

Discrete dynamics of biological networks

Focus on the regulatory circuits

Ecole Jeunes Chercheurs

Modélisation formelle de réseaux de régulation biologique

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Motivations

The logical modelling

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

Genetic regulations, a schematic view

We distinguish two types of regulations

- **Activation** : $i \rightarrow j$ or $i \xrightarrow{+} j$
the presence of proteins of gene i “favors” the expression of gene j
- **Inhibition** : $i \nrightarrow j$ or $i \xrightarrow{-} j$
the presence of proteins of gene i “inhibites” the expression of gene j

- ↪ Genetic regulations known as **threshold phenomena** (approximated with Hill or step functions)
- ↪ x_i expression level of gene i : discrete variable
- ↪ for a first approximation : **Boolean variable** (gene expressed/not expressed)

Motivations

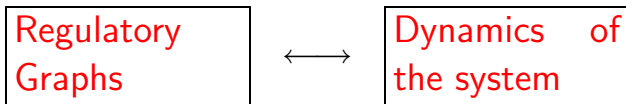
The main problem : size of the state transition graph (the graph which represents the dynamics)

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

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- Simulations
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Sommaire

- ① Overview of the logical modelling
- ② Isolated regulatory circuits
- ③ Multistability and positive circuits
- ④ Cycles and negative circuits
- ⑤ Towards the notion of functionality
- ⑥ Combination of circuits

Regulatory graph

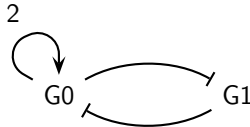
Regulatory graphs : finite, signed, labelled, directed graphs

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

Regulatory graph

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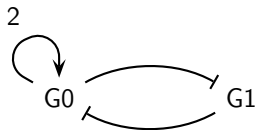


Dynamics of regulatory networks

Evolution of the transcription levels of the regulated genes

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

The formalism

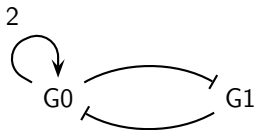


$$x_{G0} \in \{0, 1, 2\}$$

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

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



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

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

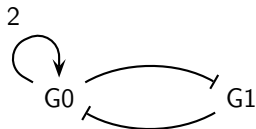
State transition graphs

Directed graphs :

- Nodes $\rightarrow$ states (tuples of expression levels)
- Arcs $\rightarrow$ transitions between two “consecutive” states

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

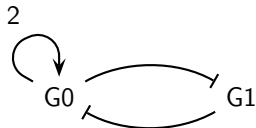


$$x_{G0} \in \{0, 1, 2\}$$

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

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



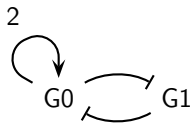
$$x_{G0} \in \{0, 1, 2\}$$

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

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

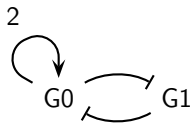
- if $x_i < f_i(x)$, gene i tends to *increase* its expression level ($\overset{+}{x}_i$)
- if $x_i > f_i(x)$, gene i tends to *decrease* its expression level ($\overset{-}{x}_i$)
- if $x_i = f_i(x)$, gene i does not modify its expression level

The formalism



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

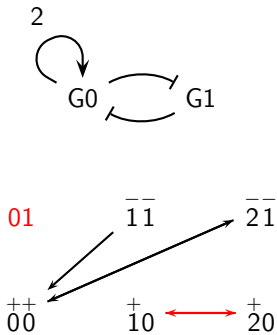
The formalism



01	$\bar{1}\bar{1}$	$\bar{2}\bar{1}$
$^{++}00$	$^{+}10$	$^{+}20$

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

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

State transition graphs

Updating rules :

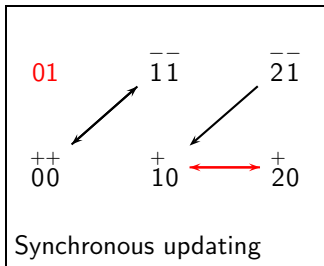
- in a **synchronous** updating :
 $\forall i$ such that $f(x)_i \neq x_i$, $y_i = x_i + \frac{f(x)_i - x_i}{|f(x)_i - x_i|}$, and
 $\forall j$ such that $f(x)_j = x_j$, $y_j = x_j$.
- in an **asynchronous** updating : $\exists i \in$ such that $y = \bar{x}^{(i,\varepsilon)}$ with
 $\varepsilon = \frac{f(x)_i - x_i}{|f(x)_i - x_i|}$
- Mixed

State transition graphs

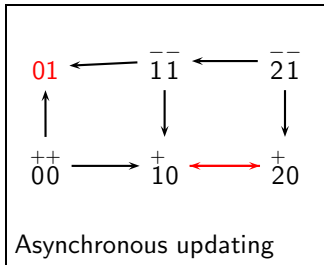
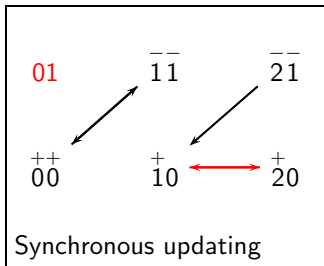
Updating rules in Boolean dynamics :

- the *synchronous* updating : $\{(x, f(x)) \text{ s.t. } x \in \{0, 1\}^n\}$, all the expression levels x_i are simultaneously updated
- the fully *asynchronous* updating :
 $\{(x, \bar{x}^i) \text{ s.t. } x \in \{0, 1\}^n, \forall i \text{ s.t. } x_i \neq f_i(x)\}$ the expression level of only one gene is updated
- Mixed

Updating rules



Updating rules



Updating rules

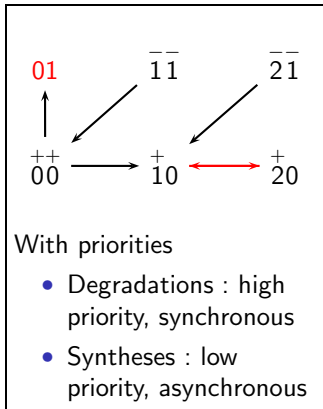
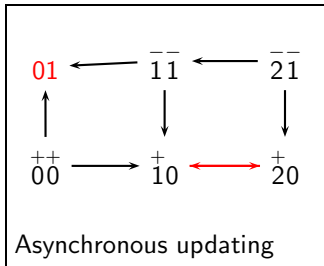
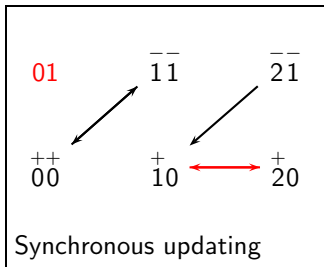


Illustration through the p53-Mdm2 network

W. Abou-Jaoudé, D.A. Ouattara and M. Kaufman. Journal of Theoretical Biology, 258 (2009).

- P53 : transcriptional regulator of genes involved in growth arrest, DNA repair, apoptosis.....
- P53 level regulated by ligase Mdm2 through a negative circuit
- large oscillations in irradiated cells
- abrupt transitions from rest state (P53 low) and stable oscillations

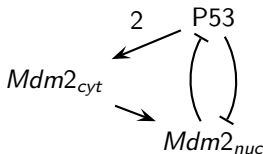
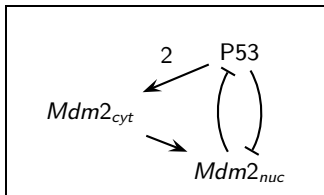


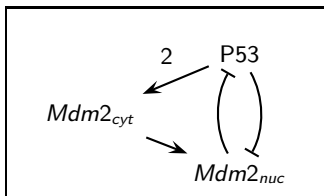
Illustration through the p53-Mdm2 network



Dynamics of P53 ?

x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0			
1	0	0			
2	0	0			
0	1	0			
0	0	1			
0	1	1			
1	0	1			
2	0	1			
1	1	0			
2	1	0			
1	1	1			
2	1	1			

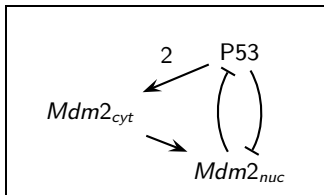
Illustration through the p53-Mdm2 network



Dynamics of $Mdm2_{cyt}$?

x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0	2		
1	0	0	2		
2	0	0	2		
0	1	0	2		
0	0	1	0		
0	1	1	0		
1	0	1	0		
2	0	1	0		
1	1	0	2		
2	1	0	2		
1	1	1	0		
2	1	1	0		

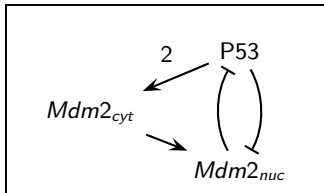
Illustration through the p53-Mdm2 network



Dynamics of $Mdm2_{nuc}$?

x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0	2	0	
1	0	0	2	0	
2	0	0	2	1	
0	1	0	2	0	
0	0	1	0	0	
0	1	1	0	0	
1	0	1	0	0	
2	0	1	0	1	
1	1	0	2	0	
2	1	0	2	1	
1	1	1	0	0	
2	1	1	0	1	

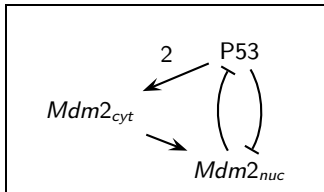
Illustration through the p53-Mdm2 network



Dynamics of $Mdm2_{nuc}$?
Several cases

x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0	2	0	
1	0	0	2	0	
2	0	0	2	1	
0	1	0	2	0	
0	0	1	0	0	
0	1	1	0	0	
1	0	1	0	0	
2	0	1	0	1	
1	1	0	2	0	
2	1	0	2	1	
1	1	1	0	0	
2	1	1	0	1	

Illustration through the p53-Mdm2 network



Case 1 :

Absence of P53 is sufficient
for expression of $Mdm2_{nuc}$

weak decay rate of
 $Mdm2_{nuc}$

x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0	2	0	1
1	0	0	2	0	0
2	0	0	2	1	0
0	1	0	2	0	1
0	0	1	0	0	1
0	1	1	0	0	1
1	0	1	0	0	0
2	0	1	0	1	0
1	1	0	2	0	0
2	1	0	2	1	0
1	1	1	0	0	0
2	1	1	0	1	0

Illustration through the p53-Mdm2 network

Case 1 :

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

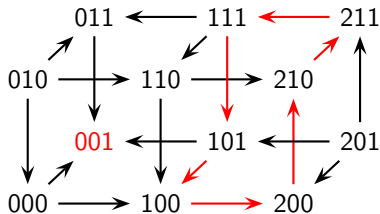
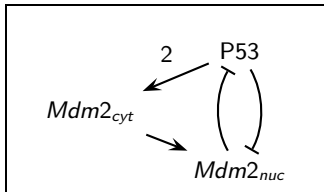


Illustration through the p53-Mdm2 network



Case 2 :

Presence of $Mdm2_{cyt}$ is sufficient for expression of $Mdm2_{nuc}$

Intermediate decay rate of $Mdm2_{nuc}$

x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0	2	0	0
1	0	0	2	0	0
2	0	0	2	1	0
0	1	0	2	0	1
0	0	1	0	0	0
0	1	1	0	0	1
1	0	1	0	0	0
2	0	1	0	1	0
1	1	0	2	0	1
2	1	0	2	1	1
1	1	1	0	0	1
2	1	1	0	1	1

Illustration through the p53-Mdm2 network

Case 2 :

One attractive cycle :

P53 concentration pulses
observed after irradiation

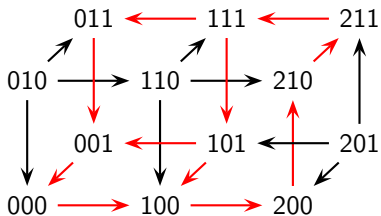
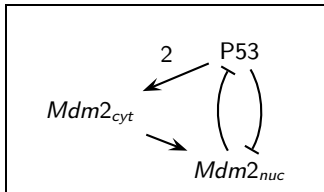


Illustration through the p53-Mdm2 network



Case 3 :

Absence of p53 AND presence of $Mdm2_{cyt}$ are necessary for expression of $Mdm2_{nuc}$

x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0	2	0	0
1	0	0	2	0	0
2	0	0	2	1	0
0	1	0	2	0	1
0	0	1	0	0	0
0	1	1	0	0	1
1	0	1	0	0	0
2	0	1	0	1	0
1	1	0	2	0	0
2	1	0	2	1	0
1	1	1	0	0	0
2	1	1	0	1	0

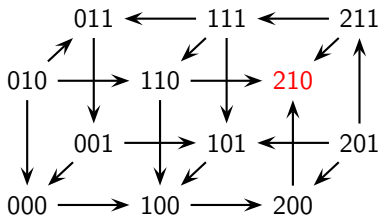
High decay rate of $Mdm2_{nuc}$

Illustration through the p53-Mdm2 network

Case 3 :

One stable state :

P53 is steadily high



Boolean dynamics of genetic regulations

Activation $i \xrightarrow{+} j \ (i \rightarrow j)$

$$x_i = 0 \Rightarrow f_j(x) = 0$$

$$x_i = 1 \Rightarrow f_j(x) = 1$$

Inhibition $i \xrightarrow{-} j$

$$x_i = 0 \Rightarrow f_j(x) = 1$$

$$x_i = 1 \Rightarrow f_j(x) = 0$$

Stable states (or Fixed points) : $f_i(x) = x_i$ for all i .

Definitions

A **Positive circuit** contains an even number of inhibitions

A **Negative circuit** contains an odd number of inhibitions

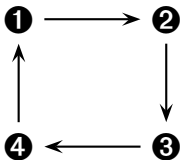
Regulatory
Graphs



Dynamics of
the system

- 1 Overview of the logical modelling
- 2 Isolated regulatory circuits**
- 3 Multistability and positive circuits
- 4 Cycles and negative circuits
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Isolated regulatory circuits



Activation : $x_i = 0 \Rightarrow x_j \searrow$
 $x_i = 1 \Rightarrow x_j \nearrow$

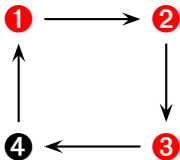
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Starting at state $(\bar{1}, 1, 1, 0^+)$

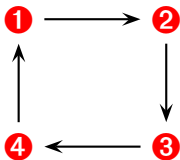
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Activating gene 4
 $\mapsto$ *Fixed point* (1, 1, 1, 1)

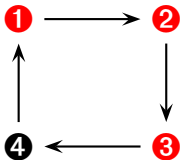
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Starting again at $(\bar{1}, 1, 1, 0^+)$

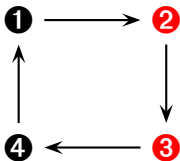
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Disactivating gene 1
 $\rightarrow (0, \bar{1}, 1, \overset{+}{0})$

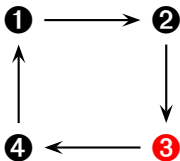
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Disactivating gene 2
 $\rightarrow (0, 0, \bar{1}, \bar{0})$

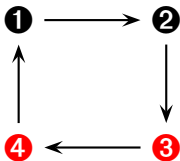
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Activating gene 4
 $\rightarrow (0, 0, \bar{1}, 1)$

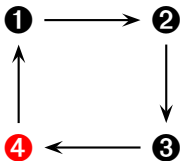
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Disactivating gene 3
 $\rightarrow (0^+, 0, 0, \bar{1})$

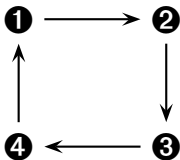
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



Disactivating gene 4
 $\mapsto$ *Fixed point* (0, 0, 0, 0)

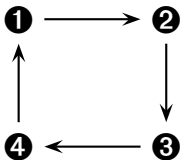
$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



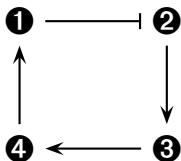
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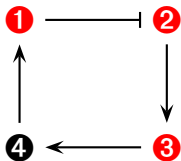
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$\overline{a}$: negation

One (trap) cycle : homeostasis

Isolated regulatory circuits



Starting at state $(\bar{1}, \bar{1}, 1, 0^+)$

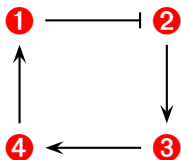
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Isolated regulatory circuits



Activating gene 4

$\rightarrow (1, \bar{1}, 1, 1)$

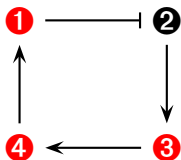
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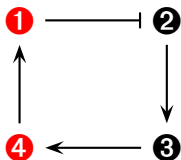
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Isolated regulatory circuits



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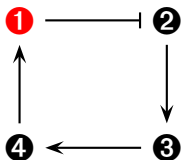
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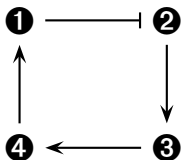
$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

$$\rightarrow (\overline{1}, 0, 0, 0)$$

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One (trap) cycle : homeostasis

Isolated regulatory circuits



$\rightarrow (0, 0^+, 0, 0)$

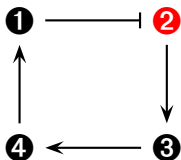
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One (trap) cycle : homeostasis

Isolated regulatory circuits



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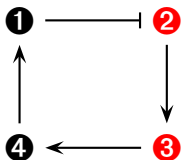
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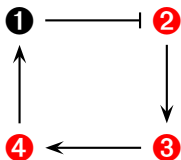
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One (trap) cycle : homeostasis

Isolated regulatory circuits



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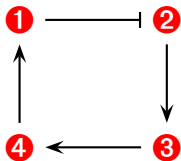
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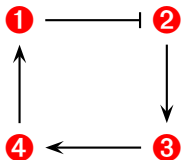
$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

$\mapsto$ *return to* $(1, \overline{1}, 1, 1)$

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One (trap) cycle : homeostasis

Isolated regulatory circuits



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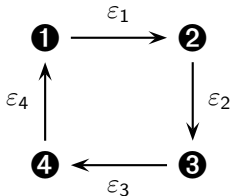
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One (trap) cycle : homeostasis

Isolated regulatory circuits

E. R., B. Mossé, C. Chaouiya, D. Thieffry. Bioinformatics, 2003



Simple modelling :

- Each gene is the source of a unique interaction, and the target of a unique interaction $\Rightarrow$ Boolean case
- Only one dynamics leads to an “interesting” behaviour

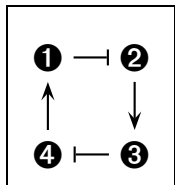
$$f_{i+1}(x) = \begin{cases} x_i & \text{if } \varepsilon_i = +1 \\ 1 - x_i & \text{if } \varepsilon_i = -1 \end{cases}$$

Isolated regulatory circuits

Complete description of the structure of the synchronous state transition graph :

- ↪ Disconnected elementary cycles
- ↪ Staged structure :
 - each stage k gathers all the states having k calls for updating
 - the states are distributed in cycles according to their configurations

Synchronous state transition graph of isolated positive circuit



$$00\bar{1}\bar{1} \longleftrightarrow \bar{1}\bar{1}00$$

$$\begin{array}{ccc} 1\bar{1}0\bar{1} & \longrightarrow & 10\bar{1}\bar{1} \\ \uparrow & & \downarrow \\ 000\bar{1} & \longleftarrow & \bar{1}000 \end{array}$$

1001

$$\begin{array}{ccc} 0\bar{1}0\bar{1} & \longrightarrow & \bar{1}\bar{1}\bar{1}\bar{1} \\ \uparrow & & \downarrow \\ 0000 & \longleftarrow & \bar{1}0\bar{1}0 \end{array}$$

$$\begin{array}{ccc} 00\bar{1}0 & \longrightarrow & 0\bar{1}00 \\ \uparrow & & \downarrow \\ \bar{1}\bar{1}10 & \longleftarrow & 0\bar{1}\bar{1}\bar{1} \end{array}$$

0110

k=4

k=2

k=0

Isolated regulatory circuits

From the synchronous state transition graph : Complete description of the structure of the asynchronous state transition graph :

- ↪ Connected graph
- ↪ Staged structure : at each stage k , each state has exactly k successors
 - either at the same stage k
 - or at the stage below $k - 2$

From synchronous to asynchronous state transition graph of isolated positive circuit

$\begin{smallmatrix} + & + & - & - \\ 0 & 0 & 1 & 1 \end{smallmatrix}$

$\begin{smallmatrix} - & - & + & + \\ 1 & 1 & 0 & 0 \end{smallmatrix}$

$\begin{smallmatrix} - & + \\ 1 & 1 \end{smallmatrix} 0 1$

$\begin{smallmatrix} + & + \\ 0 & 1 \end{smallmatrix} 0 1$

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$1 0 \begin{smallmatrix} - & - \\ 1 & 1 \end{smallmatrix}$

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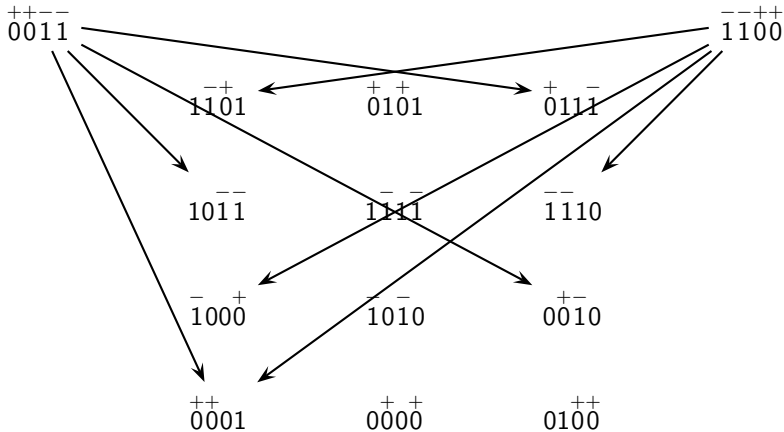
$\begin{smallmatrix} + & + \\ 0 & 0 \end{smallmatrix} 0 0$

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1001

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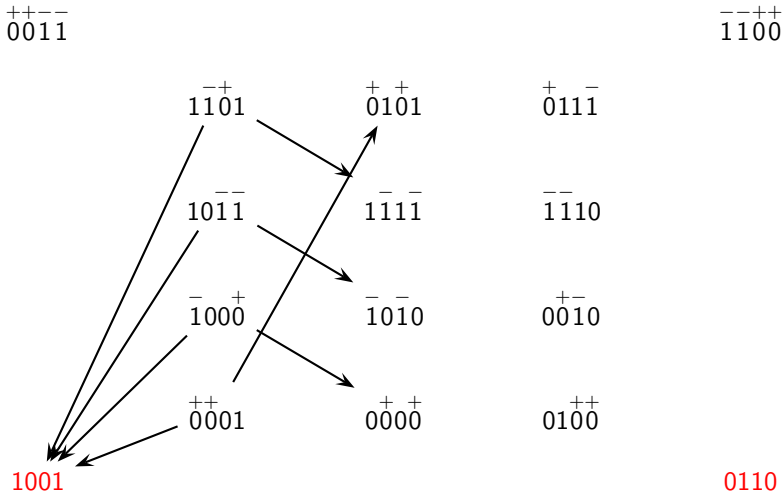
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1001

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From synchronous to asynchronous state transition graph of isolated positive circuit

$\begin{smallmatrix} + & + & - & - \\ 0 & 0 & 1 & 1 \end{smallmatrix}$

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$\begin{smallmatrix} - & + \\ 1 & 1 \end{smallmatrix} 0 1 \begin{smallmatrix} + \\ 1 \end{smallmatrix} \longleftarrow \begin{smallmatrix} + & + \\ 0 & 1 \end{smallmatrix} 0 1 \longrightarrow \begin{smallmatrix} + \\ 0 \end{smallmatrix} 1 1 \begin{smallmatrix} - \\ 1 \end{smallmatrix}$

$1 0 \begin{smallmatrix} - & - \\ 1 & 1 \end{smallmatrix} \longleftarrow 1 \begin{smallmatrix} - & - \\ 1 & 1 \end{smallmatrix} 1 1 \longrightarrow \begin{smallmatrix} - & - \\ 1 & 1 \end{smallmatrix} 1 0$

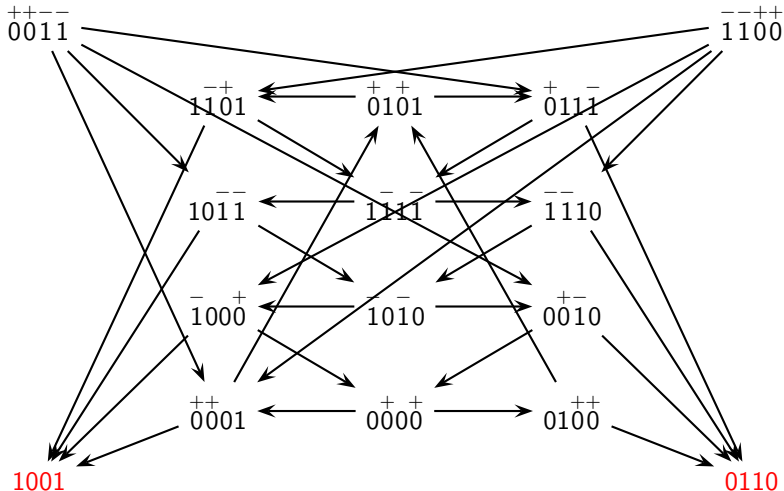
$\begin{smallmatrix} - \\ 1 \end{smallmatrix} 0 0 \begin{smallmatrix} + \\ 0 \end{smallmatrix} \longleftarrow \begin{smallmatrix} - \\ 1 \end{smallmatrix} 0 \begin{smallmatrix} - \\ 1 \end{smallmatrix} 0 \longrightarrow \begin{smallmatrix} + & - \\ 0 & 0 \end{smallmatrix} 1 0$

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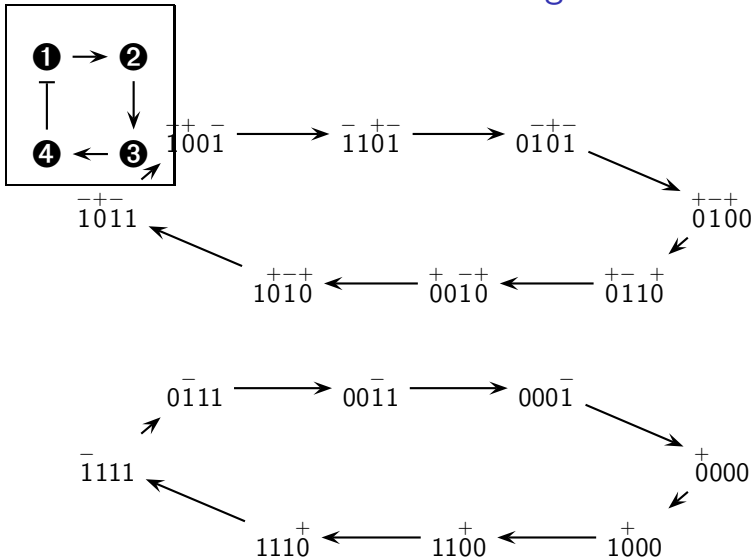
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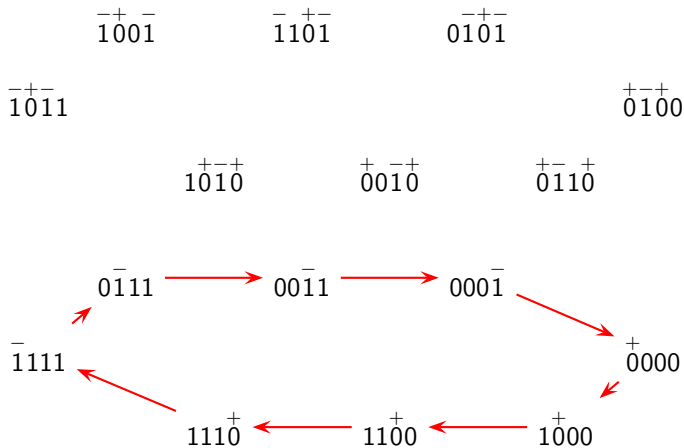
From synchronous to asynchronous state transition graph of isolated positive circuit



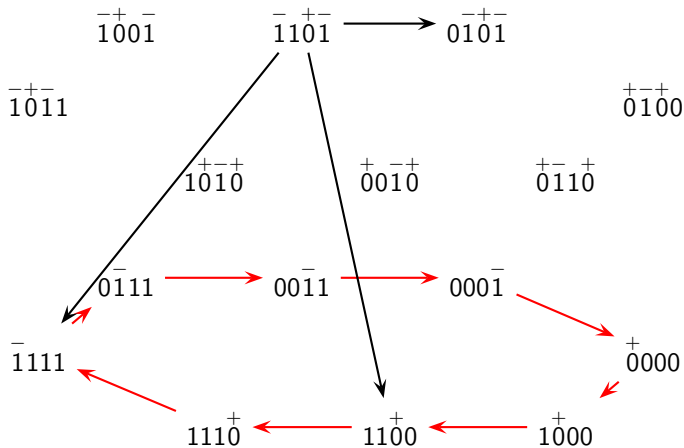
Synchronous state transition graph of isolated negative circuit



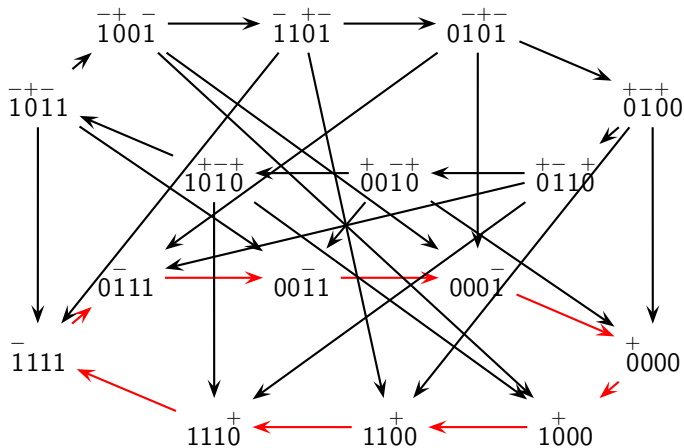
From synchronous to asynchronous state transition graph of isolated negative circuit



From synchronous to asynchronous state transition graph of isolated negative circuit



From synchronous to asynchronous state transition graph of isolated negative circuit



Isolated regulatory circuits

- Positive circuit (even number of inhibitions) $\Leftrightarrow$ multistationarity (2 fixed points) differentiation
- Negative circuit (odd number of inhibitions) $\Leftrightarrow$ sustained oscillations homeostasis

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- Negative circuit (odd number of inhibitions) $\Leftrightarrow$ sustained oscillations homeostasis

Thomas' rules (1981)

- Multistationarity $\Rightarrow$ positive circuit in the regulatory graph.
- Homeostasis $\Rightarrow$ negative circuit in the regulatory graph.

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

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

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From dynamics to regulatory graph

Asynchronous dynamics : represented by the state transition graph $(\mathcal{V}, \mathcal{E})$.
Given $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$, we have $(x, \bar{x}^i) \in \mathcal{E}$ when $x_i \neq f_i(x)$
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Global regulatory graph : $G(f) = \bigcup_x G(f)(x)$.

From dynamics to regulatory graph

Definitions with the State Transition Graph...

- $i \xrightarrow{\varepsilon} j$
-

From dynamics to regulatory graph

Definitions with the State Transition Graph...

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From dynamics to regulatory graph

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From dynamics to regulatory graph

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- i input : i input : not regulated at all. $\forall x \in \{0, 1\}^n$, we have $(x, \bar{x}^i) \notin \mathcal{E}$ if $x_i = 0$ (resp. if $x_i = 1$) and $(x, \bar{x}^i) \in \mathcal{E}$ if $x_i = 1$ (resp. if $x_i = 0$)

- 1 Overview of the logical modelling
- 2 Isolated regulatory circuits
- 3 Multistability and positive circuits**
- 4 Cycles and negative circuits
- 5 Towards the notion of functionality
- 6 Combination of circuits

Thomas' rules (1981)

- Multistationarity $\Rightarrow$ positive circuit in the regulatory graph
- f has at least two fixed points $\Rightarrow$ positive circuit in $G(f)$

Multistability and positive circuits : a first proof

Notations :

Discrete Jacobian matrix $J(x)$

$$J(x)_{i,j} = \begin{cases} 1 & \text{if } f_i(\bar{x}^j) \neq f_i(x) \\ 0 & \text{otherwise} \end{cases}$$

I -circuit, $I \subseteq \{1, \dots, n\}$, circuit whose vertices belong to I

I -subcube, $I \subseteq \{1, \dots, n\}$, $x \in \{0, 1\}^n$

$$x[I] = \{y \in \{0, 1\}^n \text{ s.t. } y_j = x_j \text{ for all } j \notin I\}$$

A κ -fixed point, κ I -subcube, is a state $x \in \kappa$ such that $f_i(x) = x_i$ for all $i \in I$

Multistability and positive circuits : a first proof

Lemma : Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ and $I \subseteq \{1, \dots, n\}$. If for each $x \in \{0, 1\}^n$, $G(f)(x)$ has no positive I -circuit, then for each I -subcube κ , f has at most one κ -fixed point

Proof : Induction on the cardinality k of I

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 - if $\#\Delta(x, y) = k + 1$
for any $i \in I$, x is a $x[I \setminus \{i\}]$ -fixed point, and $\bar{y}^i$ is not. So,
 $\exists j \in I \setminus \{i\}$ such that $f_j(\bar{y}^i) \neq \bar{y}_j^i = y_j = f_j(y)$ and this implies
 $J(y)_{j,i} = 1 \Rightarrow$ the principal submatrix of $J(y)$ has no zero-column $\Rightarrow$
 $G(y)$ has a I -circuit. Its sign has to be positive.

Multistability and positive circuits

Theorem :

f has at least two fixed points $\implies \exists a \in \{0, 1\}^n$ such that $G(f)(a)$ has a positive circuit

More precisely, if f has two fixed points x and $y = \bar{x}^{\Delta(x,y)}$, then the regulatory graph contains a positive circuit involving a subset of $\Delta(x, y)$

Multistability and positive circuits

Remark : The proof of the lemma leans on the proof of discrete version of the Jacobian conjecture

Let $\Gamma(x)$ to be the simple directed graph whose adjacency matrix is the transpose of $J(x)$ ($G(x)$ signed version of $\Gamma(x)$)

Discrete Jacobian Conjecture [Shih and Dong, 2005] :

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

Multistability and positive circuits : an other proof

An other proof :

Let x and $y = \bar{x}^{\Delta(x,y)}$ two fixed points

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

Multistability and positive circuits : an other proof

An other proof :

Let x and $y = \bar{x}^{\Delta(x,y)}$ two fixed points

- Let $i \in \Delta(x, y)$. By definition, $(y, \bar{y}^i) \notin \mathcal{E}$.
 - if $(\bar{y}^i, y) \notin \mathcal{E}$, then positive self regulation on $i \rightarrow \text{OK!}$

Multistability and positive circuits : an other proof

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Let x and $y = \bar{x}^{\Delta(x,y)}$ two fixed points

- Let $i \in \Delta(x, y)$. By definition, $(y, \bar{y}^i) \notin \mathcal{E}$.
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 - Suppose $(\bar{y}^i, y) \in \mathcal{E}$. Take $D = \Delta(x, y) \setminus \{i\}$

Multistability and positive circuits : an other proof

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 - if $(\bar{y}^i, y) \notin \mathcal{E}$, then positive self regulation on $i \rightarrow \text{OK!}$
 - Suppose $(\bar{y}^i, y) \in \mathcal{E}$. Take $D = \Delta(x, y) \setminus \{i\}$
We have $(x, \bar{x}^i) \notin \mathcal{E}$ (fixed point), and $(\bar{x}^D, \bar{x}^{D \cup i}) \in \mathcal{E}$. There exists $D' \subseteq D$ s.t., for $j \in D'$

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

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

Multistability and positive circuits : an other proof

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

$\Rightarrow \forall i \in \Delta(x, y), \exists p(i) \in \Delta(x, y)$ 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 $\{p^k(i), k \geq 0\}$. 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 different $\Rightarrow$ 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 $j \in \Delta(x, y)$ occurring 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 fixed points x and $y \implies$ for each $i \in \Delta(x, y)$ there exists $j \in \Delta(x, y)$ occurring in a positive circuit involving only components of $\Delta(x, y)$, and a path from j to i .

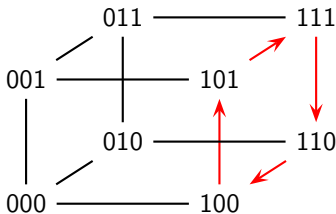
In particular the regulatory graph contains a positive circuit involving a subset of $\Delta(x, y)$

- 1 Overview of the logical modelling
- 2 Isolated regulatory circuits
- 3 Multistability and positive circuits
- 4 Cycles and negative circuits**
- 5 Towards the notion of functionality
- 6 Combination of circuits

Cycles and negative circuits

Definitions

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



Cycle $(100, 101, 111, 110, 100)$

Strategy $\varphi = (3, 2, 3, 2)$

$(x^1, \dots, x^r)$ 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

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

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

Cycles and negative circuits

Ideas of proof :

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

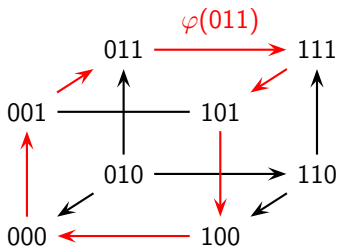
$$\varphi_i \xrightarrow{\varepsilon_i} \varphi_{i+1}$$

with $\varepsilon_i = -1$ if $x_{\varphi_i}^i \neq x_{\varphi_{i+1}}^{i+1}$

- 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 $\{\varphi_{k+1}, \dots, \varphi_{k+l-1}\}$ 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

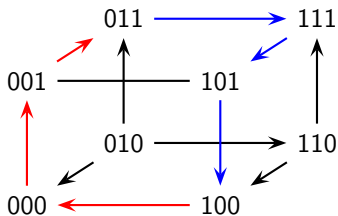
Cycles and negative circuits



$$\begin{aligned}\varphi(000) &= 3 & \varphi(001) &= 2 \\ \varphi(011) &= 1 & \varphi(111) &= 2 \\ \varphi(101) &= 3 & \varphi(100) &= 1\end{aligned}$$

Cycle $C = (000, \varphi)$

Cycles and negative circuits



$$\varphi(000) = 3 \quad \varphi(001) = 2$$

$$\varphi(011) = 1 \quad \varphi(111) = 2$$

$$\varphi(101) = 3 \quad \varphi(100) = 1$$

Cycle $C = (000, \varphi)$

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

Regulatory
Graphs



Dynamics of
the system

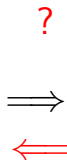
Regulatory
Graphs



Thomas' rules

Dynamics of
the system

Regulatory
Graphs

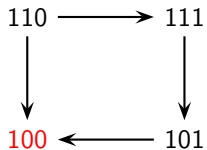
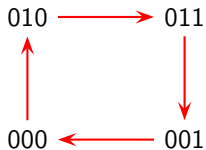
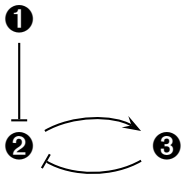


Dynamics of
the system

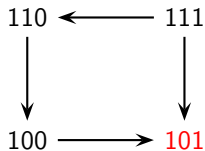
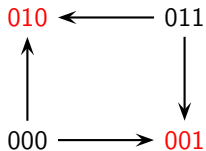
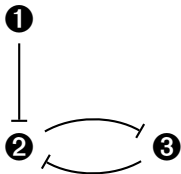
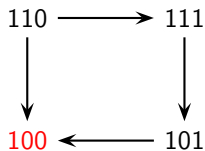
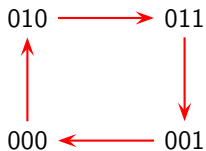
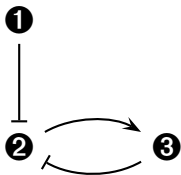
Thomas' rules

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Embedded circuits



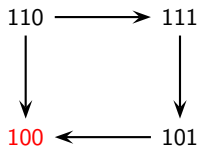
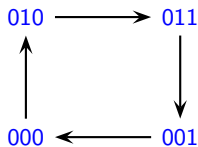
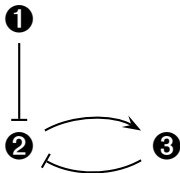
Embedded circuits



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



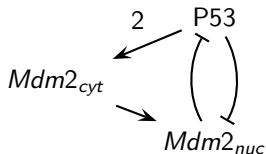
The negative circuit is functional only in the absence of gene 1

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

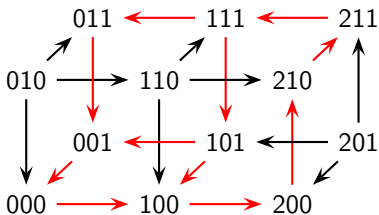
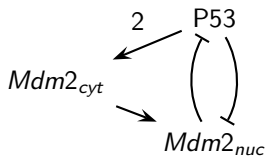


2 circuits :

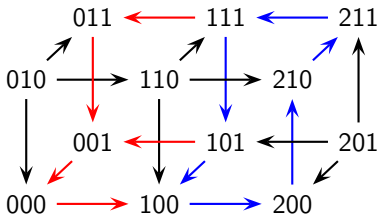
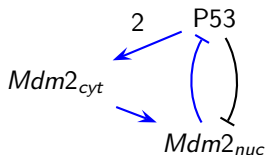
- a positive circuit (cross-inhibition between P53 and nuclear Mdm2)
- a negative circuit involving the 3 components

the p53-Mdm2 network

Which circuit is functional?

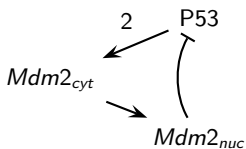


the p53-Mdm2 network



Sole the negative circuit is functional

Illustration through the p53-Mdm2 network

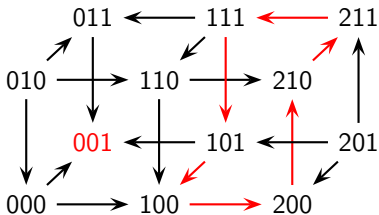
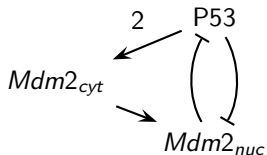


The inhibition $P53 \xrightarrow{-} Mdm2_{nuc}$ does not appear in $G(f)$!!

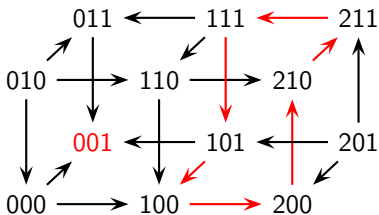
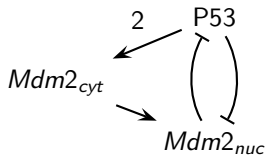
x_{P53}	x_{M_c}	x_{M_n}	$f_{p53}(x)$	$f_{M_c}(x)$	$f_{M_n}(x)$
0	0	0	2	0	0
1	0	0	2	0	0
2	0	0	2	1	0
0	1	0	2	0	1
0	0	1	0	0	0
0	1	1	0	0	1
1	0	1	0	0	0
2	0	1	0	1	0
1	1	0	2	0	1
2	1	0	2	1	1
1	1	1	0	0	1
2	1	1	0	1	1

the p53-Mdm2 network

Which circuit is functional?



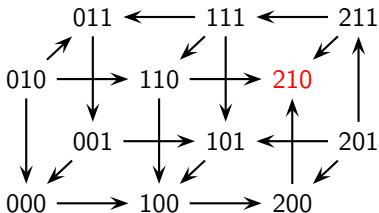
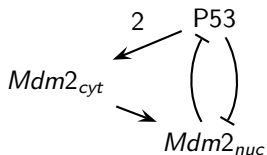
the p53-Mdm2 network



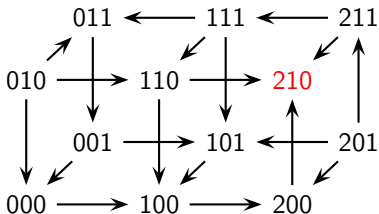
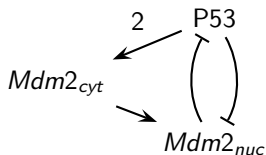
Both circuits are functional

the p53-Mdm2 network

Which circuit is functional?



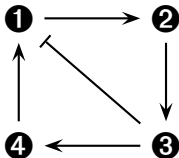
the p53-Mdm2 network



Context of the positive circuit : $x_{Mdm2_{cyt}} = 1$.

Negatif circuit not functional

Shortcuts in a positive circuit

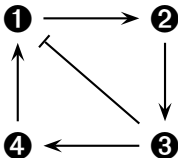


$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \overline{x_3} \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

A single fixed point $(0, 0, 0, 0)$:
No multistationarity.

Shortcuts in a positive circuit

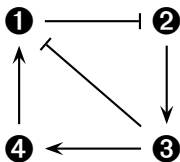


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Shortcuts in a negative circuit

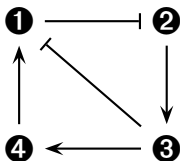


$$f \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_4 \overline{x_3} \\ \overline{x_1} \\ x_2 \\ x_3 \end{pmatrix}$$

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

One fixed point $(0, 1, 1, 1)$, one **unstable** cycle :
No homeostasis.

Shortcuts in a negative circuit



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

$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

One fixed point $(0, 1, 1, 1)$, one **unstable** cycle :
No homeostasis.

Globally minimal circuits

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

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

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

Theorem

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

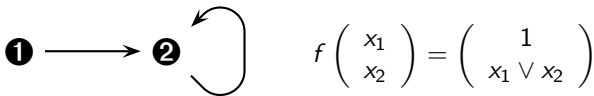
$$C = k_1 \xrightarrow{\varepsilon_1} k_2 \xrightarrow{\varepsilon_2} \dots \xrightarrow{\varepsilon_{p-1}} k_p \xrightarrow{\varepsilon_p} k_1$$

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

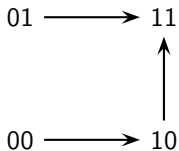
- if C is positive, the dynamics has two $\{k_1, \dots, k_p\}$ -fixed points ;
- if C is negative, the dynamics has a $\{k_1, \dots, k_p\}$ -trap cycle.

Global and local separators

The theorem does not necessarily imply a **global** behaviour : a priori **local separators**.



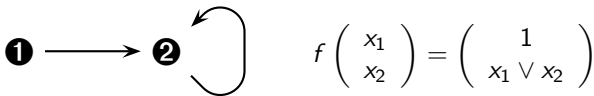
Globally min. loop on 2 with funct. context $x_1 = 0$



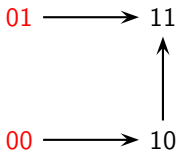
Two 2-fixed points, a single global one

Global and local separators

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Globally min. loop on 2 with funct. context $x_1 = 0$

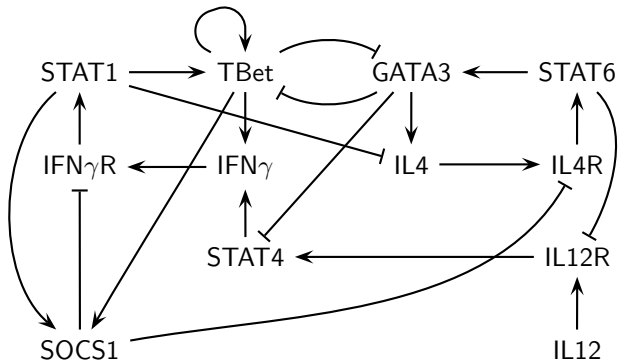


Two 2-fixed points, a single global one

Th-lymphocyte differentiation

- CD4+ T helper lymphocytes can differentiate :
 - Th1 $\Rightarrow$ cell mediated immunity $\Rightarrow$ autoimmune diseases,
 - Th2 $\Rightarrow$ humoral responses $\Rightarrow$ allergic reactions.
- Various mathematical models :
 - interactions between immunological cell populations at a macroscopic level (Antia, Bergman, Callard, Klein, Segel, Stark, Van Hemmen, Yates,...),
 - generation of antibody and T-cell receptors diversity (Buja, De Boer, Junker, Krueger, Marshall, Perelson, Schroeder, Wang, Weisbuch,...),
 - ...

Very simplified Boolean model



18 circuits, 3 stable states

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

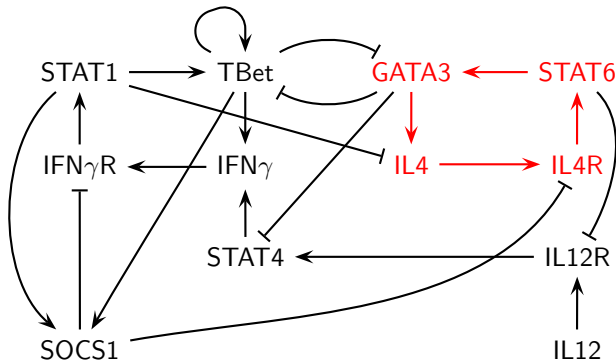
Very simplified Boolean model

Genes		Stable states		
		s_0	s_1	s_2
IFN- γ	(1)	0	0	1
IL-4	(2)	0	1	0
IL-12	(3)	0	0	0
IFN- γ R	(4)	0	0	0
IL-4R	(5)	0	1	0
IL-12R	(6)	0	0	0
STAT1	(7)	0	0	0
STAT6	(8)	0	1	0
STAT4	(9)	0	0	0
SOCS1	(10)	0	0	1
T-bet	(11)	0	0	1
GATA-3	(12)	0	1	0

s_0 corresponds to the virgin Th cells

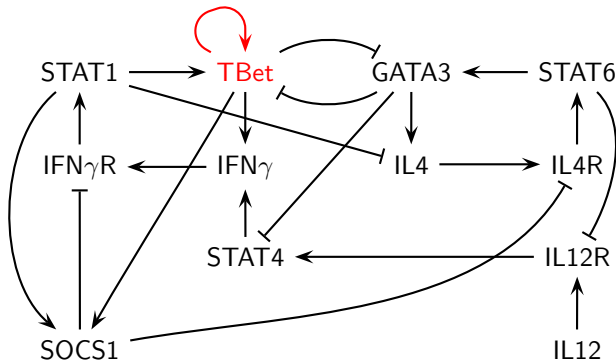
s_1 and s_2 to Th2 and Th1 differentiated lymphocytes,

Very simplified Boolean model



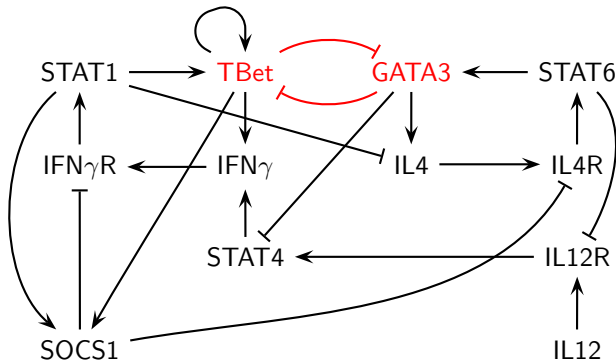
18 circuits, only 4 functional ones (C1).

Very simplified Boolean model



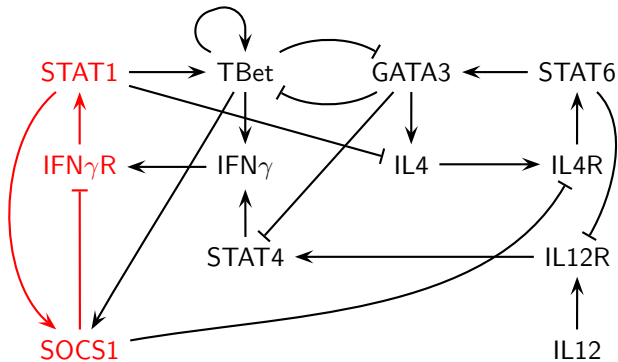
18 circuits, only 4 functional ones (C1, C2).

Very simplified Boolean model



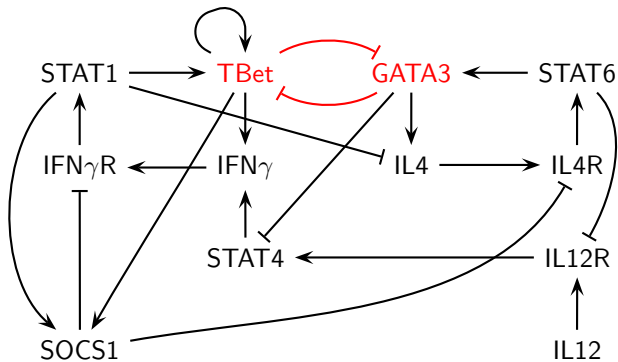
18 circuits, only 4 functional ones (C1, C2, C3).

Very simplified Boolean model



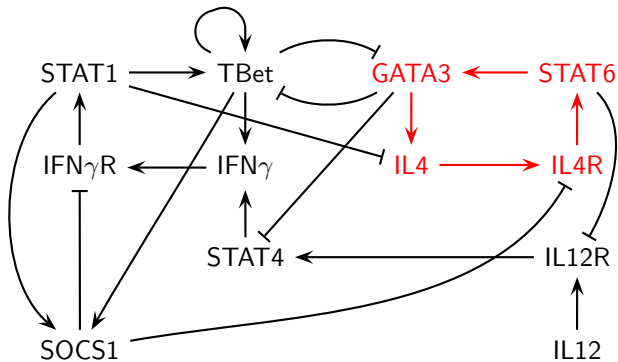
18 circuits, only 4 functional ones (C1, C2, C3, C4).

Very simplified Boolean model



18 circuits, only 4 functional ones, only 3 globally minimal ones.

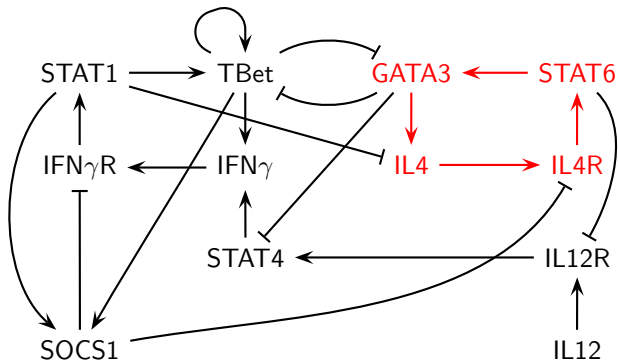
Analysis



$$\Phi(f)(C1) = \{x \mid x_{\text{Tbet}} = x_{\text{STAT1}} = x_{\text{SOCS1}} = 0\}.$$

Theorem $\Rightarrow$ two $\{\text{IL4R}, \text{STAT6}, \text{GATA3}, \text{IL4}\}$ -fixed points...

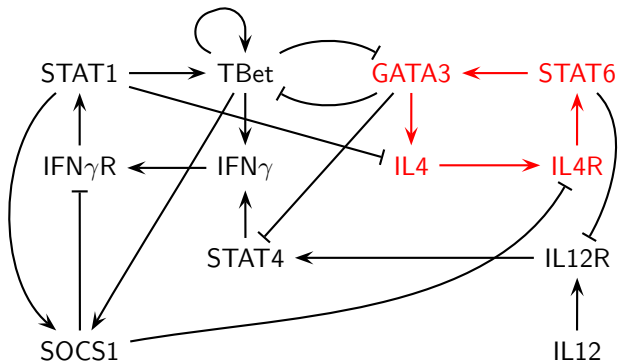
Analysis



$s_0 = 0$: virgin Th cells Th0.

$s_1 = \overline{s_0}^{\text{IL4R, STAT6, GATA3, IL4}}$: Th2 differentiated lymphocytes.

Analysis

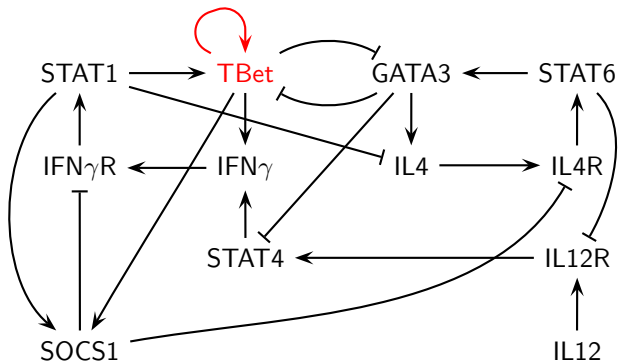


$s_0, s_1 \in \Phi(f)(C1)$ are also global fixed points.

Analysis

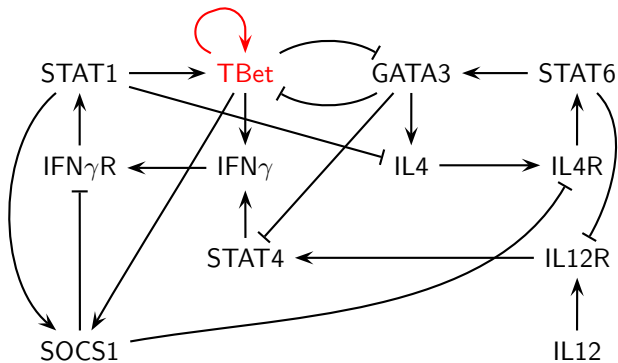
Genes		Stable states		
		s_0	s_1	s_2
IFN- γ	(1)	0	0	1
IL-4	(2)	0	1	0
IL-12	(3)	0	0	0
IFN- γ R	(4)	0	0	0
IL-4R	(5)	0	1	0
IL-12R	(6)	0	0	0
STAT1	(7)	0	0	0
STAT6	(8)	0	1	0
STAT4	(9)	0	0	0
SOCS1	(10)	0	0	1
T-bet	(11)	0	0	1
GATA-3	(12)	0	1	0

Analysis



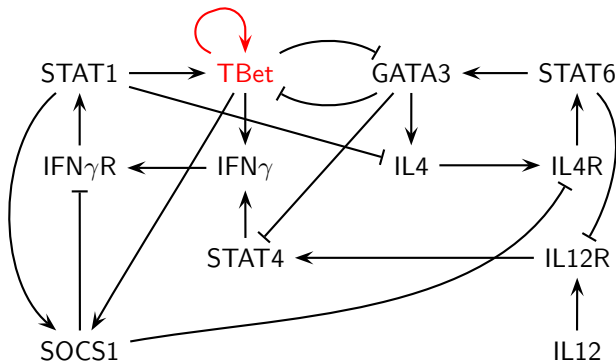
$$\Phi(f)(C2) = \{x \mid x_{\text{GATA3}} = x_{\text{STAT1}} = 0\}.$$

Analysis



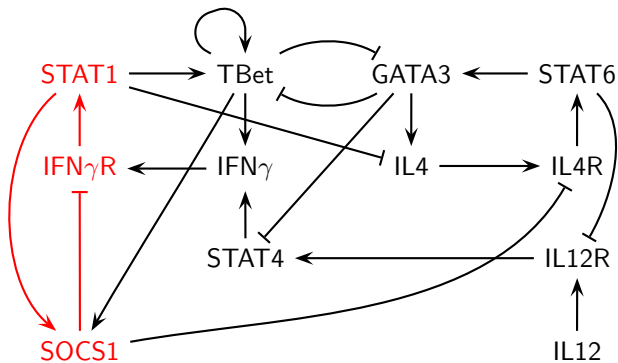
$x_{\text{Tbet}} = 0 \Rightarrow x_{\text{GATA3}} = 1$ and C1 functional
 $\Rightarrow$ reach s_1 (Th2 cells).

Analysis



Suppose IFN γ transiently expressed $\Rightarrow x_{\text{Tbet}} = 1 \Rightarrow x_{\text{GATA3}} = 0$ and C2 functional $\Rightarrow$ the system reaches fixed point s_2 (Th1 cells).

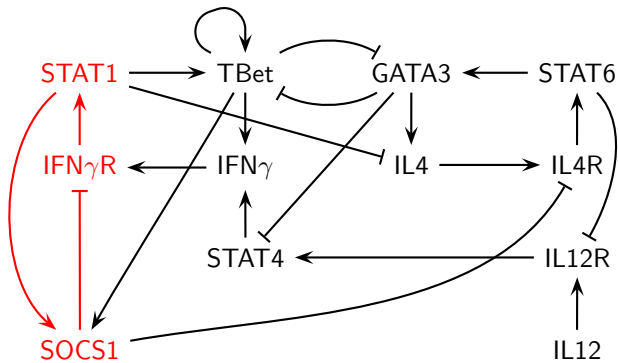
Analysis



$$\Phi(f)(C4) = \{x \mid x_{\text{IFN}\gamma} = 1, x_{\text{Tbet}} = 0\}.$$

Theorem $\Rightarrow$ dynamics restr. to $\Phi(f)(C4)$ has a trap cycle, but...

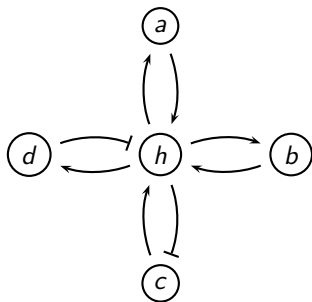
Analysis



Tbet activates lymphokine IFN γ $\Rightarrow$ functionality of C4 fragile.

- 1 Overview of the logical modelling
- 2 Isolated regulatory circuits
- 3 Multistability and positive circuits
- 4 Cycles and negative circuits
- 5 Towards the notion of functionality
- 6 Combination of circuits**

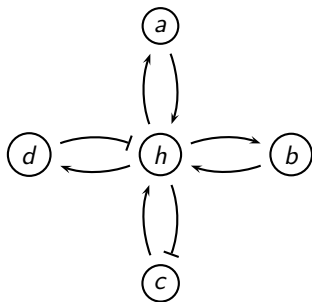
Flower-graphs



A flower-graph

- all the regulations are univocal
- there is a particular component h such that $\mathcal{E} = \{h \xrightarrow{\varepsilon_{hi}} i \mid i \neq h\} \cup \{i \xrightarrow{\varepsilon_{ih}} h \mid i \neq h\}$

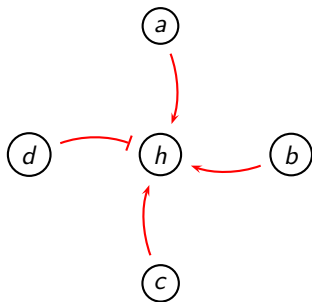
Flower-graphs



Remark :

- all regulations on h are *univocal*
- h is not self regulated

Flower-graphs

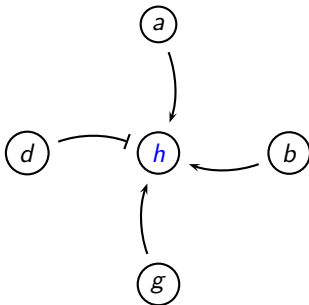


Behaviour of h ?

Multiple regulators

We define the state u by :

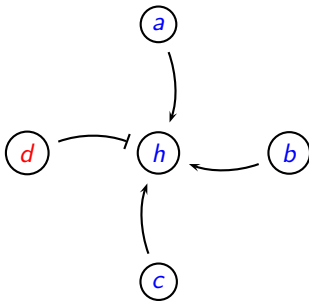
- $u_h = 0$,
- for all $i \in \mathcal{C} \setminus \{h\}$, $u_i = \begin{cases} 0 & \text{if } i \xrightarrow{+} h \\ 1 & \text{if } i \xrightarrow{-} h \end{cases}$



Multiple regulators

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Multiple regulators

Let

$$E_0 = \{y \in \{0,1\}^{\mathcal{C}} \mid y_h = 0 \text{ and } (x, \bar{x}^h) \notin \mathcal{E} \text{ for all } x \in \{0,1\}^{\mathcal{C}} \\ \text{such that } x_i = y_i \text{ for all } i \in \mathcal{C}\}$$

$$E_1 = \{y \in \{0,1\}^{\mathcal{C}} \mid y_h = 1 \text{ and } (x, \bar{x}^h) \notin \mathcal{E} \text{ for all } x \in \{0,1\}^{\mathcal{C}} \\ \text{such that } x_i = y_i \text{ for all } i \in \mathcal{C}\}$$

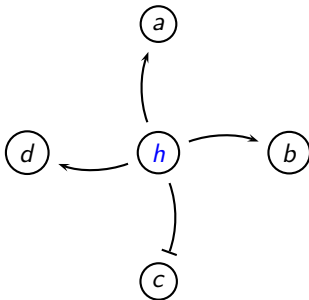
We have

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

Stable states and flower graphs

We define the state v by :

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

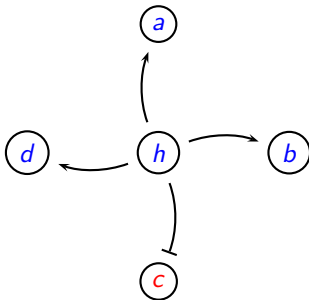


v and $\bar{v}$ are the only potential stable states

Stable states and flower graphs

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Stable states and flower graphs

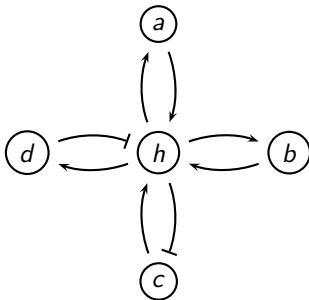
v stable state $\iff v \in E_0$

$\bar{v}$ stable state if and only if $\bar{v} \in E_1$

- If the flower graph contains only positive circuits, then $v = u$ and $\bar{v} = \bar{u} \Rightarrow 2$ stable states
- If the flower graph contains only negative circuits, then $v = \bar{u}$ and $\bar{v} = u \Rightarrow$ no stable state
- If the flower graph contains a unique negative circuit (e.g. implying a) , and at least one positive circuit $\Rightarrow$ at least one stationary configuration
- If the flower graph contains a unique positive circuit, and at least one negative circuit $\Rightarrow$ at most one stationary configuration

Stable states and flower graphs

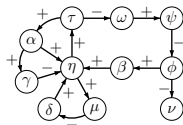
Consequence : the dynamics of such flower graph (more than two positive and negative circuits) may contain 0,1 or 2 stables states.... !



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



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 stationary configurations. In the particular case f does contain two stationary configurations, they are complementary. More precisely :

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

Stable states and flower graphs

