Analysis of feedback circuits in discrete models of regulatory networks

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TAG 08

Joint works with C.Chaouiya (IGC,Lisbonne), G.Didier (IML), P.Ruet(IML), D.Thieffry(TAGC)

Introduction

- Activity of a cell controlled by genetic regulatory networks. **Structure of the network ↔ properties of the dynamics.**
- Typically : network ↦ generate dynamical model ↦ numerical simulations and experimental observations ↦ evaluation.
- **High computational cost.**
- Looking for some abstract **principles**.

Genetic regulations, a schematic view

We distinguish two types of regulations

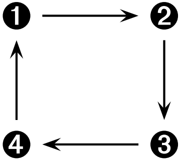
- Activation : $i \rightarrow j$ or $i \xrightarrow{+} j$
  the presence of proteins of gene i "favors" the expression of gene j
- Inhibition : $i \dashv j$ or $i \xrightarrow{-} j$
  the presence of proteins of gene i "inhibites" the expression of gene j

x_i expression level of gene i : discrete variable

↪ genetic regulations known as threshold phenomena

↪ for a first approximation : Boolean variable (gene expressed/not expressed)

Isolated regulatory circuits



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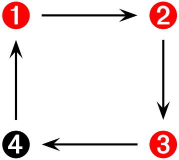
$$x_1, x_2, x_3, x_4 \in \{0, 1\}$$

$$\begin{aligned} \textit{Activation} : x_i = 0 \ &\Rightarrow \ x_j \searrow \\ x_i = 1 \ &\Rightarrow \ x_j \nearrow \end{aligned}$$

Asynchronous dynamics
(one update at a time)

Multistationarity

Isolated regulatory circuits



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Starting at state $(\overset{-}{1}, 1, 1, \overset{+}{0})$

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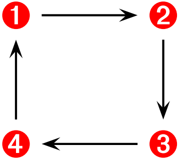

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Activating gene 4
$\mapsto$ *Fixed point* $(1, 1, 1, 1)$

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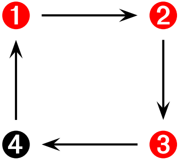

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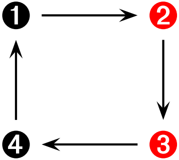

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Disactivating gene 1

$\rightarrow (0, \overset{-}{1}, 1, \overset{+}{0})$

Asynchronous dynamics

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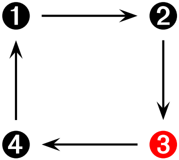

Disactivating gene 2

$\rightarrow (0, 0, \overset{-}{1}, \overset{+}{0})$

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Asynchronous dynamics

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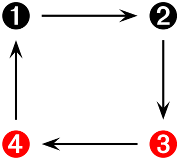

Activating gene 4

$\rightarrow (\overset{+}{0}, 0, \overset{-}{1}, 1)$

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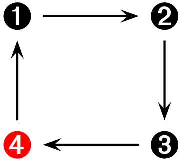

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Disactivating gene 3

$\rightarrow (\overset{+}{0}, 0, 0, \overset{-}{1})$

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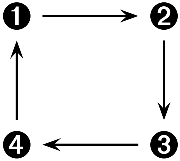

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Disactivating gene 4
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Asynchronous dynamics
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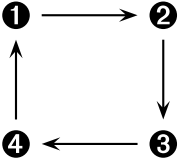
Multistationarity

Isolated regulatory circuits



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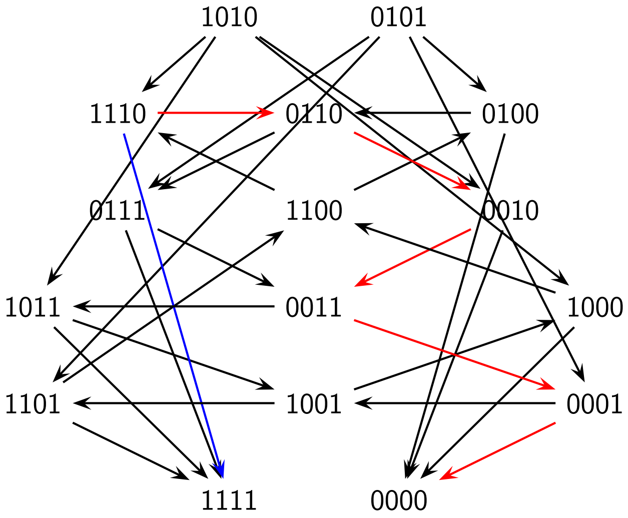
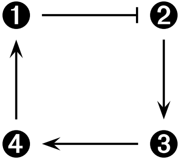
Multistationarity

Isolated regulatory circuits

The whole dynamical graph



Isolated regulatory circuits



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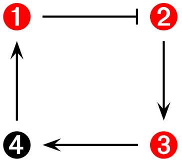
$\overline{a}$: negation

One (trap) cycle : homeostasis

Isolated regulatory circuits



Starting at state $(\overset{-}{1}, \overset{-}{1}, 1, \overset{+}{0})$

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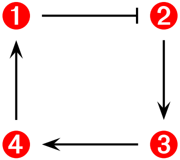

Activating gene 4

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

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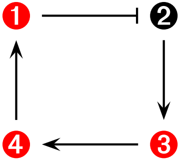

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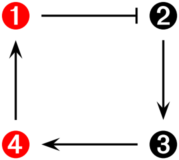

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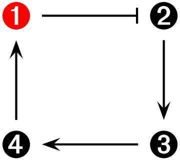

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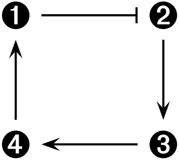

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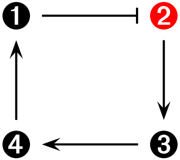

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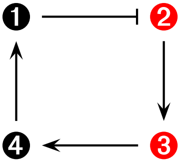

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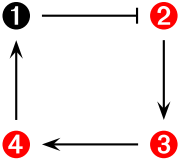

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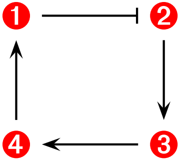

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$\mapsto$ *return to* $(1, \overline{1}, 1, 1)$

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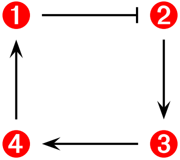

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One (trap) cycle : homeostasis

Isolated regulatory circuits

- Positive circuit (even number of inhibitions) ⇔ multistationarity (2 fixed points) . . . . differentiation
- Negative circuit (odd number of inhibitions) ⇔ sustained oscillations . . . . homeostasis

R.-Mossé-Chaouiya-Thieffry, Bioinformatics, 2003

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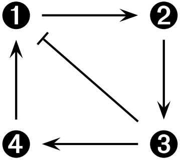
Shortcuts in a positive circuit



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

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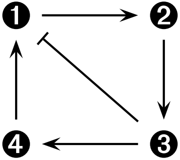

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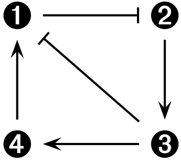
Shortcuts in a negative circuit



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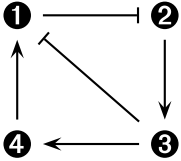
One fixed point $(0, 1, 1, 1)$, one unstable cycle :
No homeostasis.

Shortcuts in a negative circuit



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

Thomas' rules (1981)

- Multistationarity ⇒ positive circuit in the regulatory graph.
- Homeostasis ⇒ negative circuit in the regulatory graph.

Differential equations : Plathe et al. (±, 1995), Snoussi (±, 1998), Gouzé (±, 1998), Soulé (+, 2003).
Discrete framework : Aracena et al (+, 2001), R.-Ruet-Thieffry (±, 2005), Comet-Richard (2005)

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Discrete (Boolean) framework

Asynchronous (non deterministic) dynamics : given $f : \{0,1\}^n \rightarrow \{0,1\}^n$, the trajectory $x \rightsquigarrow \overline{x}^i$ is admissible when $x_i \neq f_i(x)$ (updates the expression level of i in state x). We write $(x, \overline{x}^i) \in \mathcal{E}$.

(Local) regulatory network $G(f)(x)$:

$i \rightarrow j$ when $f_j(\overline{x}^i) \neq f_j(x)$ and $x_i = f_j(x)$
$i \dashv j$ when $f_j(\overline{x}^i) \neq f_j(x)$ and $x_i \neq f_j(x)$
… discrete (partial) derivatives.

Global regulatory graph : $G(f) = \bigcup_x G(f)(x)$.

Equivalently, $i \xrightarrow{\epsilon} j$ if $(x, \overline{x}^j) \in \mathcal{E}$ and $(\overline{x}^i, \overline{x}^{i,j}) \notin \mathcal{E}$
with $\epsilon = +$ if $x_i \neq x_j$
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... discrete (partial) derivatives.

Global regulatory graph : $G(f) = \bigcup_x G(f)(x)$.

Equivalently, $i \xrightarrow{\epsilon} j$ if $(x, \overline{x}^j) \in \mathcal{E}$ and $(\overline{x}^i, \overline{x}^{i,j}) \notin \mathcal{E}$
with $\epsilon = +$ if $x_i \neq x_j$
and $\epsilon = -$ if $x_i = x_j$

Discrete (Boolean) framework

- positive self-regulation $i \overset{+}{\circlearrowleft}$:
  - when $f_i(x) \neq f_i(\overline{x}^i)$ and $x_i = f_i(x)$
  - if both $(x, \overline{x}^i) \notin \mathcal{E}$ and $(\overline{x}^i, x) \notin \mathcal{E}$
- negative self-regulation $i \overset{-}{\circlearrowleft}$
  - when $f_i(x) \neq f_i(\overline{x}^i)$ and $x_i \neq f_i(x)$
  - if both $(x, \overline{x}^i) \in \mathcal{E}$ and $(\overline{x}^i, x) \in \mathcal{E}$

Multistability and positive circuits

Theorem :
f has at least two fixed points $\Longrightarrow \exists a \in \{0,1\}^n$ such that $G(f)(a)$ has a positive circuit
More precisely, if f has two fixed points x and $y = \overline{x}^{\Delta(x,y)}$, then the regulatory graph contains a positive circuit involving a subset of $\Delta(x,y)$.

Multistability and positive circuits

Ideas of the proof :

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

- Let $i \in \Delta(x,y)$. By definition, $(y, \overline{y}^i) \notin \mathcal{E}$.
  - if $(\overline{y}^i, y) \notin \mathcal{E}$, then positive self regulation on $i \rightarrow$ OK !
  - Suppose $(\overline{y}^i, y) \in \mathcal{E}$. Take $D = \Delta(x,y) \setminus \{i\}$.
    We have $(x, \overline{x}^i) \notin \mathcal{E}$ (fixed point), 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, $i \xrightarrow{\epsilon} j$. As $x_i \neq y_i$, we can deduce that $\epsilon_i = -1$ if $x_i \neq x_j$

$\Rightarrow \forall i \in \Delta(x,y), \exists p(i) \in \Delta(x,y)$ such that $p(i) \xrightarrow{\epsilon_i} i$, with $\epsilon_i = -1$ 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 negative sign as $x_{p^j(i)} \neq x_{p^{j+1}(i)}$.

$\Rightarrow$ 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.

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 :

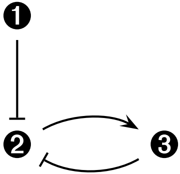
- $\forall i \in \{1, \cdots, p\}$, $(x^i, \overline{x^i}^{\varphi_{i+1}}) \notin \mathcal{E}$ (because the cycle is trap), and $(\overline{x^i}^{\varphi_i}, \overline{x^i}^{\varphi_i, \varphi_{i+1}}) \in \mathcal{E}$:

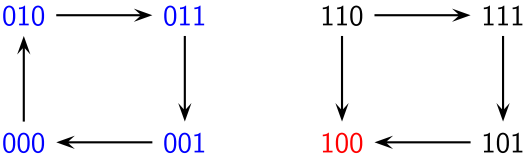
$$\varphi_i \xrightarrow{\epsilon_i} \varphi_{i+1}$$

  with $\epsilon_i = -1$ if $x^i_{\varphi_i} \neq x^{i+1}_{\varphi_{i+1}}$.
- let (x^k, x^{k+l}) be a bridge, *i.e.* such that $\varphi_k = \varphi_{k+l}$ (each gene implied in the strategy appears an even number of times) and $\{\varphi_{k+1}, \cdots, \varphi_{k+l-1}\}$ contains once all the genes of the strategy except φ_k

$\Rightarrow$ *Circuit, with negative sign*

Context of functionality





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

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 (R.-Ruet, Bioinformatics, 2008)

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

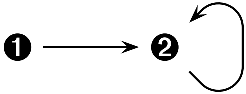
$$C = k_1 \xrightarrow{\epsilon_1} k_2 \xrightarrow{\epsilon_2} \cdots \xrightarrow{\epsilon_{p-1}} k_p \xrightarrow{\epsilon_p} k_1$$

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.*

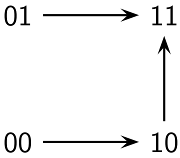
Global and local separators

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



$$f\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 1 \\ x_1 \vee x_2 \end{pmatrix}$$

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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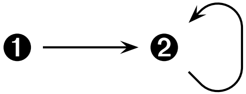

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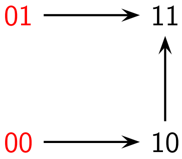
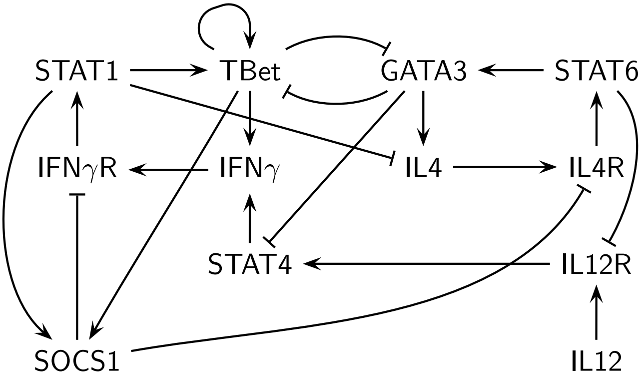


Two 2-fixed points, a single global one

Th-lymphocyte differentiation

- CD4+ T helper lymphocytes can differentiate :
  - Th1 ⇒ cell mediated immunity ⇒ autoimmune diseases,
  - Th2 ⇒ humoral responses ⇒ 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 receptorsdiversity (Buja, De Boer, Junker, Krueger, Marshall, Perelson, Schroeder, Wang, Weisbuch,. . .),
  - . . .

Very simplified Boolean model (Remy-Ruet-Mendoza-Thieffry-Chaouiya)



18 circuits, 3 stables states

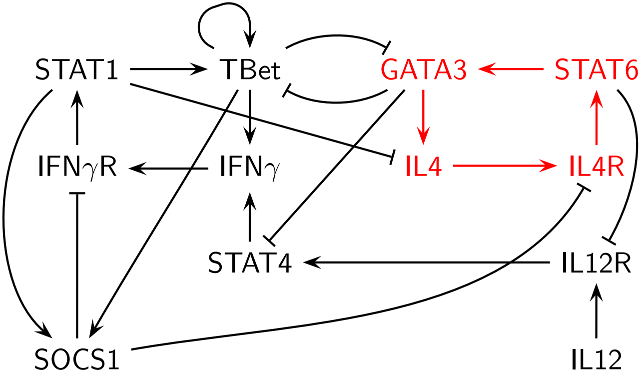
Very simplified Boolean model

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-γR	(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

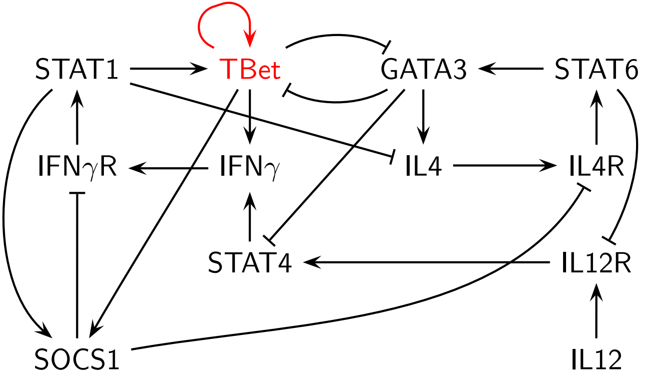
s_1 and s_2 to Th2 and Th1 differentiated lymphocytes,

Very simplified Boolean model



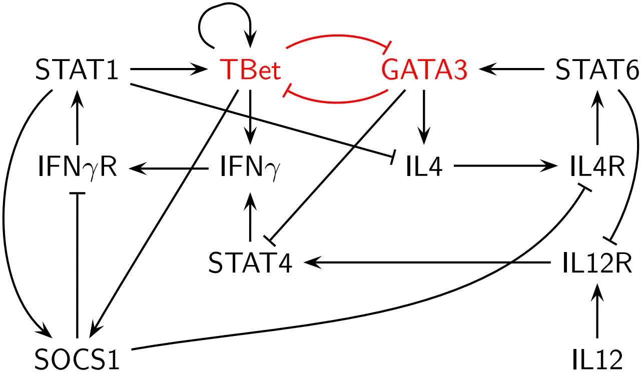
18 circuits, only 4 functional ones (C1).

Very simplified Boolean model



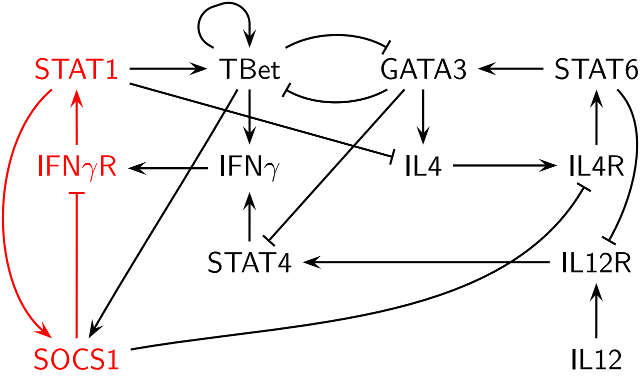
18 circuits, only 4 functional ones (C1, C2).

Very simplified Boolean model



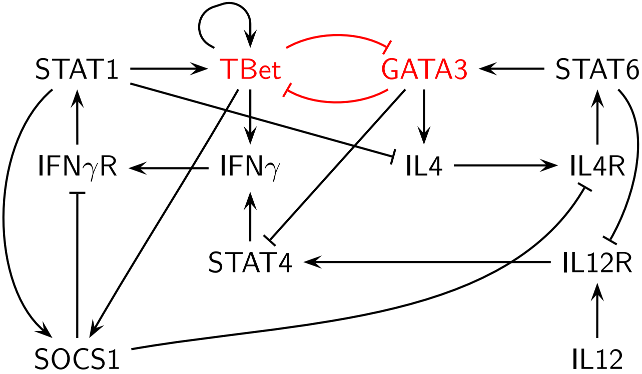
18 circuits, only 4 functional ones (C1, C2, C3).

Very simplified Boolean model



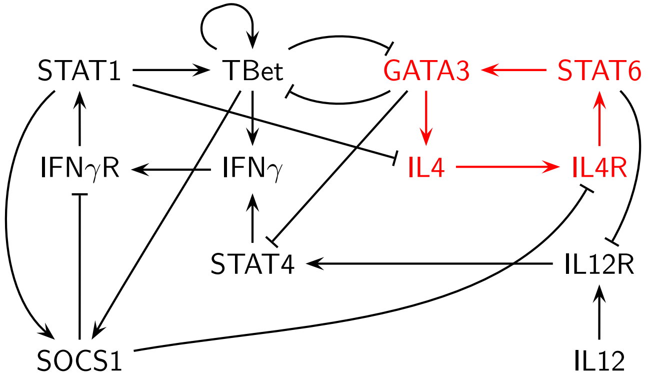
18 circuits, only 4 functional ones (C1, C2, C3, C4).

Very simplified Boolean model



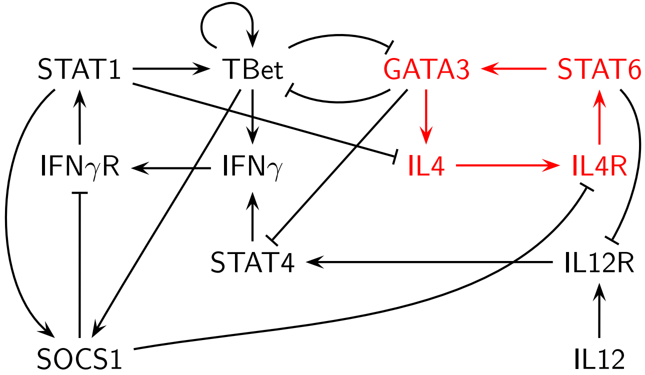
18 circuits, only 4 functional ones, only 3 globally minimal ones.

Analysis



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

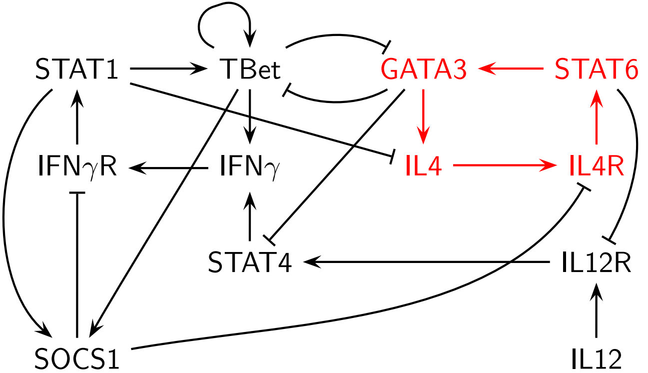
Analysis



$s_0 = 0$: 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-γR	(4)	0	0	0
IL-4R	(5)	0	1	0
IL-12R	(6)	0	0	0
STAT1	(7)	0	0	0
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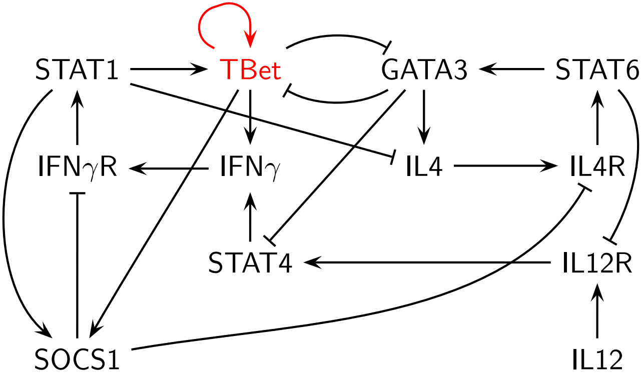
SOCS1	(10)	0	0	1
T-bet	(11)	0	0	1
GATA-3	(12)	0	1	0

Analysis



STAT1 TBet GATA3 STAT6

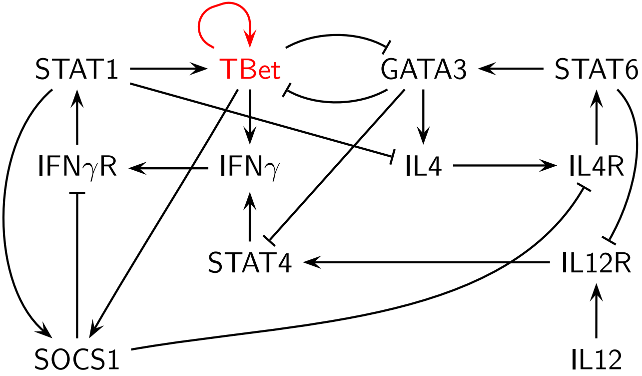
IFNγR IFNγ IL4 IL4R

STAT4 IL12R

SOCS1 IL12

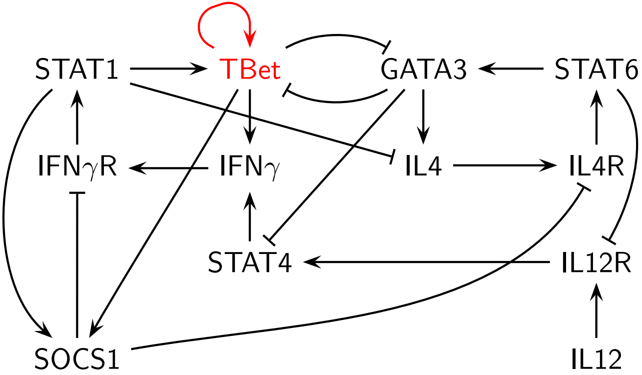
$$\Phi(f)(C2) = \{x \mid x_{\text{GATA3}} = x_{\text{STAT1}} = 0\}.$$

Analysis



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

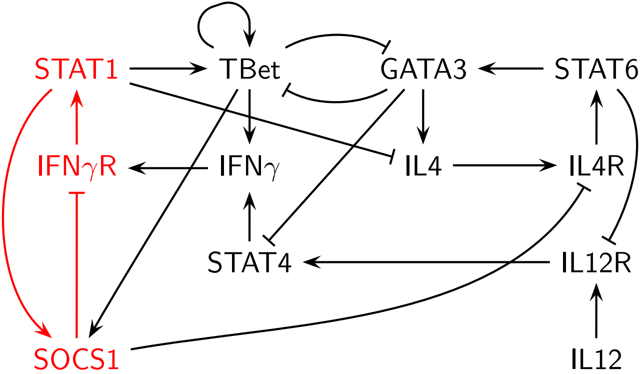
Analysis



Suppose IFNγ transiently expressed $\Rightarrow x_{\text{Tbet}} = 1 \Rightarrow x_{\text{GATA3}} = 0$ and

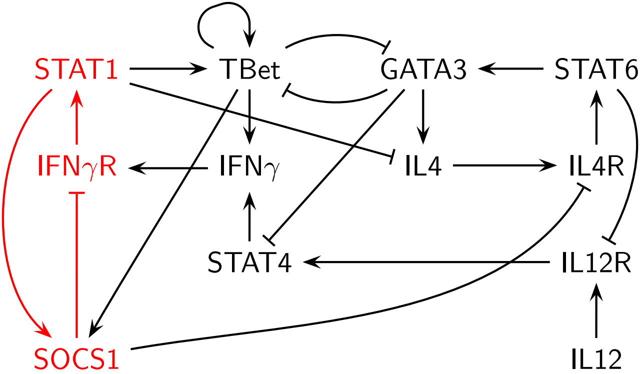
$C2$ functional $\Rightarrow$ the system reaches fixed point s_2 (Th1 cells).

Analysis



$\Phi(f)(C4) = \{x \mid x_{\mathrm{IFN}\gamma} = 1,\ x_{\mathrm{Tbet}} = 0\}$.
Theorem $\Rightarrow$ dynamics restr. to $\Phi(f)(C4)$ has a trap cycle, but...

Analysis



Tbet activates lymphokine IFNγ $\Rightarrow$ functionality of $C4$ fragile.

Conclusion

- Globally minimal positive circuit $\Rightarrow$ local separator.
- Globally minimal negative circuit $\Rightarrow$ local form of homeostasis.
- Regulatory “modules” $\simeq$ globally minimal circuits.
- Th-lymphocyte differentiation : global behaviour induced by 3 circuits.
- How do modules and basins of attraction combine in general ?