Local cycles and dynamical properties of Boolean networks

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Master MPRI 2016–2017
Computational Methods for Systems and Synthetic Biology

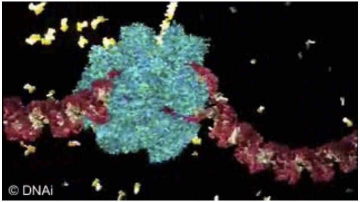
Outline

1. Boolean networks, attractors, interaction graphs, subnetworks
2. Dynamics and structure, Thomas' rules
3. Classes of networks: cycles, and-nets, non-expansive networks…
4. Generalized discrete networks

Cell biology

	definition	function
DNA	long double-helix chain of ($\simeq 10^9$) pairs of nucleotides A, T, C, G (Watson-Crick) organized in chromosomes (or circular)	programme
RNA	short chain of ($\simeq 10^3$) nucleotides A, U, C, G	product of transcription (messenger RNA), translation (transfer RNA, ribosomal RNA): machines
Proteins	polymers ($10 - 10^3$) made of 22 amino acids	transcription, translation, catalysis (enzymes), transport, intra- and inter-cellular communication, replication, membrane: machines, structure
Sugars, acids,...		ressources-products, structure
Lipids		membrane: structure
Water		structure

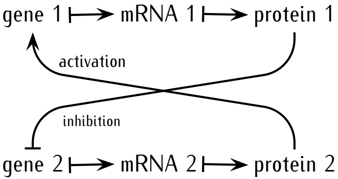
Gene networks

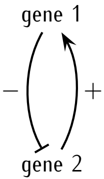


Pictures: Dolan DNA Learning Center

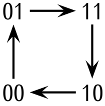
Discrete dynamical systems
Each of n agents takes 2 values (states) $0, 1$. State space $\{0, 1\}^n$
Models of, e.g., neural (McCulloch–Pitts), genetic (Kauffman, Thomas...) networks
Gene networks: abstraction of regulatory transcription / translation processes
Agents $1, \ldots, n =$ genes, $x_i =$ discretized expression level of gene i
Motivations:

1. qualitative nature of biological questions
2. in vivo measurements capabilities
3. many non-linear (sigmoid-shaped) interactions with strong threshold effects





map $f : \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \mapsto \begin{pmatrix} f_1(x) = x_2 \\ f_2(x) = \neg x_1 \end{pmatrix}$ dynamics



Boolean networks

Notation. $\mathbb{F}_2$ is the two-element field, with sum $+$ (xor). The canonical basis of the vector space $\mathbb{F}_2^n$ is $\{e^1, \dots, e^n\}$, and for each $I \subseteq \{1, \dots, n\}$, $e^I = \sum_{i \in I} e^i$. We may remove brackets and write $e^{1,2}$ for $e^{\{1,2\}}$. For $x, y \in \mathbb{F}_2^n$, $d(x, y)$ is the Hamming distance (cardinality of the unique subset $I \subseteq \{1, \dots, n\}$ such that $x + y = e^I$).

Definition. A Boolean network is a map from $\mathbb{F}_2^n$ to $\mathbb{F}_2^n$.

Definition. The synchronous dynamics (iteration) associated to a Boolean network $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$ is the directed graph with vertex set $\mathbb{F}_2^n$ and an edge from x to $f(x)$ for all x.

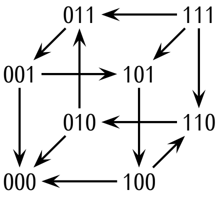
Definition. The asynchronous dynamics associated to f is the directed graph $\Gamma(f)$ with vertex set $\mathbb{F}_2^n$ and an edge from x to y when for some i, $y = x + e^i$ and $f_i(x) \neq x_i$.

Example.

Boolean network

$$x \mapsto \begin{pmatrix} (x_2 + 1)x_3 \\ (x_3 + 1)x_1 \\ (x_1 + 1)x_2 \end{pmatrix}$$

asynchronous dynamics



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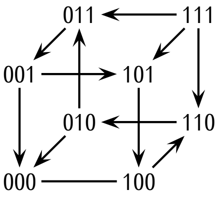

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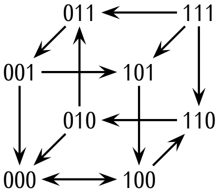


Proposition. Γ is a bijection between maps from $\mathbb{F}_2^n$ to $\mathbb{F}_2^n$ and partial orientations of the hypercube $\mathbb{F}_2^n$.

Proofs. Cf notes (and blackboard).

Remarks.

1. The synchronous dynamics is deterministic, the asynchronous dynamics non-deterministic.
2. Informal justification of asynchrony: trajectories of (piecewise-linear) differential equation models a.s. cross 1 threshold hyperplane at a time $\Rightarrow$ 1 variable update at a time.

Definition. Both dynamics agree on fixed points. A trajectory is a path in $\Gamma(f)$. An attractor is a terminal strongly connected component of $\Gamma(f)$. A cyclic attractor is an attractor which is not a singleton (*i.e.* does not consist in a fixed point). An attractive cycle is a cyclic trajectory θ such that for each point $x \in \theta$, $d(x, f(x)) = 1$. The antipode of $x \in \mathbb{F}_2^n$ is $\overline{x} = x + e^{1,\dots,n}$. Antipodal attractive cycles are those of the form

$$(x^1, \dots, x^n, x^{n+1}, \dots, x^{2n}, x^1) = (x^1, \dots, x^n, \overline{x^1}, \dots, \overline{x^n}, x^1).$$

Remarks.

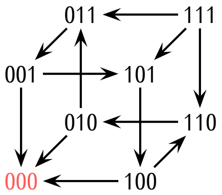
1. If f has no fixed point, then $\Gamma(f)$ has a cyclic attractor.
2. Attractive cycles are examples of cyclic attractors.
3. In an antipodal attractive cycle as above, $d(x^i, x^{i+n}) = n$ for each $i \in \{1, \dots, n\}$.

Definition. A network f is weakly terminating if for any $x \in \mathbb{F}_2^n$, $\Gamma(f)$ has a trajectory from x to a fixed point, directly terminating if moreover such a trajectory exists in which the distance to the fixed point decreases, and collapsing if it is directly terminating to a unique fixed point.

Remark. Weak termination is equivalent to the absence of cyclic attractor.

Example.

fixed point
cyclic trajectory
attractive cycle
cyclic attractor
weak termination
direct termination
collapse



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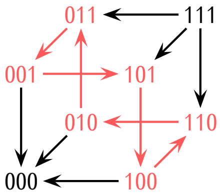

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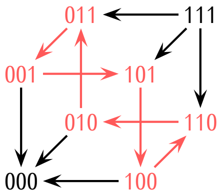

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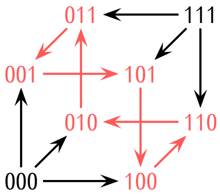

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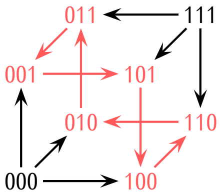

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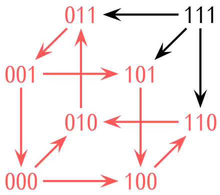

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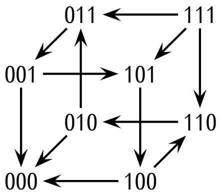

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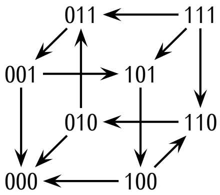

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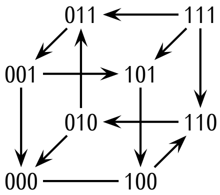

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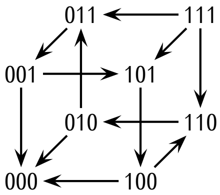


yes

Definition. Given $\varphi : \mathbb{F}_2^n \to \mathbb{F}_2$ and $i \in \{1, \ldots, n\}$, the discrete i^{th} partial derivative $\partial\varphi/\partial x_i = \partial_i\varphi : \mathbb{F}_2^n \to \mathbb{F}_2$ maps each $x \in \mathbb{F}_2^n$ to

$$\partial_i\varphi(x) = \varphi(x) + \varphi(x + e^i).$$

Given $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$ and $x \in \mathbb{F}_2^n$, the discrete Jacobian matrix $\mathscr{J}(f)(x)$ is the $n \times n$ matrix with entries $\mathscr{J}(f)(x)_{i,j} = \partial_j f_i(x)$.

Remarks.

1. $\partial_i\varphi(x) = 1$ if and only if $\varphi(x) \neq \varphi(x + e^i)$. In that case, the influence of variable x_i on φ at x is either covariant when the map

$$\mathbb{F}_2 \to \mathbb{F}_2, \;\; \alpha \mapsto \varphi(x_1, \ldots, x_{i-1}, \alpha, x_{i+1}, \ldots, x_n)$$

is increasing (identity), or contravariant when it is decreasing (negation).

2. Variant of Leibniz rule: $\partial_i(\varphi\psi) + \partial_i\varphi\partial_i\psi = \varphi\partial_i\psi + \psi\partial_i\varphi$.

Definition. A signed directed graph is a directed graph with a sign, $+1$ or -1, attached to each edge. The sign of a cycle (or more generally of a path) is the product of the signs of its edges.

Remark. All cycles will be assumed to be directed and elementary.

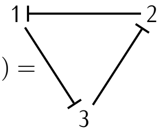
Definition. The interaction graph $\mathscr{G}(f)(x)$ of f at x is the signed directed graph on vertex set $\{1, \ldots, n\}$ which has an edge from j to i when $\mathscr{J}(f)(x)_{i,j} = 1$, with positive (resp. negative) sign when the influence of x_j on f_i is covariant (resp. contravariant). The global interaction graph $\mathscr{G}(f)$ has the same vertices, and a positive (resp. negative) edge from j to i when for some x, $\mathscr{G}(f)(x)$ has. A cycle, or more generally a path, of $\mathscr{G}(f)$ is said to be local when it lies in $\mathscr{G}(f)(x)$ for some x.

Remarks.

1. The condition for an edge to be positive in $\mathscr{G}(f)(x)$ is equivalent to $x_j = f_i(x)$.
2. A global interaction graph may have two edges of opposite signs from some vertex to another.
3. $\mathscr{J}(f)(x)$ is the adjacency matrix of the transpose of (the graph underlying) $\mathscr{G}(f)(x)$.

Example.

$$f(x) = \begin{pmatrix} (x_2+1)x_3 \\ (x_3+1)x_1 \\ (x_1+1)x_2 \end{pmatrix} \qquad \mathscr{G}(f)(111) =$$



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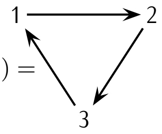

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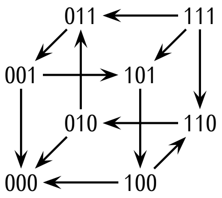
Definition. For any subcube κ, the subnetwork $f\restriction_\kappa : \kappa \to \kappa$ is defined in the obvious way: if $\kappa = x[I]$ and $y \in \kappa$,

$$(f\restriction_\kappa(y))_i = \begin{cases} f_i(y) & \text{if } i \in I \\ x_i & \text{otherwise.} \end{cases}$$

subcube

subnetwork $f\restriction_\kappa : \kappa \to \kappa$ of $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$



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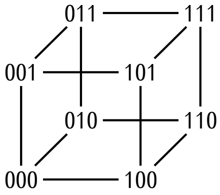

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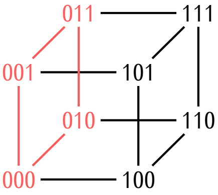

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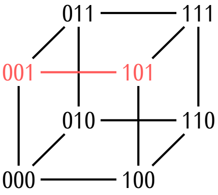

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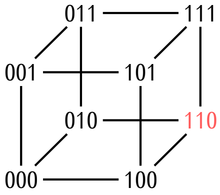

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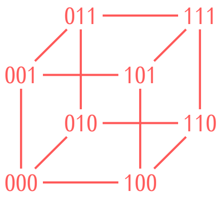

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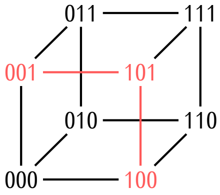
Definition. For any subcube κ, the subnetwork $f\restriction_\kappa : \kappa \to \kappa$ is defined in the obvious way: if $\kappa = x[I]$ and $y \in \kappa$,

$$(f\restriction_\kappa(y))_i = \begin{cases} f_i(y) & \text{if } i \in I \\ x_i & \text{otherwise.} \end{cases}$$

subcube

subnetwork $f\restriction_\kappa : \kappa \to \kappa$ of $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$



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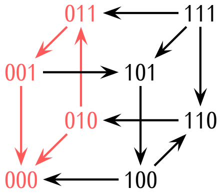


yes

Proposition.

1. Compatibility with asynchronous dynamics: $\Gamma(f\restriction_\kappa)$ is the subgraph of $\Gamma(f)$ induced by κ.
2. Compatibility with interaction graphs: $\mathscr{G}(f\restriction_\kappa)(y)$ is the signed subgraph of $\mathscr{G}(f)(y)$ induced by I.

Lemma. If f has $\geqslant 2$ attractors, then some subnetwork $f\restriction_\kappa$ has $\geqslant 2$ fixed points.

Definition. If $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$ is such that $\mathscr{G}(f)$ has no loop on n (no edge (n, n)), the reduced Boolean network $f' : \mathbb{F}_2^{n-1} \to \mathbb{F}_2^{n-1}$ is defined by substitution:

$$f_i'(x) = f_i(x, f_n(x, 0)) = f_i(x, f_n(x, 1))$$

for each $x \in \mathbb{F}_2^{n-1}$ and $i < n$. If f reduces to f', we say that f is expanded from f'.

Remarks.

1. The hypothesis on $\mathscr{G}(f)$ entails $f_n(x, 0) + f_n(x, 1) = \partial_n f(x, 0) = \partial_n f(x, 1) = 0$. We shall write $f'(x) = f(x, f_n(x, -))$.
2. Generalization: reductions and expansions over any variable(s) can be considered.

Proposition. Assume $\mathscr{G}(f)$ has no loop on n.

1. Fixed points are preserved by reduction and expansion: x is a fixed point of f' if and only if $(x, f_n(x, -))$ is a fixed point of f.
2. Attractive cycles are preserved by reduction: the projection $\pi : \mathbb{F}_2^n \to \mathbb{F}_2^{n-1}$ maps attractive cycles of f to attractive cycles of f'.

Remark. Attractive cycles are not preserved by expansion:

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} \mapsto \begin{pmatrix} x_2 + 1 \\ x_1 \\ x_1 + x_2 \end{pmatrix} \text{ has no attractive cycle, but reduces to } \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \mapsto \begin{pmatrix} x_2 + 1 \\ x_1 \end{pmatrix}.$$

Exercise. Arbitrary cyclic attractors are generally neither preserved by reduction, nor by expansion.

Rules (René Thomas).

1. Differentiation ($\geqslant 2$ fixed points) $\Rightarrow$ 'functional' positive cycle.
2. Homeostasis (sustained oscillations) $\Rightarrow$ 'functional' negative cycle.

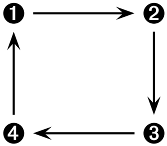
Contributions of Aracena, Chaouiya, Comet, Dong, Goles, Ho, Mossé, Naldi, Remy, Richard, Ruet, Shih, Thieffry...

Differential framework: contributions of Demongeot, Gouzé, Snoussi, Soulé...

Theorem. If $\mathscr{G}(f)(x)$ is independent of x and consists in a Hamiltonian positive (resp. negative) cycle, then f has 2 fixed points and no cyclic attractor (resp. f has no fixed point, and a unique attractor which is an attractive cycle).

Example.

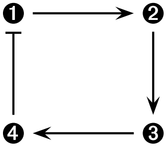
positive



$$x \mapsto \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

2 fixed points: 0000, 1111
direct termination (to 0000 and 1111)

negative



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unique attractor =
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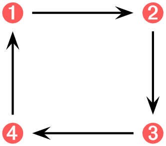

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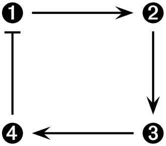

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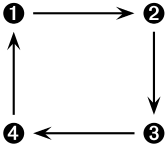

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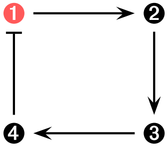

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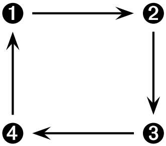

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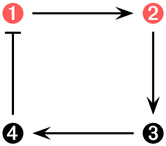

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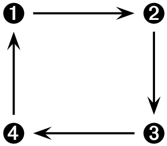

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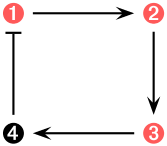

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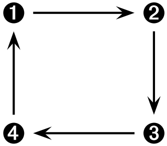

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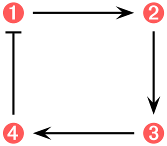

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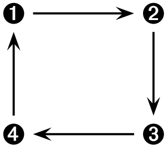

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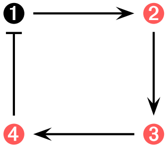

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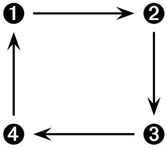

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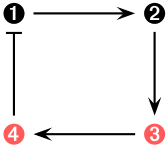

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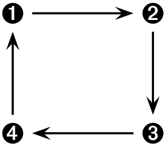

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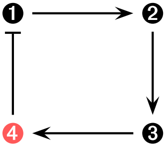

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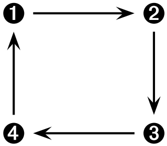

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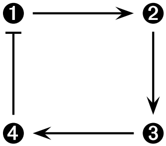

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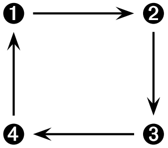

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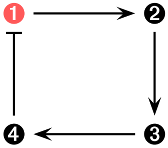

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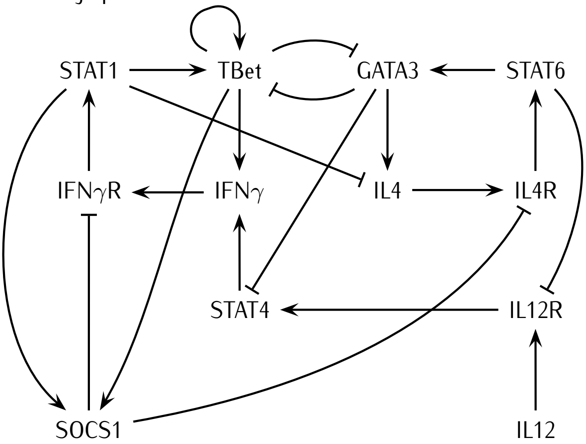
Example: Th lymphocyte differentiation

Exercise. Implement $f : \mathbb{F}_2^{12} \to \mathbb{F}_2^{12}$ in GINsim.

index i	gene	$f_i(x)$
1	IFNγ	$x_9 \vee x_{11}$
2	IL4	$x_{12} \wedge \neg x_7$
3	IL12	constant
4	IFNγR	$x_1 \wedge \neg x_{10}$
5	IL4R	$x_2 \wedge \neg x_{10}$
6	IL12R	$x_3 \wedge \neg x_8$
7	STAT1	x_4
8	STAT6	x_5
9	STAT4	$x_6 \wedge \neg x_{12}$
10	SOCS1	$x_7 \vee x_{11}$
11	TBet	$(x_7 \vee x_{11}) \wedge \neg x_{12}$
12	GATA3	$x_8 \wedge \neg x_{11}$

Example: Th lymphocyte differentiation

Global interaction graph



Theorem (Robert). If $\mathscr{G}(f)$ has no cycle, then f has a unique fixed point and the iteration of f terminates in $\leqslant n$ steps.

Theorem (Bahi-Michel). If $\mathscr{G}(f)$ has no cycle, then $\Gamma(f)$ is collapsing.

Proofs. Exercise.

Theorem. If $\mathscr{G}(f)$ has no local cycle, then f has a unique fixed point.

Proof. The group $\mathbb{F}_2^n$ acts on the set of Boolean networks by translation, and $\mathscr{J}(f + x)(-) = \mathscr{J}(f)(-)$.

Lemma.

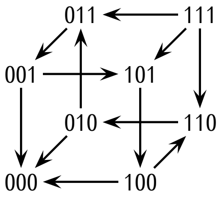
1. An orbit of Boolean networks contains a network with no fixed point if and only if it contains a network with $\geqslant 2$ fixed points.
2. The set of networks such that each subnetwork $f\restriction_{\kappa}$ has a unique fixed point is closed under translation.

Definition. $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$ is called hereditarily bijective (resp. hereditarily ufp) when for any subcube κ, $f\restriction_\kappa$ is bijective (resp. has a unique fixed point).

Proposition. f is hereditarily ufp if and only if $f + \text{id}$ is hereditarily bijective.

Corollary. If $f + \text{id}$ is hereditarily bijective, then $\Gamma(f)$ is collapsing.

$f + \text{id}$ hereditarily bijective



Theorem. If $f + \text{id}$ is not bijective, then there exist two different points $x, y \in \mathbb{F}_2^n$ such that $\mathscr{G}(f)(x)$ and $\mathscr{G}(f)(y)$ have a cycle.

Corollary. If $\mathscr{G}(f)$ has no local cycle, then $\Gamma(f)$ is collapsing.

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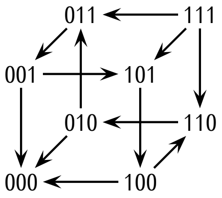

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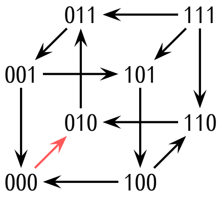

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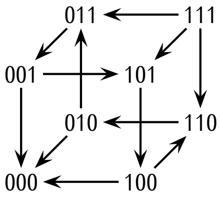

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Corollary. If $\mathscr{G}(f)$ has no local cycle, then $\Gamma(f)$ is collapsing.

Theorem. There exists a 4-dimensional Boolean network f such that $\mathscr{G}(f)$ has no local cycle and the iteration of f does not terminate.

The iteration of

$$f(x) = \begin{pmatrix} (x_3 \vee x_4)\neg x_2 \\ x_3 \neg x_4 \\ x_4 \neg x_1 \neg x_2 \\ x_1 x_2 \neg x_3 \end{pmatrix}$$

has a cycle $((0,0,0,1),(1,0,1,0),(1,1,0,0),(0,0,0,1))$, but $\mathscr{G}(f)$ has no local cycle.

Proof. GINsim.

Positive cycles

Lemma. If C is a cycle of $\mathscr{G}(f)(x)$ with vertex set I, then C is positive (resp. negative) when x has an even (resp. odd) out-degree in $\Gamma(f)$, *i.e.*, when

$$\sum_{i\in I}(x_i + f_i(x)) = 0 \text{ (resp. 1)}.$$

In particular, if x is a fixed point and C is any cycle in $\mathscr{G}(f)(x)$, then C is positive.

Theorem. If $\mathscr{G}(f)$ has no local positive cycle, then f has $\leqslant 1$ fixed point.

Theorem. If $\mathscr{G}(f)$ has no local positive cycle, then f has a unique attractor.

Theorem. If $\Gamma(f)$ has an attractive cycle, then $\mathscr{G}(f)$ has a negative cycle.

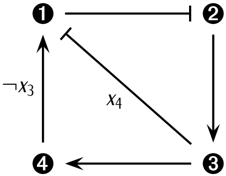
Lemma. Let $p \geqslant 1$ and $(x^0, \ldots, x^p)$ be a trajectory of $\Gamma(f)$. If $f(x^0) = x^0 + e^i$ and $f_j(x^p) \neq x_j^p$, then $\mathscr{G}(f)$ has a path from i to j whose sign is positive if and only if $x_i^0 = x_j^p$.

Theorem. If $\Gamma(f)$ has a cyclic attractor (in particular if f has no fixed point), then $\mathscr{G}(f)$ has a negative cycle.

Definition. A map $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$ is non-expansive if $d(f(x), f(y)) \leqslant d(x, y)$ for any x, y.

Theorem. If f is non-expansive and has no fixed point, then $\mathscr{G}(f)$ has a local negative cycle.

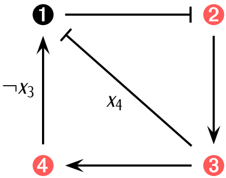
Chord in a cyclic Boolean network



$$f\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4\overline{x_3} \\ \overline{x_1} \\ x_2 \\ x_3 \end{pmatrix}$$

unique fixed point $(0, 1, 1, 1)$

non-attractive cycle



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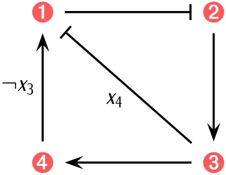

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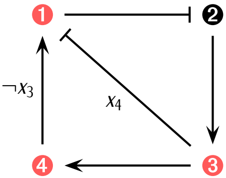
Chord in a cyclic Boolean network



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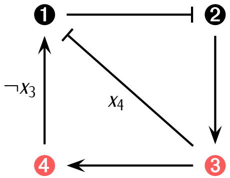

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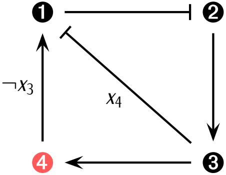
Chord in a cyclic Boolean network



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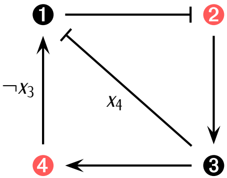

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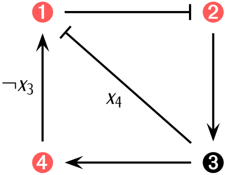
Chord in a cyclic Boolean network



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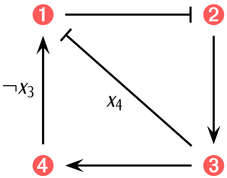

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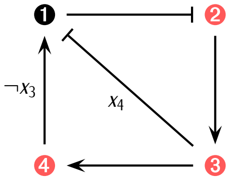
Chord in a cyclic Boolean network



$$f\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4\overline{x_3} \\ \overline{x_1} \\ x_2 \\ x_3 \end{pmatrix}$$

unique fixed point $(0, 1, 1, 1)$

non-attractive cycle

Definition. A network f is an and-net when for each i, f_i is a product of literals, *i.e.* there exist disjoint subsets P_i and N_i of $\{1, \dots, n\}$ such that

$$f_i(x) = \prod_{j \in P_i} x_j \prod_{j \in N_i} (x_j + 1),$$

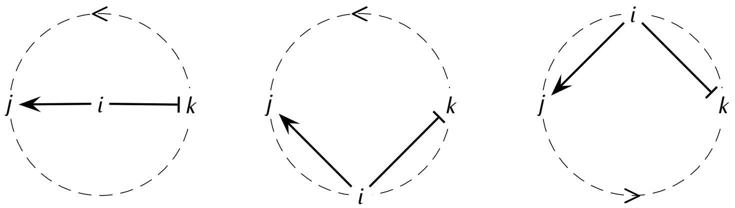
with the convention that the empty product is 1. Indices in P_i (resp. in N_i) are called the positive (resp. negative) inputs of f_i.

Remarks.

1. The positive (resp. negative) inputs are the vertices j of $\mathscr{G}(f)$ such that (j, i) is a positive (resp. negative) edge of $\mathscr{G}(f)$.
2. For an and-net, the global interaction graph $\mathscr{G}(f)$ determines f: given a signed directed graph G which is simple (*i.e.* without parallel edges), define the and-net f by

$$f_i(x) = \prod_{(j,i) \in E^+(G)} x_j \prod_{(j,i) \in E^-(G)} (x_j + 1),$$

where $E^+(G)$ (resp. $E^-(G)$) is the set of positive (resp. negative) edges of G. Then f is the unique and-net such that $\mathscr{G}(f) = G$.



Definition. A triple $(i, j, k) \in \{1, \ldots, n\}^3$ is said to be a delocalizing triple of C when j, k are distinct vertices of C and $(i, j), (i, k)$ are two edges of G that are

- not edges of C,
- and of different signs.

A delocalizing triple (i, j, k) of C is said internal when i is a vertex of C, external otherwise.

Proposition. For an and-net f, a cycle C of $\mathscr{G}(f)$ is local if and only if it has no delocalizing triple.

Theorem.

1. If f is an and-net and every cycle of $\mathscr{G}(f)$ has a delocalizing triple, then f has a unique fixed point.
2. If f is an and-net and every positive cycle of $\mathscr{G}(f)$ has a delocalizing triple, then f has $\leqslant 1$ fixed point.

Theorem. If f is an and-net and has an antipodal attractive cycle, then $\mathscr{G}(f)$ has a local negative cycle.

Theorem. If f is an and-net and every negative cycle of $\mathscr{G}(f)$ has an internal delocalizing triple, then f has $\geqslant 1$ fixed point.

Definition. A vertex i in a directed graph G dominates a vertex j when G has an edge from i to j. A set I of vertices of G is called independent when no edge of G links two vertices in I, and absorbent when every vertex not in I dominates some vertex in I. A kernel is an independent and absorbent set of vertices.

Theorem (von Neumann). If a directed graph G has no cycle, then it has a unique kernel.

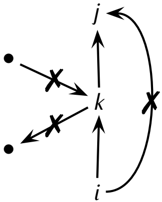
Theorem (Boros–Gurvich). If G has no even cycle, then it has $\leqslant 1$ kernel.

Theorem (Richardson). If G has no odd cycle, then it has $\geqslant 1$ kernel.

Definition. An and-net f is negative if for all i, f_i has only negative inputs.

Remark. Every directed graph G with vertex set $\{1, \ldots, n\}$ determines a unique negative and-net $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$ such that the graph underlying $\mathscr{G}(f)$ is G. Positive and negative cycles of $\mathscr{G}(f)$ correspond to even and odd cycles of G, where the parity of a cycle is the parity of the number of its edges.

Proposition. Let f be the negative and-net associated to the directed graph G. The fixed points of f are in bijection with the kernels of G^{op} (the opposite of G, obtained by reversing the direction of edges).



Definition. Given vertices i, j of G (not necessarily distinct), a vertex $k \neq i, j$ is said to be a subdivision of (i, j) when (i, k) and (k, j) are edges of D, and the in-degree and out-degree of k both $= 1$. Given a cycle C of G and vertices u, v_1, v_2 of G, (u, v_1, v_2) is called a killing triple of C when:

1. v_1 and v_2 are distinct vertices of C,
2. (v_1, u) has a subdivision in G, but no subdivision of (v_1, u) belongs to C,
3. (v_2, u) is an edge of G that is not in C.

A killing triple (u, v_1, v_2) of C is internal when u is a vertex of C, external otherwise.

Theorem.

1. If every cycle of a directed graph G has a killing triple, then G has a unique kernel.
2. If every even cycle of G has a killing triple, then G has $\leqslant 1$ kernel.

Theorem. If every odd cycle of G has an internal killing triple, then G has $\geqslant 1$ kernel.

Definition.

1. To an and-net f is associated a directed graph f^* obtained by replacing positive inputs $i \to^+ j$ by $i \to^- (i,j) \to^- j$, and forgetting signs.
2. To a directed graph G is associated an and-net $G^{\pm}$.

Proposition. The constructions relate fixed points to kernels, positive and negative cycles to even and odd cycles, and (good) delocalizing triples to killing triples.

Definition. Let X be the metric space $X_1 \times \cdots \times X_n$, where $n \geqslant 1$ and for each i, $X_i = \{m_i, m_i + 1, \ldots, M_i\}$ with $m_i < M_i$, and distance $d(x, y) = \sum_i |x_i - y_i|$. A discrete asynchronous network is a directed graph γ with vertex set X satisfying the following two conditions:

1. if γ has an edge from x to y, then $d(x, y) = 1$,
2. for each i, γ does not have edges from x to both $x + e^i$ and $x - e^i$,

where $e^i \in X$ is defined by the Kronecker symbol $e^i_j = \delta^i_j$. Given $x, y \in X$, $[x, y]$ is the set of all z such that $d(x, y) = d(x, z) + d(z, y)$, and a subspace is a set of the form $[x, y]$. For any subspace κ, the subnetwork $\gamma\restriction_\kappa$ is the subgraph of γ induced by κ. The diameter of a subspace $[x, y]$ is $d(x, y)$.

Remark. The diameter of κ depends only on κ, not on the choice of x, y such that $\kappa = [x, y]$.

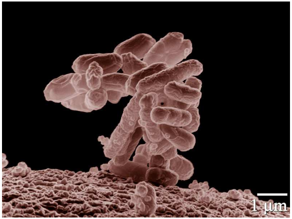
Definition. If $\max_i |x_i - y_i| = 1$ and I is the set of i such that $x_i \neq y_i$, the map

$$\beta : [x, y] \to \mathbb{F}_2^I, \quad z \mapsto (z_i - \min(x_i, y_i))_{i \in I}$$

is an increasing bijection, and the local interaction graph $\mathscr{G}(\gamma)(x, y)$ of γ at x in the direction of y is the interaction graph, at $\beta(x)$, of the Boolean network $\beta(\gamma\restriction_{[x,y]})$ image of the subnetwork $\gamma\restriction_{[x,y]}$. The global interaction graph $\mathscr{G}(\gamma)$ has vertex set $\{1, \ldots, n\}$ and a positive (resp. negative) edge from i to j when for some x, y as above, $\mathscr{G}(\gamma)(x, y)$ has.

Generalized discrete networks: λ bacteriophage

λ is a virus infecting E. coli bacteria.



Picture: E. Erbe, C. Pooley

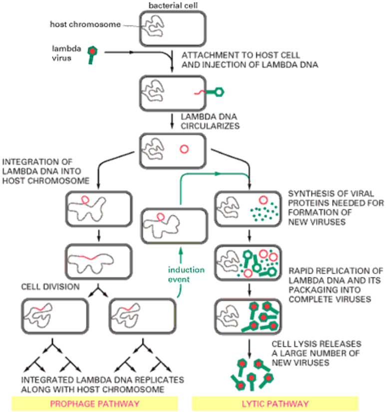
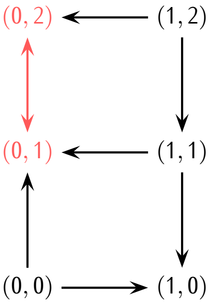
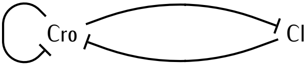


Diagram: *Essential Cell Biology*, Alberts, Bray, Johnson, Lewis, Raff, Roberts, Walter (2009)

Generalized discrete networks: λ bacteriophage

Lytic cycle and lysogenic state

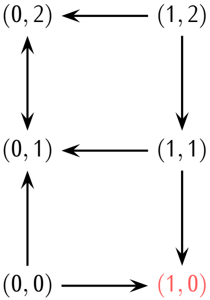




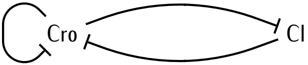
x_1–axis CI, x_2–axis Cro

Generalized discrete networks: λ bacteriophage

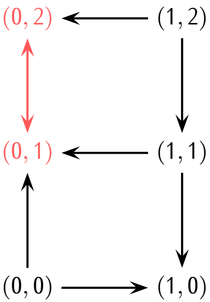
Lytic cycle and lysogenic state

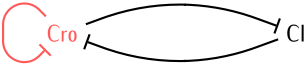


x_1-axis CI, x_2-axis Cro



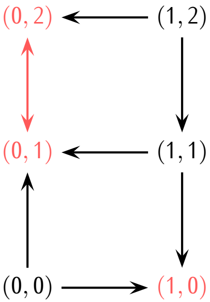
Lytic cycle and lysogenic state





x_1–axis CI, x_2–axis Cro

Lytic cycle and lysogenic state

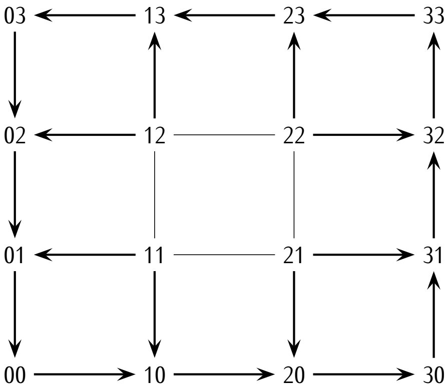


x_1–axis CI, x_2–axis Cro

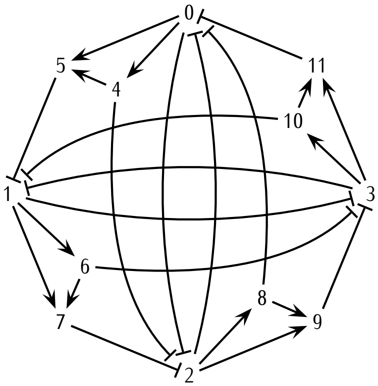
Theorem. If γ is a discrete network such that $\mathscr{G}(\gamma)$ has no local positive cycle, then γ has $\leqslant 1$ fixed point.

Theorem. If γ is a discrete network such that $\mathscr{G}(\gamma)$ has no local cycle, then γ has a unique fixed point.

Theorem. There exists a 2-dimensional discrete network with no fixed point, an attractive cycle and no local negative cycle.



Theorem. There exists a 12-dimensional and-net with no fixed point (hence a cyclic attractor) and no local negative cycle.

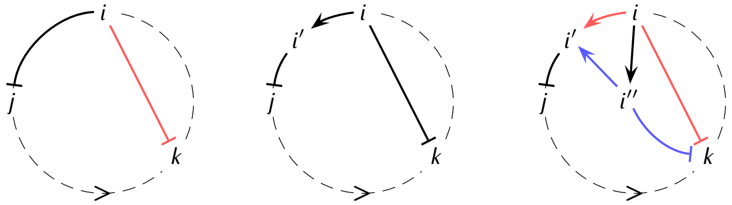


Question. Does there exist an and-net with an attractive cycle and no local negative cycle?

Definition. Let f be a negative and-net and S be a set of cycles of $\mathscr{G}(f)$. An S-quasi-delocalizing function of f is a function χ from S to the set of pairs of edges of $\mathscr{G}(f)$ such that:

- $\chi_1(C)$ is a chord (i,k) of C;
- $\chi_2(C)$ is an edge (i,j) of C;
- $\mathrm{Im}(\chi_1) \cap \mathrm{Im}(\chi_2) = \varnothing$.

Remark. $\chi_2(C)$ is determined by $\chi_1(C)$: it is the unique edge of C starting from the same vertex as $\chi_1(C)$.



Lemma. Let f be a negative and-net and S be a set of cycles of $\mathscr{G}(f)$. If f has an S-quasi-delocalizing function, then f can be expanded to an and-net g such that every cycle of $\mathscr{G}(g)$ above a cycle of S is delocalized.

Corollary. Let f be a negative and-net and S be the set of negative cycles of $\mathscr{G}(f)$. If f has an S-quasi-delocalizing function, then f can be expanded to an and-net without local negative cycle.

Theorem. There exists a 7-dimensional Boolean network with an antipodal attractive cycle and no local negative cycle.