Fixed points and feedback cycles in Boolean networks

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Joint work with

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A **boolean network** is a function

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

The dynamics is described by the successive iterations of f

$$x \to f(x) \to f^2(x) \to f^3(x) \to \cdots$$

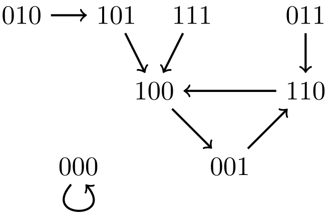
Fixed points correspond to stable states

Example with $n = 3$ and f defined by

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

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

Dynamics



The **interaction graph** of f is the digraph G defined by

- the vertex set is $[n] := \{1, \dots, n\}$
- there is an arc $j \to i$ if f_i *depends on* x_j

The **signed interaction graph** of f is the signed digraph G_σ where σ is the arc-labelling function defined by

$$\sigma(j \to i) = \begin{cases} 1 & \text{if } f_i \text{ is non-decreasing with } x_j \\ -1 & \text{if } f_i \text{ is non-increasing with } x_j \\ 0 & \text{otherwise} \end{cases}$$

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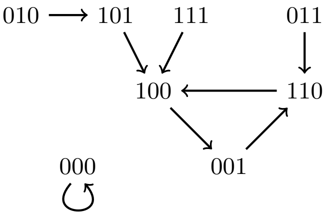
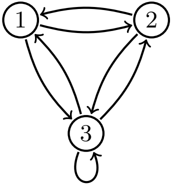


Interaction graph



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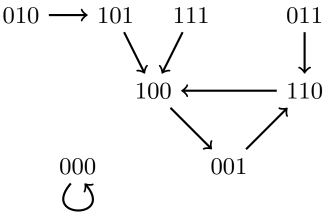
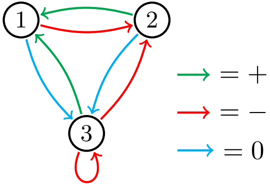


Signed interaction graph



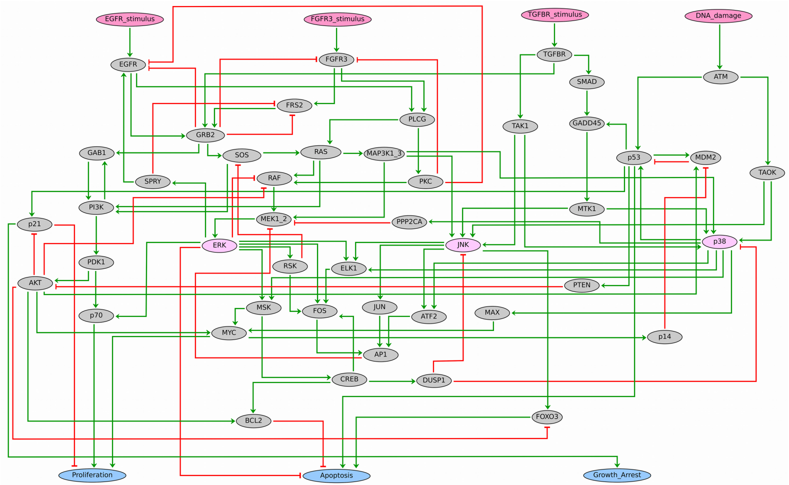
Many applications

- Neural networks [McCulloch & Pitts 1943]
- **Gene networks** [Kauffman 1969, Tomas 1973]
- Epidemic diffusion, social network, etc

Very often, reliable information concern the (signed) interaction graph

Natural questions

- *What can be said on the dynamics of a system according to its interaction graph ?*


EGFR_stimulus
FGFR3_stimulus
TGFBR_stimulus
DNA_damage
EGFR
FGFR3
TGFBR
SMAD
ATM
FRS2
PLCG
TAK1
GADD45
GRB2
GAB1
SOS
RAS
MAP3K1_3
p53
MDM2
TAOK
SPRY
RAF
PKC
PI3K
MTK1
MEK1_2
PPP2CA
p21
ERK
JNK
p38
PDK1
RSK
ELK1
AKT
PTEN
p70
MSK
FOS
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Very often, reliable information concern the (signed) interaction graph

Natural questions

- *What can be said on the dynamics of a system according to its interaction graph ?*
- *What can be said on the* **number of fixed points** *a* **boolean network** *according to its interaction graph ?*

Number fixed points in the gene network of a multicellular organism $\approx$ Number of cellular types

Quantities of interest

$\phi(G)$:= maximum number of fixed points in a boolean network with G as interaction graph

$\phi(G_\sigma)$:= maximum number of fixed points in a boolean network with G_σ as signed interaction graph

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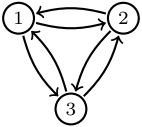

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(100 networks)

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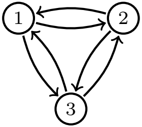

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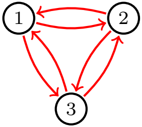

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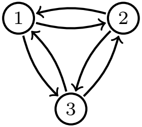

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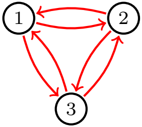

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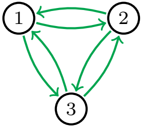

$\phi(G_+) = 2$

(8 networks)

Notations

$f : \{0,1\}^n \to \{0,1\}^n$ is a boolean network

G is the interaction graph of f (the vertex set is $[n]$)

G_σ is the signed interaction graph of f

Given $x, y \in \{0,1\}^n$ we set $\Delta(x,y) := \{i \in [n] \,:\, x_i \neq y_i\}$

Upper bound on $\phi(G)$

Lemma *If x and y are two distinct fixed points of f, then the subgraph of G induced by $\Delta(x, y)$ has a cycle.*

Proof If $i \in \Delta(x, y)$ then

$$f_i(x) = x_i \neq y_i = f_i(y)$$

thus f_i depends on at least one component j such that $x_j \neq y_j$, that is, G has an arc $j \to i$ with $j \in \Delta(x, y)$.

Thus $G[\Delta(x, y)]$ is of minimal in-degree at least one. □

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Remark $$G \text{ is acyclic } \iff \phi(G) = 1$$

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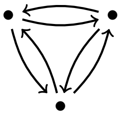

$\tau = 2$

Remark τ is invariant under subdivisions of arcs ($\rightarrow$ replaced by $\rightarrow\rightarrow$)

Theorem (Classical upper bound) [Riis, 2007]

f has at most 2^τ fixed points

Proof Let I be a FVS of size $|I| = \tau$, and let x and y be fixed points.
If $x \neq y$ then $G[\Delta(x,y)]$ has a cycle C (lemma) and $I \cap C \neq \emptyset$ by def.
Hence $I \cap \Delta(x,y) \neq \emptyset$ so that $x_I \neq y_I$.
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Reformulation $\phi(G) \leq 2^\tau$

Remark G is acyclic $\Rightarrow$ $\tau = 0$ $\Rightarrow$ $\phi(G) \leq 1$

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Binary network coding problem

Given a digraph G, is there exists $H \subseteq G$ such that $\phi(H) = 2^{\tau(G)}$?

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Binary network coding problem

Given a digraph G, is there exists $H \subseteq G$ such that $\phi(H) = 2^{\tau(G)}$?

Surprisingly, the following question has deserved very few attention

Given a digraph G, do we have $\phi(G) = 2^{\tau(G)}$?

Upper bounds on $\phi(G_\sigma)$

In G_σ the **sign of a cycle** (or path) is the product of the sign of its arcs

$$\boldsymbol{\tau^+(G_\sigma)} := \textbf{positive transversal number}$$
$$:= \text{minimum size of a set of vertices meeting every } \textbf{non-negative} \text{ cycle}$$

Remark 1 $\tau^+ \leq \tau$

Remark 2 τ^+ is invariant under subdivisions of arcs preserving signs
e.g. $\rightarrow$ replaced by $\rightarrow\rightarrow$, or $\rightarrow$ replaced by $\rightarrow\rightarrow$

Theorem [Aracena, 2008]

For every signed digraph G_σ

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No lower bounds on $\phi(G)$ *neither* $\phi(G_\sigma)$ *!*

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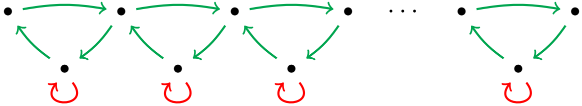

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$$2^{\tau^+} \sim 2^{n/4}$$

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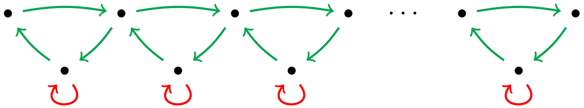

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We think that improvements could be obtained by considering **negative cycles** too. This is a difficult problem...

What happen when there is ***only positive cycles*** *?*

$\hookrightarrow$ This essentially corresponds to the case where f **is monotone**

Monotone networks

$\{0,1\}^n$ is equipped with the usual partial order

$$x \leq y \iff x_i \leq y_i \text{ for all } i$$

f is **monotone** if for all $x, y \in \{0,1\}^n$

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Proposition *If G_σ is strong and has only positive cycles then*

$$\phi(G_\sigma) = \phi(G_+)$$

Fixed points in monotone networks

Theorem [Knaster-Tarski, 1928]

If f is monotone then $\textsc{Fixe}(f)$ is a non-empty lattice

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To go further we need another graph parameter about cycles

$$\begin{aligned} \boldsymbol{\nu(G)} &:= \textbf{packing number} \\ &:= \text{maximum number of vertex-disjoint cycles} \end{aligned}$$

Remark $\nu \leq \tau$

Theorem [Aracena-Salinas-R, 2016+]

If f is monotone then $\textsc{Fixe}(f)$ a isomorphic to a subset $L \subseteq \{0,1\}^\tau$ s.t.

1. *L is a non-empty lattice*
2. *L has no chains of size $\nu + 2$*

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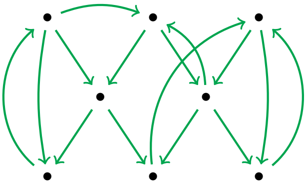

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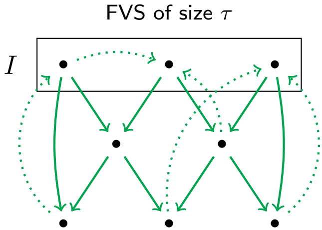

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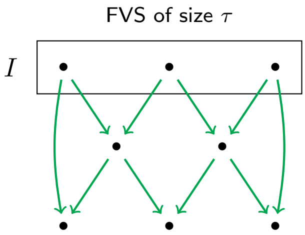

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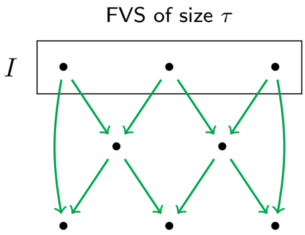

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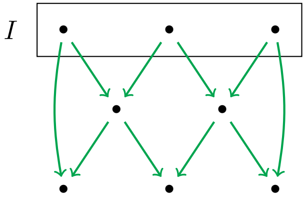
Proof of the isomorphism $\forall x, y \in \mathrm{FIXE}(f) \quad x_I \leq y_I \iff x \leq y$

$$\mathrm{FIXE}(f) \text{ is isomorphic to } L = \{x_I : x \in \mathrm{FIXE}(f)\}$$



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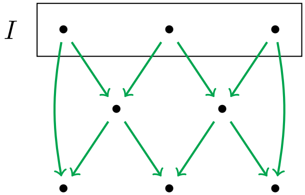

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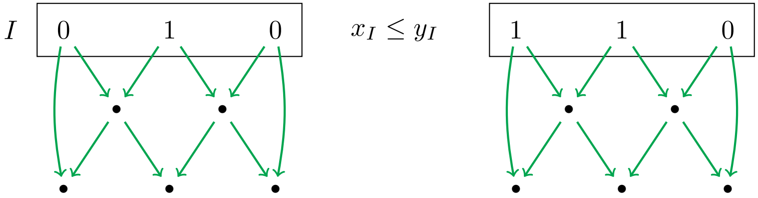

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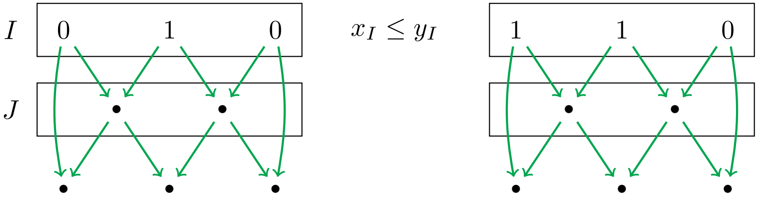

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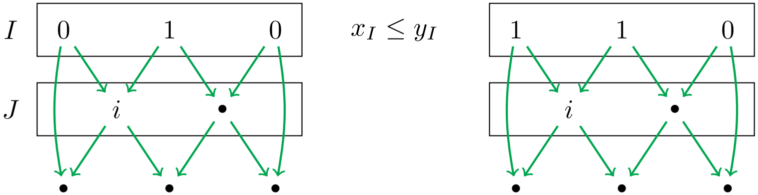

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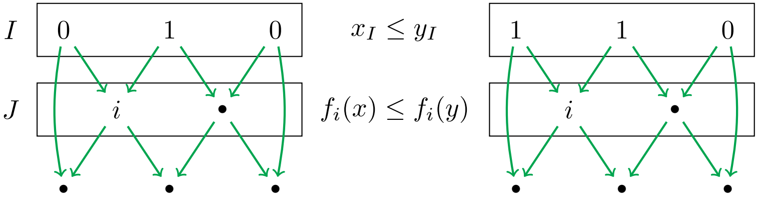

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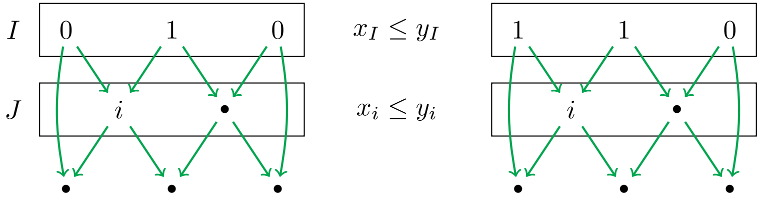

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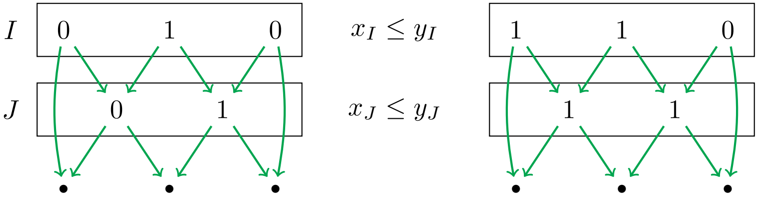

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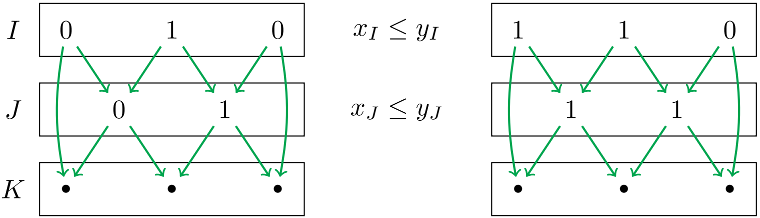

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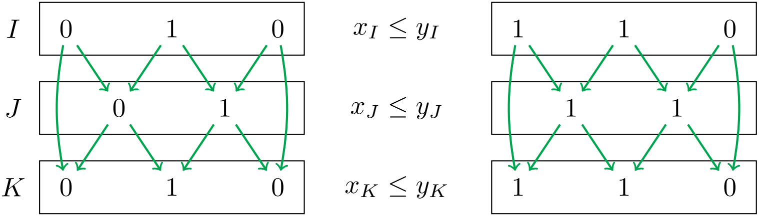

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$$
\begin{array}{rcllllllllllllllllll}
x^5 & = & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} & \mathbf{1} \\
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$x^4 =$	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0	0	0
$x^3 =$	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0	0	0	0	0	0	0
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x^4	=	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0	0	0
x^3	=	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0	0	0	0	0	0	0
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Thus $\textsc{Fixe}(f)$ has no chains of length $\nu+2$ and so L

x^5	$=$	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
x^4	$=$	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0	0	0
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Remark The case $\ell = 1$ is Sperner's lemma on antichains

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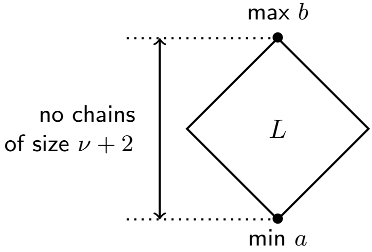

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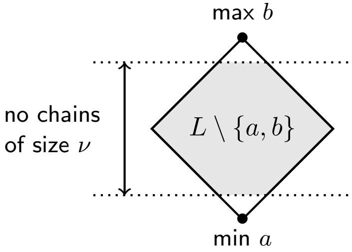

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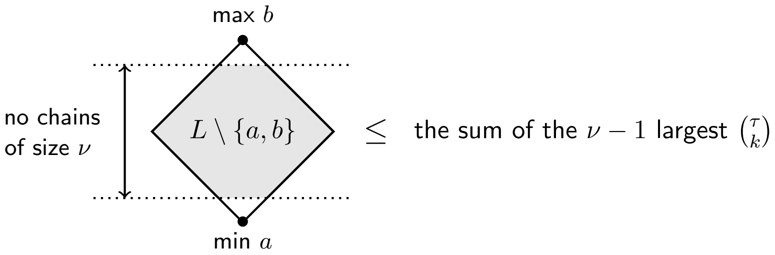

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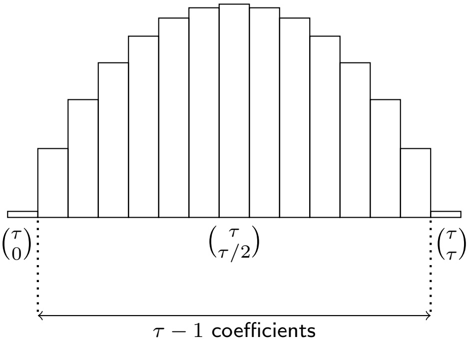

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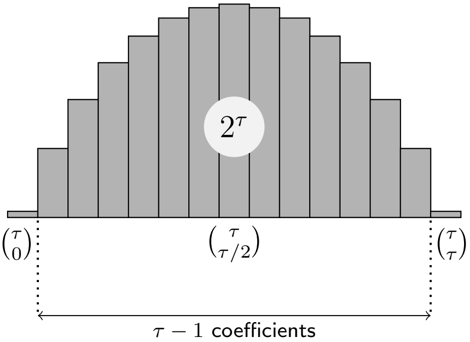

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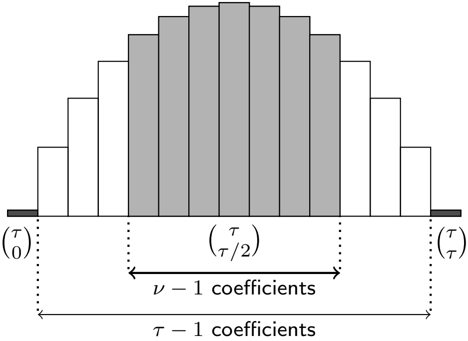

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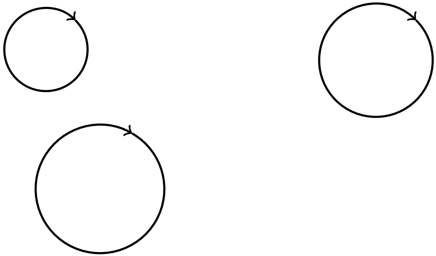
More on fixed points in monotone networks

Special packing



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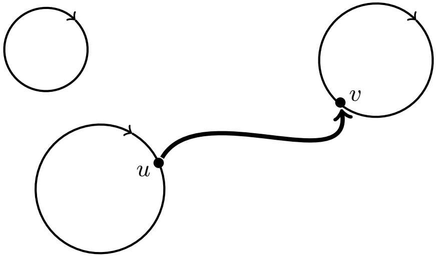

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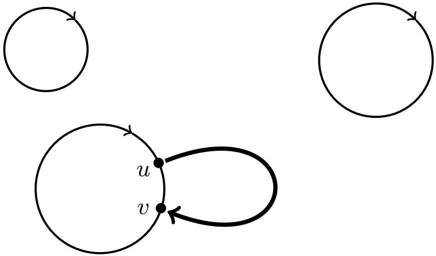

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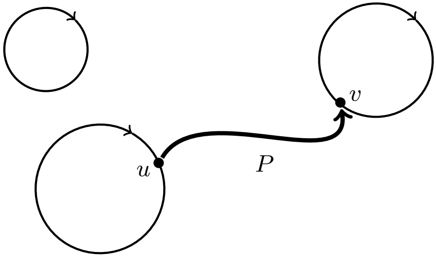

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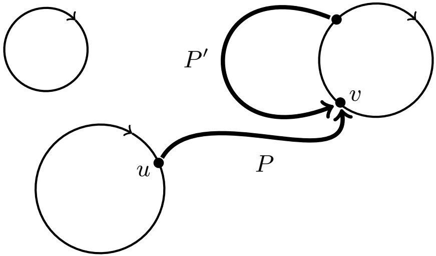

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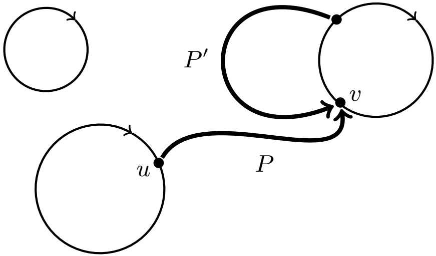

We denote by $\boldsymbol{\nu^*(G)}$ the maximum size of a special packing

Remark $\nu^* \leq \nu \leq \tau$

A ***k*-pattern** in $X \subseteq \{0,1\}^n$ is a sequence $(x^1,\dots,x^k) \in X^k$ such that

$$(\overline{x^1},\dots,\overline{x^k}) \in X^k \qquad \text{and} \qquad x^p \leq \overline{x^q} \iff p \neq q$$

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Example (e_1, e_2, e_3) is a 3-pattern of $\{0,1\}^3$

$$\overline{e_1} = 011 \qquad \overline{e_2} = 101 \qquad \overline{e_3} = 110$$

$$e_1 = 100 \qquad e_2 = 010 \qquad e_3 = 001$$

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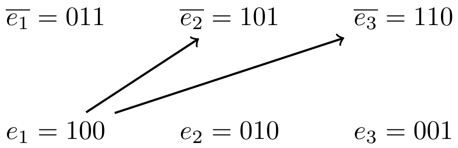

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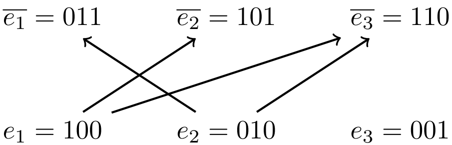

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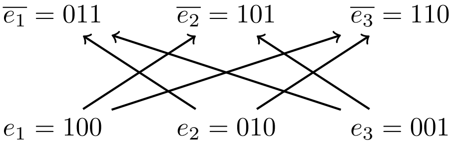

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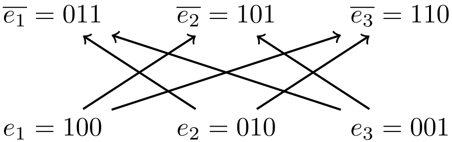

More generally $(e_1, e_2, \dots, e_n)$ is an n-pattern of $\{0,1\}^n$

Theorem [Aracena-Salinas-R, 2016+]

If f is monotone then $\textsc{Fixe}(f)$ *a isomorphic to a subset* $L \subseteq \{0,1\}^\tau$ *s.t.*

1. L *is a non-empty lattice*
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2. *L has no chains of size $\nu + 2$*
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Remark If $L = \{0,1\}^\tau$ then L has a has a τ-pattern, so $\tau < \nu^* + 1$. Thus $\tau \leq \nu^*$ and since $\nu^* \leq \tau$ we deduce that $\nu^* = \tau$.

Theorem [Aracena-Salinas-R, 2016+]

If f is monotone then $\textsc{Fixe}(f)$ a isomorphic to a subset $L \subseteq \{0,1\}^\tau$ s.t.

1. *L is a non-empty lattice*
2. *L has no chains of size $\nu + 2$*
3. *L has no $(\nu^* + 1)$-pattern*

Corollary $\phi(G_+) = 2^\tau \;\Rightarrow\; \nu^* = \tau$

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Corollary $\boldsymbol{\phi(G_+) = 2^\tau \iff \nu^* = \tau}$

Open problems

Problem 1 For $k, \ell \leq n$ what is the max size of a subset $X \subseteq \{0,1\}^n$ s.t.

1. X is a lattice
2. X has no chain of size $\ell + 1$
3. X has no $(k+1)$-pattern

$\rightarrow$ Erdős proved the max size of X subject to 2. only

$\rightarrow$ What is the max size of X subject to 3. only ?

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Problem 2 Is the lower bound $\nu + 1 \leq \phi(G)$ tight ?

$\rightarrow$ We known that the lower bound is tight in the monotone case

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$\rightarrow$ We known that $\tau \leq h(\nu)$ and we may think that $\tau \leq c\nu \log \nu$

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$$\tau^+ \leq h^+(\nu^+)$$

$\rightarrow$ Positive answer in the undirected case [Thomassen 88]

Thank you!

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