# Revisiting and extending probabilistic Boolean networks

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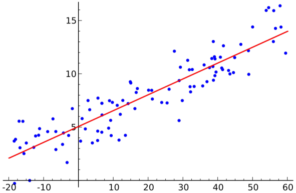
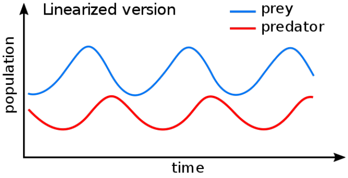
# Mathematical models

## Applied to many fields of science

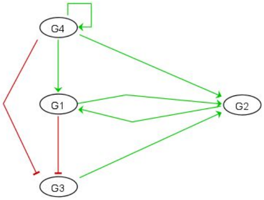
- Elaborated from ground data
- Used to reproduce, understand, and predict behaviors




*Linear regression.*




*Differential equations.*

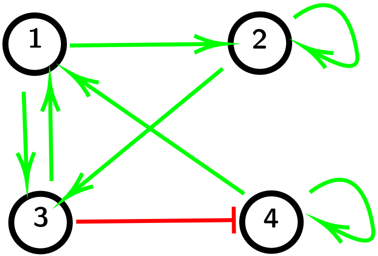



*Boolean networks.*

# Gene Regulatory Networks

## Interaction between genes

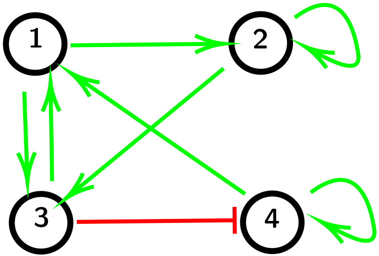
- Positive interactions
- Negative interactions



# Boolean Networks

## Transition functions

- One boolean function associated to each gene
- Computes the next state depending on the current one




$$f_1(x) = \begin{cases} 1 \text{ if } (x_3 = 1) \vee (x_4 = 1) \\ 0 \text{ otherwise} \end{cases}$$

$$f_2(x) = \begin{cases} 1 \text{ if } (x_1 = 1) \vee (x_2 = 1) \\ 0 \text{ otherwise} \end{cases}$$

$$f_3(x) = \begin{cases} 1 \text{ if } (x_1 = 1) \wedge (x_2 = 1) \\ 0 \text{ otherwise} \end{cases}$$

$$f_4(x) = \begin{cases} 1 \text{ if } (x_3 = 0) \wedge (x_4 = 1) \\ 0 \text{ otherwise} \end{cases}$$

# Boolean Networks

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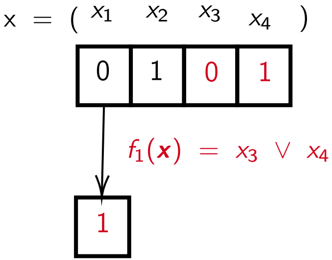


$$f_1(x) = \begin{cases} 1 \text{ if } (x_3 = 1) \lor (x_4 = 1) \\ 0 \text{ otherwise} \end{cases}$$

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# Boolean Networks

## Transition functions

- One associated to each gene
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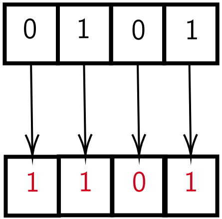
$$x = (\ x_1 \quad x_2 \quad x_3 \quad x_4\ )$$




$$f(x) = (\ f_1(x) \quad f_2(x) \quad f_3(x) \quad f_4(x)\ )$$

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# Boolean Networks

## State transitions

$$
\begin{aligned}
0000 &\longrightarrow 0000\\
0001 &\longrightarrow 1001\\
0010 &\longrightarrow 1000\\
0011 &\longrightarrow 1000\\
0100 &\longrightarrow 0100\\
0101 &\longrightarrow 1101\\
0110 &\longrightarrow 1100\\
0111 &\longrightarrow 1100\\
1000 &\longrightarrow 0100\\
1001 &\longrightarrow 1101\\
1010 &\longrightarrow 1100\\
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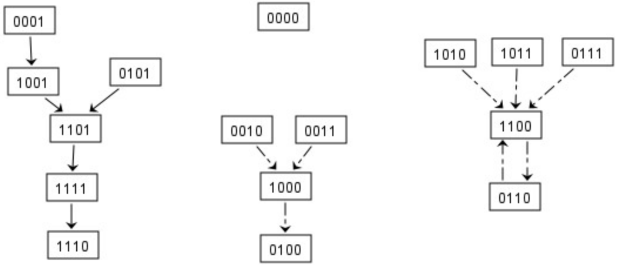
1111 &\longrightarrow 1110
\end{aligned}
$$

## State Transition Graph (STG)



# Boolean Networks

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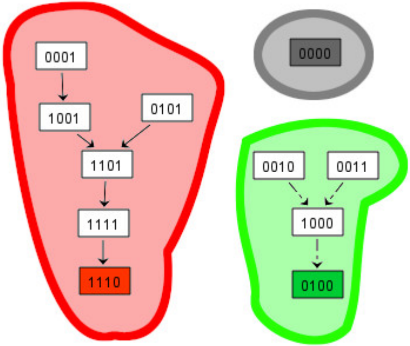
$$

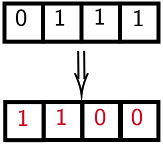
## State Transition Graph (STG) with attractors



# Boolean Networks : update mode

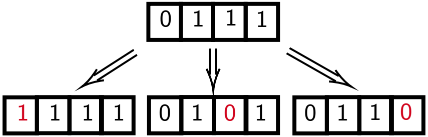
## Synchronous

Updates all the genes simultaneously




## Asynchronous

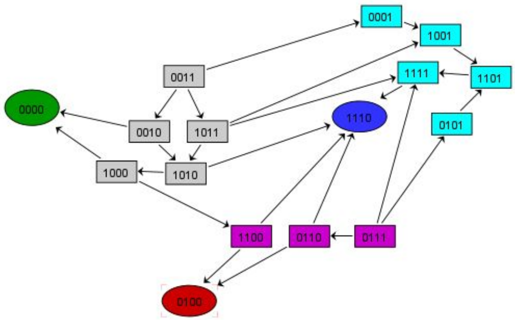
Updates one randomly-chosen gene at a time




$\rightarrow$ Also modifies the attractors.

# Boolean Networks : update mode

## Example : STG for asynchronous update




- Attracted by the blue attractor
- Attracted by the blue and red attractors
- Attracted by all three attractors

# Software tools

## Analyze a Boolean network with GINSIM

- Takes a set of transition functions as an input
- Computes the state transition graph
- Identifies attractor states and their basins of attraction

## Complexity

- With $n$ genes, the STG contains $2^n$ states...

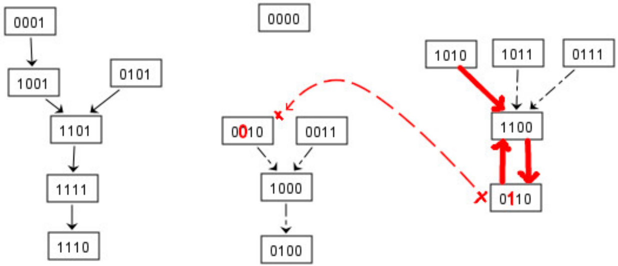
## Reduction model

- Methods to approximate the attractors without combinatorial explosion

# Extensions I

## Perturbations

- Each iteration, a random gene is flipped with probability $p \ll 1$
- Emanates from biological noise

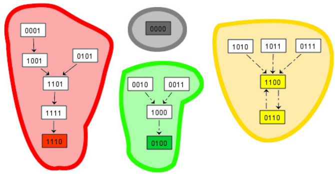



In this example, the gene n°2 is **flipped** from a '1' to a '0', and the current state moves to another attractor.

# Extensions II

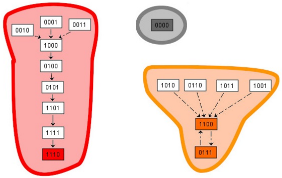
## Probabilistic Boolean Networks (PBNs)

- Each iteration, the transition functions are re-drawn from a set with probability $q \ll 1$
- It can alter the 'attractor landscape' of the state space.




$f_4(x) = \neg x_3 \wedge x_4$

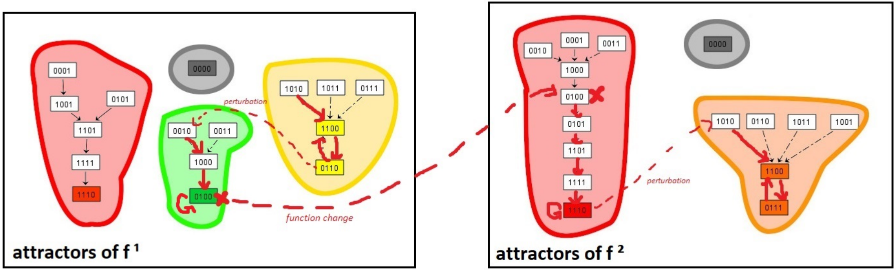
$\Longrightarrow$




$f_4(x) = \neg x_3 \wedge x_2$

# Extensions

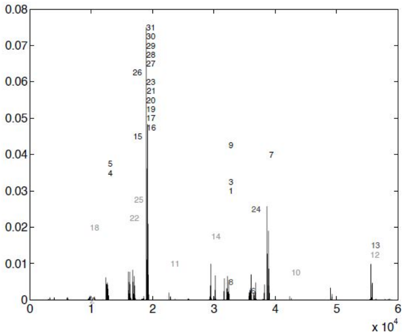
## Example of a PBN evolution



# Software tools

## Sample the stationary law

- Simulating the model a large number of times
- Identify the recurrent states (=attractors)




*Example with $n = 10$ [Kim et al., 2003].*

# Future extensions - My internship

## Asynchronous PBNs

- Extend the formalism
- Study dynamical properties
- Adapt the algorithms

# Thank you for your attention.

Selected sources :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- W. Abou-Jaoudé, P. Traynard, P.T. Monteiro, J. Saez-Rodriguez, T. Helikar, D. Thieffry, and C. Chaouiya. Logical Modeling and Dynamical Analysis of Cellular Networks. Frontiers in Genetics, 7(94), 2016. doi :10.3389/fgene.2016.00094.
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