Interaction networks and their environment

a basic view

Sylvain Sené

Archamps, June 10, 2014

Outline

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Biology et computer science: a long story

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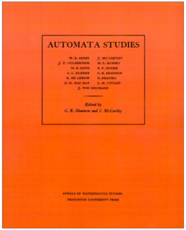

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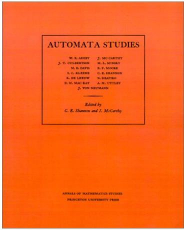

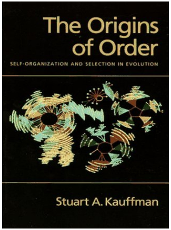

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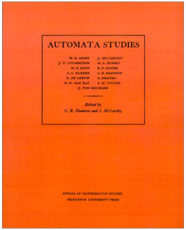

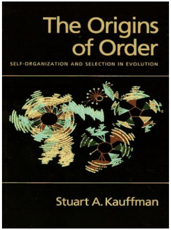

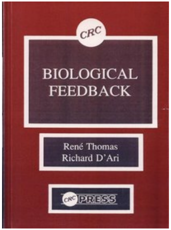

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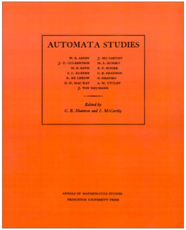

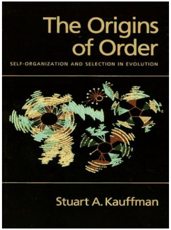

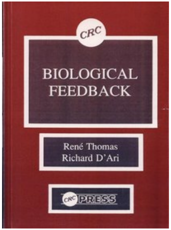

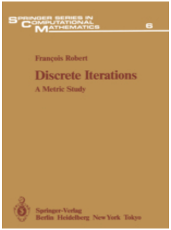

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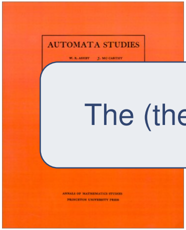
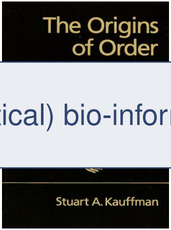
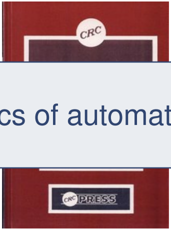






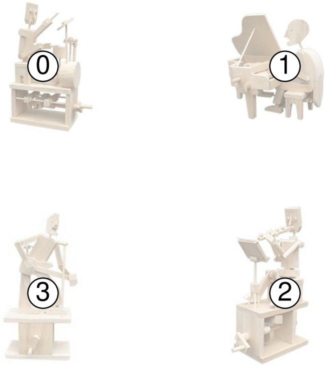
The (theoretical) bio-informatics of automata networks

Automata and configurations

The automata

$V = \{0, \ldots, n-1\}$: a set of n automata

Automata and configurations



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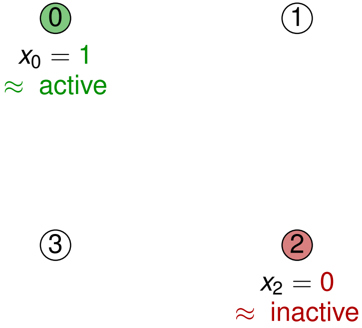


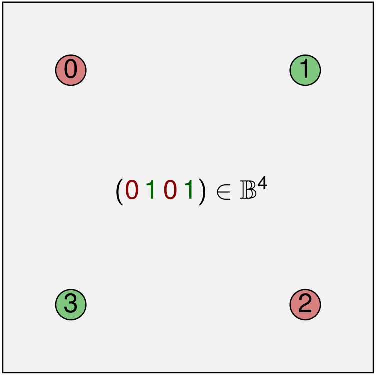
Their (Boolean) state

$$\forall i \in V,\ x_i \in \mathbb{B} = \{0, 1\}$$

Automata and configurations

The configurations

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



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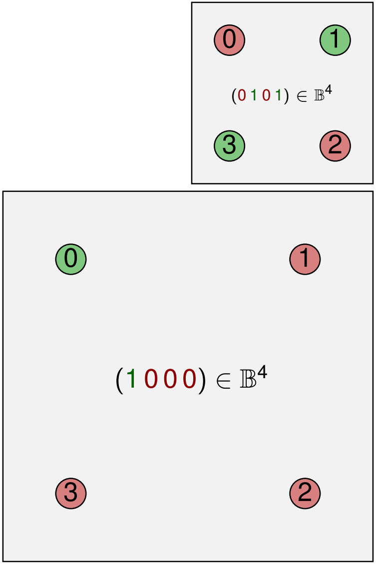

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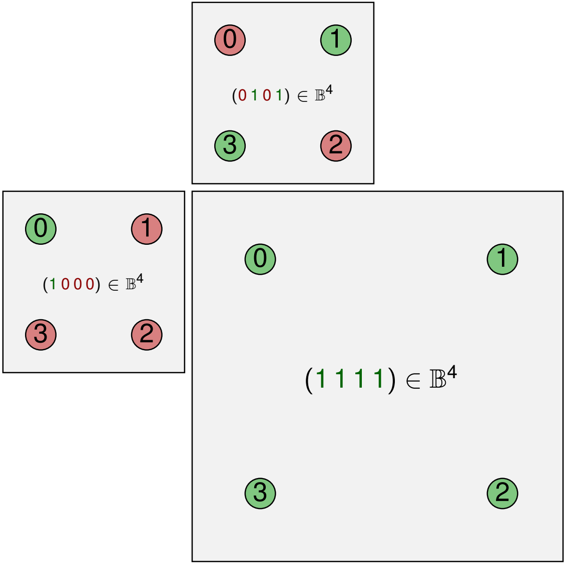

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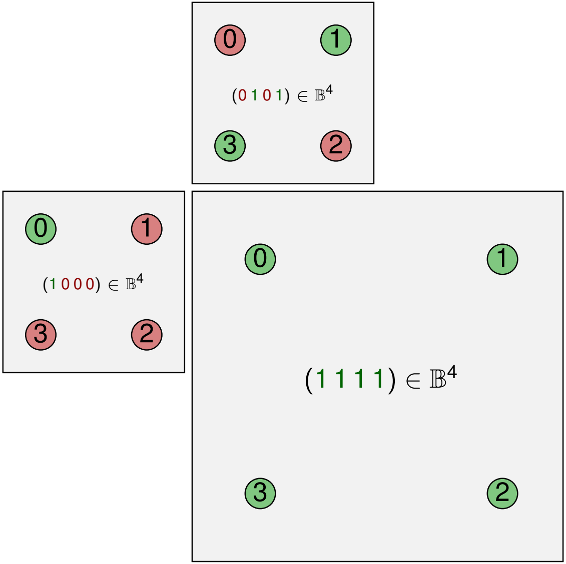
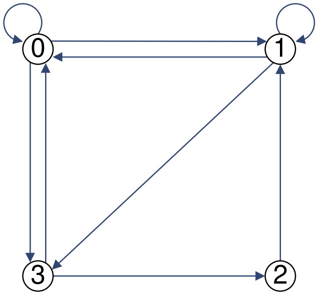


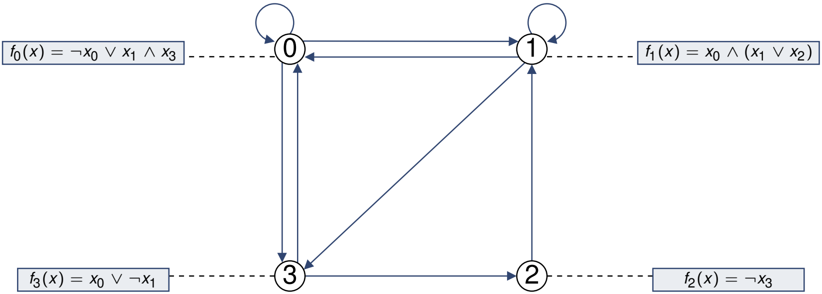
Interactions between automata



The *architecture* $G = (V, A)$ of the network – the *interaction graph*

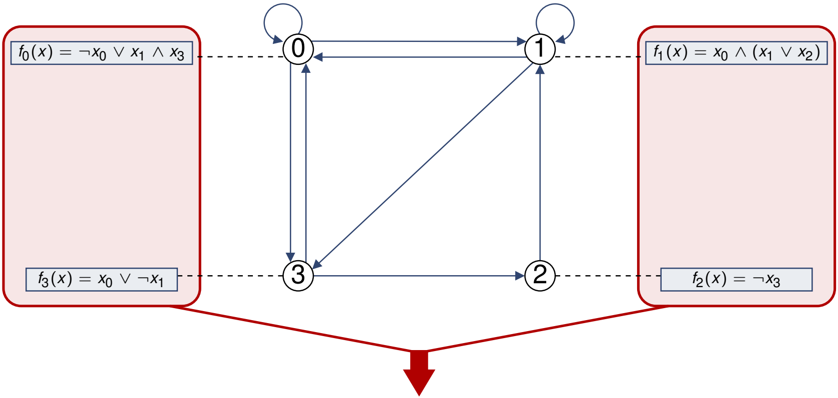
$$A \subseteq V \times V$$

Interactions between automata



The *local transition functions*

Automata network



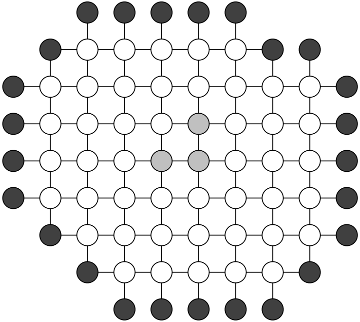
The *network* $N = \{f_i \mid i \in V\}$

defined as the set of n local transition functions

Automata network centre and boundaries

Let $G = (V, A)$ be an arbitrary digraph and let N be an automata network with G its interaction graph

- The *eccentricity* $\epsilon(u)$ of a vertex $u \in V$ of G is the maximal distance (in terms of graph) between u and any other vertex of G
- The *centre* of N is the set of vertices of G whose eccentricity is minimal
- The *boundaries* (*i.e.*, the environment) of N is the set of sources of G



Automata updates

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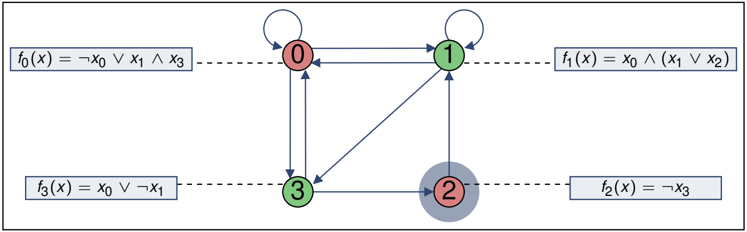

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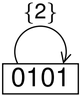

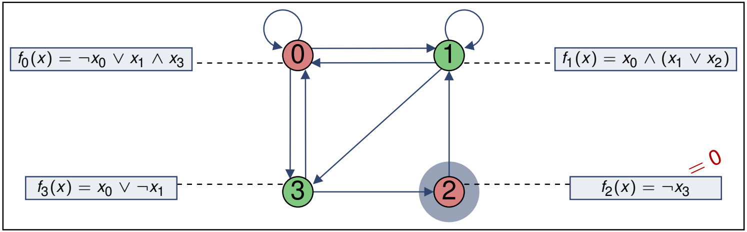

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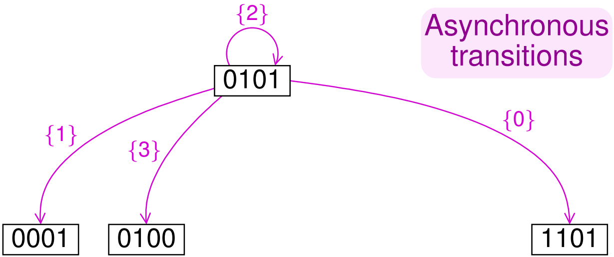

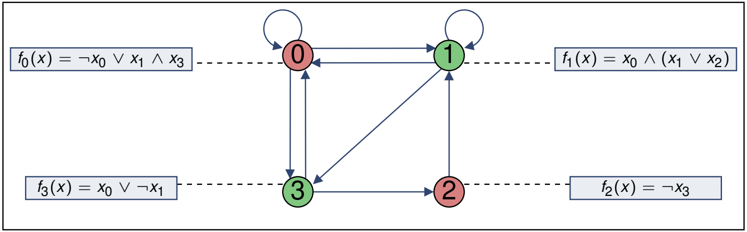

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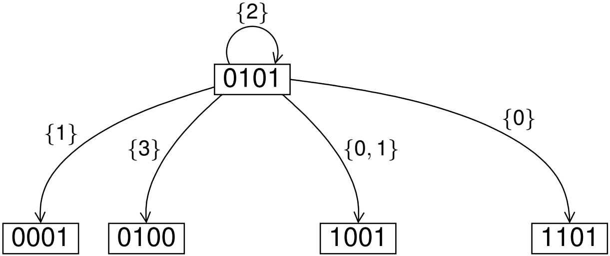

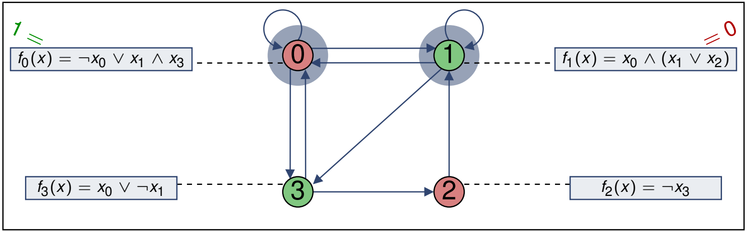

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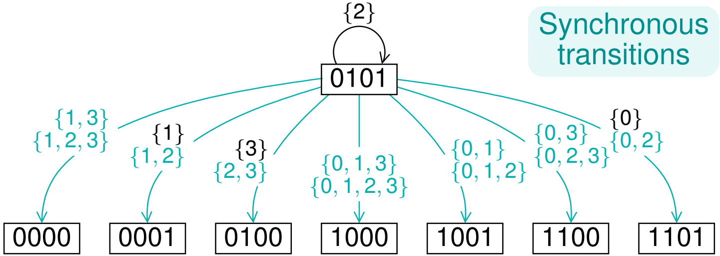

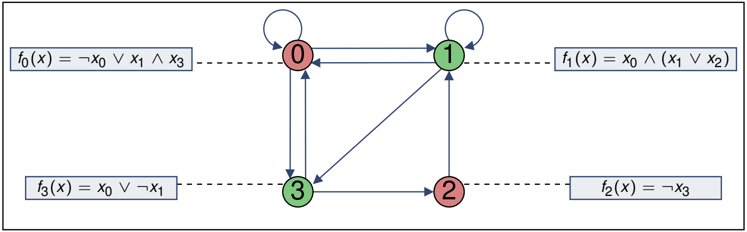

Automata network behaviour

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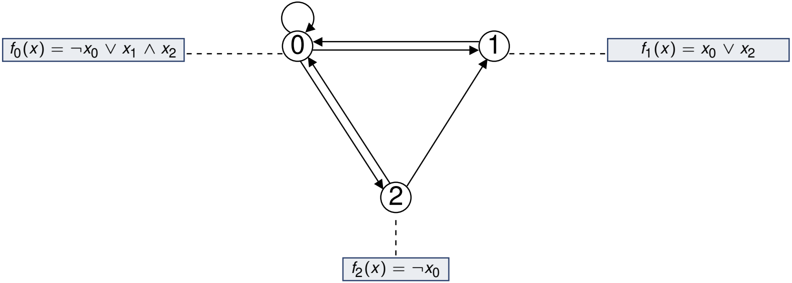

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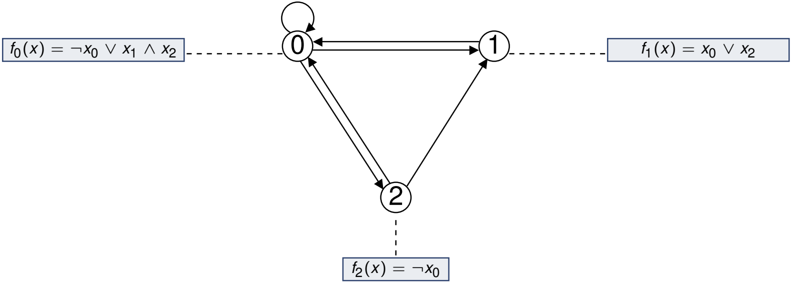

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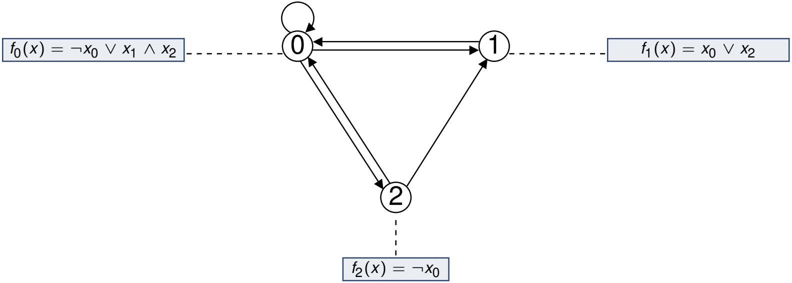

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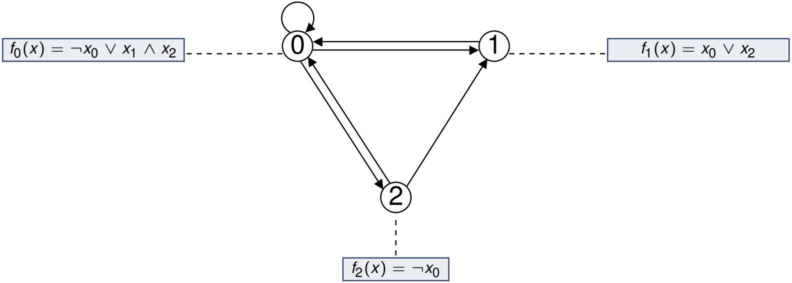

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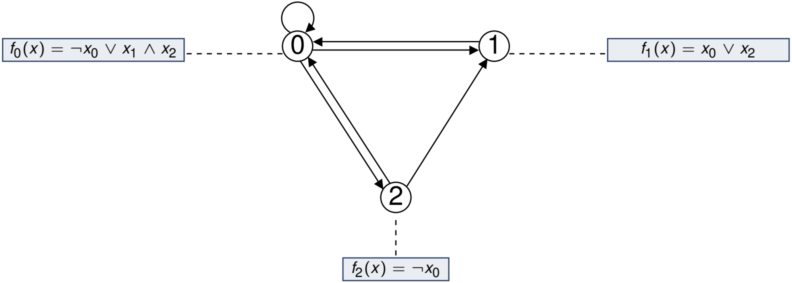

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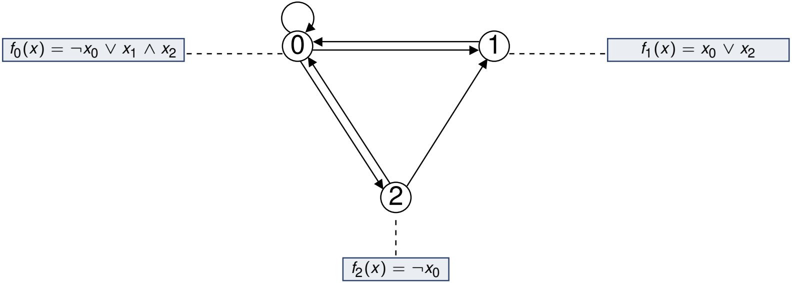
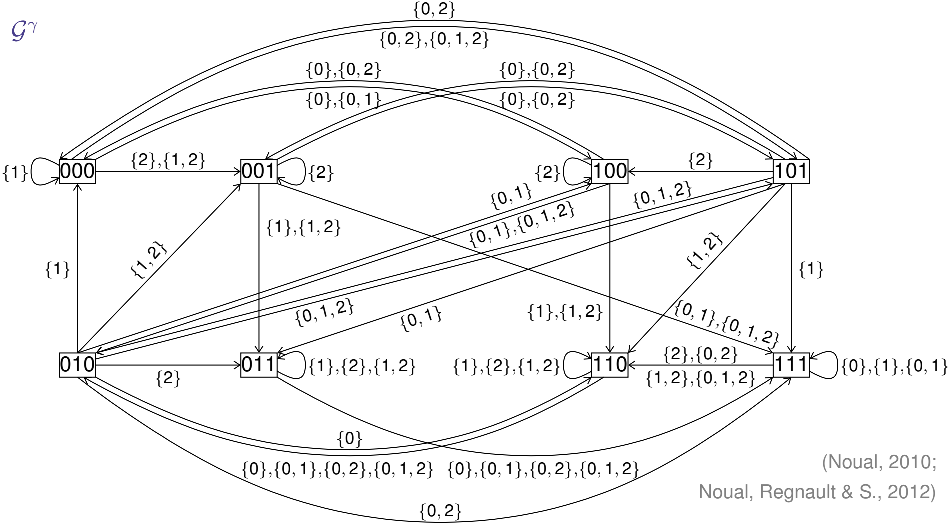


Automata network behaviour

General updating mode

$\mathcal{G}^\gamma$

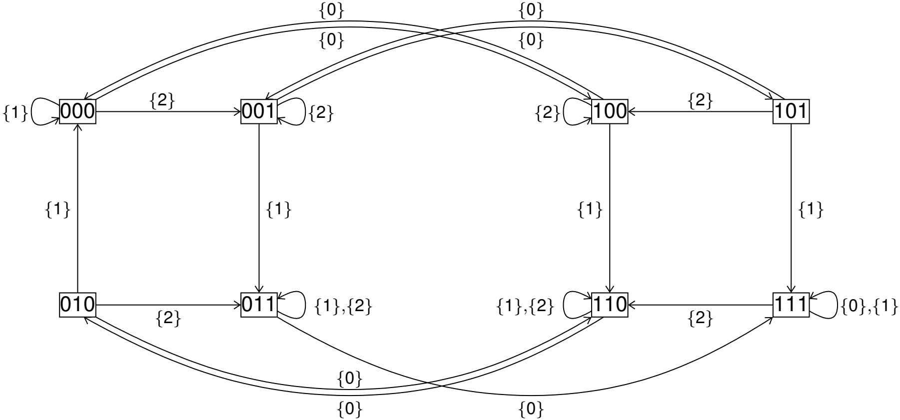


(Noual, 2010;
Noual, Regnault & S., 2012)

Automata network behaviour

Asynchronous updating mode

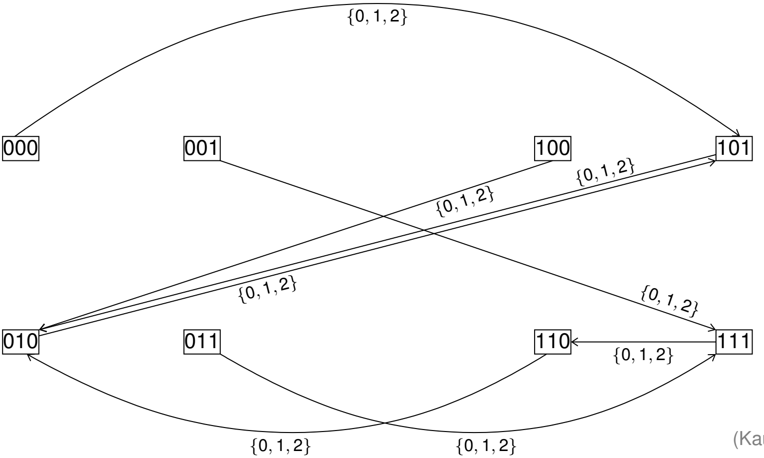
$\mathcal{G}^{\alpha}$



(Thomas, 1973; Thomas, 1991)

Automata network behaviour
Parallel updating mode

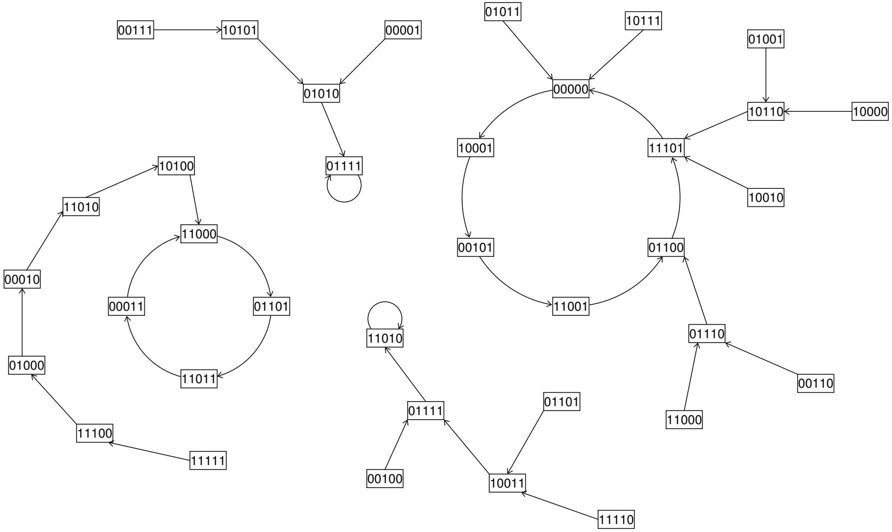
$\mathcal{G}^{\pi}$



(Kauffman, 1969; Robert, 1969; Robert, 1986)

Automata network behaviour

Last definitions, well almost!



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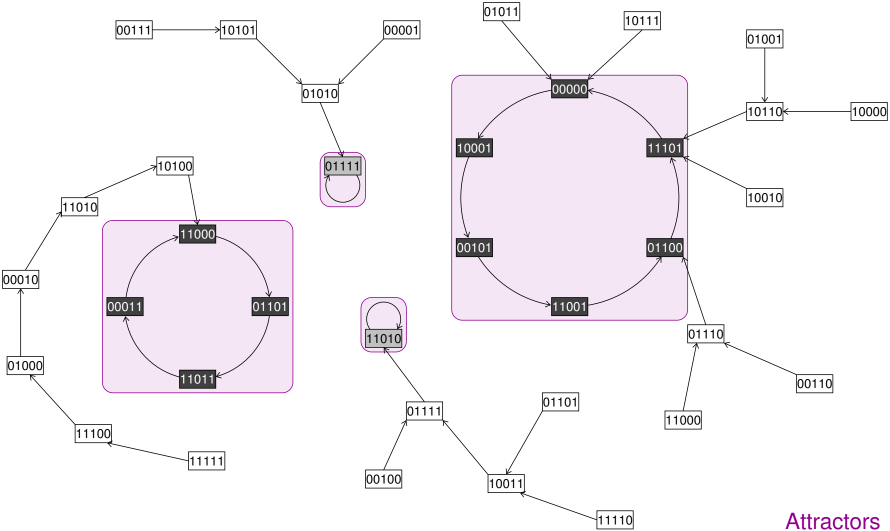

Attractors

Automata network behaviour

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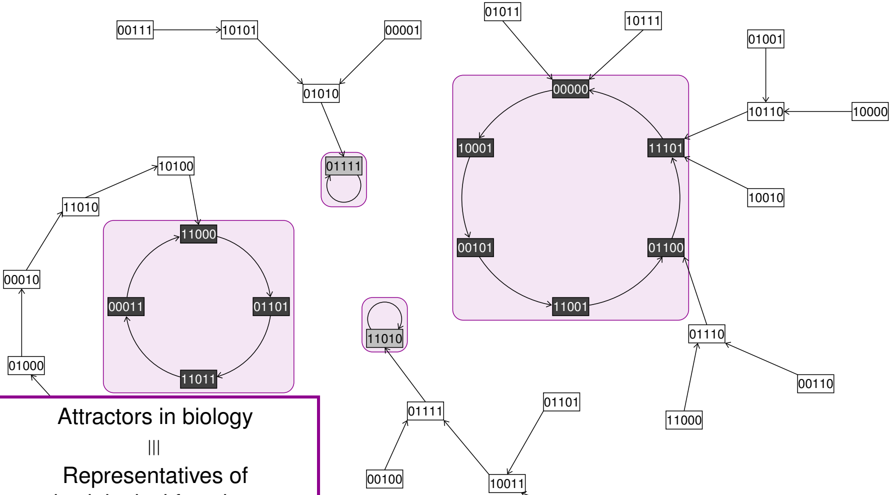

Attractors in biology

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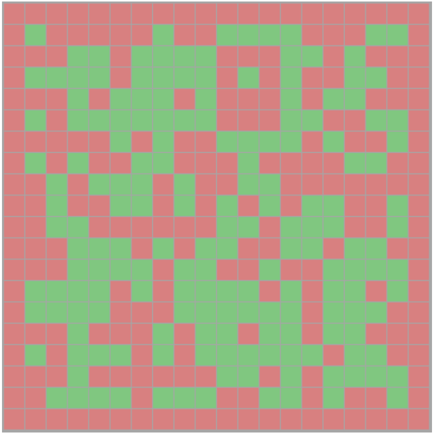
Representatives of physiological functions, cellular types. . .

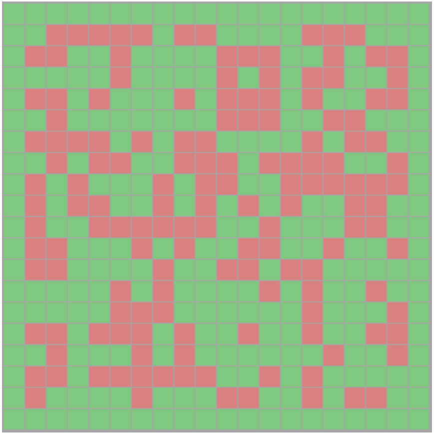
Attractors

Outline

An insight with Majority



$t = 0$



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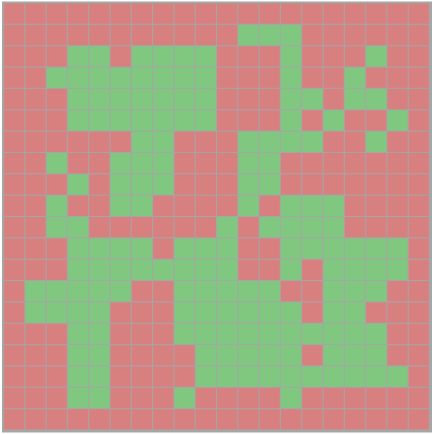
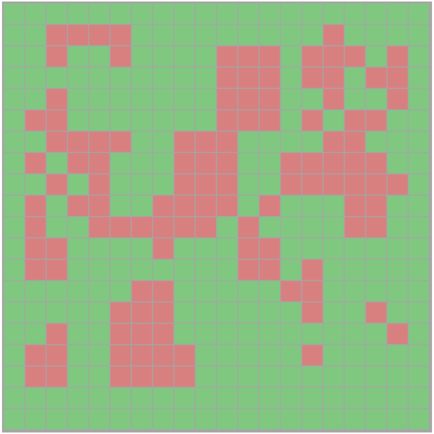


$t = 1$



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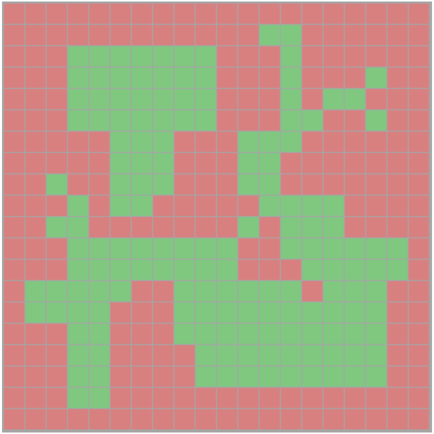
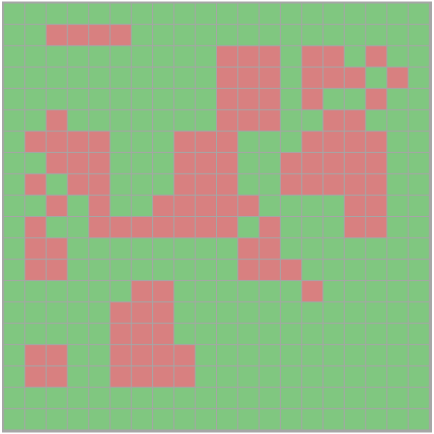
An insight with Majority



$t = 2$



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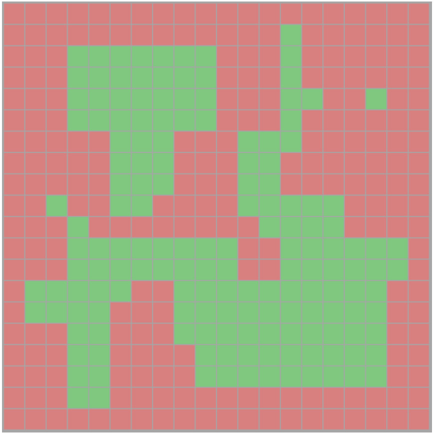
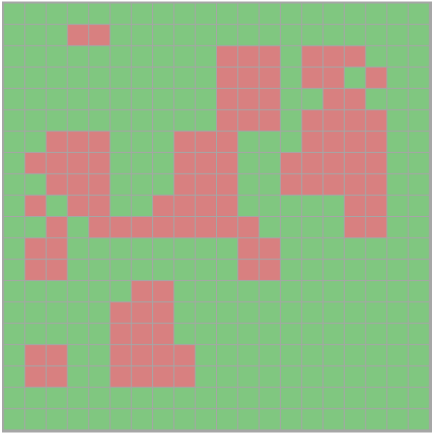


$t = 3$



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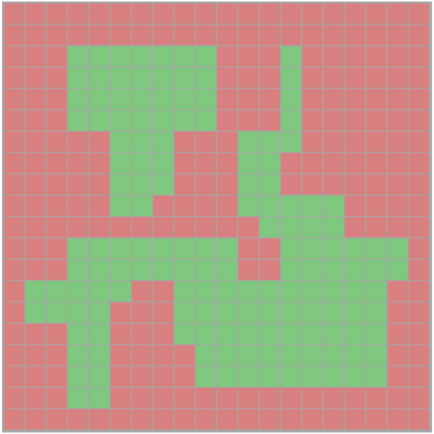
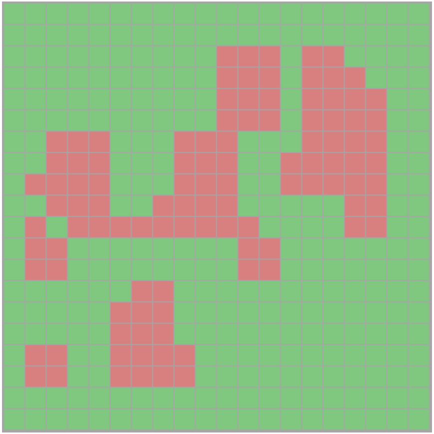


$t = 4$



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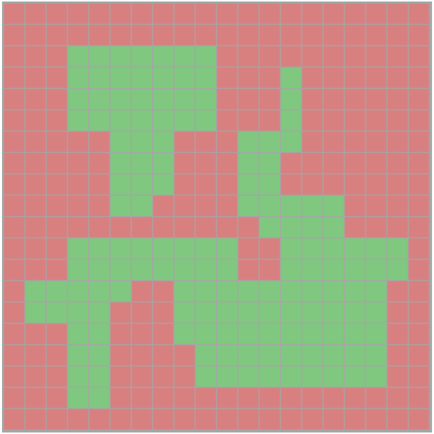
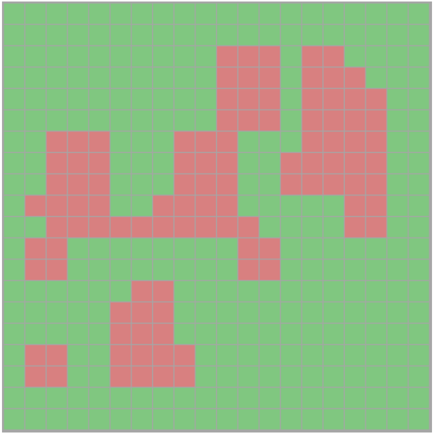
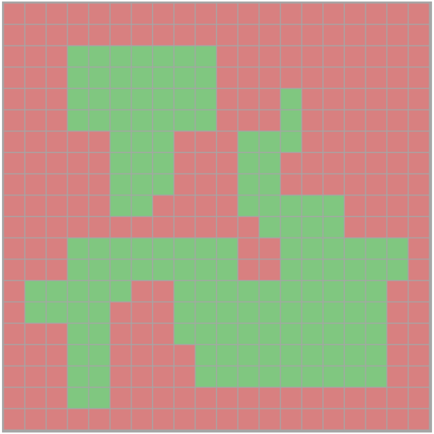


$t = 5$

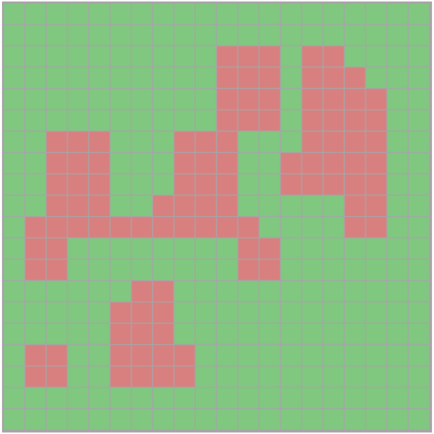


$t = 5$

An insight with Majority

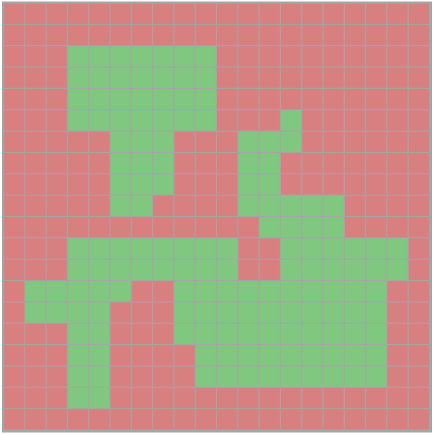


$t = 6$

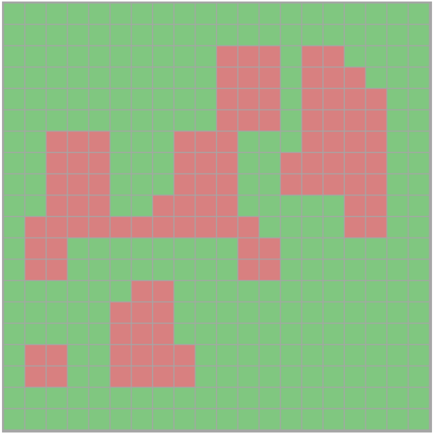


$t = 6$

An insight with Majority

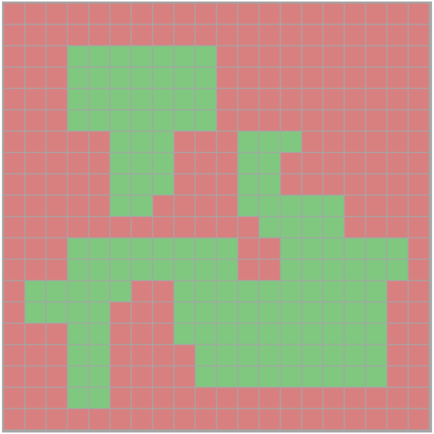


$t = 7$

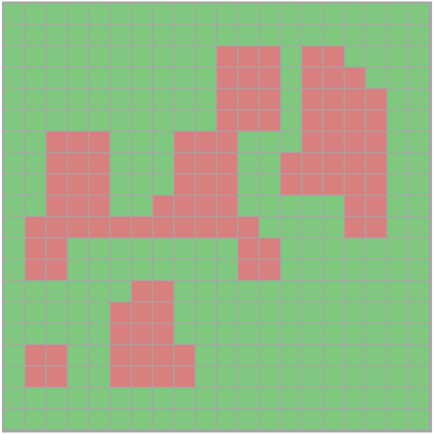


$t = 7$

An insight with Majority

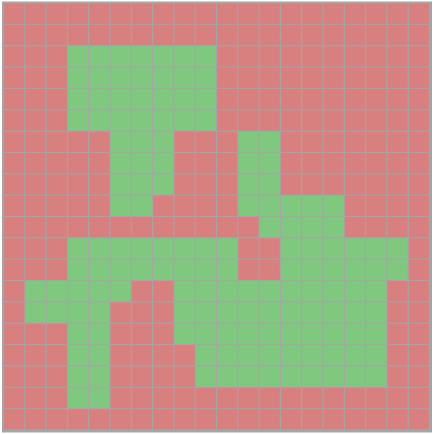


$t = 8$

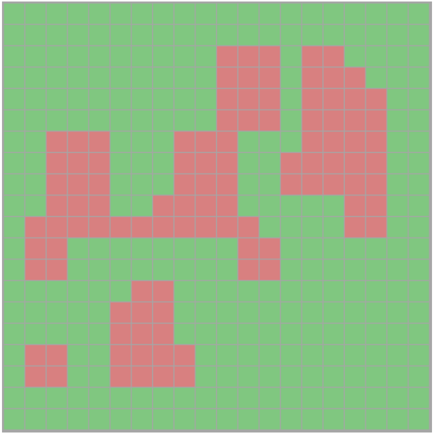


$t = 8$

An insight with Majority

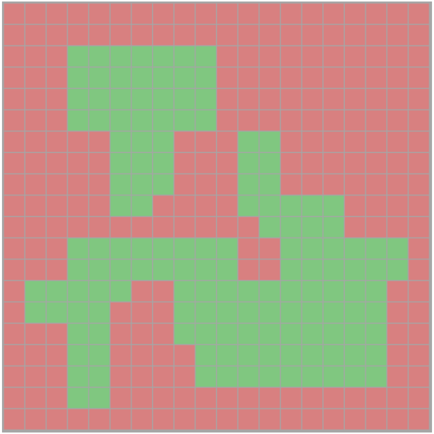


$t = 9$

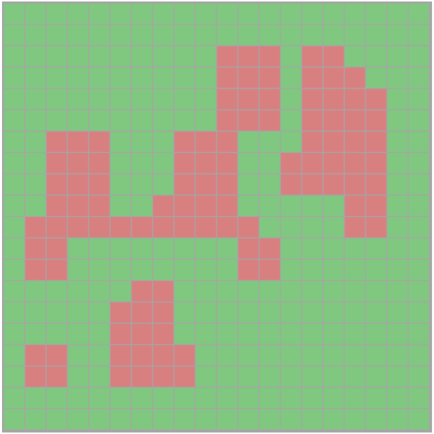


$t = 9$

An insight with Majority



$t = 10$



$t = 10$

2 distincts attractors $\iff$ Impact of the environment

Linear threshold PCA

◇ Deterministic function (McCulloch & Pitts, 1943; Goles, 1980's):

$$\forall i \in V, \forall t,\ x_i(t+1) = \begin{cases} 1 & \text{if } \sum_{j \in \mathcal{N}_i} w_{i,j} \cdot x_j(t) - \theta_i > 0 \\ 0 & \text{otherwise} \end{cases}$$

Linear threshold PCA

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◇ Probabilistic function:

$$\forall i \in V, \forall t,\ P(x_i(t+1) = \alpha \mid x(t)) = \frac{e^{\alpha \cdot (\sum_{j \in \mathcal{N}_i} w_{i,j} \cdot x_j(t) - \theta_i)/T}}{1 + e^{(\sum_{j \in \mathcal{N}_i} w_{i,j} \cdot x_j(t) - \theta_i)/T}}$$

where $T \in \mathbb{N}$ is a "temperature" parameter such that:

(i) if $T \to 0$, the deterministic function is retrieved,

(ii) if $T \to +\infty$, then:

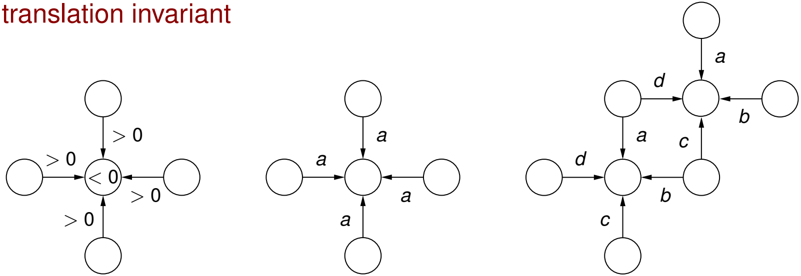
$$\forall i \in V, \forall t,\ P(x_i(t) = 1) = \frac{1}{2}$$

Attractive PCA at stake here

- Neighbourhoods of cell *i*:
  - → $\mathcal{N}_i$: the von Neumann neighbourhood (*i* and its nearest neighbours)
  - → $\mathcal{N}_i^* = \mathcal{N}_i \setminus \{i\}$

We will only focus on PCA that are:

- attractive
- isotropic (a.k.a. totalistic)
- translation invariant



Global behaviour et stochastic process

◇ Stationary Markov chains:

$$\forall t \in \mathbb{N}^*,\ P(x(t+1) = D \mid x(t) = E) \ = \ P(x(t) = D \mid x(t-1) = E)$$

→ Markovian matrix $\mathcal{P}$:

$$\mathcal{P} = \left(\begin{array}{c} \vdots \\ \cdots \quad P\,(x\,(t+1) \;=\; D \mid x\,(t) \;=\; E) = p_{E,D} \quad \cdots \\ \vdots \end{array} \right) \quad \text{row } E,\ \text{column } D$$

→ Invariant measure μ:

$$\mu_y \ = \ \sum_{x \in \mathbb{B}^n} \mu_x \cdot p_{x,y} \qquad\qquad \mu \ = \ \mu \cdot \mathcal{P}$$

Method and general results

(Demongeot, Jézéquel & S., 2008; Demongeot & S., 2008)

Definition

(Dobrushin, 1968) N is not robust against its environment $\iff$ phase transition $\iff$ $\mu^{\circ}(R) \neq \mu^{\bullet}(R)$.

Method and general results

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Definition

(Dobrushin, 1968) N is not robust against its environment $\iff$ *phase transition* $\iff \mu^\circ(R) \neq \mu^\bullet(R)$.

Theorem

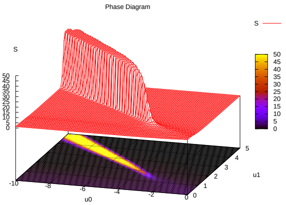
Linear PCA robustness does not depend on periodic updating modes.

Theorem

1-D PCA are entirely robust against their environment.

Theorem

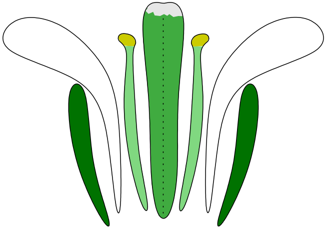
Let $u_0 = \frac{w_{i,i}}{T}$, $u_1 = \frac{w_{i,j}}{T}$ *and* $d > 1$. *If d-D linear PCA are non-robust against their environment, then* $u_0 + d \cdot u_1 = 0$.

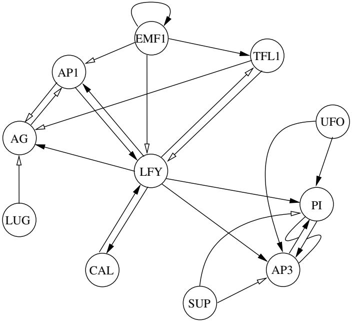


Outline

Floral morphogenesis of *Arabidopsis thaliana*

(Mendoza & Alvarez-Buylla, 1998)





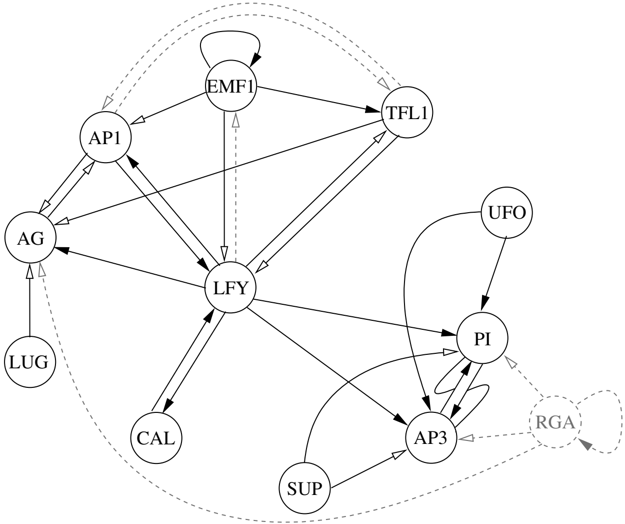
Attractors	Tissues
Fixed point 1	Sepals
Fixed point 2	Petals
Fixed point 3	Stamens
Fixed point 4	Carpels
Fixed point 5	Inflorescence
Fixed point 6	Mutant
Limit cycle 1	—
⋮	⋮
Limit cycle 7	—

Experimental results on the influence of Gibberellin

(Goto & Pharis, 1999)

Variation around the Mendoza network

Deterministic functions and sequential updating mode



Robustness against state perturbations

- Probability $P(c \to c' \mid p_k)$ for configuration c to become c' knowing perturbation p_k of k (given) elements:

$$P(c \to c' \mid p_k) \;=\; 0 \text{ or } 1$$

- Probability $P(c \to c' \mid k)$ for c to become c' knowing any perturbation of k elements:

$$P(c \to c' \mid k) \;=\; \frac{\sum_{p_k \in P_k} P(c \to c' \mid p_k)}{\binom{|V|}{k}}$$

- Probability $P_\alpha(k)$ to make k state changes in c according to the state perturbation rate α:

$$P_\alpha(k) \;=\; \binom{|V|}{k} \cdot \alpha^k \cdot (1-\alpha)^{|V|-k}$$

Robustness against state perturbations

- Probability $P_\alpha(c \to c')$ for c to become c' depending on α whatever k:

$$P_\alpha(c \to c') = \sum_{k=0}^{n} (P(c \to c' \mid k) \cdot P_\alpha(k))$$

- Probability $P_\alpha(c \to B_j)$ for c to become a configuration of attraction basin B_j:

$$P_\alpha(c \to B_j) = \sum_{c' \in B_j} P_\alpha(c \to c')$$

- Probability $P_\alpha(B_i \to B_j)$ "to go" from B_i to B_j:

$$P_\alpha(B_i \to B_j) = \frac{\sum_{c \in B_i} P_\alpha(c \to B_j)}{|B_i|}$$

Robustness against state perturbations – Summary

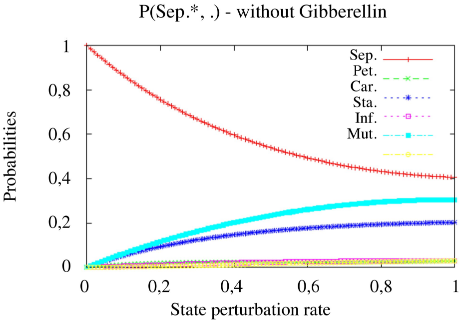
Characteristic polynomials of the probabilities for initial configurations to become configurations of other attraction basins according to a stochastic parameter of state perturbation α:

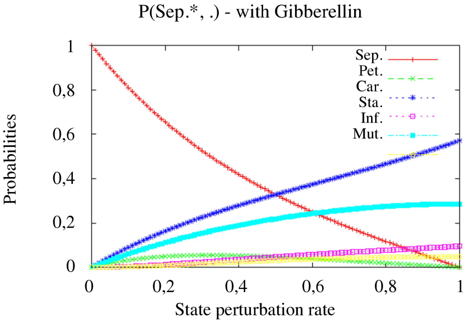
$$P_\alpha(B_i \to B_j) \;=\; \frac{1}{|B_i|} \cdot \sum_{c \in B_i} \sum_{k \leq |V|} a_k(c) \cdot \alpha^k \cdot (1-\alpha)^{|V|-k},$$

where $a_k(c)$ is the number of configurations $c' \in B_j$ located at Hamming distance k to c.

Robustness against state perturbations – Results

(Demongeot, Goles, Morvan, Noual & S., 2010)





Outline

What are these objects?

◇ Reminder – the linear rule

$$\forall i \in V, \forall t,\ P(x_i(t+1) = \alpha \mid x(t)) = \frac{e^{\alpha \cdot (\sum_{j \in \mathcal{N}_i} w_{i,j} \cdot x_j(t) - \theta_i)/T}}{1 + e^{(\sum_{j \in \mathcal{N}_i} w_{i,j} \cdot x_j(t) - \theta_i)/T}}$$

◇ *Interaction potentials* (functions of the interaction weights):

$u_{0,i}$

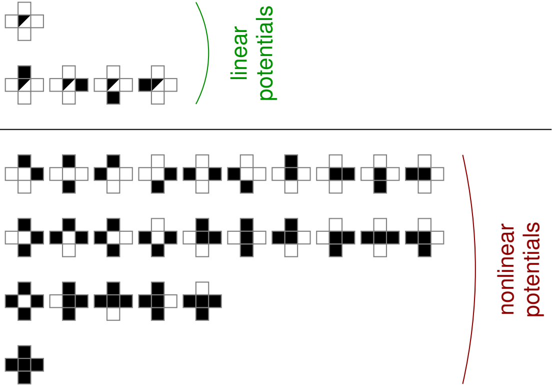
$u_{1,i,j}$

$u_{2,i,\langle j_1,j_2 \rangle}$

$u_{3,i,\langle j_1,j_2,j_3 \rangle}$

$u_{4,i,\langle j_1,j_2,j_3,j_4 \rangle}$

$u_{5,i,\langle i,j_1,j_2,j_3,j_4 \rangle}$



What are these objects?

- Our probabilistic rule *for CA of order* $k \geq 2$:

$$P(x_i(t+1) = 1 \mid x(t)) \;=\; \Phi_i(x(t)) \;=\; \frac{e^{u_0 + \sum_{j \in \mathcal{N}_i^*} u_1 \cdot x_j(t) + \eta_i^k(x(t))}}{1 + e^{u_0 + \sum_{j \in \mathcal{N}_i^*} u_1 \cdot x_j(t) + \eta_i^k(x(t))}},$$

where $\eta_i^k(x(t))$ is the *nonlinear term* and stands for accounting collective interaction potentials such that:

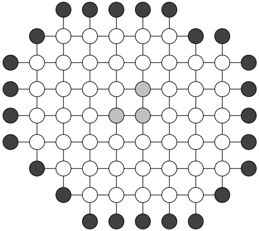
$$\eta_i^k(x(t)) = \begin{cases} 0 & \text{if } k = 2, \\ \sum_{\substack{j_1, j_2 \in \mathcal{N}_i \\ j_1 \neq j_2}} u_2 \cdot x_{j_1}(t) \cdot x_{j_2}(t) & \text{if } k = 3, \\ \sum_{\substack{j_1, \dots, j_{k-1} \in \mathcal{N}_i \\ j_1 \neq \dots \neq j_{k-1}}} u_2 \cdot x_{j_1}(t) \cdot x_{j_2}(t) + \dots & \\ \qquad\qquad + u_{k-1} \cdot x_{j_1}(t) \cdot \ldots \cdot x_{j_{k-1}}(t) & \text{otherwise.} \end{cases}$$

- Specific constraints:
  - Finite PCA on $\mathbb{Z}^2$
  - Isotropy (totalistic PCA)
  - Arbitrarily large sizes
  - $\forall i, \theta_i = 0$
  - u_0 always taken into account
  - $u_1 \geq 0$

Environmental robustness

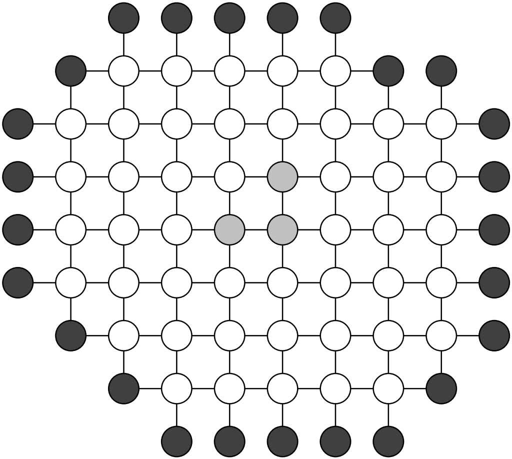
- ◇ Finite stationary Markov chains
- ◇ Perron-Frobenius theorem: convergence towards a unique invariant measure μ
- ◇ Invariant measure $\sim$ attractor

- General idea:

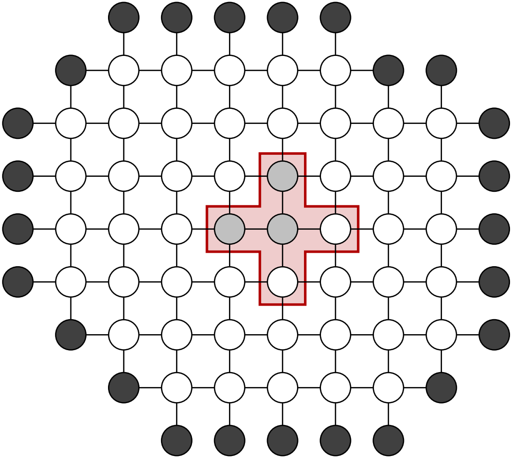


- The PCA $\mathcal{A}$ and its boundary $=$ the system $\mathcal{S}$
- Let $\mathcal{S}^\circ$ and $\mathcal{S}^\bullet$ be two distinct instances of $\mathcal{S}$
- $\mathcal{A}$ admits a phase transition w.r.t. its boundary conditions (or environment) when $\mu^\circ \neq \mu^\bullet$ (Dobrushin, 1968)
- Phase transition $\iff$ non-robustness of $\mathcal{A}$
- Main objective: characterise the family of PCA non robust against their environment, that is the values of interaction potentials u_0, u_1, u_2. . . under which phase transitions emerge

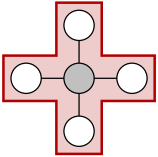
Reduction of the problem



Reduction of the problem



Reduction of the problem



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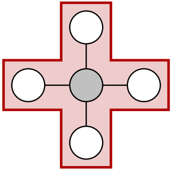

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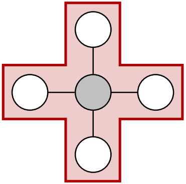

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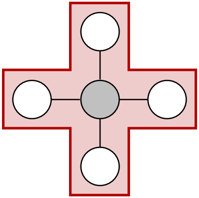

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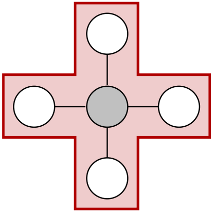

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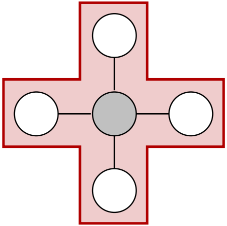
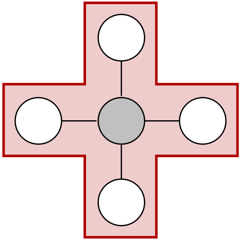


Reduction of the problem



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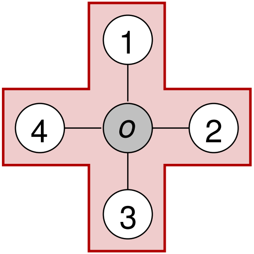

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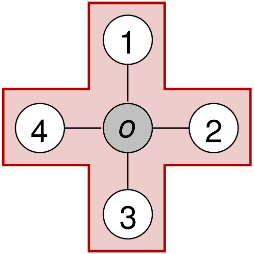


The transfer matrix

$$
\begin{cases}
\mu([\{1,2,3,4\},\emptyset]) + \mu([\{2,3,4\},\{1\}]) & = \mu([\{2,3,4\},\emptyset]) \\
\mu([\{1,2,3,4\},\emptyset]) + \mu([\{1,3,4\},\{2\}]) & = \mu([\{1,3,4\},\emptyset]) \\
\mu([\{1,2,3,4\},\emptyset]) + \mu([\{1,2,4\},\{3\}]) & = \mu([\{1,2,4\},\emptyset]) \\
\mu([\{1,2,3,4\},\emptyset]) + \mu([\{1,2,3\},\{4\}]) & = \mu([\{1,2,3\},\emptyset]) \\
\mu([\{2,3,4\},\{1\}]) + \mu([\{3,4\},\{1,2\}]) & = \mu([\{3,4\},\{1\}]) \\
\mu([\{2,3,4\},\{1\}]) + \mu([\{2,4\},\{1,3\}]) & = \mu([\{2,4\},\{1\}]) \\
\mu([\{2,3,4\},\{1\}]) + \mu([\{2,3\},\{1,4\}]) & = \mu([\{2,3\},\{1\}]) \\
\mu([\{1,3,4\},\{2\}]) + \mu([\{1,4\},\{2,3\}]) & = \mu([\{1,4\},\{2\}]) \\
\mu([\{1,3,4\},\{2\}]) + \mu([\{1,3\},\{2,4\}]) & = \mu([\{1,3\},\{2\}]) \\
\mu([\{1,2,4\},\{3\}]) + \mu([\{1,2\},\{3,4\}]) & = \mu([\{1,2\},\{3\}]) \\
\mu([\{3,4\},\{1,2\}]) + \mu([\{4\},\{1,2,3\}]) & = \mu([\{4\},\{1,2\}]) \\
\mu([\{3,4\},\{1,2\}]) + \mu([\{3\},\{1,2,4\}]) & = \mu([\{3\},\{1,2\}]) \\
\mu([\{2,4\},\{1,3\}]) + \mu([\{2\},\{1,3,4\}]) & = \mu([\{2\},\{1,3\}]) \\
\mu([\{1,4\},\{2,3\}]) + \mu([\{1\},\{2,3,4\}]) & = \mu([\{1\},\{2,3\}]) \\
\mu([\{4\},\{1,2,3\}]) + \mu([\emptyset,\{1,2,3,4\}]) & = \mu([\emptyset,\{1,2,3\}]) \\
\sum_{[A,B]\in\{0,1\}^{|\mathcal{N}_o^*|}} \Phi_o([A,B]) \cdot \mu([A,B]) & = \mu([\{o\},\emptyset])
\end{cases}
$$

The transfer matrix

$$
\mathcal{M} = \left(\begin{array}{c|cccc|cccccc|cccc|c}
\mathbf{1} & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\mathbf{1} & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\mathbf{1} & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\mathbf{1} & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \mathbf{1} & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \mathbf{1} & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mathbf{1} & 0 & 0 & 0 & \mathbf{1} \\
\Phi_o^4 & \multicolumn{4}{c|}{\Phi_o^3} & \multicolumn{6}{c|}{\Phi_o^2} & \multicolumn{4}{c|}{\Phi_o^1} & \Phi_o^0
\end{array}\right)
$$

A theoretical necessary condition for phase transitions

Theorem

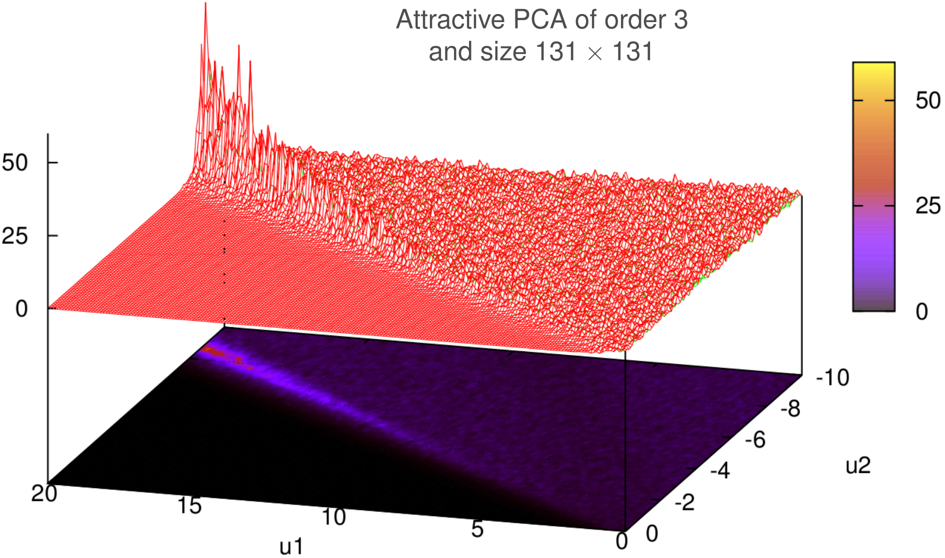
If threshold attractive PCA of order $k > 2$ (nonlinear PCA) admit a phase transition w.r.t. their environment, then

$$\frac{\sum_{j\in\mathcal{N}_o^*} u_1}{2} + \frac{\eta_o^k(\mathcal{N}_o^*)}{2} = 0 \iff Det\mathcal{M} = 0$$

Idea of the proof

- ◇ A symmetric nonlinear term ($\forall K \subseteq \mathcal{N}_i^*,\ \eta_i^k(\mathcal{N}_i^*) = \eta_i^k(K) + \eta_i^k(\mathcal{N}_i^* \setminus K)$) allows to counter-balance the influence of linear interaction potentials, which is necessary for the emergence of phase transitions
- ◇ Show that the nonlinear term is symmetric iff $u_0 + \frac{\sum_{j\in\mathcal{N}_o^*} u_1}{2} + \frac{\eta_o^k(\mathcal{N}_o^*)}{2} = 0$
- ◇ Attractive PCA $\implies$ Super-modularity (Preston, 1974; Demongeot, 1983) and concavity
- ◇ Deduce that: $\frac{\sum_{j\in\mathcal{N}_o^*} u_1}{2} + \frac{\eta_o^k(\mathcal{N}_o^*)}{2} = 0 \iff \mathrm{Det}\mathcal{M} = 0$

An empirical sufficient condition



Outline

On-going works

- ◇ Towards a formal characteristation. . . ?
- ◇ Constraint relaxation to become closer to biology:
  - → Attractiveness
  - → Isotropy
  - → Translation invariance
  - → Perfect synchronism
  - → . . .
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  - → Cell coalitions in extra-cellular networks

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- ◇ Other problematics:
  - → Towards the study of the evolution of genetic regulation networks. . .
  - → Towards a better understanding of the relation between regulations and time. . .

Thanks and credits

- ◇ Jacques Demongeot
- ◇ Eric Goles
- ◇ Michel Morvan
- ◇ Mathilde Noual

Thank you for your attention

Super-modularity and concavity

Definition

A function $g : \mathbb{B}^n \to \mathbb{R}^+$ is *super-modular* iff

$$\forall K, L \subseteq \mathbb{B}^n,\ g(K \cup L) + g(K \cap L) \geq g(K) + g(L). \quad (1)$$

Definition

Let V be a set s.t. $|V| = n$. A function $g : \mathbb{B}^n \to \mathbb{R}^+$ is *concave* iff

$$\forall K, L \subseteq \mathbb{B}^n, |K| \geq |L|,\ g(K) + g(V \setminus K) \leq g(L) + g(V \setminus L). \quad (2)$$

Lemma

Let $\mathscr{A}$ be a PCA of order $k > 2$ in $\mathbb{Z}^2$ and size n, whose interaction graph is $G = (V, A)$. If its local transition function f is super-modular and concave, then

$$\forall K \subseteq \mathbb{B}^n, f(V) + f(\emptyset) = f(K) + f(V \setminus K).$$