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FUNDAÇÃO CALOUSTE GULBENKIAN
Instituto Gulbenkian de Ciência

On the structure and robustness of gene regulatory network Boolean functions

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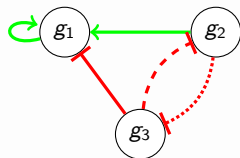
Biological motivation

Structure of Boolean functions

Stochasticity & robustness in regulatory networks

Background

Logical (Boolean) regulatory graphs

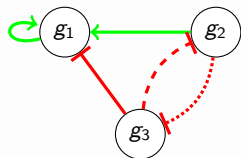


Logical (Boolean) regulatory graph $\mathcal{R} = (G, F)$:

- G is a set of n regulatory components g_i
- $\prod_{g_i \in G} \{0, 1\}$ defines the state space \mathcal{S}
- F is a set of regulatory functions $F_{g_i} \in F : \mathcal{S} \rightarrow \{0, 1\}$

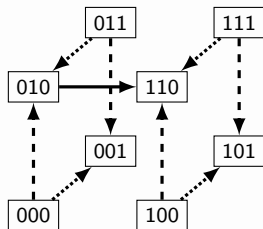
Background

Logical (Boolean) regulatory graphs



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State transition graph

represents the dynamical behaviour of a LRG, where:

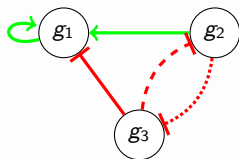
- nodes - represent states
- edges - possible transitions between successor states

Biological motivation

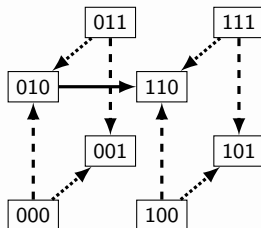
Dynamic behaviour of a GRN

Modelling procedure (simplified):

- Define the set of components
- Define their signed influences
- Define the functions regulating each component

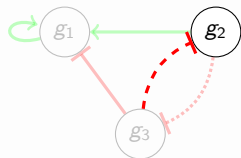


\Rightarrow

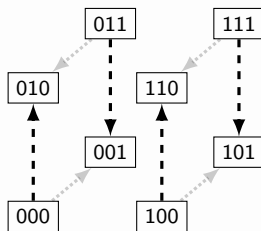


Biological motivation

Dynamic behaviour of a GRN



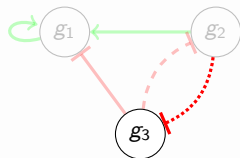
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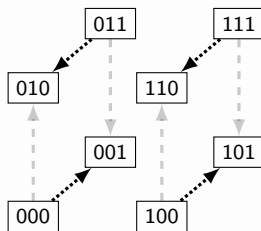
$$f_{g_2} = \neg g_3$$

Biological motivation

Dynamic behaviour of a GRN



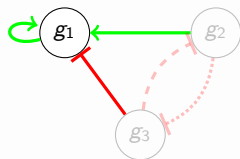
\Rightarrow



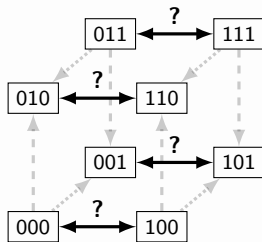
$$f_{g_3} = \neg g_2$$

Biological motivation

Dynamic behaviour of a GRN



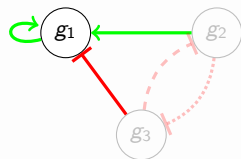
\Rightarrow



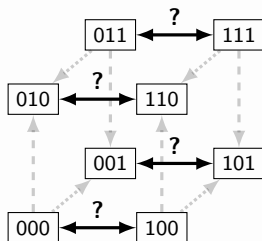
$$f_{g_1} = \neg g_1 \vee \neg g_2 \vee \neg g_3$$

Biological motivation

Dynamic behaviour of a GRN



\Rightarrow



$$f_{g_1} = \overset{?}{\neg} g_1 \vee \overset{?}{\wedge} \overset{?}{\neg} g_2 \vee \overset{?}{\wedge} \overset{?}{\neg} g_3$$

Q: How to choose the “correct” function(s)?

- Are all regulatory interactions functional?
- Is the function compliant with the regulator sign?
- Is the function “robust” to changes?

Biological motivation

Structure of Boolean functions

Stochasticity & robustness in regulatory networks

Boolean functions

Number of Boolean functions

1 regulator

A	F	\bar{A}	A	F
0	0	1	0	1
1	0	0	1	1

Boolean functions

Number of Boolean functions

1 regulator

A	F	\bar{A}	A	T
0	0	1	0	1
1	0	0	1	1

2 regulators

A	B	F	$\bar{A} \wedge \bar{B}$	$\bar{A} \wedge B$	\bar{A}	$A \wedge \bar{B}$	\bar{B}	$A \oplus B$	$\bar{A} \vee \bar{B}$	$A \wedge B$	$A \leftrightarrow B$	B	$\bar{A} \vee B$	A	$A \vee \bar{B}$	$A \vee B$	T
0	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
0	1	0	0	1	1	0	0	1	1	0	0	1	1	0	1	1	1
1	0	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1
1	1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1

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0	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
0	1	0	0	1	1	0	0	1	1	0	0	1	1	0	1	1	1
1	0	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1
1	1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1

n regulators

$$|K_{g_i}| = 2^{2^n} \text{ Combinatorial explosion!}$$

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Includes functions which are:

- Degenerate (non-functional regulators)

Boolean functions

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0	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
0	1	0	0	1	1	0	0	1	1	0	0	1	1	0	1	1	1
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n regulators

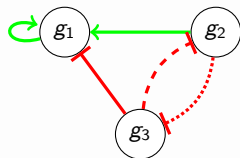
$$|K_{g_i}| = 2^{2^n} \text{ Combinatorial explosion!}$$

Includes functions which are:

- Degenerate (non-functional regulators)
- Non-monotone (regulators with dual role)

Boolean functions

Compatible with a GRN topology



Given an LRG (G, \mathcal{K}) , we denote G_g the set of regulators of g .

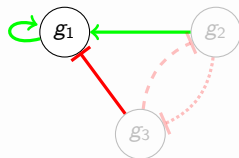
$$G_g = G_g^+ \cup G_g^-$$

G_g^+ : set of positive regulators

G_g^- : set of negative regulators

Boolean functions

Compatible with a GRN topology



$$G_{g_1} = \{g_1, g_2, g_3\}$$

$$G_{g_1}^+ = \{g_1, g_2\} \quad G_{g_1}^- = \{g_3\}$$

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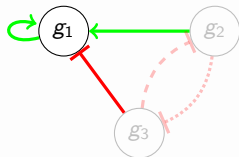
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$$G_g = G_g^+ \cup G_g^-$$

G_g^+ : set of positive regulators

G_g^- : set of negative regulators

Recall that F_g denotes the set of functions f_g compatible with the structure defined by G_g

Boolean functions

Compatible with a GRN topology

$f_g \in F_g$ can be written in the Disjunctive Normal Form (DNF)

$$f_g = C_1 \vee \dots \vee C_m$$

$$C_i = \bigwedge_{k \in E_i \subseteq G_g} u_k \quad i = \{1, \dots, m\}$$

which must satisfy the following conditions:

- $\forall g_k \in G_g, \exists j$ for which $k \in E_j$
all regulators are functional
- $u_k = \begin{cases} q_k, & \text{if } g_k \in G_g^+ \\ \neg q_k, & \text{if } g_k \in G_g^- \end{cases}$
regulators do not have a dual role

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Compatible with a GRN topology

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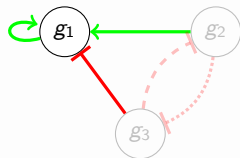
Also known as:

- Blake canonical form
- Complete DNF, *i.e.*, the complete list of the [prime implicants of \$f\$](#)

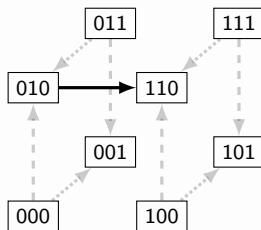
(Blake 1937)

Boolean functions

Compatible with a GRN topology



\Rightarrow

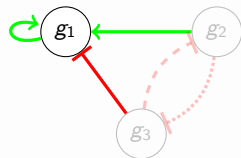


Examples:

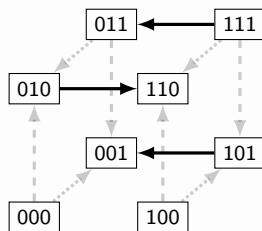
$$f_{g_1} = g_1 \vee (g_2 \wedge \neg g_3)$$

Boolean functions

Compatible with a GRN topology



\Rightarrow



Examples:

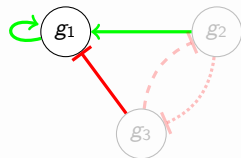
$$f_{g_1} = g_1 \vee (g_2 \wedge \neg g_3)$$

$$f_{g_2} = (g_1 \wedge \neg g_3) \vee (g_2 \wedge \neg g_3)$$

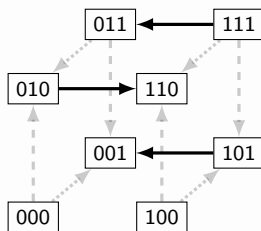
...

Boolean functions

Compatible with a GRN topology



\Rightarrow



Examples:

$$f_{g_1} = g_1 \vee (g_2 \wedge \neg g_3)$$

$$f_{g_2} = (g_1 \wedge \neg g_3) \vee (g_2 \wedge \neg g_3)$$

...

$$f_{g_3} = g_1 \vee (g_2 \wedge \neg g_1)$$

Boolean functions

What is the size of $|F_g|$?

Given n variables:

- 2^{2^n} - number of all Boolean functions
- $|D(n)|$ - number of all monotone Boolean functions (Dedekind number)
- $|F(n)|$ - number of non-degenerate monotone Boolean functions

n	2^{2^n}	$D(n)$		$ F(n) $
1	4	3	(Dedekind 1897)	1
2	16	6	(Dedekind 1897)	2
3	256	20	(Dedekind 1897)	9
4	65 536	168	(Dedekind 1897)	114
5	4 294 967 296	7 581	(Church 1940)	6 894
6	1.8×10^{19}	7 828 354	(Ward 1946)	7 785 062
7	3.4×10^{38}	2 414 682 040 998	(Church 1965)	2 414 627 396 434
8	1.2×10^{77}	5.6×10^{22}	(Wiedemann 1991)	5.6×10^{22}

$D(n)$ not known for $n > 8$!

$$|F(n)| = D(n) - 2 - \sum_{i=1}^{n-1} \frac{n}{i!(n-i)!} |F(i)|$$

Boolean functions

How is the set F_g organised?

Given any two Boolean functions f, f' , in n variables:

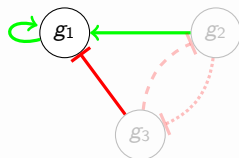
$$f \preceq f' \quad \text{iff} \quad f(x) = 1 \implies f'(x) = 1$$

Given the set F_g and the relation \preceq :

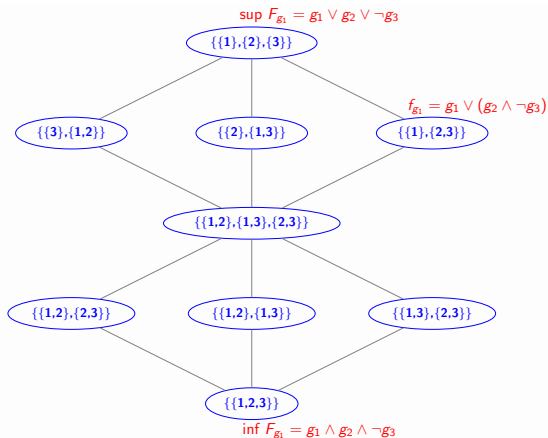
- \preceq is a Partial Order relation on F_g
- (F_g, \preceq) defines a **Partial Order set**

Boolean functions

F_g organised as a Partial Order set



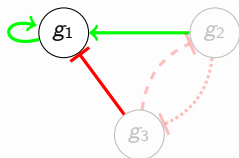
Set representation of f_g
(indices of the literals in the clauses)



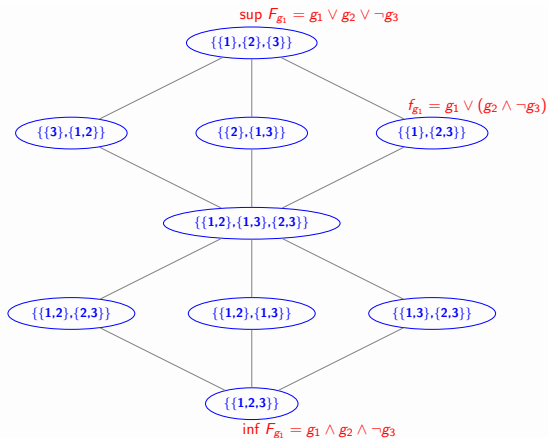
Hasse Diagram of $F(3)$, with its 9 functions

Boolean functions

F_g organised as a Partial Order set



Set representation of f_g
(indices of the literals in the clauses)



Hasse Diagram of $F(3)$, with its 9 functions

$$\inf F_{g_1} \preceq f_{g_1} \preceq \sup F_{g_1}$$

Boolean functions

F_g organised as a Partial Order set



Hasse Diagram of $F(4)$ - has 114 functions

Boolean functions

Neighbourhood characterization of f_g in the PO Set

Given g and its regulators, for two functions $f, f' \in F_g$:

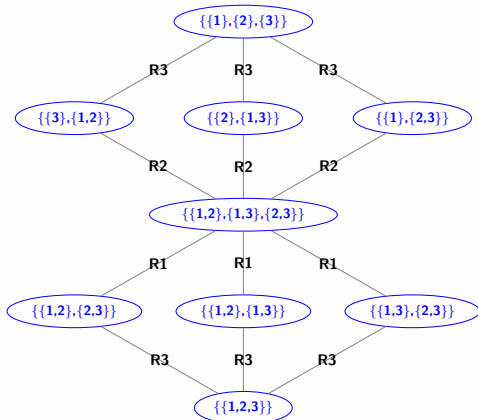
- f' is said to be a "parent" of f (resp. f a "children" of f') in the PO-Set (F_g, \preceq) iff:

$$f \preceq f' \text{ and } \nexists f'' \in F_g \text{ s.t. } f \preceq f'' \text{ and } f'' \preceq f'$$

For each function f , we define two sets of rules to compute:

- the set of all its "parents": 3 rules
- the set of all its "children": 3 rules

(Cury, Monteiro, Chaouiya, *in preparation*)

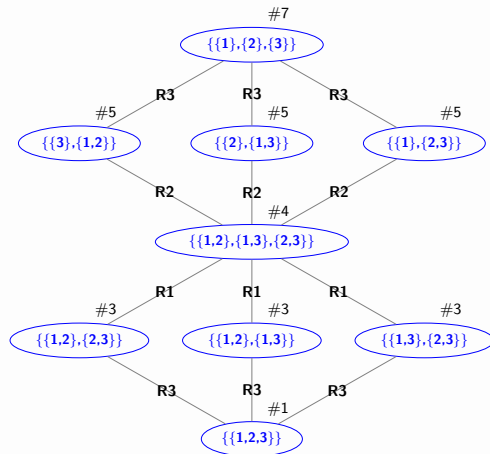


Boolean functions

Number of states where f is true

Given any two functions f, f' s.t. f' is a “parent” of f :

- there is never more than 2 states of difference



(Cury, Monteiro, Chaouiya, *in preparation*)

Biological motivation

Structure of Boolean functions

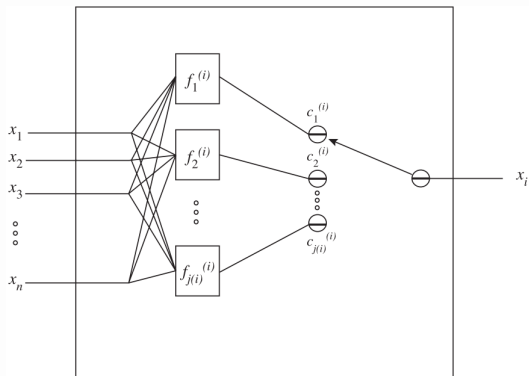
Stochasticity & robustness in regulatory networks

Stochasticity in gene regulatory networks

PBN - Probabilistic Boolean networks

PBN - Probabilistic Boolean networks

- Model the choice between alternate biological functions for activation of gene/protein



(Shmulevich et al., *Bioinformatics* 2002)

SIN - Stochasticity in nodes

- Nodes are flipped from 0 to 1 (or vice-versa) with some predefined probability
- Regardless of the susceptibility to stochasticity of the underlying function

(Ribeiro and Kauffman, *J. Theor. Biol.* 2007)

(Davidich and Bornholdt, *PLoS ONE* 2008)

(Álvarez-Buylla *et al.*, *PLoS ONE* 2008)

SIF - Stochasticity in functions

(Garg et al., *Bioinformatics* 2009)

- associates a probability of failure with different functions
- models stochasticity in these functions depending upon the expression of the input nodes

$$BUFF: f^B(x_a) = [(x_c \leftrightarrow \mathbf{0}) \wedge \Delta] \vee [(x_c \leftrightarrow x_a) \wedge \neg \Delta]$$

$$NOT: f^N(x_a) = [(x_c \leftrightarrow \mathbf{1}) \wedge \Delta] \vee [(x_c \leftrightarrow \neg x_a) \wedge \neg \Delta]$$

$$OR: f^O(x_1, \dots, x_p) = (x_c \leftrightarrow \bigvee_{i=1}^p x_i)$$

$$AND: f^A(x_1, \dots, x_p) = [(x_c \leftrightarrow \mathbf{0}) \wedge \Delta] \vee$$

$$\left[(x_c \leftrightarrow \bigwedge_{i=1}^p x_i) \wedge \neg \Delta \right]$$

$$IAND: f^{IA}(x_1, \dots, x_p) = \left[\{x_c \leftrightarrow \bigwedge_{j=1}^{p^a + p^n} x_j\} \wedge \Delta \right] \vee$$

$$\left[\{x_c \leftrightarrow (\bigwedge_{i=1}^{p^n} \neg x_i^{in} \wedge \bigwedge_{j=1}^{p^a} x_j^a)\} \wedge \neg \Delta \right]$$

Stochasticity in gene regulatory networks



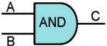

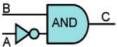
SIF - Stochasticity in functions

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(Garg et al., *Bioinformatics* 2009)

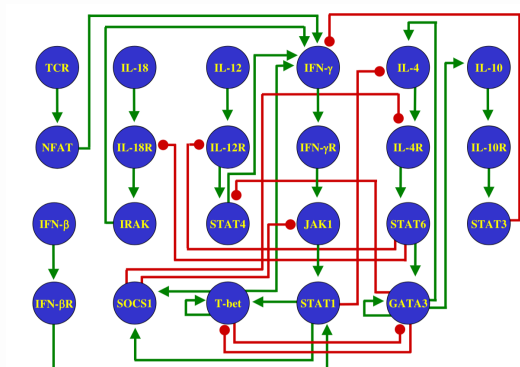
- associates a probability of failure with different functions
- models stochasticity in these functions depending upon the expression of the input nodes

Table 1. Truth tables representing the transfer function of different Boolean logic gates. A and B are the input genes, C represents the output gene expression in the absence of stochasticity and \tilde{C} represents the output gene expression in the presence of stochasticity under the SIF model.

																																																																																		
<table border="1" data-bbox="237 688 360 774"><thead><tr><th>A</th><th>C</th><th>\tilde{C}</th></tr></thead><tbody><tr><td>0</td><td>0</td><td>0</td></tr><tr><td>1</td><td>1</td><td>0</td></tr></tbody></table>	A	C	\tilde{C}	0	0	0	1	1	0	<table border="1" data-bbox="395 688 518 774"><thead><tr><th>A</th><th>C</th><th>\tilde{C}</th></tr></thead><tbody><tr><td>0</td><td>1</td><td>1</td></tr><tr><td>1</td><td>0</td><td>1</td></tr></tbody></table>	A	C	\tilde{C}	0	1	1	1	0	1	<table border="1" data-bbox="552 635 717 774"><thead><tr><th>A</th><th>B</th><th>C</th><th>\tilde{C}</th></tr></thead><tbody><tr><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>0</td><td>1</td><td>0</td><td>0</td></tr><tr><td>1</td><td>0</td><td>0</td><td>0</td></tr><tr><td>1</td><td>1</td><td>1</td><td>0</td></tr></tbody></table>	A	B	C	\tilde{C}	0	0	0	0	0	1	0	0	1	0	0	0	1	1	1	0	<table border="1" data-bbox="751 635 916 774"><thead><tr><th>A</th><th>B</th><th>C</th><th>\tilde{C}</th></tr></thead><tbody><tr><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>0</td><td>1</td><td>1</td><td>1</td></tr><tr><td>1</td><td>0</td><td>1</td><td>1</td></tr><tr><td>1</td><td>1</td><td>1</td><td>1</td></tr></tbody></table>	A	B	C	\tilde{C}	0	0	0	0	0	1	1	1	1	0	1	1	1	1	1	1	<table border="1" data-bbox="943 635 1108 774"><thead><tr><th>A</th><th>B</th><th>C</th><th>\tilde{C}</th></tr></thead><tbody><tr><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>0</td><td>1</td><td>1</td><td>0</td></tr><tr><td>1</td><td>0</td><td>0</td><td>0</td></tr><tr><td>1</td><td>1</td><td>0</td><td>1</td></tr></tbody></table>	A	B	C	\tilde{C}	0	0	0	0	0	1	1	0	1	0	0	0	1	1	0	1
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Model application

T-helper differentiation network



The Th network. The regulatory network that controls the differentiation process of T helper cells. Positive regulatory interactions are in green and negative interactions in red.

(Mendoza and Xenarios, *Theor. Biol. Med. Model.* 2006)

- From precursor Th0 cells to Th1 or Th2 effector cells upon the presence of cytokines $IFN\gamma$ or IL4, respectively

Model application

T-helper differentiation network

Cell type signatures (stable states):

	GATA3	IFN γ	IL4	IL4R	JAK1	SOCS1	STAT1	Tbet	IFN β
Th0	0	0	0	0	0	0	0	0	0
Th1	0	1	0	0	0	1	0	1	0
Th2	1	0	1	1	0	0	0	0	0

Th0 cells in response to an IFN γ stimuli

- differentiate to Th1
- **cannot** differentiate to Th2

(Murphy and Reiner, *Nat. Rev. Immunol.* 2002)

Stochasticity in gene regulatory networks

T-helper differentiation network

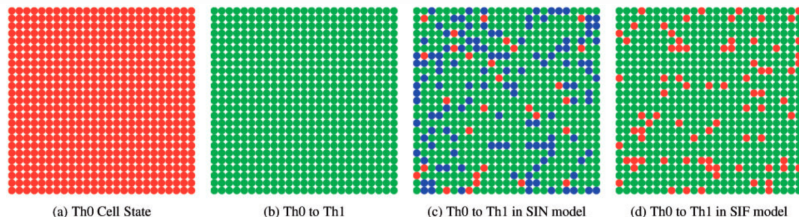


Fig. 4. Simulation results showing the effect of noise on T-helper cell differentiation process with an external stimulus of $\text{IFN}\gamma$. Each small circle is representative of a T-helper cell and each cell is modeled to behave independent of the neighboring cells. Red cells represent the naive undifferentiated Th0 cells, green cells represent Th1 cell state and blue cells represent Th2 cell state. Ratio of number of red (green or blue) cells to total number of cells in a panel is representative of the probability of differentiating into Th0 (Th1 or Th2) cell state. **(a)** Cell culture maintained in Th0 state. **(b)** In absence of any stochasticity all Th0 cells differentiate to Th1 cell state on receiving $\text{IFN}\gamma$. **(c)** Th0 cells differentiate into Th1 and Th2 under the SIN model of stochasticity. Few cells revert to Th0 state as seen by the few patches of red color. **(d)** SIF model of stochasticity shows that Th0 cells differentiate into Th1 cells while some cells cannot differentiate on receiving $\text{IFN}\gamma$ and revert to Th0 cell state. None of the cells differentiate into Th2 cell state. The probability of failure (i.e. ϵ_j) is 0.5 for all the nodes (functions) in the SIN model (SIF model).

(Garg *et al.*, *Bioinformatics* 2009)

Experimental results

Deterministic setting - f_{GATA3}

- Synchronous simulation
- All monotone non-degenerate functions for f_{GATA3}
- Reference $f_{\text{GATA3}} =$
 $(\text{Tbet} \ \& \ \text{GATA3}) \mid (\text{Tbet} \ \& \ \text{STAT6})$

Legend:

1 - !Tbet

2 - GATA3

3 - STAT6

Th1 - green nodes

Th2 - blue nodes

Solid node - non-degenerate function

Dashed node - degenerate function

Experimental results

Deterministic setting - f_{GATA3}

- Synchronous simulation
- All monotone **non-degenerate** functions for f_{GATA3}
- Reference $f_{GATA3} = (!Tbet \ \& \ GATA3) \mid (!Tbet \ \& \ STAT6)$

Legend:

1 - !Tbet

2 - GATA3

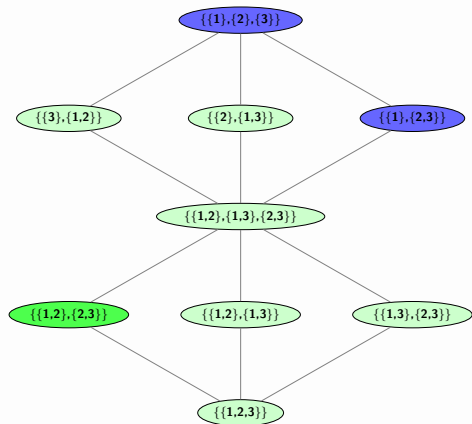
3 - STAT6

Th1 - green nodes

Th2 - blue nodes

Solid node - non-degenerate function

Dashed node - degenerate function



Experimental results

Deterministic setting - f_{GATA3}

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Legend:

1 - !Tbet

2 - GATA3

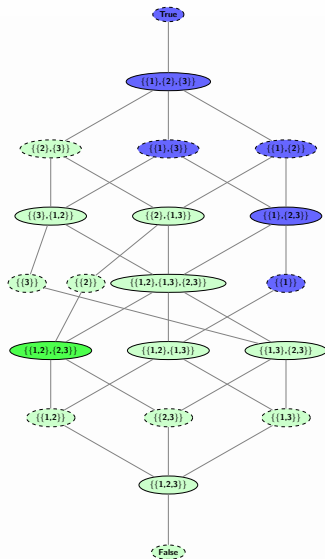
3 - STAT6

Th1 - green nodes

Th2 - blue nodes

Solid node - non-degenerate function

Dashed node - degenerate function



Experimental results

Deterministic setting - f_{IL4}

- Synchronous simulation
- All monotone non-degenerate functions for f_{IL4}
- Reference $f_{IL4} =$
GATA3 & !STAT1

Legend:

1 - GATA3

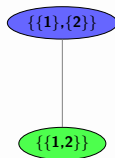
2 - !STAT1

Th1 - green nodes

Th2 - blue nodes

Solid node - non-degenerate function

Dashed node - degenerate function



Experimental results

Deterministic setting - f_{IL4}

- Synchronous simulation
- All monotone functions for f_{IL4}
- Reference $f_{IL4} =$
GATA3 & !STAT1

Legend:

1 - GATA3

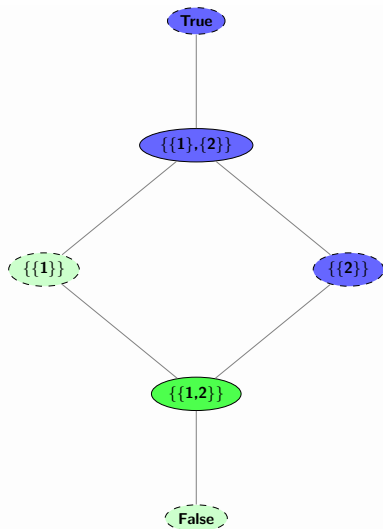
2 - !STAT1

Th1 - green nodes

Th2 - blue nodes

Solid node - non-degenerate function

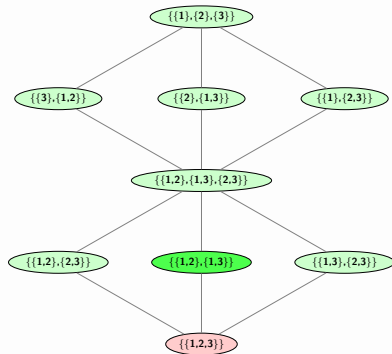
Dashed node - degenerate function



Experimental results

Deterministic setting - f_{Tbet}

- Synchronous simulation
- All monotone **non-degenerate** functions for f_{Tbet}
- Reference $f_{Tbet} =$
(!GATA3 & STAT1) | (!GATA3 & Tbet)



Legend:

1 - !GATA3

2 - STAT1

3 - Tbet

Th0 - red nodes

Th1 - green nodes

Solid node - non-degenerate function

Dashed node - degenerate function

Experimental results

Deterministic setting - f_{Tbet}

- Synchronous simulation
- All monotone functions for f_{Tbet}
- Reference $f_{Tbet} = (!GATA3 \ \& \ STAT1) \mid (!GATA3 \ \& \ Tbet)$

Legend:

1 - !GATA3

2 - STAT1

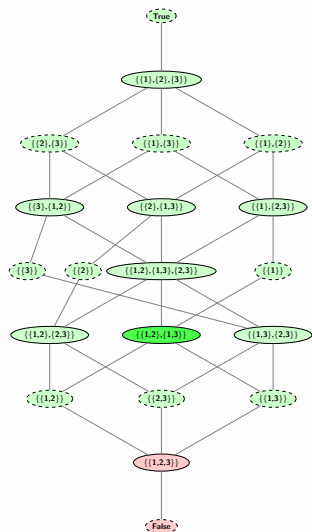
3 - Tbet

Th0 - red nodes

Th1 - green nodes

Solid node - non-degenerate function

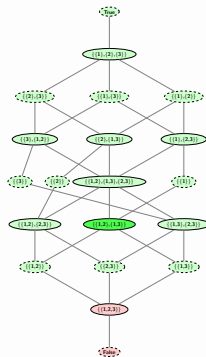
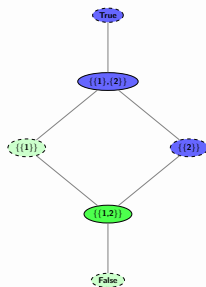
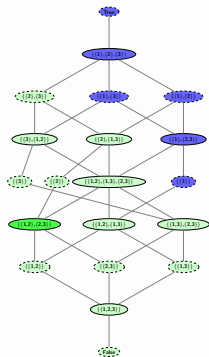
Dashed node - degenerate function



Experimental results

Deterministic setting

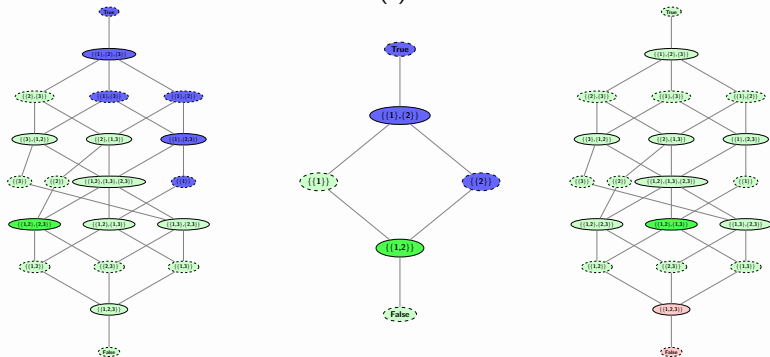
Q: How to choose the “correct” function(s)?



Experimental results

Deterministic setting

Q: How to choose the “correct” function(s)?

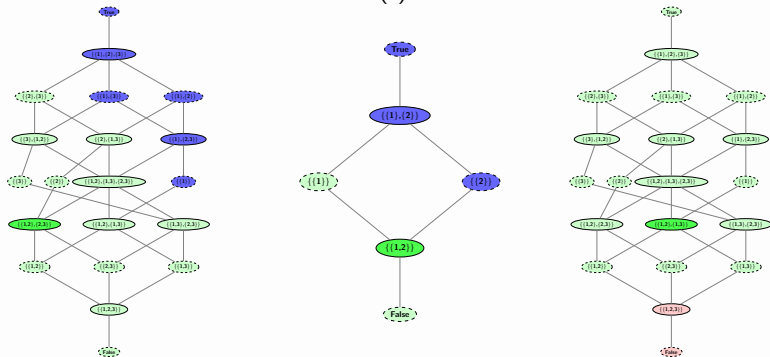


Given a **reference** function could we suggest alternative functions which are:

Experimental results

Deterministic setting

Q: How to choose the “correct” function(s)?



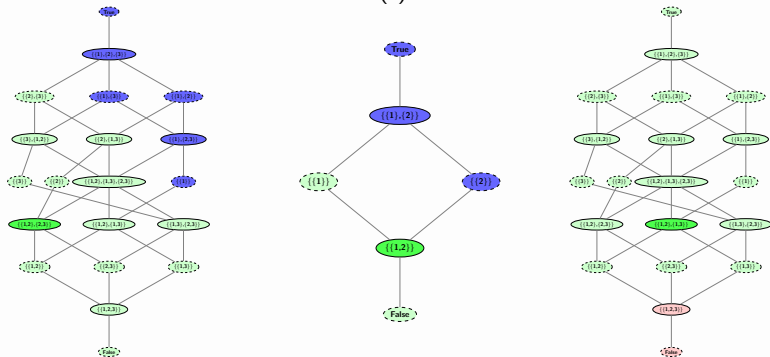
Given a **reference** function could we suggest alternative functions which are:

- at maximum distance d

Experimental results

Deterministic setting

Q: How to choose the “correct” function(s)?



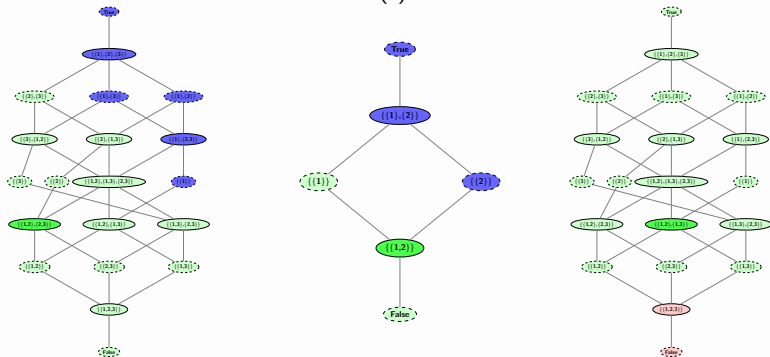
Given a **reference** function could we suggest alternative functions which are:

- at maximum distance d
- more general/specific functions

Experimental results

Deterministic setting

Q: How to choose the “correct” function(s)?



Given a **reference** function could we suggest alternative functions which are:

- at maximum distance d
- more general/specific functions
- add/remove degenerate functions
- ...

Experimental results

Non-deterministic setting - f_{GATA3}

At each time step, choose between:

- All (20) monotone functions for f_{GATA3} with equal probability (of 0.05)

Experimental results

Non-deterministic setting - f_{GATA3}

At each time step, choose between:

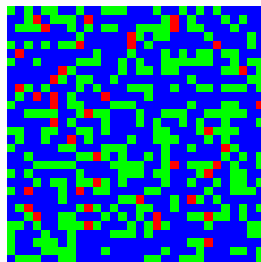
- All (20) monotone functions for f_{GATA3} with equal probability (of 0.05)

900 simulations:

Th0 - 41

Th1 - 305

Th2 - 554



Experimental results

Non-deterministic setting - f_{GATA3}

At each time step, choose between:

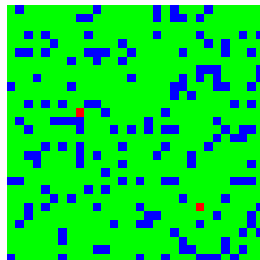
- 0.8 reference $f_{\text{GATA3}} =$
(!Tbet & GATA3) | (!Tbet & STAT6)
- 0.2 its neighbours

900 simulations:

Th0 - 2

Th1 - 744

Th2 - 154



Experimental results

Non-deterministic setting - f_{GATA3}

At each time step, choose between:

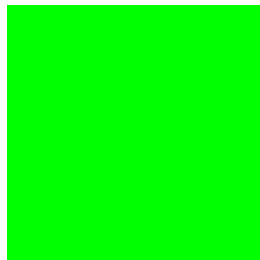
- 0.8 reference $f_{\text{GATA3}} =$
(!Tbet & GATA3) | (!Tbet & STAT6)
- 0.2 its **more specific** neighbours

900 simulations:

Th0 - 0

Th1 - 900

Th2 - 0



Questions for the working group

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Using the Boolean functions PO set:

- is the reference function **robust** to changes?
- should we define instead **classes of models** (sets of functions)?

Questions for the working group

Using the Boolean functions PO set:

- is the reference function **robust** to changes?
- should we define instead **classes of models** (sets of functions)?

Building Boolean models from regulatory maps, upon insufficient knowledge:

- should a **default function** be attributed?
if so, a more specific or more general one (lower or higher in the PO set)?
 - e.g. at least one activator and no inhibitor
 - e.g. canalizing functions
 - ...
- or should we consider (algorithmically support?) **incomplete models**?

Thank you!

Questions?!

Acknowledgements:

FCT

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Claudine Chaouiya

