Discrete dynamics of biological networks
Focus on the regulatory circuits

"Méthodes informatiques pour la biologie systémique et synthétique"
M2 MPRI

Lundi 31 Janvier 2011

Motivations

Modelisation and analysis of the dynamics of regulatory networks :

- Insights from the dynamical properties, attractors (stable states, cyclical behaviours, trajectories...)
- Analysis of perturbations, confrontation of model predictions to experimental data

Main problem : size of the state transition graph (the dynamics)

- Simulations
- isolated modules
- focus on specific motives : the regulatory circuits (feedback circuits)

Thomas' rules (1981)

- Presence of several stable states in the dynamics (multistationarity) $\Rightarrow$ positive circuit in the regulatory graph.

- Presence of sustained oscillations in the dynamics (homeostasis) $\Rightarrow$ negative circuit in the regulatory graph.

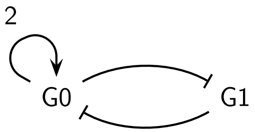
Regulatory Graphs	$\longleftrightarrow$	Dynamics of the system

Sommaire

Regulatory graph

Regulatory graphs : finite, signed, labelled, directed graphs

- Nodes → genes
- Arcs → interactions between genes
- Sign → type of regulation (activation/inhibition)
- Label → threshold



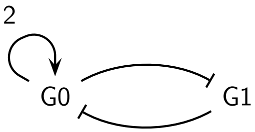
Dynamics of regulatory networks

Evolution of the transcription levels of the regulated genes

- n number of genes
- $x_i \in \{0, 1, \ldots, Max_i\}$ expression level of gene i
- $x = (x_1, \ldots, x_n)$ a state of the system
- $f : \prod_{i=1}^{n} \{0, \ldots, Max_i\} \rightarrow \prod_{i=1}^{n} \{0, \ldots, Max_i\}$,
  $f(x) = (f_1(x), \ldots, f_n(x))$ the dynamics

The formalism

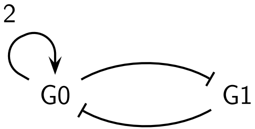
x_{G0} x_{G1}	$f_{G0}(x)$ $f_{G1}(x)$
0 0	2 1
1 0	2 0
2 0	1 0
0 1	0 1
1 1	0 0
2 1	0 0



$x_{G0} \in \{0, 1, 2\}$
$x_{G1} \in \{0, 1\}$

The formalism

x_{G0}	x_{G1}	$f_{G0}(x)$	$f_{G1}(x)$
$\overset{+}{0}$	$\overset{+}{0}$	2	1
$\overset{+}{1}$	0	2	0
$\overset{-}{2}$	0	1	0
0	1	0	1
$\overset{-}{1}$	$\overset{-}{1}$	0	0
$\overset{-}{2}$	$\overset{-}{1}$	0	0

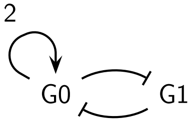


$x_{G0} \in \{0, 1, 2\}$
$x_{G1} \in \{0, 1\}$

$f_i(x)$: value to which x_i tends when the system is in state x

- if $x_i < f_i(x)$, gene i tends to *increase* its expression level ($\overset{+}{x}_i$)
- if $x_i > f_i(x)$, gene i tends to *decrease* its expression level ($\overset{-}{x}_i$)
- if $x_i = f_i(x)$, gene i does not modify its expression level

State transition graphs



01 $\overset{-}{1}\overset{-}{1}$ $\overset{-}{2}\overset{-}{1}$

$\overset{+}{0}\overset{+}{0}$ $\overset{+}{1}0$ $\overset{+}{2}0$

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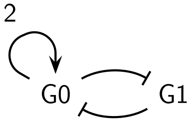
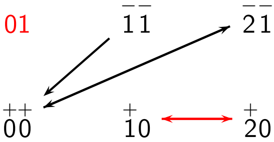
$\overset{-}{2}$ $\overset{-}{1}$	0 0

State transition graphs





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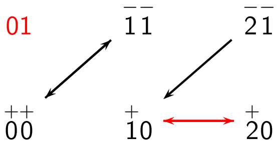
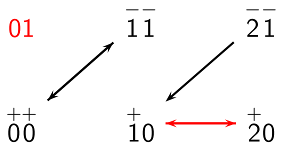
Updating rules



Synchronous updating

Updating rules



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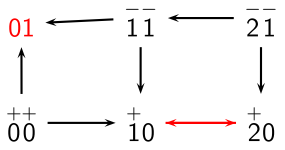

Asynchronous updating

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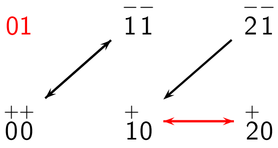

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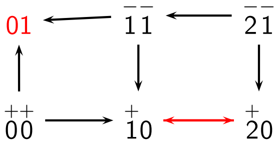

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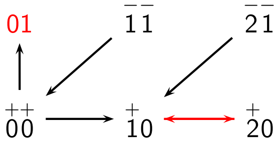

With priorities

- Degradations : high priority, synchronous
- Syntheses : low priority, asynchronous

Boolean Asynchronous Dynamics

- Boolean Dynamics : $Max_i = 1, \forall i \in \{1, \ldots n\}$
- Asynchronous updating : $\{(x, \overline{x}^i)$ s.t. $x \in \{0,1\}^n, \forall i$ s.t. $x_i \neq f_i(x)\}$

Définitions :

- Stable states : $f_i(x) = x_i$ for all i
- Positive circuit contains an even number of inhibitions
- Negative circuit contains an odd number of inhibitions

Thomas' rules (1981)

- Presence of several stable states in the dynamics (multistationarity) $\Rightarrow$ positive circuit in the regulatory graph.
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From dynamics to regulatory graph

Asynchronous dynamics : represented by the state transition graph $(\mathcal{V}, \mathcal{E})$. Given $f : \{0,1\}^n \to \{0,1\}^n$, we have $(x, \overline{x}^i) \in \mathcal{E}$ when $x_i \neq f_i(x)$ (updates the expression level of i in state x).

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Local regulatory network $G(f)(x)$
$i \xrightarrow{\varepsilon} j$ when $f_j(\overline{x}^i) \neq f_j(x)$,
with $\varepsilon = +$ if $x_i = f_j(x)$ and $\varepsilon = -$ if $x_i \neq f_j(x)$
... discrete (partial) derivatives.
Global regulatory graph : $G(f) = \bigcup_x G(f)(x)$.

From dynamics to regulatory graph

Definitions with the State Transition Graph

- $i \xrightarrow{\varepsilon} j$ if $\exists x$ s.t. $(x, \overline{x}^j) \in \mathcal{E}$ and $(\overline{x}^i, \overline{x}^{i,j}) \notin \mathcal{E}$ with $\varepsilon = +$ if $x_i \neq x_j$ and $\varepsilon = -$ if $x_i = x_j$

From dynamics to regulatory graph

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- positive self-regulation $i \overset{+}{\circlearrowleft}$:
  - when $f_i(x) \neq f_i(\overline{x}^i)$ and $x_i = f_i(x)$
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Sommaire

Thomas' conjectures (1981)

- f has at least two stable states $\Rightarrow$ there exits a positive circuit in $G(f)$

- f has a trap cycle $\Rightarrow$ there exists a negative circuit in $G(f)$

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Differential equations : Plathe et al. ($\pm$, 1995), Snoussi ($\pm$, 1998), Gouzé ($\pm$, 1998), Cinquin-Demongeot ($+$, 2002), Soulé ($+$, 2003).

Discrete framework : Aracena et al ($+$, 2001), R.-Ruet-Thieffry ($\pm$, 2005), Comet-Richard (2005)

Multistability and positive circuits : a proof

Let x and $y = \overline{x}^{\Delta(x,y)}$ two stable states

- Let $i \in \Delta(x, y)$. By definition, $(y, \overline{y}^i) \notin \mathcal{E}$.

Multistability and positive circuits : a proof

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  - Suppose $(\overline{y}^i, y) \in \mathcal{E}$. Take $D = \Delta(x,y) \setminus \{i\}$
    We have $(x, \overline{x}^i) \notin \mathcal{E}$ (stable state), and $(\overline{x}^D, \overline{x}^{D \cup i}) \in \mathcal{E}$. There exists $D' \subseteq D$ s.t., for $j \in D'$

    $$(\overline{x}^{D' \setminus j}, \overline{x}^{(D' \setminus j) \cup i}) \notin \mathcal{E} \text{ and } (\overline{x}^{D'}, \overline{x}^{D' \cup i}) \in \mathcal{E}.$$

    Hence, $j \xrightarrow{\varepsilon} i$. As $x_i \neq y_i$, we can deduce that $\varepsilon_i = -1$ if $x_i \neq x_j$

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$\Rightarrow \forall i \in \Delta(x,y), \exists p(i) \in \Delta(x,y)$ such that $p(i) \xrightarrow{\varepsilon_i} i$, with $\varepsilon_i = -1$ if $x_i \neq x_{p(i)}$

Multistability and positive circuits

• Let $i \in \Delta(x,y)$, and the sequence $\{p^k(i), k \geqslant 0\}$. There exists j and l s.t.$p^j(i) = p^{j+l}(i)$ and $p^j(i), \dots p^{j+l-1}(i)$ are all differents $\Rightarrow$ circuit $p^j(m), \dots p^{j+l-1}(i)$, with an even number of negative edges, (as $i \xrightarrow{-} j$ if $x_{p^j(i)} \neq x_{p^{j+1}(i)}$).

$\Rightarrow$ For each $i \in \Delta(x,y)$, there exists $j \in \Delta(x,y)$ occuring in a positive circuit involving only components of $\Delta(x,y)$, and a path from i to j.

Multistability and positive circuits

Theorem :
f has two stable states x and $y \Longrightarrow$ for each $i \in \Delta(x,y)$ there exists $j \in \Delta(x,y)$ occuring in a positive circuit involving only components of $\Delta(x,y)$, and a path from j to i.
In particular the regulatory graph contains a positive circuit involving a subset of $\Delta(x,y)$

Didier, R. Submitted.

Multistability and positive circuits

An other proof leans on the proof of discrete version of the Jacobian conjecture

Discrete Jacobian Conjecture [Shih and Dong, 2005] :

$\forall x \in \{0,1\}^n$, $\Gamma(x)$ (non signed version of $G(x)$) has no circuit $\implies$ f has a unique fixed point

Theorem :

f has at least two stable states $\implies \exists a \in \{0,1\}^n$ such that $G(f)(a)$ has a positive circuit involving a subset of $\Delta(x,y)$.

R., Ruet, Thieffry. 2008

Cycles and negative circuits

Theorem :
If f has a trap cycle

$$C = x^1 \xrightarrow{i_1} x^2 \xrightarrow{i_2} \cdots \xrightarrow{i_{p-1}} x^p \xrightarrow{i_p} x^1 ,$$

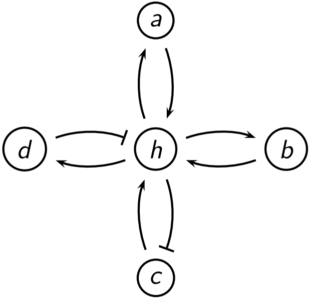
then the regulatory graph contains a negative circuit with vertices $i_1, \ldots i_p$

Thomas'rules : from the dynamics to the regulatory graph

From the regulatory graph to the dynamics ?

- When RG $\equiv$ isolated circuit :OK [R., Mossé, Chaouiya, Thieffry. Bioinformatics, 2003]
- When RG $\equiv$ combination of circuits : nb of stable states [Didier, R.. Submitted]
- When RG is general ? ? $\longrightarrow$ toward the functional circuits ?

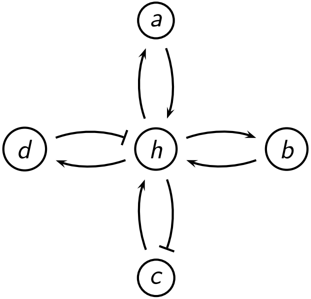
Flower-graphs



A flower-graph

- there is a particular component h such that $\mathcal{E} = \{h \xrightarrow{\varepsilon_{h\,i}} i \mid i \neq h\} \cup \{i \xrightarrow{\varepsilon_{i\,h}} h \mid i \neq h\}$
- all regulations are *univocal*
- h is not self regulated

Flower-graphs



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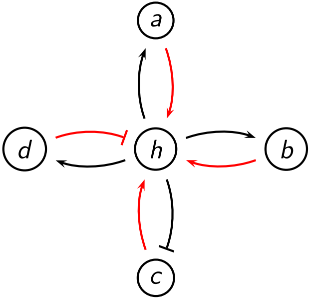
Number of stable states ?

Flower-graphs



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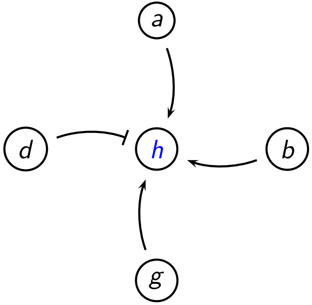
Number of stable states ?

Multiple regulators

We define the state u by :

- $u_h = 0$,
- for all $i \in \mathcal{C}_{\setminus\{h\}}$, $u_i = \begin{cases} 0 & \text{if } i \xrightarrow{+} h \\ 1 & \text{if } i \xrightarrow{-} h \end{cases}$



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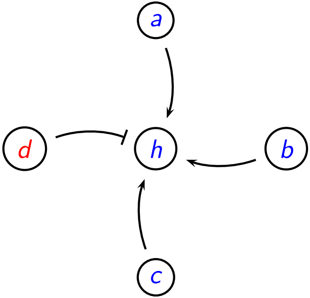


Multiple regulators

Let

$$
\begin{aligned}
E_0 &= \{y \in \{0,1\}^{\mathcal{C}} \mid y_h = 0 \text{ and } f_h(y) = 0\} \\
E_1 &= \{y \in \{0,1\}^{\mathcal{C}} \mid y_h = 1 \text{ and } f_h(y) = 1\}
\end{aligned}
$$

Multiple regulators

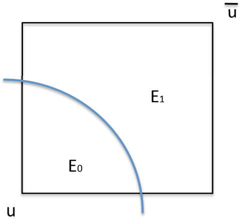
Let

$$E_0 = \{y \in \{0,1\}^{\mathcal{C}} \mid y_h = 0 \text{ and } f_h(y) = 0\}$$
$$E_1 = \{y \in \{0,1\}^{\mathcal{C}} \mid y_h = 1 \text{ and } f_h(y) = 1\}$$

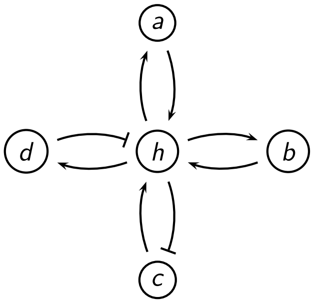
We have

- $u \in E_0$ and $\overline{u} \in E_1$
- For all $\mathcal{D} \subseteq \mathcal{C}_{\setminus\{h\}}$, if $\overline{u}^{\mathcal{D}} \in E_0$ then, $\forall \mathcal{F} \subset \mathcal{D}$, $\overline{u}^{\mathcal{F}} \in E_0$ (antichain).

Multiple regulators



Stable states and Flower-graphs



Number of stable states ?

Stable states and flower graphs

We define the state v by :

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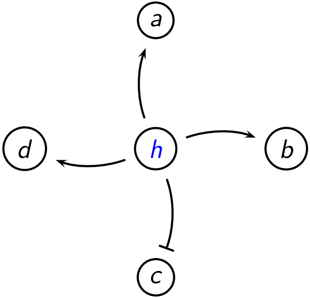

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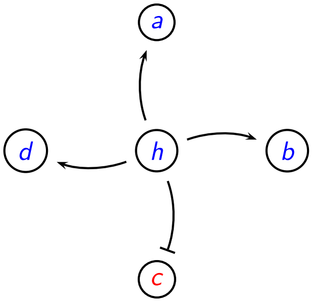
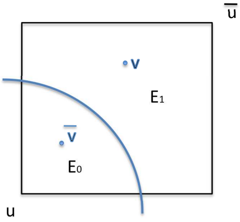


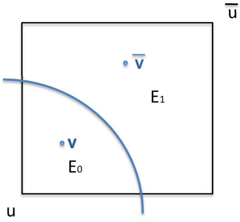
Stable states and flower graphs

$\hookrightarrow$ v and $\overline{v}$ are the only potential stable states

- v stable state if and only if $v \in E_0$
- $\overline{v}$ stable state if and only if $\overline{v} \in E_1$

Stable states and flower graphs

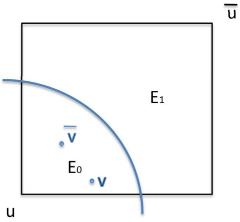


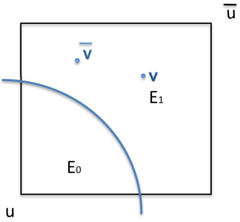


no stable state

2 stable states

Stable states and flower graphs





1 stable state

Stable states and flower graphs

- If the flower graph contains only positive circuits,
then $v = u$ and $\overline{v} = \overline{u} \Rightarrow$ 2 stable states

Stable states and flower graphs

- If the flower graph contains only positive circuits, then $v = u$ and $\overline{v} = \overline{u} \Rightarrow$ 2 stable states

- If the flower graph contains only negative circuits, then $v = \overline{u}$ and $\overline{v} = u \Rightarrow$ no stable state

Stable states and flower graphs

• If the flower graph contains a unique negative circuit (*e.g.* implying a) and at least one positive circuit then $v = \overline{u}^a$ and $\overline{v} = \overline{u}^{\mathcal{C} \setminus a}$.
Suppose there is no stable state, $\overline{u}^a \notin E_0$ and $\overline{u}^{\mathcal{C} \setminus a} \notin E_1$. Then, $\overline{u}^{\mathcal{D}} \in E_0$ iff $a \notin \mathcal{D} \rightarrow a$ unique regulator of h, a contradiction.
$\Rightarrow$ there exists at least one stable state

Stable states and flower graphs

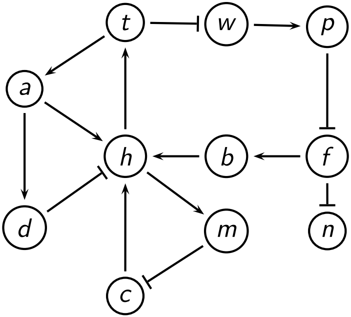
• If the flower graph contains a unique negative circuit (*e.g.* implying a) and at least one positive circuit then $v = \overline{u}^a$ and $\overline{v} = \overline{u}^{\mathcal{C} \setminus a}$.
Suppose there is no stable state, $\overline{u}^a \notin E_0$ and $\overline{u}^{\mathcal{C} \setminus a} \notin E_1$. Then, $\overline{u}^{\mathcal{D}} \in E_0$ iff $a \notin \mathcal{D} \rightarrow a$ unique regulator of h, a contradiction.
$\Rightarrow$ there exists at least one stable state

• If the flower graph contains a unique positive circuit, and at least one negative circuit $\Rightarrow$ at most one stable state

Hub-graphs

A hub-graph

- all the regulations are univocal
- there is a particular component h, called the hub, such that :
  - h is the only component which can have more than one regulator
  - for all components $i \in \mathcal{C}$, there is a path from h to i
  - h is not self-regulated



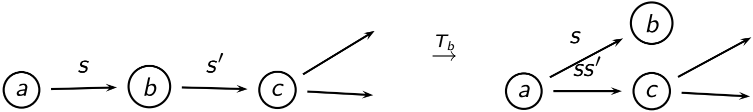
From hub- to flower-graphs

Given a hub-graph, there exists a flower graph

- which contains the same number of positive and negative circuits
- with the same number of stable states

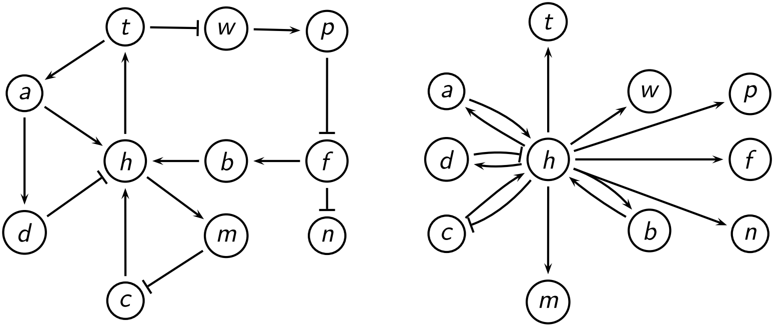
From hub- to flower-graphs : 2 transformations

1- Transformation T_b, with component b such that : b has a unique input a and $\mathcal{O}(b) \cap \mathcal{O}(a) = \varnothing$ or $\{a\}$

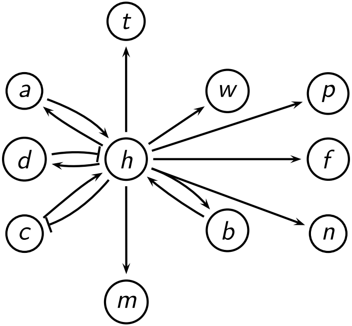


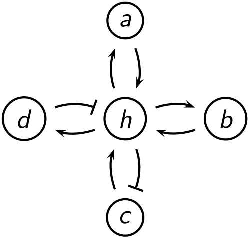
2- Transformation P_b : elimination of the output b

From hub- to flower-graphs : Iterations of transformation T.



From hub- to flower-graphs : Iterations of transformation P.





Stable states and hub-graphs

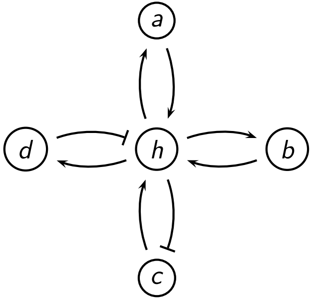
Theorem Let f be an asynchronous Boolean dynamics. If $G(f)$ is a hub-graph then f contains at most two stable states. In the particular case f does contain two stable states, they are complementary. More precisely :

- if $G(f)$ contains only positive circuits then f contains two stable states ;
- if $G(f)$ contains only negative circuits then f has no stable state ;
- if $G(f)$ contains a unique negative circuit and at least one positive circuit, then f contains at least one stable state ;
- if $G(f)$ contains a unique positive circuit and at least one negative circuit, then f contains at most one stable state.

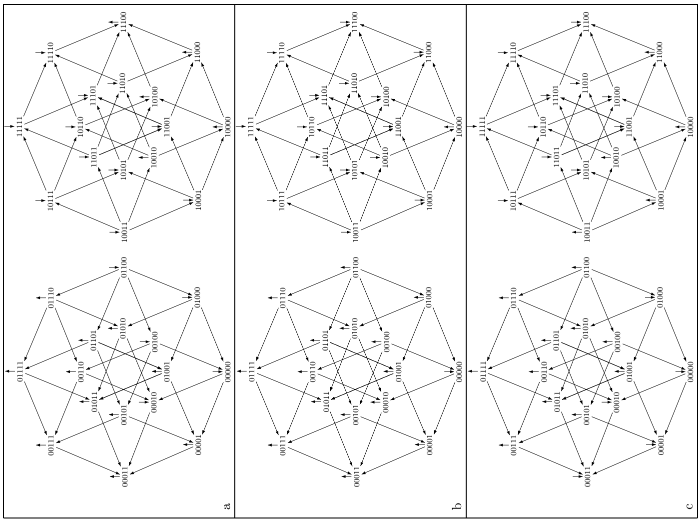
Didier-R., Soumis

Stable states and flower graphs

Consequence : the dynamics of such flower graph (more than two positive and negative circuits) may contain 0,1 or 2 stables states.... !



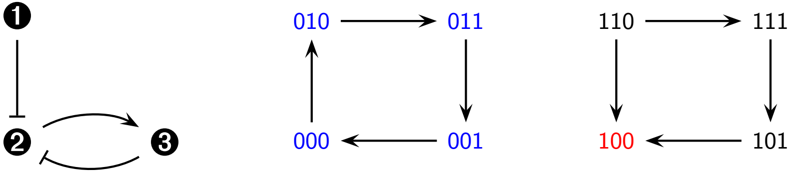
Stable states and flower graphs



Context of functionality

The loop is functional, i.e. *it actually generates homeostasis if it is a negative loop and multistationarity if it is a positive loop*

E.H. Snoussi and R. Thomas, Bull.Math.Biol, 1995



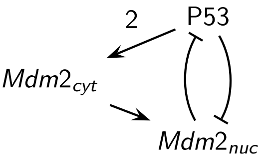
The negative circuit is functional only in the absence of gene 1

Context of functionality of circuit C ($\Phi(f)(C)$) : set of constraints on the expression levels of regulators

$\Phi(f)(C) = \{x_1 = 0\}$

the p53-Mdm2 network

W.Abou-Jaoude, DA.Ouattara, M.Kaufman From structure to dynamics : frequency tuning in the p53-Mdm2 network I. Logical approach. J Theor Biol 258(4) :561-77

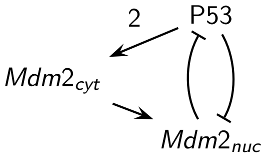


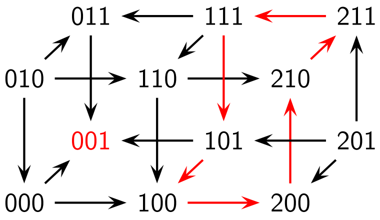
2 circuits :

- a positive circuit (cross-inhibition between P53 and nuclear Mdm2)
- a negative circuit involving the 3 components

the p53-Mdm2 network

Case 1 :*Weak decay rate of* $Mdm2_{nuc}$: Absence of P53 is sufficient for expression of $Mdm2_{nuc}$

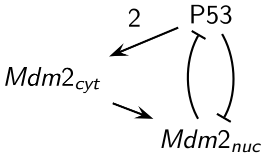


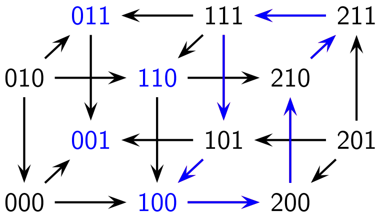


One stable state and one non-attractive cycle : Coexistence of cells in resting state and cells showing sustained P53 oscillations

the p53-Mdm2 network

Case 1 : *Weak decay rate of* $Mdm2_{nuc}$: Absence of P53 is sufficient for expression of $Mdm2_{nuc}$



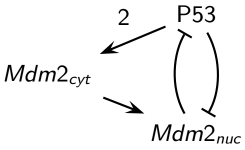


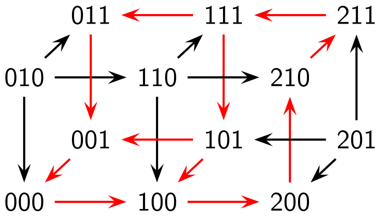
One stable state and one non-attractive cycle : Coexistence of cells in resting state and cells showing sustained P53 oscillations

Both circuits are functional

Illustration through the p53-Mdm2 network

Case 2 : *Intermediate decay rate of $Mdm2_{nuc}$* : Presence of $Mdm2_{cyt}$ is sufficient for expression of $Mdm2_{nuc}$

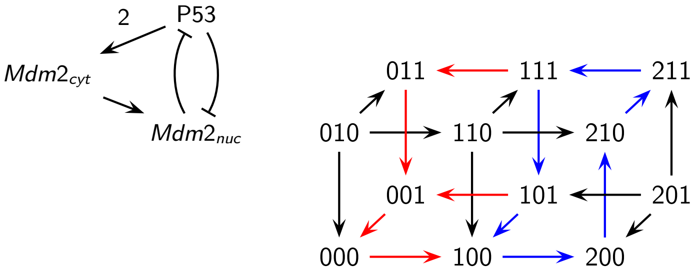




One attractive cycle : P53 concentration pulses observed after irradiation

Illustration through the p53-Mdm2 network

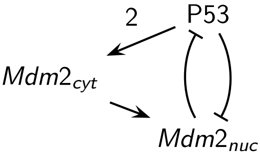
Case 2 : *Intermediate decay rate of* $Mdm2_{nuc}$: Presence of $Mdm2_{cyt}$ is sufficient for expression of $Mdm2_{nuc}$

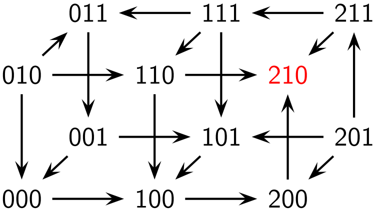


The negative circuit is functional

the p53-Mdm2 network

Case 3 :*High decay rate of* $Mdm2_{nuc}$:Absence of p53 AND presence of $Mdm2_{cyt}$ are necessary for expression of $Mdm2_{nuc}$

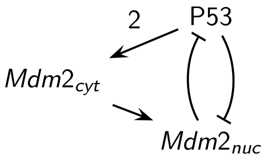


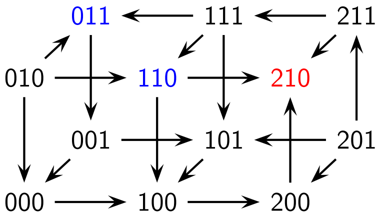


One stable state : P53 is steadily high

the p53-Mdm2 network

Case 3 :*High decay rate of* $Mdm2_{nuc}$:Absence of p53 AND presence of $Mdm2_{cyt}$ are necessary for expression of $Mdm2_{nuc}$





Context of the positive circuit : $x_{Mdm2_{cyt}} = 1$.
Negatif circuit not functional

Globally minimal circuits

Globally minimal circuit : circuit in some local $G(f)(x)$ which is minimal (no shortcut) in $G(f)$.

I-subcube, $I \subseteq \{1, \cdots, n\}$

$$x[\![I]\!] = \{y \in \{0,1\}^n \text{ such that } y_j = x_j \text{ for all } j \notin I\}$$

Theorem

Let $f : \{0,1\}^n \to \{0,1\}^n$, $x \in \{0,1\}^n$, and suppose that $G(f)(x)$ contains a circuit

$$C = k_1 \xrightarrow{\varepsilon_1} k_2 \xrightarrow{\varepsilon_2} \cdots \xrightarrow{\varepsilon_{p-1}} k_p \xrightarrow{\varepsilon_p} k_1$$

which is globally minimal. Then $\Phi(f)(C) \supseteq x[\![k_1, \ldots, k_p]\!]$ and :

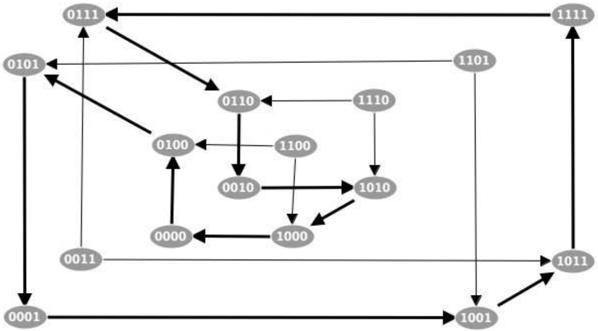
- *if C is positive, the dynamics has two $\{k_1, \ldots, k_p\}$-fixed points ;*
- *if C is negative, the dynamics has a $\{k_1, \ldots, k_p\}$-trap cycle.*

R.-Ruet, Bioinformatics, 2008

Cooperation/ Synergy of circuits

When/ How does the combination of local behaviors give coherent global properties ?

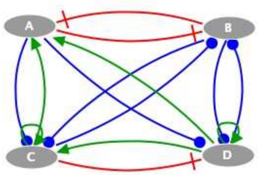
Attractive cycles and functional circuits



Attractor cycle :

$$(1,1,1,1), A^- \ D^- \ B^- \ A^+ \ C^- \ A^- \ B^+ \ D^+ \ B^- \ A^+ \ C^+ \ B^+$$

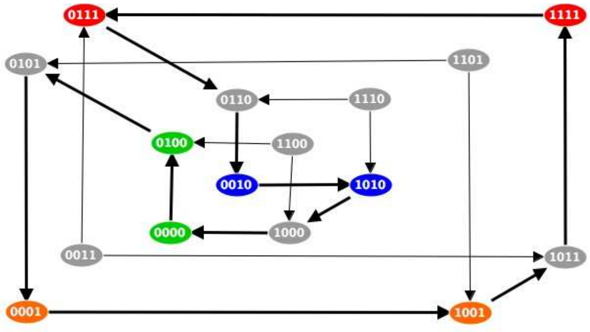
Attractive cycles and functional circuits



6 negative circuits "functional"

- $C \leftrightarrow B$ with $FC = \{(1, *, 0, 1)\}$
- $C \rightarrow B \rightarrow A$ with $FC = \{(0, 0, 0, 1), (0, 0, 1, 0), (1, 0, 0, 1)\}$
- $B \rightarrow A \rightarrow D$ with $FC = \{(*, 1, 1, 1)\}$
- $D \leftrightarrow B$ with $FC = \{(0, *, 0, 0), (0, *, 1, 1)\}$
- $B \rightarrow D \rightarrow A$ with $FC = \{(0, 0, 0, 0)\}$
- $C \leftrightarrow A$ with $FC = \{(*, 0, 1, 0)\}$

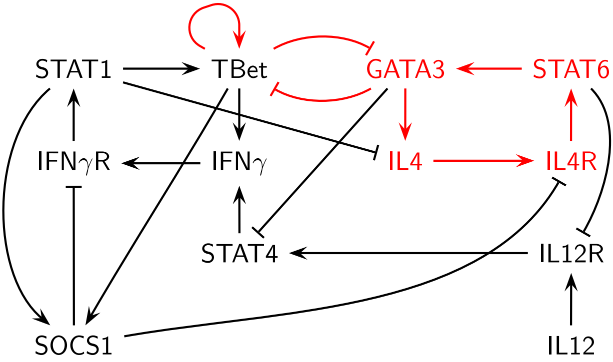
Attractive cycles and functional circuits



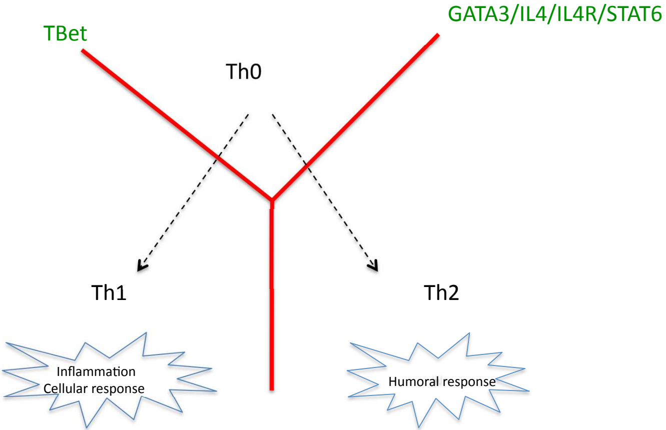
$A^- \ D^- \ B^- \ A^+ \ C^- \ A^- \ B^+ \ D^+ \ B^- \ A^+ \ C^+ \ B^+$

$A^- \ D^- \ B^- \ A^+ \ C^- \ A^- \ B^+ \ D^+ \ B^- \ A^+ \ C^+ \ B^+$

Very simplified Boolean model

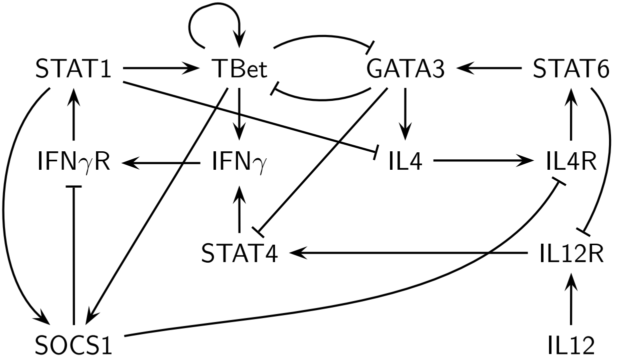


18 circuits, only 4 are functional, and 3 positive ones



TBet
GATA3/IL4/IL4R/STAT6
Th0
Th1
Th2
Inflammation
Cellular response
Humoral response

Th-lymphocyte differentiation : Very simplified Boolean model

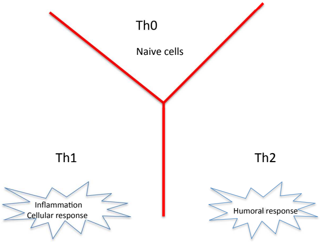


18 circuits, 3 stables states

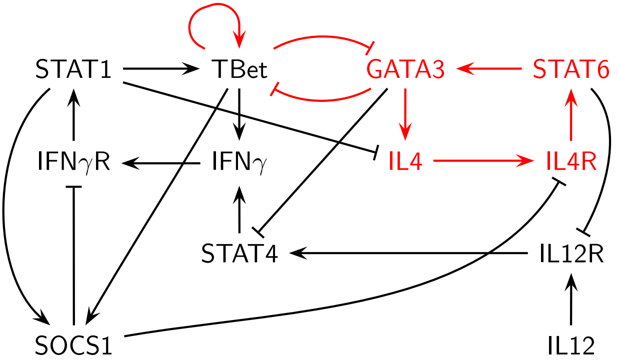
R-Ruet-Mendoza-Thieffry-Chaouiya. LNCS. 2006

Very simplified Boolean model

Genes	Stable states		
	Th0	Th2	Th1
IFN-γ	0	0	1
IL-4	0	1	0
IL-12	0	0	0
IFN-γR	0	0	0
IL-4R	0	1	0
IL-12R	0	0	0
STAT1	0	0	0
STAT6	0	1	0
STAT4	0	0	0
SOCS1	0	0	1
T-bet	0	0	1
GATA-3	0	1	0

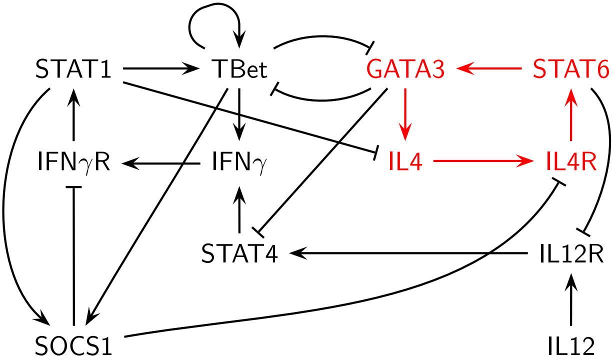


Very simplified Boolean model



18 circuits, only 4 are functional, and 3 positive ones

Analysis



$\Phi(f)(C1) = \{x \mid x_{\text{Tbet}} = x_{\text{STAT1}} = x_{\text{SOCS1}} = 0\}$.
Theorem $\Rightarrow$ two $\{\text{IL4R}, \text{STAT6}, \text{GATA3}, \text{IL4}\}$-fixed points...

Analysis

Genes	Stable states		
	Th0	Th2	Th1
IFN-γ	0	0	1
IL-4	0	1	0
IL-12	0	0	0
IFN-γR	0	0	0
IL-4R	0	1	0
IL-12R	0	0	0
STAT1	0	0	0
STAT6	0	1	0
STAT4	0	0	0
SOCS1	0	0	1
T-bet	0	0	1
GATA-3	0	1	0

Analysis

Genes	Stable states		
	Th0	Th2	Th1
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IL-4	0	1	0
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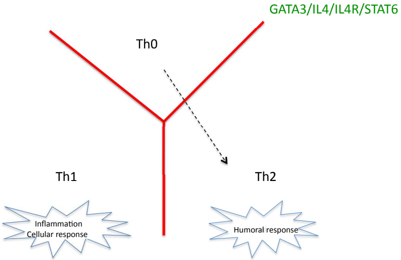
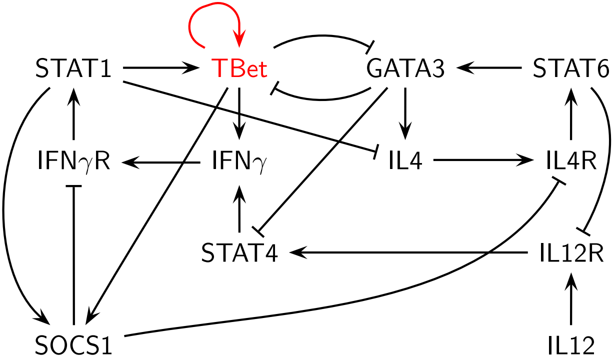
IFN-γR	0	0	0
IL-4R	0	1	0
IL-12R	0	0	0
STAT1	0	0	0
STAT6	0	1	0
STAT4	0	0	0
SOCS1	0	0	1
T-bet	0	0	1
GATA-3	0	1	0



Analysis



$\Phi(f)(C2) = \{x \mid x_{\text{GATA3}} = x_{\text{STAT1}} = 0\}.$

Analysis

Genes	Stable states		
	Th0	Th2	Th1
IFN-γ	0	0	1
IL-4	0	1	0
IL-12	0	0	0
IFN-γR	0	0	0
IL-4R	0	1	0
IL-12R	0	0	0
STAT1	0	0	0
STAT6	0	1	0
STAT4	0	0	0
SOCS1	0	0	1
T-bet	0	0	1
GATA-3	0	1	0

Analysis

Genes	Stable states		
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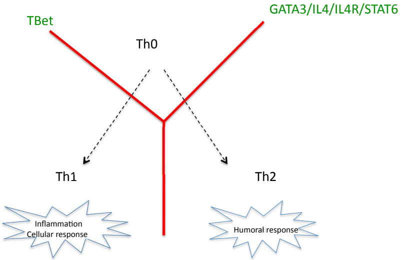
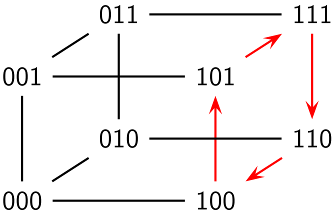
IL-12	0	0	0
IFN-γR	0	0	0
IL-4R	0	1	0
IL-12R	0	0	0
STAT1	0	0	0
STAT6	0	1	0
STAT4	0	0	0
SOCS1	0	0	1
T-bet	0	0	1
GATA-3	0	1	0



Cycles and negative circuits

Definitions

A cycle $(x^1, \ldots, x^r, x^1) = (x^1, \varphi)$ with φ its strategy : $x^{i+1} = \overline{x^i}^{\varphi(i)}$



Cycle $(100, 101, 111, 110, 100)$
Strategy $\varphi = (3, 2, 3, 2)$

$(x^1, \ldots, x^r)$ with strategy φ is a trap cycle $\Rightarrow f(x^i) = \overline{x^i}^{\varphi(i)} = x^{i+1}$

Cycles and negative circuits

Theorem :
If f has a trap cycle

$$C = x^1 \xrightarrow{\varphi_1} x^2 \xrightarrow{\varphi_2} \cdots \xrightarrow{\varphi_{p-1}} x^p \xrightarrow{\varphi_p} x^1 \,,$$

then the regulatory graph contains a negative circuit with vertices $\varphi_1, \ldots, \varphi_p$

Cycles and negative circuits

Ideas of proof :

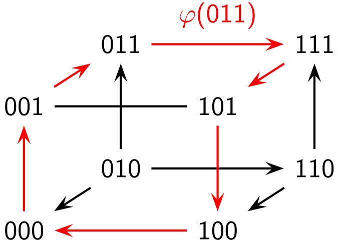
- $\forall i \in \{1, \cdots, p\}$, $(x^i, \overline{x^i}^{\varphi_{i+1}}) \notin \mathcal{E}$ (because the cycle is trap), and $(\overline{x^i}^{\varphi_i}, \overline{x^i}^{\varphi_i,\varphi_{i+1}}) \in \mathcal{E}$:

$$\varphi_i \xrightarrow{\varepsilon_i} \varphi_{i+1}$$

  with $\varepsilon_i = -1$ if $x^i_{\varphi_i} \neq x^{i+1}_{\varphi_{i+1}}$
- Each gene appears an even number of times in the strategy $\Rightarrow$ existence of a *bridge* (x^k, x^{k+l}), *i.e. such that* $\varphi_k = \varphi_{k+l}$ *and* $\{\varphi_{k+1}, \cdots, \varphi_{k+l-1}\}$ *contains once all the genes of the strategy except* φ_k
- *if* x^i *belongs to the bridge, then* $G(x^i)$ *has an edge from* φ_i *to* φ_{i+l}

$\Rightarrow$ *Circuit, with negative sign*

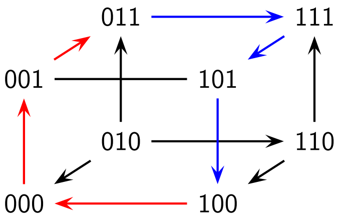
Cycles and negative circuits



$\varphi(000) = 3$ $\varphi(001) = 2$
$\varphi(011) = 1$ $\varphi(111) = 2$
$\varphi(101) = 3$ $\varphi(100) = 1$

Cycle $C = (000, \varphi)$

Cycles and negative circuits



$\varphi(000) = 3$ $\varphi(001) = 2$
$\varphi(011) = 1$ $\varphi(111) = 2$
$\varphi(101) = 3$ $\varphi(100) = 1$

Cycle $C = (000, \varphi)$
Bridge $(011,\ 100)$ $(\varphi(011) = \varphi(100))$ which contains all the genes implied in the cycle