Modelling of multi-cellular regulatory networks

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L3 SV Bioinformatique: Réseaux et régulation
COURSE 5

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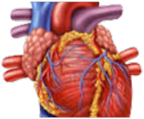
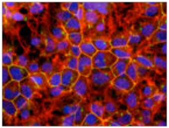
Contents

Motivation

From cellular networks to physiology

cells → tissues → organs → organism

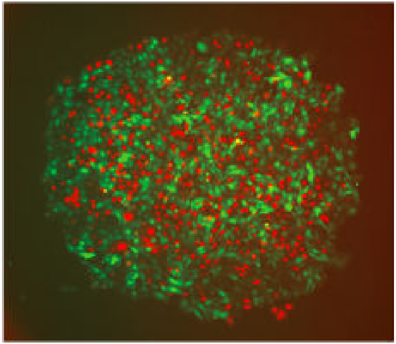


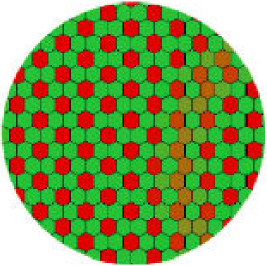


Patterns in nature... driven by cell-cell communication

Patterns in nature... driven by cell-cell communication
The case of salt-and-pepper pattern (red cells and green cells)

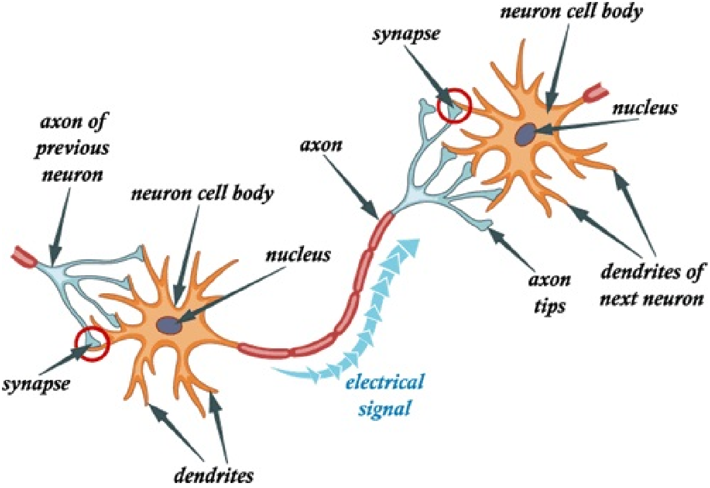
Cells engineered with a synthetic gene circuit *versus* Simulation





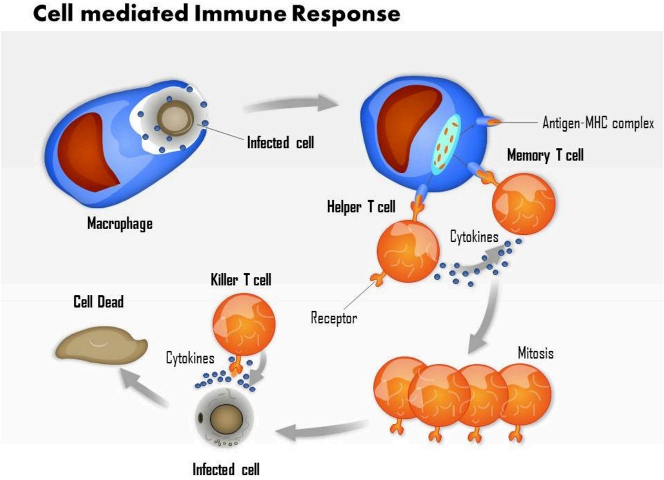
Matsuda M, et al. Nature Communications 6. 6195 (2015)

The case of neurons



biology.stackexchange.com/

The case of immune cells



https://www.slideteam.net

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Introduction to cellular automata

S. Wolfram Nature 311, 1984

Natural systems from snowflakes to mollusc shells show a great diversity of complex patterns. The origins of such complexity can be investigated through mathematical models termed 'cellular automata'.

Cellular automata [...] are analysed both as discrete dynamical systems, and as information-processing systems.

Use of Cellular Automata (CA) to model a wide range of physical & biological processes

Ideal to study / understand that "the whole is more than the parts"

$\rightarrow$ **emergent properties**

Cellular automata

A bit of history...

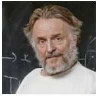
John von Neumann
1903-1957

Stanislaw Ulam
1909-1984

How to construct "self-replicating machines" $\rightarrow$ Define rules and states to prove universal constructibility

Cellular automata were born...

John Conway, 1937-



Aimed to identify properties of cellular automata, depending on their rules

- Ever growing patterns
- Stable patterns
- Oscillatory patterns
- Patterns that translate themselves across the grid
- Garden of Eden
- Etc.

Complexity arises from simple rules

Each cell lives in a square in a rectangular grid, it is either dead or alive. The game starts from an initial distribution of cells alive in a 2D grid and, at each time step, a cell fate depends on the state of its 8 closest neighbours (the grid utilises wrapping $\rightarrow$ a cell on the far left is a neighbour of a cell on the far right, the same principle applies at the top and bottom):

1. If a cell is alive, and 2 or 3 of it's neighbours are also alive, the cell remains alive.
2. If a cell is alive and it has more than 3 alive neighbours, it dies of overcrowding.
3. If a cell is alive and it has fewer than 2 alive neighbours, it dies of loneliness.
4. If a cell is dead and it has exactly 3 neighbours it becomes alive again.

Cellular automata

John Conway's game of life

No wrapping

00	01	02	03	04
10	11	12	13	14
20	21	22	23	24

Moore neighbouring

00	01	02	03	04
10	11	12	13	14
20	21	22	23	24

Generation 0
Living cells are in green

1	2	3	2	1
1	1	2	1	1
1	2	3	2	1

Generation 0
# of living neighbours

0	2	1	2	0
0	3	2	3	0
0	2	1	2	0

Generation 1

1	2	3	2	1
1	1	2	1	1
1	2	3	2	1

Generation 2

0	2	1	2	0
0	3	2	3	0
0	2	1	2	0

Generation 3

With wrapping

00	01	02	03	04
10	11	12	13	14
20	21	22	23	24

Moore neighbouring

1	2	3	2	1
1	1	2	1	1
1	2	3	2	1

Generation 0

0	2	2	2	0
0	3	2	3	0
0	2	2	2	0

Generation 2

Can you continue??

Rules of the game of life

- A dead cell surounded by 3 living cells becomes alive again
- A living cell surounded by 2 or 3 living cell remains alive
- In all other cases, the cell dies or remains dead

https://academo.org/demos/conways-game-of-life/

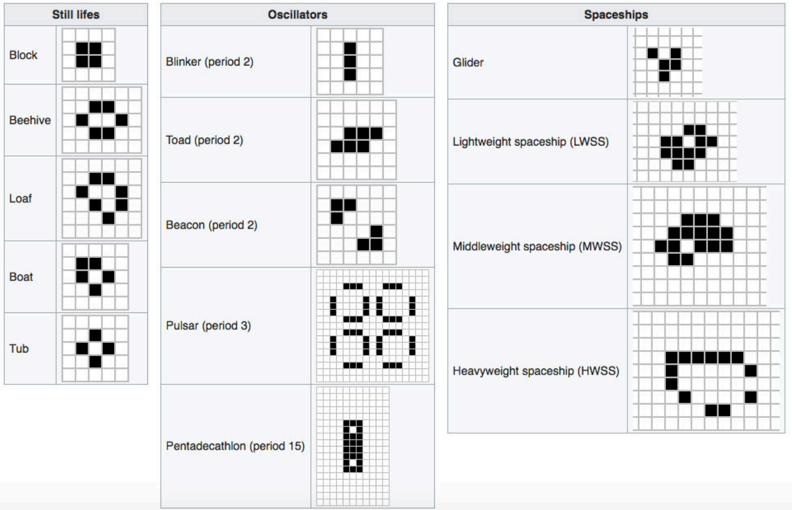
No apparent correspondence between the size of the initial pattern and the time needed to stabilize
Adding or removing one cell in the initial pattern may completely change the behaviour

Fundamental properties:

1. Parallelism: constituants evolve simultaneously and independently
2. Locality: next state of a cell only depends on its current state and states of its neighbours
3. Homogeneity: rules are universal, *i.e.* are the same for all the cells

Cellular automata

John Conway's game of life



https://en.wikipedia.org/wiki/Conway's_Game_of_Life

Formal definition

A cellular automata is defined by a tuple (L, S, N, f) where

1. L is a regular network (nodes are cells, all with the same degree)
2. S is a finite set of states
3. N is a finite set of neighbouring indices of size n
4. f is a transition function: $f : S^n \to S$

A configuration is a function associating a state to each cell: $C_i : L \to S^{|L|}$

The transition function defines the evolution of the configurations:

$$\forall c \in L, C_{i+1}(c) = f(\{C_i(\delta_i), \delta_i \in N(c)\})$$

where $N(c)$ is the set of neighbours of cell c

Wolfram's cellular automata

Simpler case of a line of cells

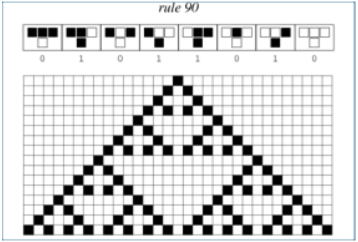
f transition function: $s_{t+1}(c) = f(s_t(\delta_1), \ldots s_t(\delta_n))$, δ_i are the n neighbours of c

There are $p^{(p^n)}$ such functions (with p the number of states)

S. Wolfram was the first to conduct a systematic study of CA

1D, $n = 3, p = 2 \rightarrow 2^{(2^3)} = 256$ different CA

2D, $n = 9, p = 2 \rightarrow 2^{(2^9)} = 2^{512} \sim 10^{154}$ different CA

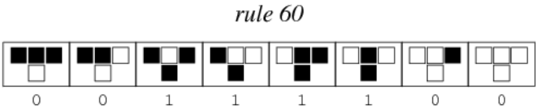


Elementary rules of Wolfram CA

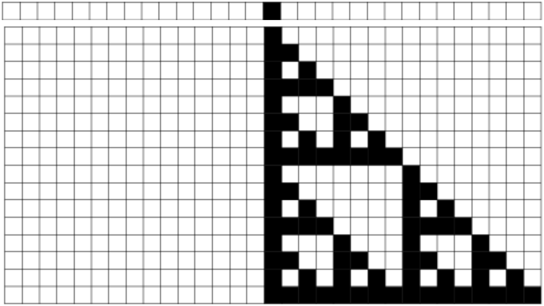
- The next colour of a cell depends on its colour and that of its immediate neighbours
- Rule outcomes are encoded in a binary representation e.g. $2 + 2^3 + 2^4 + 2^6 = 90$

Wolfram's cellular automata

Rule 60



Exercice: give the next 2 states for this initial configuration

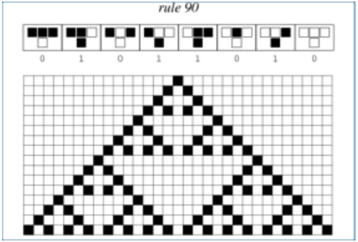


http://mathworld.wolfram.com/ElementaryCellularAutomaton.html

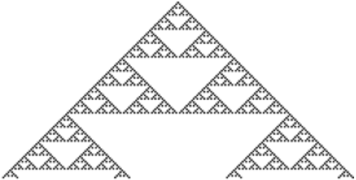
Rule 90, the Sierpinski Triangle

Each cell's next value (0/1) is the exclusive or of the values of its two neighbours

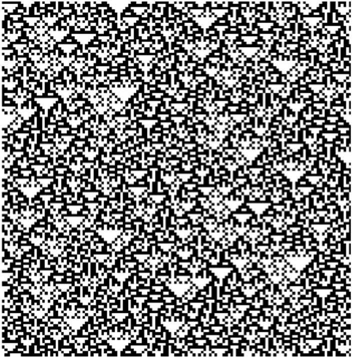
20 iterations, starting from a unique black cell



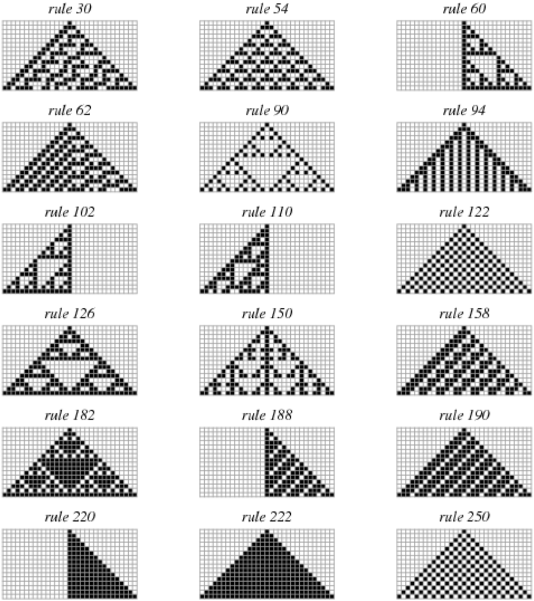
100 iterations, starting from a unique black cell



starting from a random distribution of black cells



Wolfram's cellular automata



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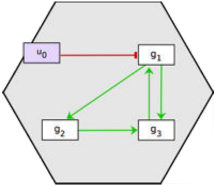
Cellular regulatory graph



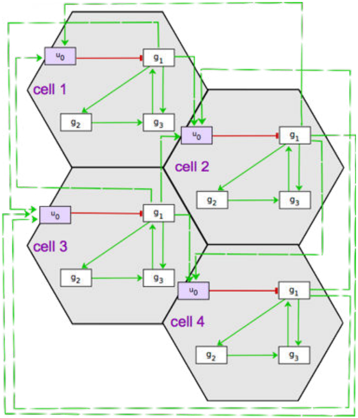
Logical functions:

$$\begin{cases} f_0(x) = & x_0 \\ f_1(x) = & !x_0 \& x_3 \\ f_2(x) = & x_1 \\ f_3(x) = & x_1 | x_2 \end{cases}$$

Truth table:

x	x_1	x_2	x_3
0000	0	0	0
0001	1	0	0
0010	0	0	1
0011	1	0	1
0100	0	1	1
0101	1	1	1
0110	0	1	1
0111	1	1	1
1000	0	0	0
1001	0	0	0
1010	0	0	1
1011	0	0	1
1100	0	1	1
1101	0	1	1
1110	0	1	1
1111	0	1	1

Composed regulatory graph



Cells 1 & 4 $\rightarrow$ 2 neighbours

Cells 2 & 3 $\rightarrow$ 3 neighbours

Integration function h_0

Logical rule defining the value of the input u_0 in a cell, depending on the signals emitted by components of neighbouring cells

OR

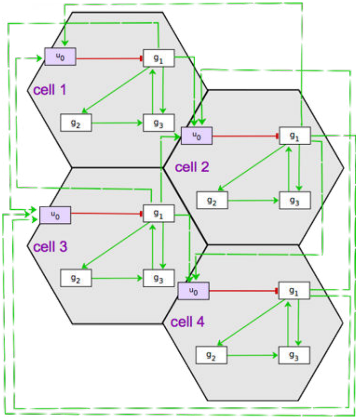
at-least-1 neighbour with $x_1 = 1$

$h_0^1(x) = x_1^2 \,|\, x_1^3$

6 stable states

x_1^1	x_2^1	x_3^1	x_1^2	x_2^2	x_3^2	x_1^3	x_2^3	x_3^3	x_1^4	x_2^4	x_3^4
0	0	0	0	0	0	0	0	0	0	0	0
1	1	1	0	0	0	0	0	0	0	0	0
0	0	0	1	1	1	0	0	0	0	0	0
0	0	0	0	0	0	1	1	1	0	0	0
0	0	0	0	0	0	0	0	0	1	1	1
1	1	1	0	0	0	0	0	0	1	1	1

Composed regulatory graph



Cells 1 & 4 $\rightarrow$ 2 neighbours

Cells 2 & 3 $\rightarrow$ 3 neighbours

Integration function h_0

Logical rule defining the value of the input u_0 in a cell, depending on the signals emitted by components of neighbouring cells

AND

at-least-v neighbours with $x_1 = 1$

$h_0^1(x) = x_1^2 \,\&\, x_1^3$

13 stable states

x_1^1	x_2^1	x_3^1	x_1^2	x_2^2	x_3^2	x_1^3	x_2^3	x_3^3	x_1^4	x_2^4	x_3^4
0	0	0	0	0	0	0	0	0	0	0	0
1	1	1	0	0	0	0	0	0	0	0	0
1	1	1	1	1	1	0	0	0	0	0	0
1	1	1	0	0	0	1	1	1	0	0	0
1	1	1	0	0	0	0	0	0	1	1	1
1	1	1	1	1	1	0	0	0	1	1	1
1	1	1	0	0	0	1	1	1	1	1	1
0	0	0	1	1	1	0	0	0	0	0	0
0	0	0	1	1	1	1	1	1	0	0	0
0	0	0	1	1	1	0	0	0	1	1	1
0	0	0	0	0	0	1	1	1	0	0	0
0	0	0	0	0	0	1	1	1	1	1	1
0	0	0	0	0	0	0	0	0	1	1	1

- What are the stable states / attractors?
- Given an initial state, what are the reachable attractors?
- What are the effects of perturbations (all cells, / clones)
- What are the effects of modifications in cell-cell communication *i.e.*
  - topology (number & shape of the cells, border conditions, etc.)
  - neighbouring relation and/or integration rule,

Challenges

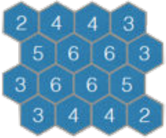
- Model definition: integration functions often unknown
- Model simulation: updating schemes at the cellular *versus* grid levels?
- Worsen combinatorial explosion of the number of states (configurations)

Composition of logical regulatory graphs

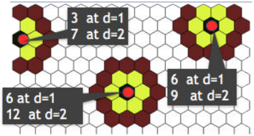
Grid configuration & sets of neighbours

Hexagonal grid

(no wrapping)

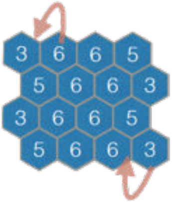


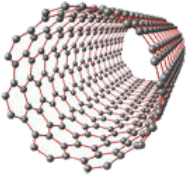
Various signalling distances



Cylinder

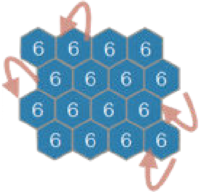
(vertical or horizontal wrapping)

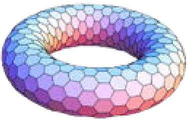




Torus

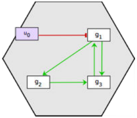
(vertical & horizontal wrapping)





Composition of n cellular models with p components $\rightarrow 2^{np}$ states

Rather than identifying the stable states of the composed model, compose the stable states $\rightarrow$ compatibility condition



Truth table:

x	x_1	x_2	x_3
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0111	1	1	1
1000	0	0	0
1001	0	0	0
1010	0	0	1
1011	0	0	1
1100	0	1	1
1101	0	1	1
1110	0	1	1
1111	0	1	1

Logical functions:

$$\begin{cases} f_1(x) = & !x_0 \& x_3 \\ f_2(x) = & x_1 \\ f_3(x) = & x_1 | x_2 \end{cases}$$

Integration function:

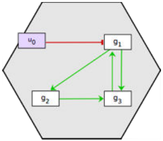
$$h_0^i(x) = x_1^{k1} \mid x_1^{k2} \mid \ldots, x_1^{k6}$$

at-least one neighbour with g_1 active

- (000) compatible with both input values
- (111) is compatible with the input value 0

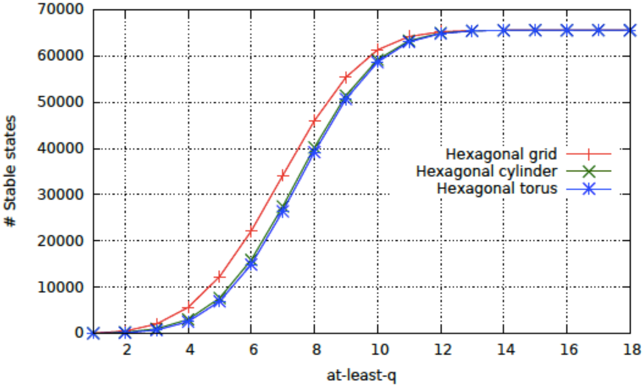
- if at-least-1 neighbour is in (111) then the cell is in (000)
- if all neighbours are in (000) then the cell is in (000) or (111)

P. Varela et al (2018) ENTCS



Hexagonal grid 4x4, distance 2

- if at-least **q** neighbours in (111) then the cell is (000)
- if not at-least **q** neighbours in (000) then the cell is (000) or (111)

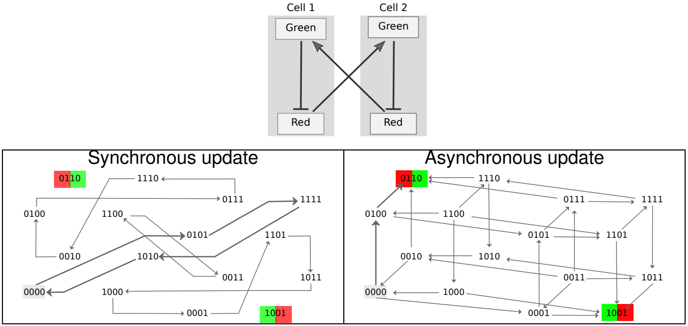


$\rightarrow$ too many to be listed explicitly!

P. Varela et al (2018) ENTCS

Composition of logical regulatory graphs

Lateral inhibition & updating schemes



Synchronous update may lead to spurious cyclical behaviours
$\rightarrow$ need to break the synchrony...

N. Fatès, *Asynchronous Cellular Automata*, Encyclopedia of Complexity and Systems Science, Springer 2018.

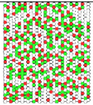
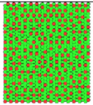
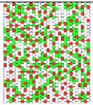
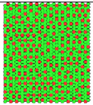
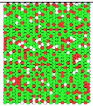
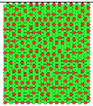
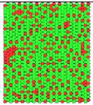
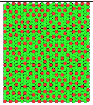
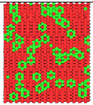
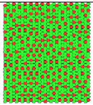
in Nature, there is no global clock to synchronise the transitions of the elements that compose a system

α-asynchronous updating scheme

At each iteration, each cell is updated with a probability α, and is left in the same state with probability 1-α.

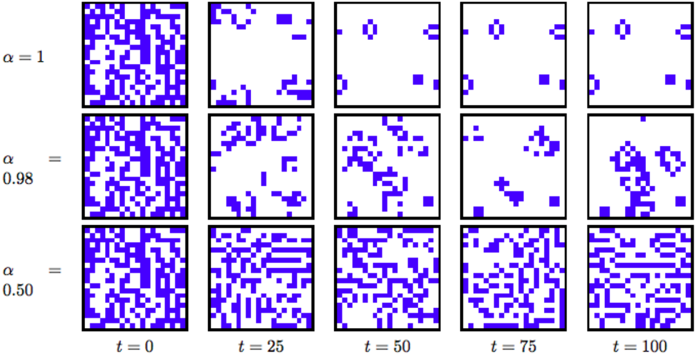
α is called the synchrony rate

How to define asynchronous updates and to assess the impact on the dynamics is challenging...

α	Steps	Transient grid	Steps	Final grid
0	400		900	
0.01	70		370	
0.5	4		12	
0.8	6		20	
0.99	11		132	

Configurations obtained with the α-asynchronous game of life

- $\alpha = 1$, synchronous updating $\rightarrow$ the system is stable at $t = 50$
- $\alpha = 0.98$ small asynchrony $\rightarrow$ the system is still evolving at t = 100
- $\alpha = 0.5$ $\rightarrow$ the qualitative behaviour of the system has changed



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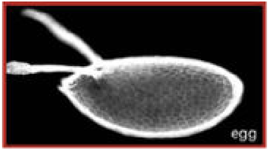
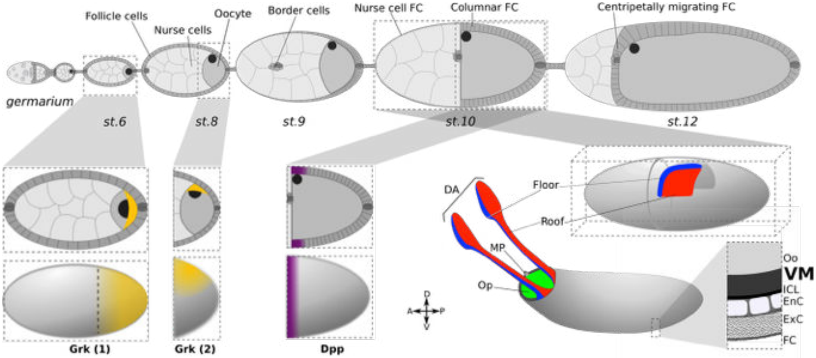


Gene expression patterns:

- Roof: **Broad**
- Floor: **Rhomboid**

Follicle cells receive two types of signals: **Grk** & **Dpp**



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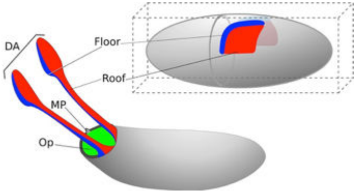
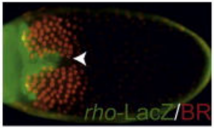
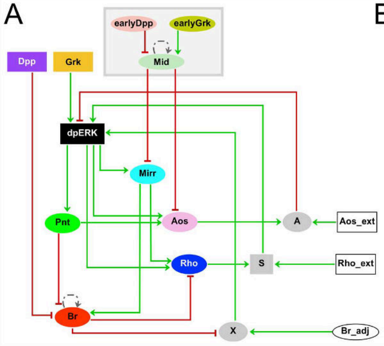




Logical model of the cellular network



B

Component	Level	Logical function
Mid	1	Mid | (earlyGrk & !earlyDpp)
A	1	Aos_ext:2 | (Aos & Aos_ext:1)
S	2	Rho:2 | Rho_ext:2
	1	(Rho:1 | Rho_ext:1) & !(Rho:2 | Rho_ext:2)
X	1	!Br & Br_adj
Aos	1	Pnt & dpERK & !Mid
Br	1	(Mirr | Br) & !Dpp & !Pnt
dpERK	2	[Grk:3] | [Grk:2 & ((S:2 & !A) | X)] | [Grk:1 & ((S:2 & !A) | (S & X))] | [!Grk & S:2 & (!A | X)]
	1	[Grk:2 & ((S:2 & A & !X) | (!S:2 & !X))] | [Grk:1 & ((S:2 & A & !X) | (S:1 & !X) | (!S & X))] | [!Grk & S:1 & (!A | X)]
Mirr	1	dpERK & !Mid
Pnt	1	dpERK:2
Rho	2	dpERK:2 & Mirr & !Br
	1	dpERK:1 & Mirr & !Br

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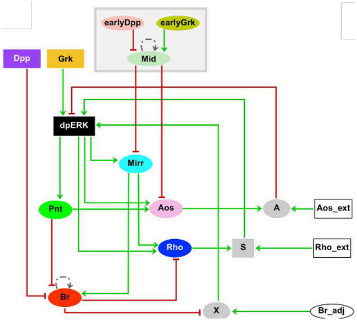
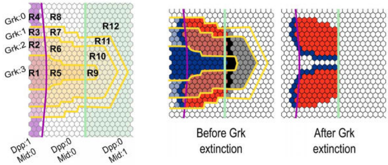
Cellular model

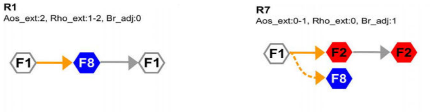


	dpERK	Mirr	Pnt	Rho	Aos	Br
F1	0	0	0	0	0	0
F2	0	0	0	0	0	1
F3	1	0	0	0	0	0
F4	1	0	0	0	0	1
F5	1	1	0	0	0	1
F6	1	1	0	1	0	0
F7	2	0	1	0	0	0
F8	2	1	1	2	1	0

Stable states



Regions & final patterns before & after Grk extinction



Reachability analysis

With a delay in Pnt activity, F8 is not reachable

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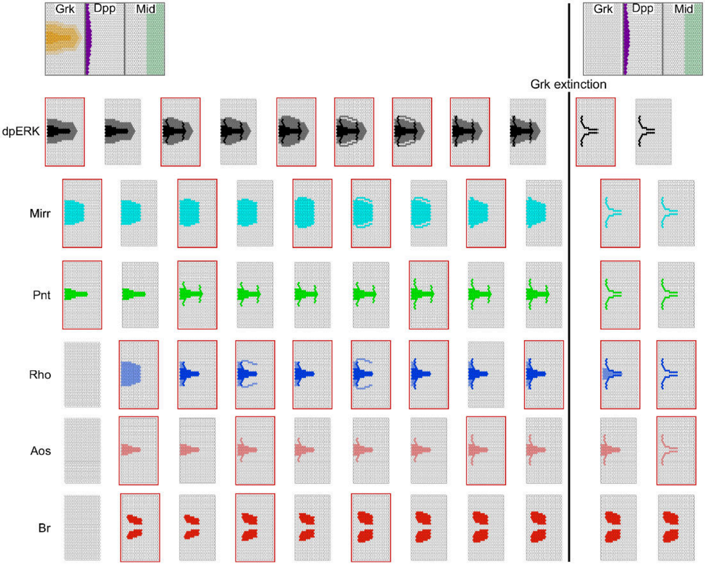
Multi-cellular model Follicular epithelium → grid of hexagonal cells



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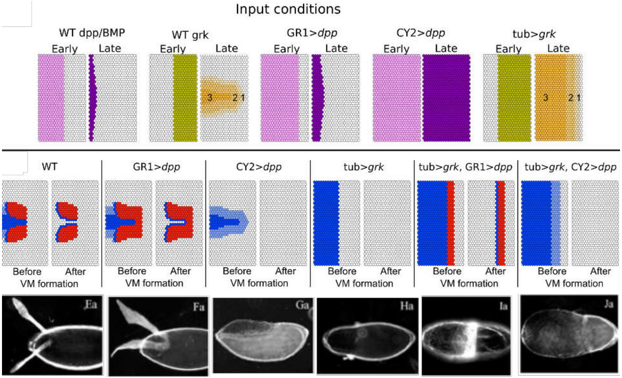
Multi-cellular model *in silico* assessment of mutant conditions (input conditions)



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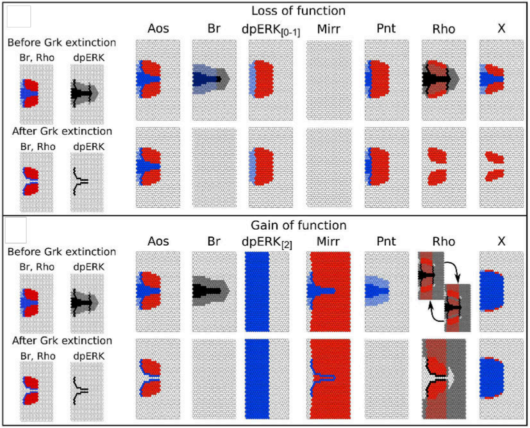
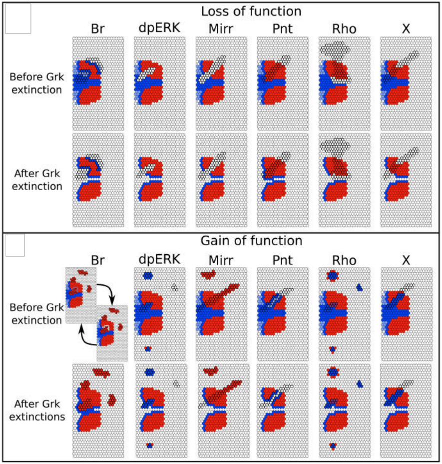
Multi-cellular model *in silico* assessment of mutant conditions (internal components)



A. Fauré et al. (2014) Plos Comp. Bio 10(3):e1003527

Multi-cellular model *in silico* assessment of mutant conditions (internal components, clonal analysis)

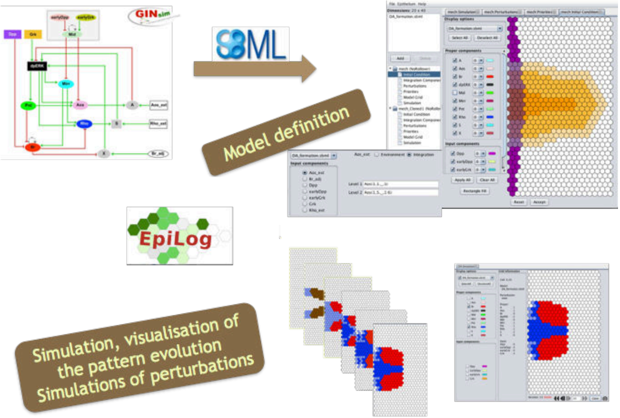


Contents

GINsim & EpiLog: from cellular to multi-cellular logical models

P. Varela et al. (2018) F1000Research, 7:1145

http://ginsim.org http://epilog-tool.org



- Define and analyse the cellular model with GINsim
- Integrate this model in an epithelium (i.e. an hexagonal grid of cells) with EpiLog
- Integration inputs $\rightarrow$ signals from neighbouring cells, Positional inputs $\rightarrow$ other environmental cues (constant)
- Simulate wild-type and perturbations

Contents

Further reading

- P. Varela *et al.* (2018) EpiLog: A software for the logical modelling of epithelial dynamics. F1000Research, 7:1145 https://doi.org/10.12688/f1000research.15613.1
- A. Fauré *et al* (2014) A Discrete Model of *Drosophila* Eggshell Patterning Reveals Cell-Autonomous and Juxtacrine Effects. *PLoS Computational Biology*, 10(3): e1003527. http://dx.doi.org/10.1371/journal.pcbi.1003527
- Nicolas Bredèche (2019) Automates Cellulaires 1D et 2D, support de cours http://pages.isir.upmc.fr/~bredeche/Teaching/2i013/2018-2019/cours_2i013_2019_CA1DCA2D.pdf
- Jean-Philippe Rennard (2000) Introduction aux Automates Cellulaires, support de cours http://www.rennard.org/alife/french/ac.pdf
- Nazim Fatès (2017) Asynchronous cellular automata https://hal.inria.fr/hal-01653675