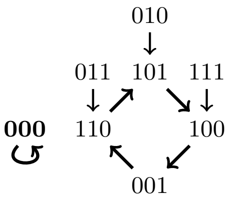
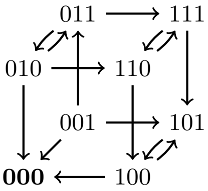
Interaction graph



Synchronous graph



Asynchronous graph



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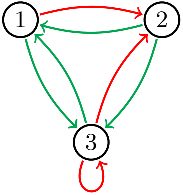

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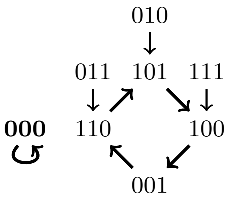
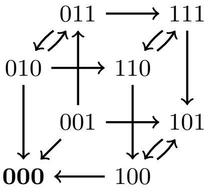


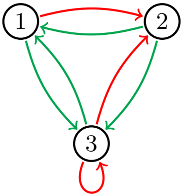
[Kauffman 69]

Asynchronous graph



[Thomas 73]

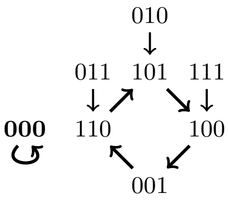
Interaction graph



Question

What can be said on the synchronous and asynchronous attractors of f according to the interaction graph $G(f)$ only?

Synchronous graph



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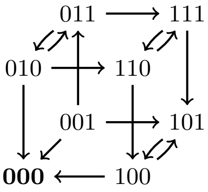

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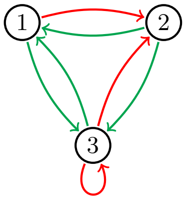

The importance of feedback cycles

Theorem [Robert 1980]

If $G(f)$ is acyclic then f has a unique fixed point and has no other synchronous or asynchronous attractor.

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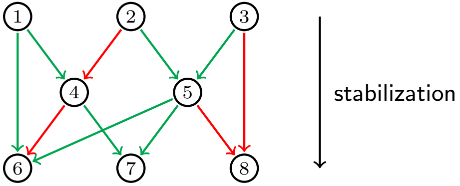

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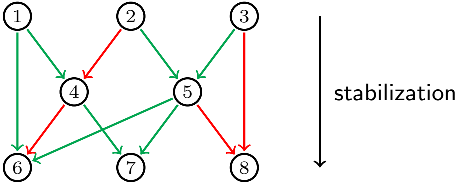

"Feedback cycles are the engines of the complexity"

According to **René Thomas**, there are **two kings of cycles**:

- positive cycles : even number of negative arcs.
- negative cycles : odd number of negative arcs.

Thomas' rules:

- Positive cycles are necessary for multistationarity.
- Negative cycles are necessary for sustained oscillations.

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Theorem [Aracena 2008]

If $G(f)$ has no positive cycle, then f has at most one fixed point.

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Theorem [Aracena 2008]

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Theorem

If $G(f)$ has no negative cycle, then f has no cyclic asynchronous att.

The dynamics of isolated cycles

Some basic facts about isolated cycles:

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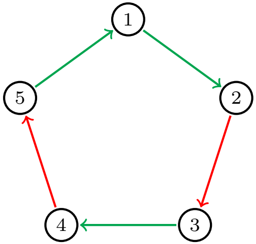
- Given a cycle C, there is a unique network f with $G(f) = C$.



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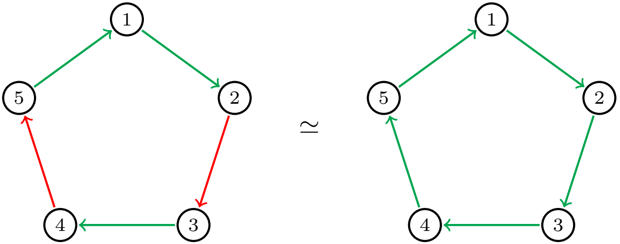
Some basic facts about isolated cycles:

- Given a cycle C, there is a unique network f with $G(f) = C$.
- Networks associated with positive cycles are pairwise isomorphic



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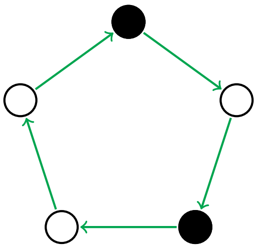

$t = 0$

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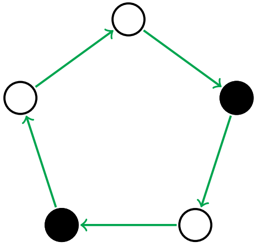

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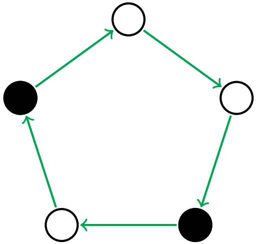

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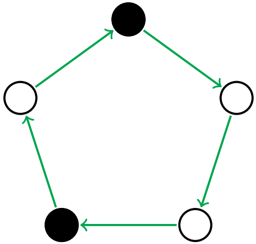

$t = 3$

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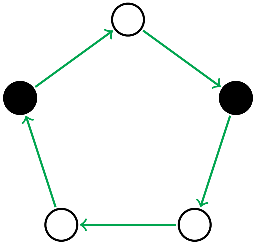

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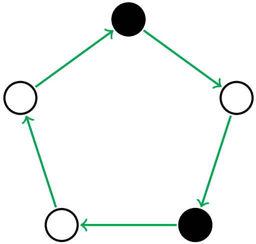

$t = 5$

Some basic facts about isolated cycles:

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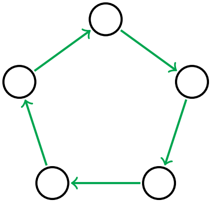

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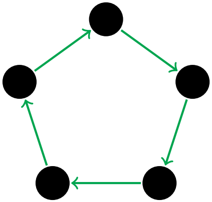

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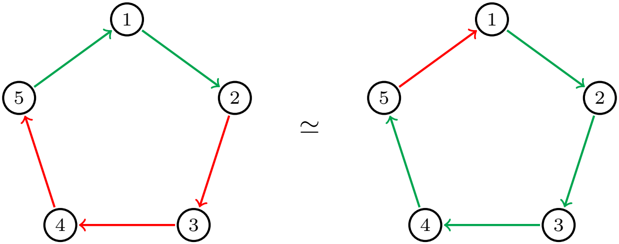

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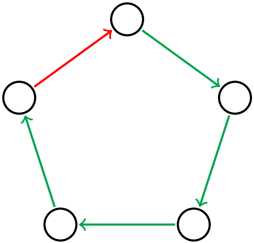

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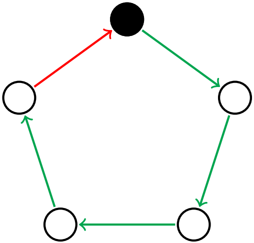

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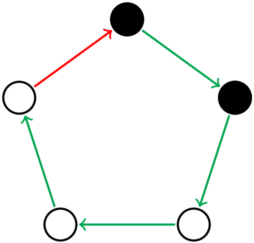

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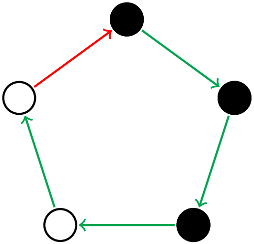

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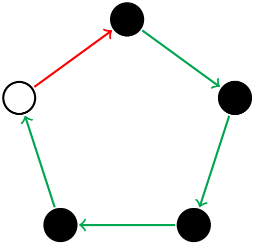

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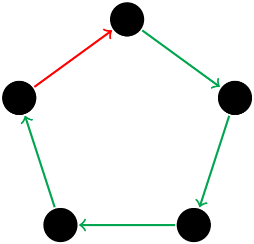

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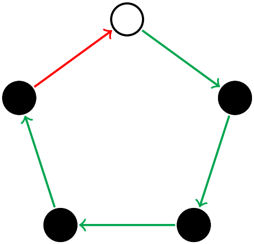

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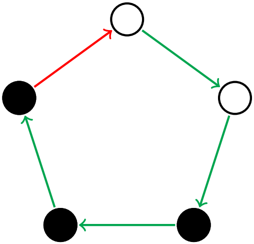

$t = 7$

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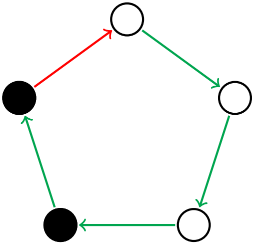

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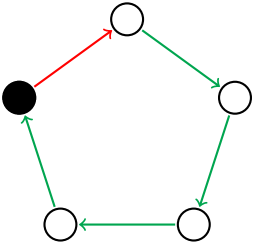

$t = 9$

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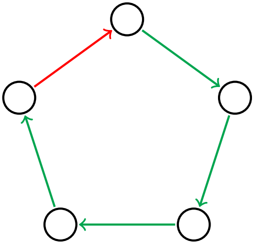

$t = 10$

Some basic facts about isolated cycles:

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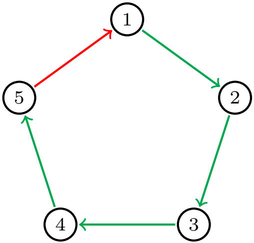

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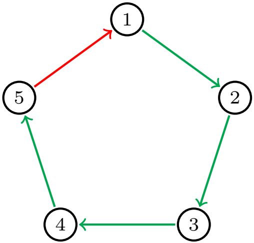

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Theorem (Synchronous isolated cycle) [Demongeot-Sené-Noual 2012]

- If $G(f)$ is a positive cycle then the nb of limit cycles of length p is

$$\begin{cases} c_p^+ & \text{if } p \mid n \\ 0 & \text{otherwise} \end{cases}$$

- If $G(f)$ is a negative cycle then the nb of limit cycles of length p is

$$\begin{cases} c_p^- & \text{if } p \mid 2n \text{ and } p \nmid n \\ 0 & \text{otherwise} \end{cases}$$

Theorem (Synchronous isolated cycle) [Demongeot-Sené-Noual 2012]

- If $G(f)$ is a positive cycle then the nb of limit cycles of length p is

$$\begin{cases} c_p^+ := \frac{1}{p}\sum_{d|p} \mu\left(\frac{p}{d}\right) 2^d & \text{if } p \mid n \\ 0 & \text{otherwise} \end{cases}$$

- If $G(f)$ is a negative cycle then the nb of limit cycles of length p is

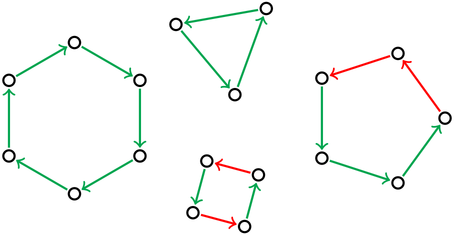
$$\begin{cases} c_p^- := \frac{1}{p}\sum_{\text{odd } d|\frac{p}{2}} \mu(d) 2^{\frac{p}{2d}} & \text{if } p \mid 2n \text{ and } p \nmid n \\ 0 & \text{otherwise} \end{cases}$$

Here, μ is the Möbius function:

$$\mu(n) := \begin{cases} 0 & \text{if } n \text{ is not square-free,} \\ 1 & \text{if } n \text{ is square-free and has an even number prime factors,} \\ -1 & \text{if } n \text{ is square-free and has an odd number prime factors.} \end{cases}$$

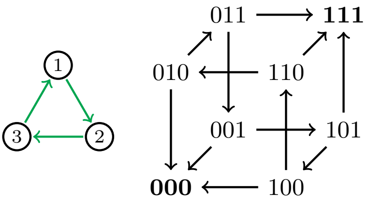
Corollary

If $G(f)$ is a disjoint union of cycles, then the number of limit cycles of a each length is known.



Proposition (Asynchronous isolated cycles) [Remy *et al* 2003]

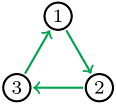
- If $G(f)$ is a positive cycle, then f has two asynchronous attractors, which are both fixed points.

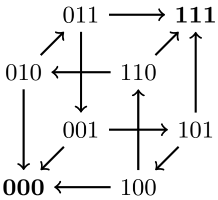


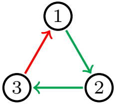
Proposition (Asynchronous isolated cycles) [Remy *et al* 2003]

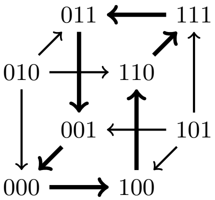
- If $G(f)$ is a positive cycle, then f has two asynchronous attractors, which are both fixed points.
- If $G(f)$ is a negative cycle, then f has a unique asynchronous att, which is cyclic attractor A of size $2n$ such that

$$\forall x \in A \qquad d(x, f(x)) = 1.$$









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If $G(f)$ is a disjoint union of cycles, with k^+ positive and k^- negative,

- f has exactly 2^{k^+} asynchronous attractors, pairwise isomorphic,
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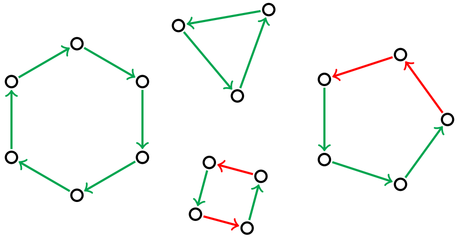
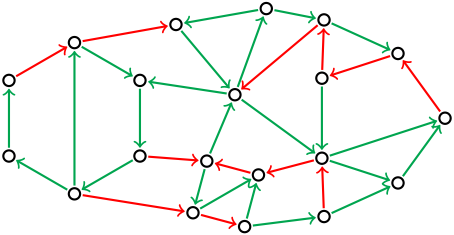


Given some synchronous/asynchronous attractors, is-it possible to identify some positive / negative cycles in $G(f)$ that could "explain" the presence of these attractors?



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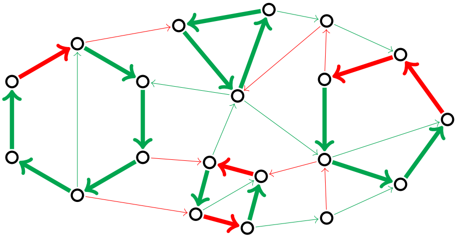

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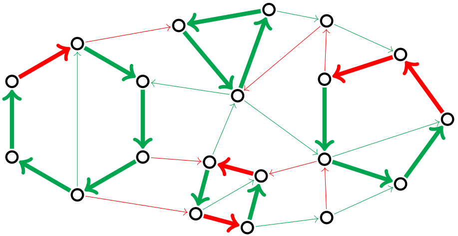
Given *two fixed points*, is-it possible to identify some *positive cycles* in $G(f)$ that could "explain" the presence of these two fixed points?



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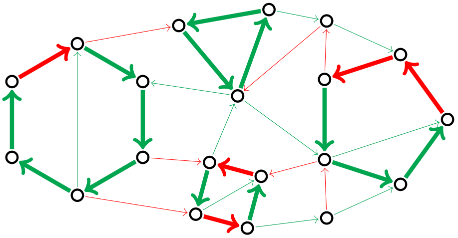

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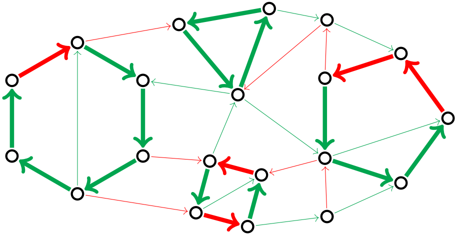
Intuition: *"key cycles are those that, in some way, behave as if isolated".*



Non-expansive networks

f is **non-expansive** if

$$\forall x, y \in \{0,1\}^n \qquad d(f(x), f(y)) \leq d(x, y)$$

Remark f is non-expansive if and only if

$$\forall x, y \in \{0,1\}^n \qquad d(x, y) = 1 \;\Rightarrow\; d(f(x), f(y)) \leq 1$$

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$\hookrightarrow$ Introduced by Shih and Ho in 1999 to establish a boolean version of the Markus-Yamabe conjecture in differential equations.

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Proposition

f is an isometry $\iff$ f is bijective and non-expansive

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f is an isometry $\iff$ f is bijective and non-expansive

$\iff$ **$G(f)$ is a disjoint union of cycles**

f is a **quasi-isometry** if

$G(f)$ is a disjoint union of cycles plus some isolated vertices

Theorem 1 [Formenti-Richard]

If f is non-expansive, there exists a unique quasi-isometry h such that:

- $G(h)$ is a spanning subgraph of $G(f)$,
- every limit cycle of f is a limit cycle of h.

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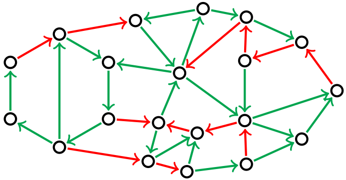

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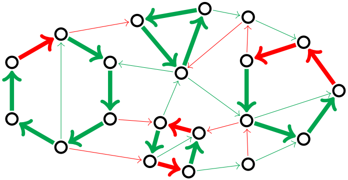

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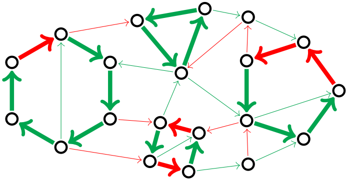

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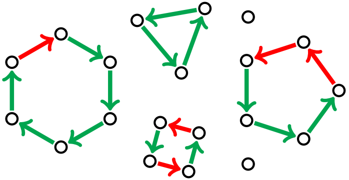

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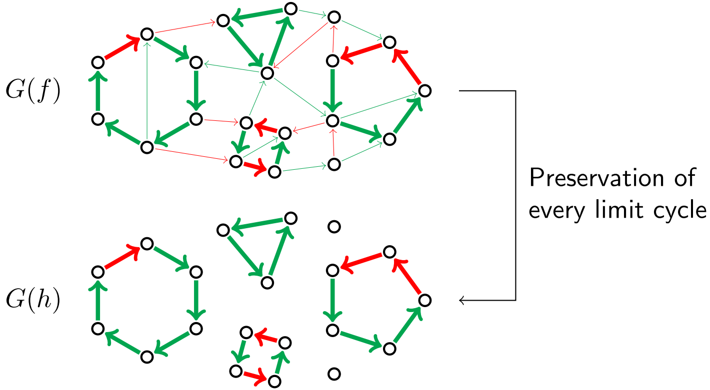

Lemma 1 If f is non-expansive and has two fixed points a and b, and no other fixed point in $[a, b]$, then $f([a, b]) = [a, b]$.

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Let Ω be the set of synchronous periodic points.

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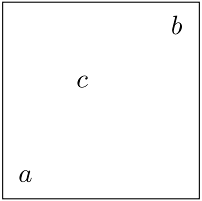

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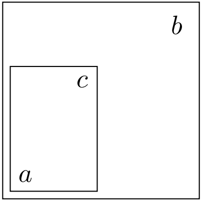

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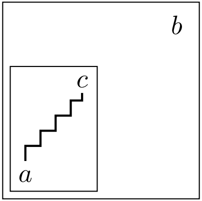

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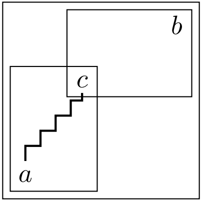

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Let p be such that $f^p(x) = x$ for all $x \in \Omega$. Then, all the synchronous periodic point of f^p are fixed points, Ω is the set of fixed points of f^p.

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Since $\Omega \cap [a, b] = \{a, b\}$, by the first lemma, $f^p([a, b]) = [a, b]$, thus all the points $c \in [a, b] \setminus \{a, b\}$ are periodic with period ≥ 2, a contradiction.

The definition of h

We suppose that there is no $i \in [n]$ and $c \in \{0,1\}$ such that $x_i = c$ for all $x \in \Omega$. This removes the case where $G(h)$ has some isolated vertices.

- Let $i \in [n]$ and $\alpha, \beta \in \Omega$ with $\alpha_i < \beta_i$ (which exists by hypothesis). Since $Q_n[\Omega]$ is connected, it has a path from α to β, and this path has an edge ab such that $a_i < b_i$.

  Let p be the period of a and q those of b.

  $$d(a,b) \geq d(f(a), f(b)) \geq \cdots \geq d(f^{pq}(a), f^{pq}(b)) = d(a,b).$$

  So $f(a)$ and $f(b)$ differs in one component j. Thus $G(f)$ has an arc from i to j of sign $f_j(b) - f_j(a)$, and we denote this signed arc A_i.

- The arcs $A_1, \ldots, A_n$ then form an union of disjoint cycles in $G(f)$, which define the isometry h.

Let $\boldsymbol{\nu}$ be the max size of a set of **disjoint cycles** in $G(f)$.
Let $\boldsymbol{\nu}^+$ be the max size of a set of **disjoint posititive cycles** in $G(f)$.
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Let ν be the max size of a set of **disjoint cycles** in $G(f)$.
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Corollary 1 If f is non-expansive, then f has at most 2^{ν^+} fixed points.

Proof

Let h be the quasi-isometry associated with f.

Let k^+ be the number of positive cycles in $G(h)$. Then

$$\text{fix}(f) \leq \text{fix}(h) \leq 2^{k^+} \leq 2^{\nu^+}.$$

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Conjecture 1 There exists $\phi : \mathbb{N} \to \mathbb{N}$ such that, for every network f,

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$$\begin{cases} (c_p)^{\nu^+} & \text{if } p \text{ is odd} \\ (c_p)^{\nu} & \text{if } p \text{ is even} \end{cases}$$

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Furthermore, $c_p \leq \sum_{d|p} c_p^+$ works, and $c_1 = 2$, $c_2 = 3$ and $c_3 = 5$.

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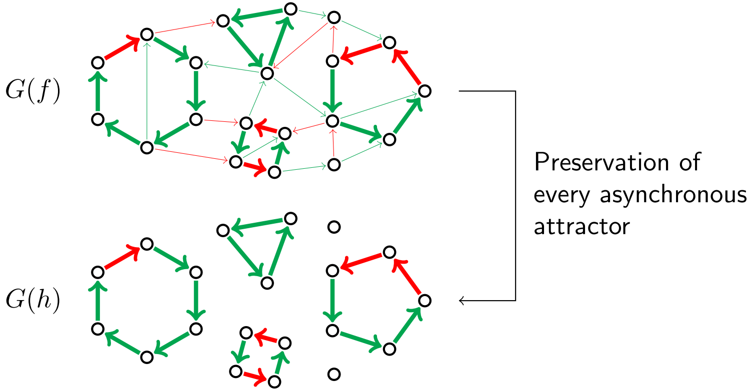

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- Let k^- be the number of negative cycles in $G(h)$.
  For every asynchronous periodic point x of f,

$$d(x, f(x)) = d(x, h(x)) = k^- \leq \nu^-.$$

Discussion

Are there many non-expansive boolean networks?

- The number of n-component BNs is

$$(2^n)^{2^n}$$

- The number of isometries with n components is

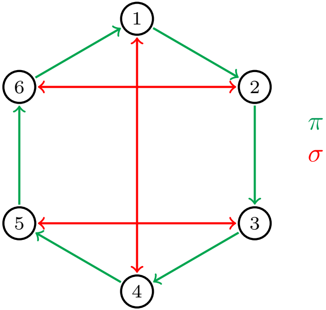
$$\mathrm{iso}(n) = 2^n n!$$

- Denoting $\mathrm{ne}(n)$ the number of non-expansive n-component BNs,

$$\mathrm{iso}(n/2) \cdot \mathrm{iso}(n) \;\leq\; \mathrm{ne}(n) \;\leq\; 2^n (n+1)^{2^n}.$$

1. Take n even, and two permutations π and σ of $[n]$ such that, $\forall i \in [n]$,

$$\pi(i) \neq i, \quad \sigma(i) \neq i, \quad \sigma^2(i) = i, \quad \pi(i) \neq \sigma(i).$$



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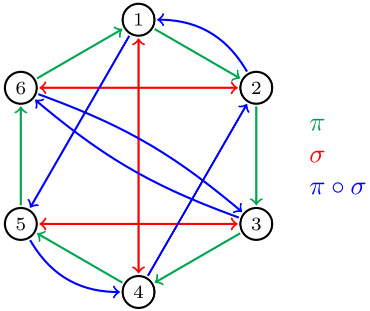
2. Let H be the union of the graph of π and $\pi \circ \sigma$; then H is 2-regular.



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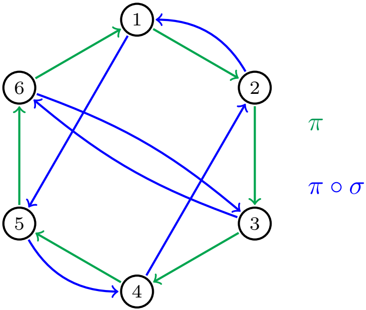

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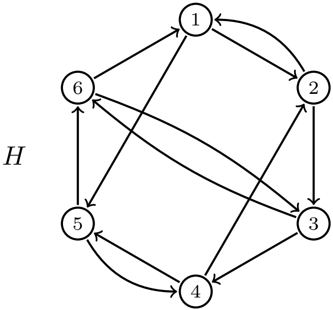

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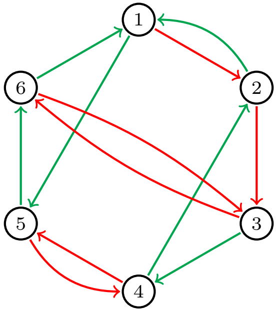
3. Put different signs on the two arcs that leave each vertex, to obtain G.

G



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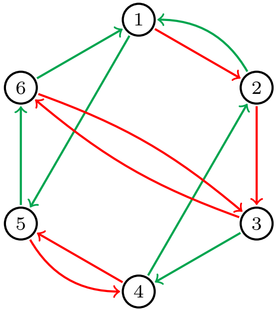
Proposition There are at least $2^{\frac{n}{2}}$ non-expansive BNs on G.

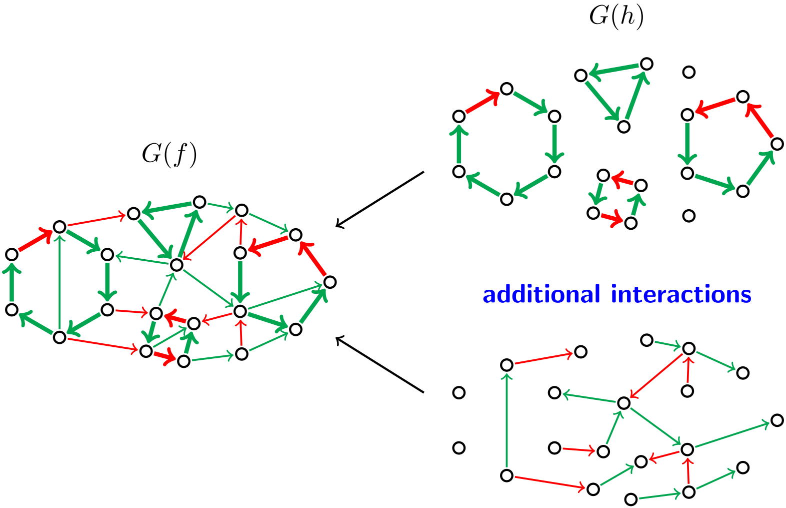
G



$$\begin{aligned}
f_1(x) &= x_2 \wedge x_6 \\
f_2(x) &= \overline{x_1} \wedge x_4 \\
f_3(x) &= \overline{x_2} \wedge \overline{x_6} \\
f_4(x) &= x_3 \wedge \overline{x_5} \\
f_5(x) &= x_1 \wedge \overline{x_4} \\
f_6(x) &= \overline{x_3} \wedge x_5
\end{aligned}$$

Perspectives

Is-it possible to quantify the missing limit cycles according to the additional interactions?



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Given the interaction graph G of a gene network, this method uses some reasonable biological hypotheses to construct a very specific set of functions $\mathcal{F}(G)$ considered as potential models for the gene network.

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with G as interaction graph, and with some properties implying

$$\forall x, y \in X, \qquad d_{\mathrm{Man}}(x, y) = 1 \quad \Rightarrow \quad d_{\mathrm{Ham}}(x, y) \leq 1.$$

$$\left(\quad d_{\mathrm{Man}}(x, y) := \sum_{i=1}^{n} |x_i - y_i| \qquad d_{\mathrm{Ham}}(x, y) := \sum_{i=1}^{n} \min(1, |x_i - y_i|) \quad \right)$$

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Is it possible to establish similar results for these class of functions?