Tutorial T04

LOGICAL MODELLING OF REGULATORY NETWORKS

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INSTITUTO GULBENKIAN DE CIÊNCIA

Network Modelling

OUTLINE & SCHEDULE

- 13:45-14:15 **Introduction to the logical modelling framework**
- 14:15-14:45 Software tools, and overview, SBML & CoLoMoTo
- 14:45-15:15 Logical models of T helper cells activation and differentiation
- 15:15-15:30 The Cell Collective (http://www.thecellcollective.org/), Short demo
- 15:30-16:00 **Coffee Break**
- 16:00-16:50 SQUAD, BoolSim (http://www.vital-it.ch/software/genYsis/), Demo & hands on
- 16:50-17:40 GINsim (http://www.ginsim.org/), Model checking - Demo & hands on

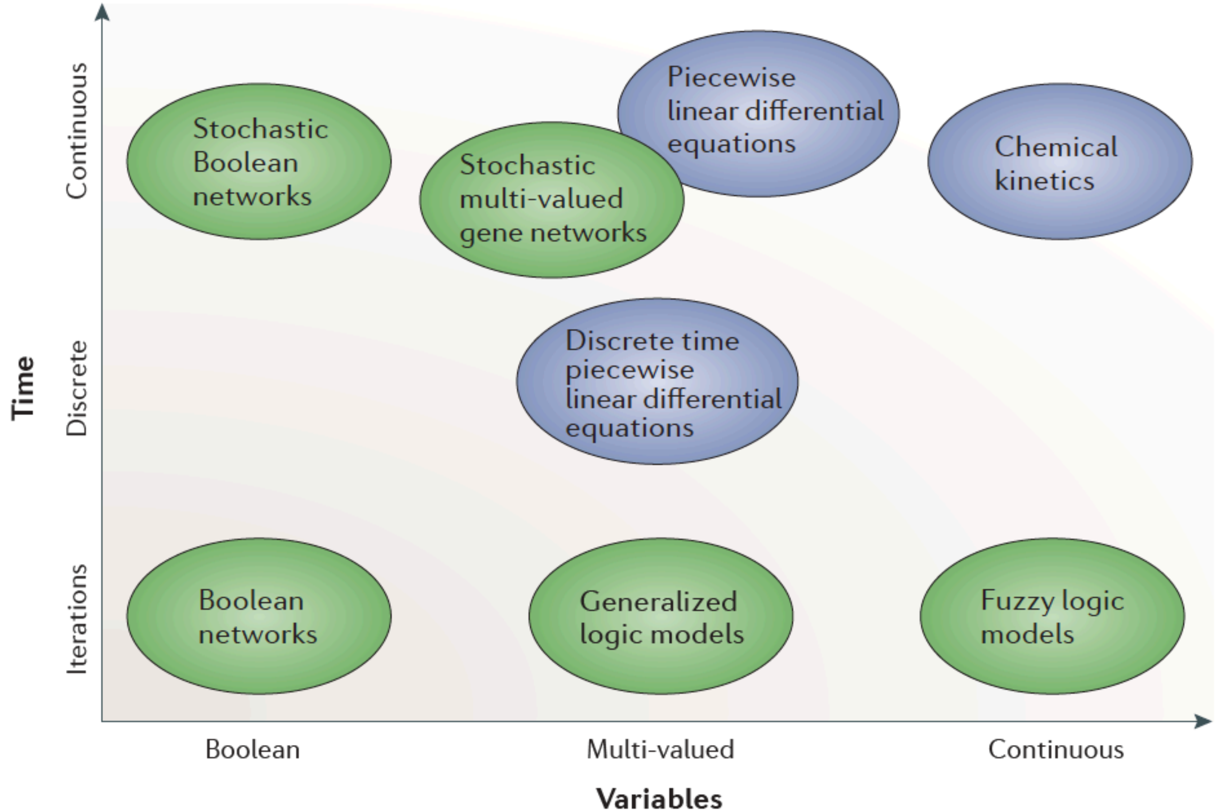
The logical modelling framework

Essentially, all models are wrong, but some are useful

(George Box, 1987)

A variety of modelling formalisms for molecular and genetic networks

Logical networks
Bayesian networks
Petri nets
Process algebras
Constraint-based models
Differential equations
Rule-based models
Cellular automata
Agent-based models
and others…

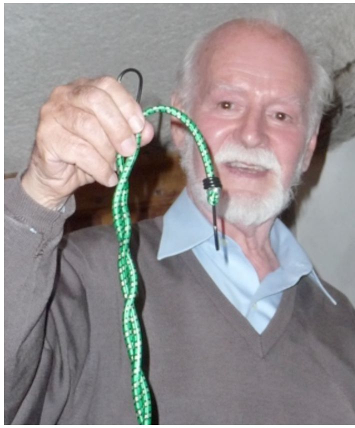


N Le Novère, Nat Rev Genet 2015, doi:10.1038/nrg3885

The logical modelling framework

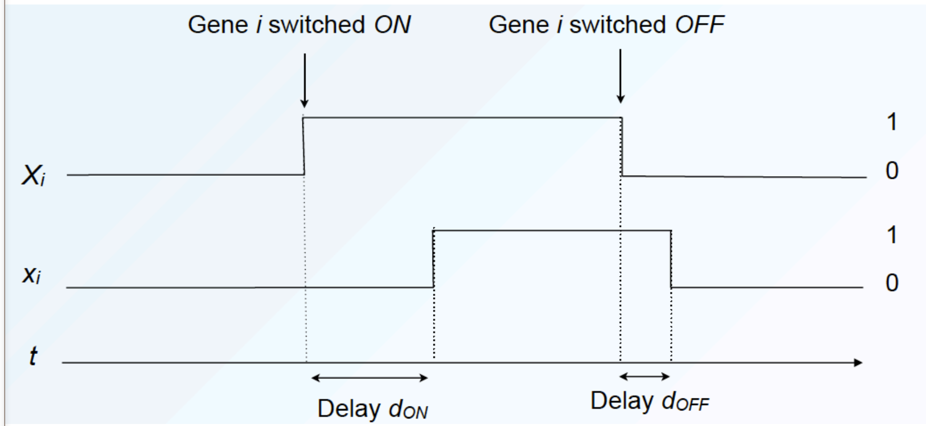
Boolean networks
S. Kauffman (1969)

Kinetic logic
R. Thomas (1973)



- Random connections, nodes with predefined in-degrees
- Deterministic behaviour (exactly one successor state) defined by a Boolean function (randomly assigned) $x_{t+1}=B(x_t)$
- Focus on asymptotic behaviours

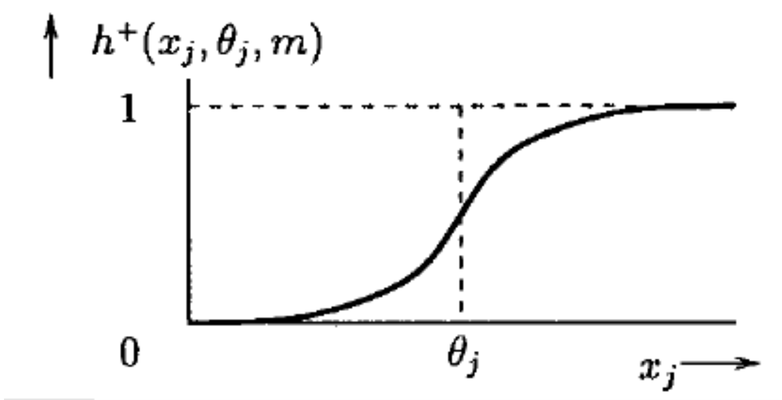
- $X=B(x)$
- X_i specifies whether gene *i* is currently transcribed
- x_i is the current level of the functional product of gene *i*

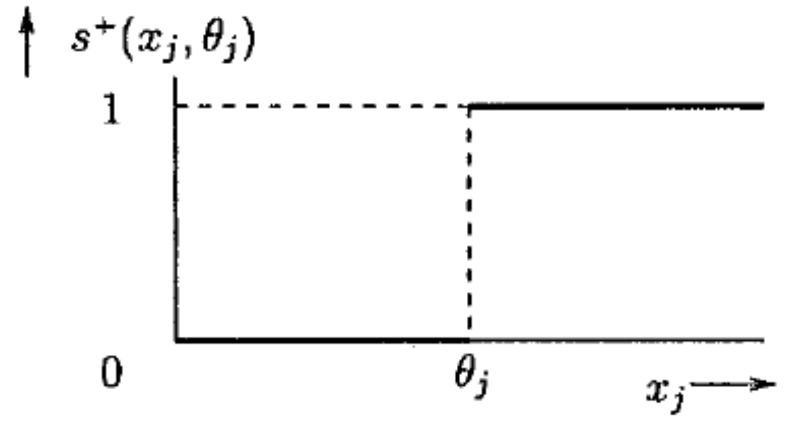


The logical modelling framework

Motivation

- Lack of precise quantitative data (concentrations, kinetic parameters…)
- Threshold effects in regulation, bi-stable behaviours



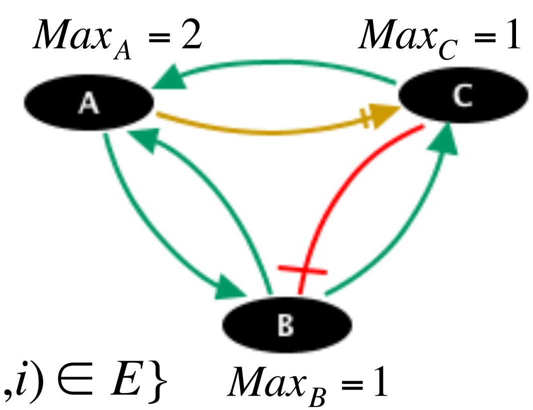


Boolean abstraction: each regulatory component is associated to a Boolean variable representing its functional levels of activity, of concentration, etc...

→ extension to multi-valued variables

The logical modelling framework

Model definition



Logical Regulatory Graph (LRG) (G,E,K)

Nodes regulatory components with discrete (activity) levels (Boolean or multi-valued) $i \in G, x_i \in \{0,\ldots,Max_i\}$

Edges regulatory interactions $E \subseteq G \times G,$

$$i \in G,\ Reg(i) = \{j \in G, (j,i) \in E\}$$

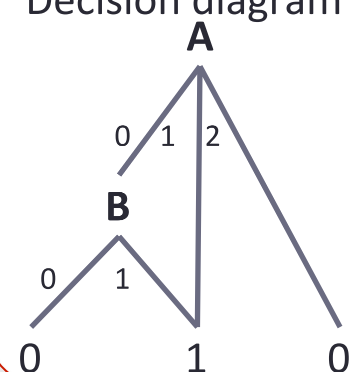
Logical rules governing the dynamics $K_i : \prod_{j \in Reg(i)} x_j \mapsto \{0,\ldots,Max_i\}$

$$K_C(x_A, x_B) = \begin{cases} 1 & if\ (x_A = 1)\ OR\ (x_A = 0\ AND\ x_B = 1) \\ 0 & otherwise \end{cases}$$

Truth table

A	B	C
0	0	0
0	1	1
1	0	1
1	1	1
2	0	0
2	1	0

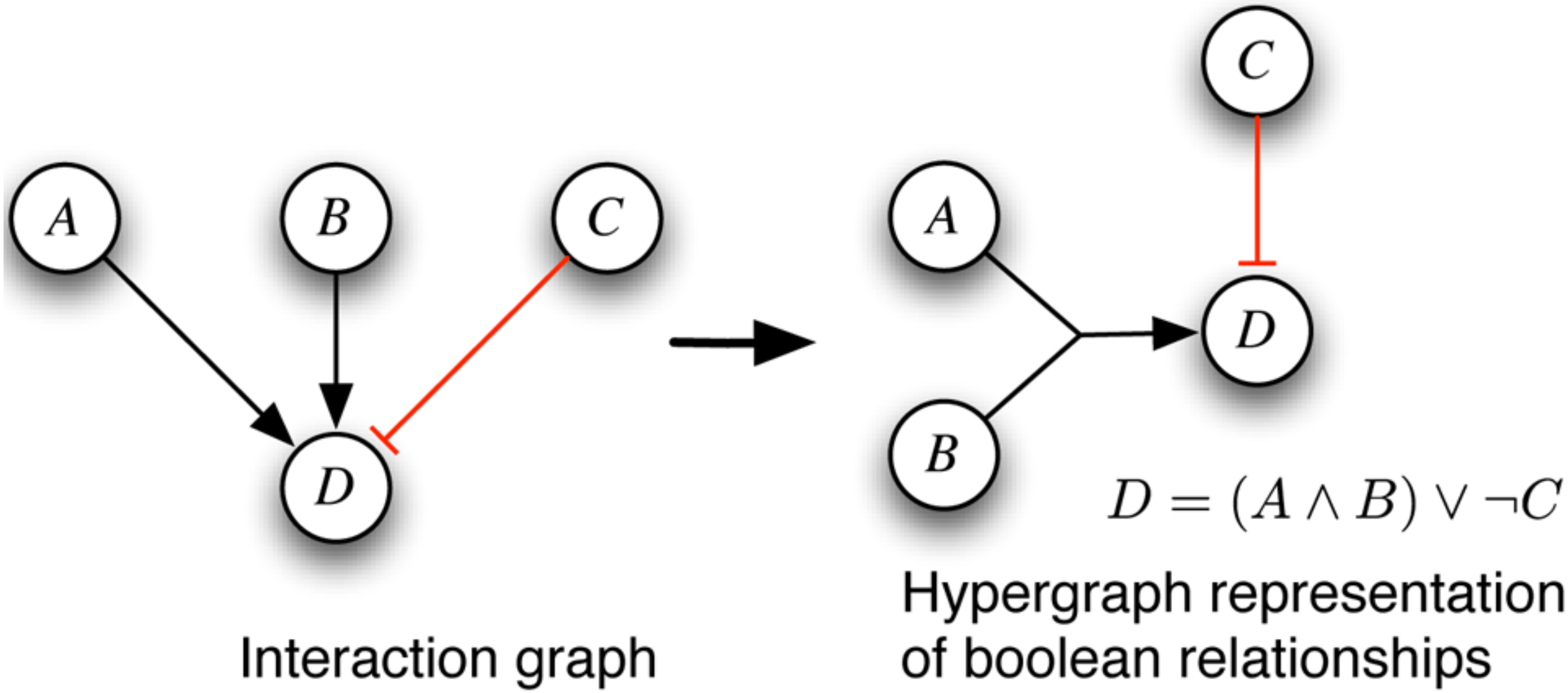
Decision diagram



The logical modelling framework

Alternate Boolean model definition

AND NOT networks encode logical rules



Klamt S, Haus U-U, Theis F (2009) PLoS Comput Biol 5(5): e1000385

(Standard) Logical rules

A node is ON in the presence of at least one of its activators and none of its inhibitors

$$x_i(t+1) = \left(x_1^a(t) \vee x_2^a(t) \ldots \vee x_n^a(t) \right) \wedge \neg\left(x_1^i(t) \vee x_2^i(t) \ldots \vee x_m^i(t)\right)$$

$\vee, \wedge,$ and $\neg$ are the logical operators OR, AND, and NOT

$x_i \in \{0,1\}$

$\{x_n^a\}$ is the set of activators of x_i

$\{x_m^i\}$ is the set of inhibitors of x_i

Mendoza L. and Xenarios I. (2006) *Theoretical Biology and Medical Modelling*, 3:13
doi:10.1186/1742-4682-3-13

(Standard) Logical rules

Canalysing functions

a single regulator being in a fixed state is sufficient to force the target to a fixed state, regardless of the state of any other regulator

AND is canalysing, but XOR is not

(Standard) Logical rules

Majority rule (threshold Boolean networks)

Sign of the interaction (i,j)

$$S_i(t+1) = 1 \quad \text{if} \quad \sum_{j=1}^{N} J_{ij} S_j(t) + h > 0,$$

Threshold (in most cases h=0)

$$S_i(t+1) = 0 \quad \text{if} \quad \sum_{j=1}^{N} J_{ij} S_j(t) + h \leq 0,$$

Bornholdt, S. (2008) *Journal of the Royal Society Interface*, *5*(Suppl 1), S85–S94

$$S_i(t+1) = \begin{cases} 0, & \sum_j a_{ij} S_j(t) > \theta_i \\ 1, & \sum_j a_{ij} S_j(t) < \theta_i \\ S_i(t), & \sum_j a_{ij} S_j(t) = \theta_i \end{cases}$$

McCulloch-Pitts neural model)

Davidich MI, Bornholdt S (2008) PLoS One 3: e1672

(Standard) Logical rules

Any rule such as the interactions are functional (or have the prescribed sign)

Definition 1. *Let consider an interaction* (i,j)*, member of a circuit* $\mathcal{C}$ *with a threshold* $\theta_{i,j}$*. Let* (j,k) *be the next interaction in* $\mathcal{C}$*, with a threshold* $\theta_{j,k}$*. The interaction* (i,j) *is said to be functional in* $\mathcal{C}$ *if and only if there exists a variable assignment for all regulators of* g_j *except* g_i *such that:*

$$\mathcal{K}_j(x_1,\ldots,x_{i-1},\theta_{i,j}-1,\ldots,x_n) < \theta_{j,k} \leq \mathcal{K}_j(x_1,\ldots,x_{i-1},\theta_{i,j},\ldots,x_n), \quad (1)$$

$$\text{or} \quad \mathcal{K}_j(x_1,\ldots,x_{i-1},\theta_{i,j},\ldots,x_n) < \theta_{j,k} \leq \mathcal{K}_j(x_1,\ldots,x_{i-1},\theta_{i,j}-1,\ldots,x_n). \quad (2)$$

A	B	C
0	0	1
0	1	1
1	0	0
1	1	0

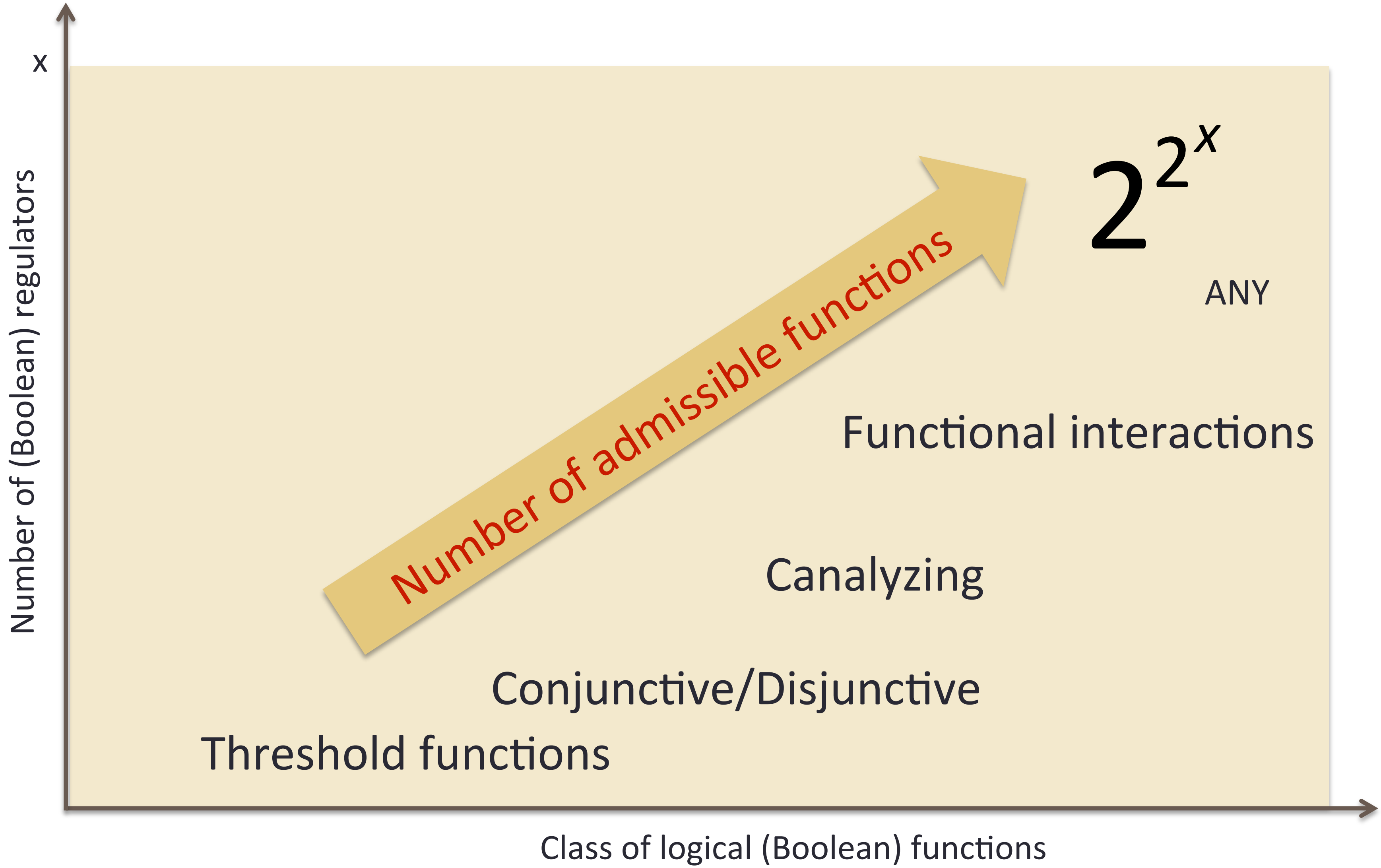
The sign (+,-,±) of the interaction derives from the rule

(A,C) is functional, negative
(B,C) is not functional

A. Naldi *et al.* (2007) LNCS/LNBI 4695:233-247

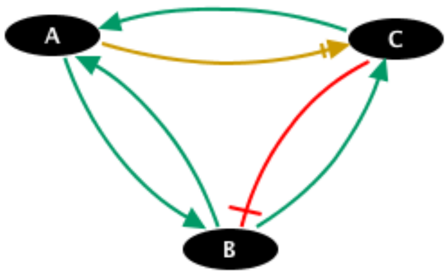
Defining large regulatory models

Logical functions



The logical modelling framework

Model dynamics



State Transition Graph (S,T)

Nodes: states $S = \prod_{i \in G} \{0,\ldots,Max_i\}$

Edges: transitions $T \subseteq S^2$ define successor state(s)

$x_0, x_1 \ldots x_j \ldots, x_n$

$\downarrow$

?

if $K_j(x) \neq x_j$, component g_j receives a **call to update its level**

if $K_j(x) > x_j$ then g_j is called to **increase**

if $K_j(x) < x_j$ then g_j is called to **decrease**

The logical modelling framework

State Transition Graph (S,T)

Nodes: states $S = \prod_{i \in G} \{0,\ldots,Max_i\}$

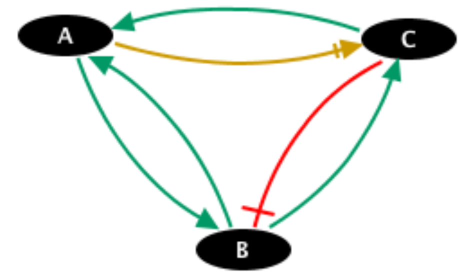
Edges: transitions $T \subseteq S^2$

$$K_A : \begin{cases} 1 \ \mathit{if}\ (B \vee C) \wedge \overline{(B \wedge C)} \\ 2 \ \mathit{if}\ B \wedge C \end{cases}$$

$$K_B : 1 \ \mathit{if}\ A \wedge \bar{C}$$

$$K_C : \overline{(A^2)} \wedge (A^1 \vee B)$$

Model dynamics

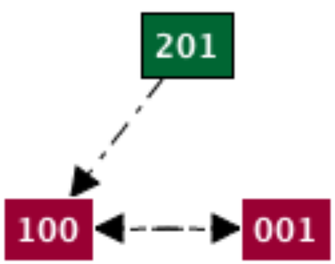


State 201: **A** *should decrease as well as* **C**

Synchronous

all updates performed

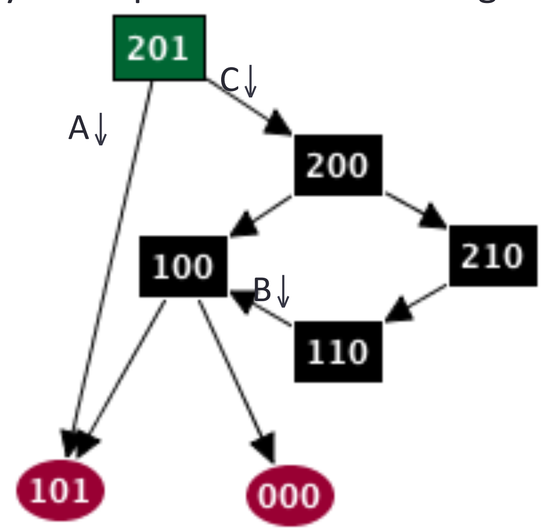
simultaneously



Asynchronous

a unique update performed at each step

lack of delay $\Rightarrow$ all possible transitions generated



The logical modelling framework

State Transition Graph (S,T)

Nodes: states $S = \prod_{i \in G} \{0,\ldots,Max_i\}$

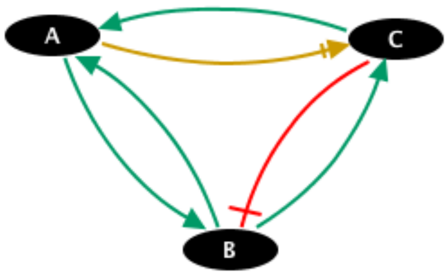
Edges: transitions $T \subseteq S^2$

$$K_A : \begin{cases} 1 \; if \; (B \vee C) \wedge \overline{(B \wedge C)} \\ 2 \; if \; B \wedge C \end{cases}$$

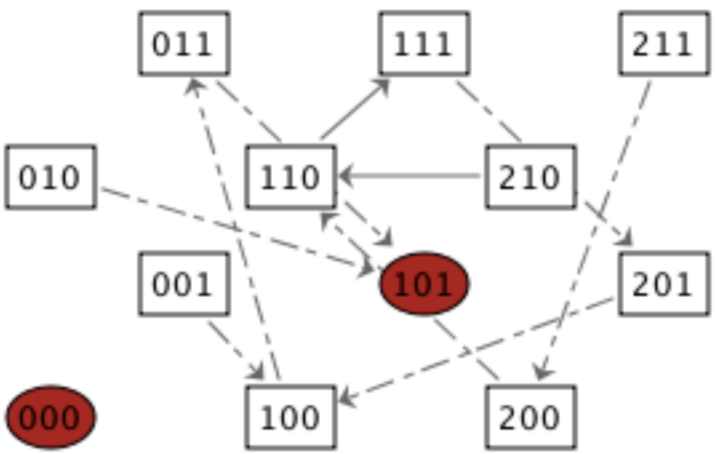
$$K_B : 1 \; if \; A \wedge \bar{C}$$

$$K_C : \overline{(A^2)} \wedge (A^1 \vee B)$$

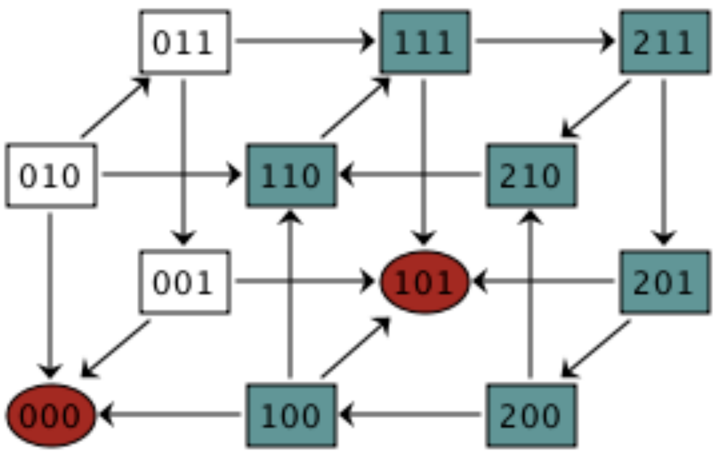
Model dynamics



Synchronous



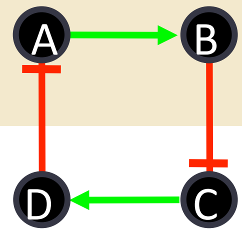
Asynchronous



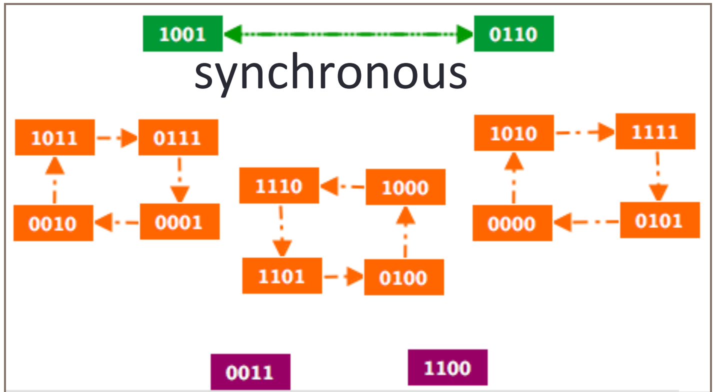
Updating schemes

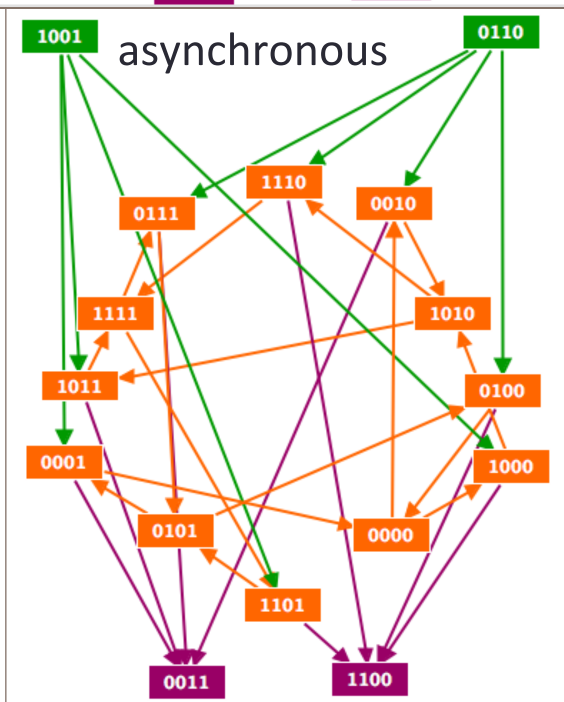
- **Synchronous**
- Block sequential (blocks of components sequentially updated, components being synchronously updated within the blocks)
- **Asynchronous**
- Random asynchronous
- Full asynchronous
- Priority classes
- …

Updating schemes



Priority classes

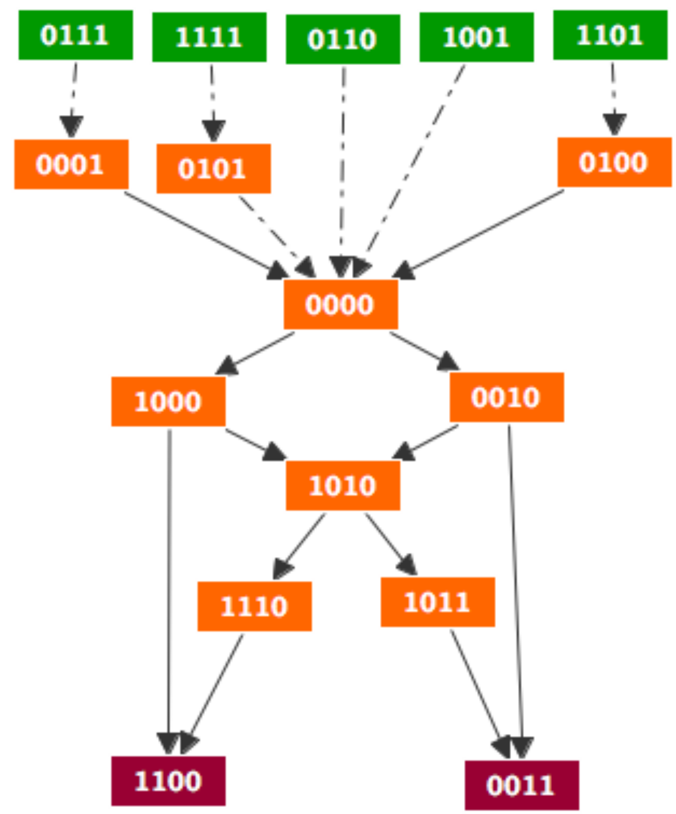




Priority classes (example)

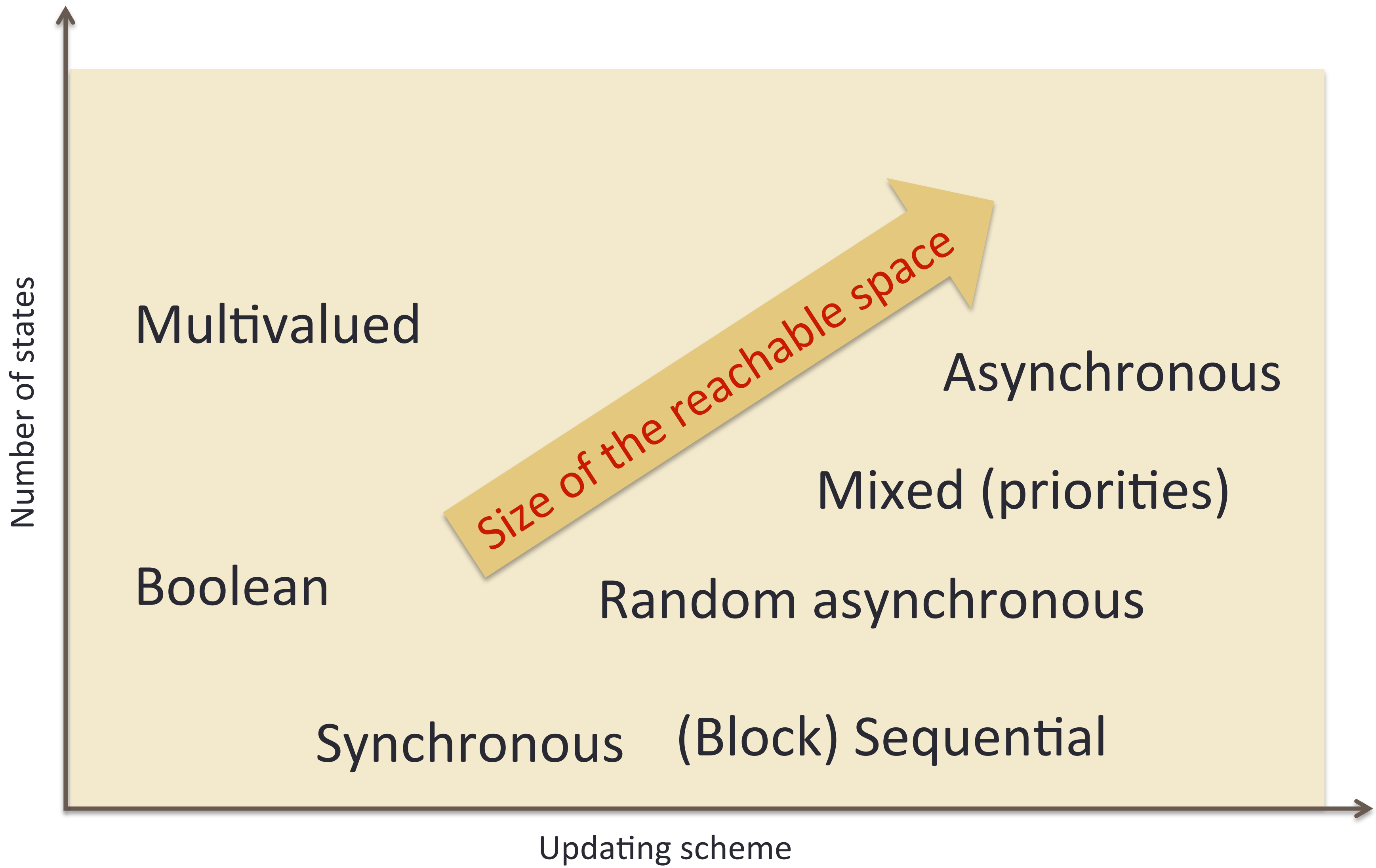
Decreases→ **high** priority, <u>synchronous</u>

Increases → **low** priority, <u>asynchronous</u>



Fauré A, Naldi A, Chaouiya C, Thieffry D (2006) Bioinformatics **22**(14):124-31.

Constructing the dynamics of large networks



Properties of interest

- Long term behaviours (attractors)
  - Terminal Strongly Connected Components (SCCs) in the STG i.e. a set A of states

    $\forall$ s,s' in A are mutually reachable

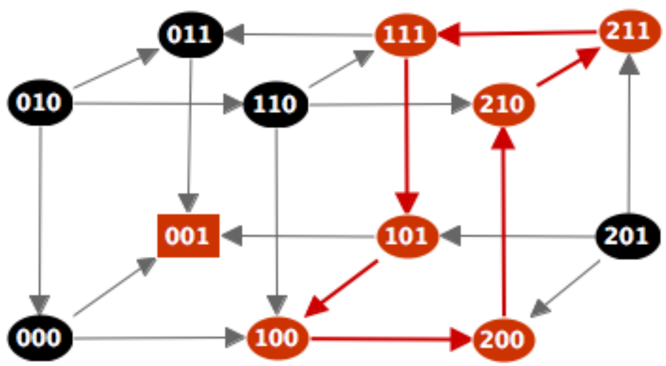
    no transition leaves A
  - Stable states (or steady states): SCC reduced to one state i.e. a state with no successor
  - Elementary cycles: each state has a unique successor
  - Complex attractors
- Reachability: is there a path (a series of transitions) leading from a given state to another)
- Properties along trajectories
- Impact of perturbations (input variations, mutants, etc)

Properties of interest

In a synchronous dynamics

- Attractors are either stable states or elementary cycles
- From any state, a unique attractor is reachable

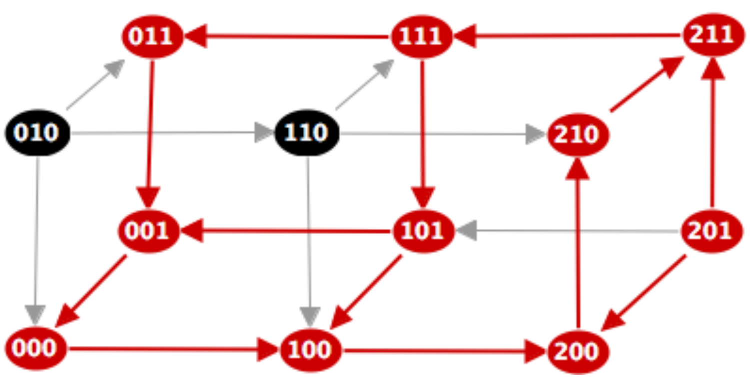
In an asynchronous dynamics, the situation is more complex (non-deterministic)



Two attractors

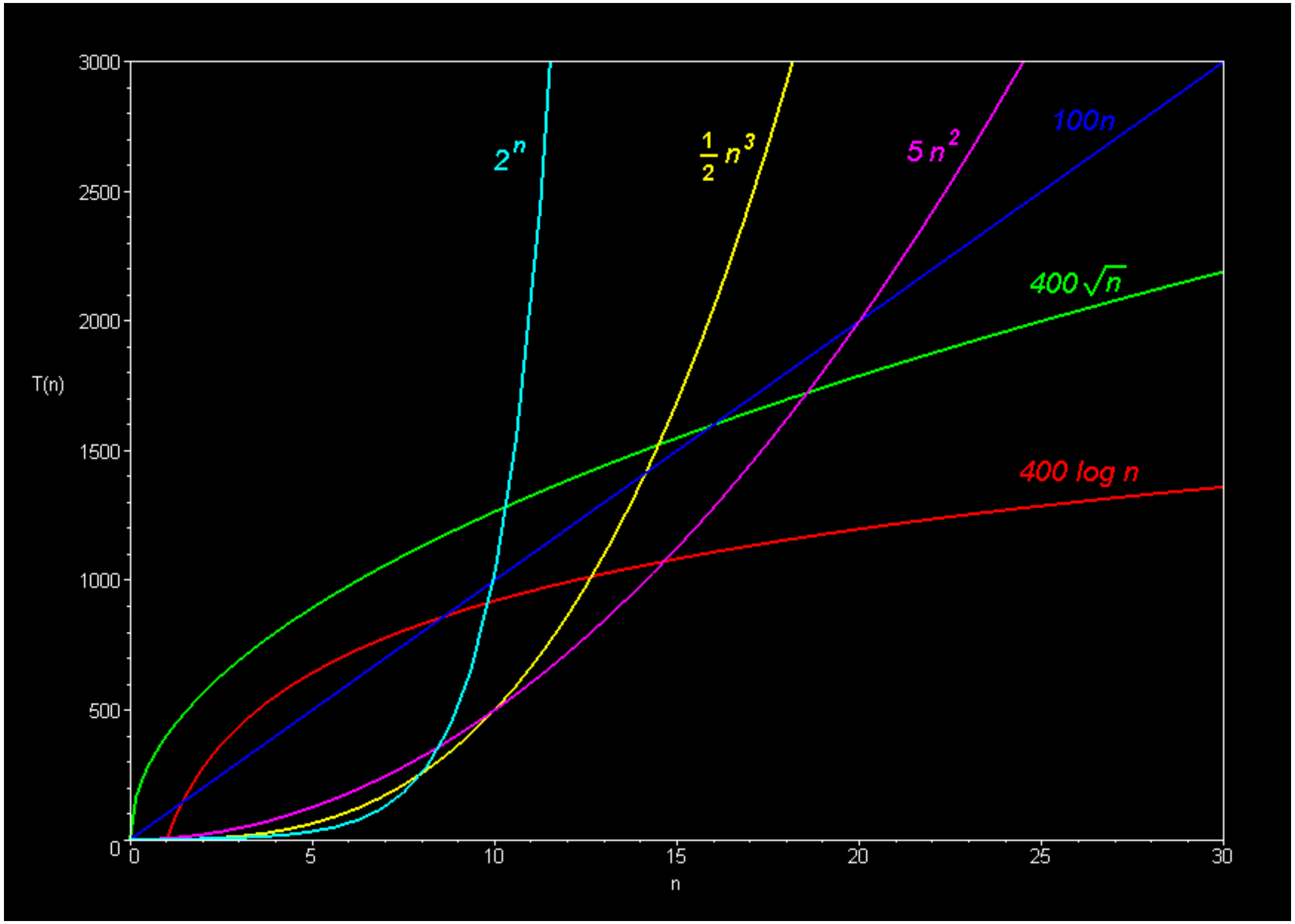
- One stable state (001)
- One elementary, terminal cycle
- The sole cyclical attractor is reachable from 201
- Both attractors are reachable from 010

A unique, complex attractor



Analysing the dynamics of large models

Combinatorial explosion of the number of states with the number of components

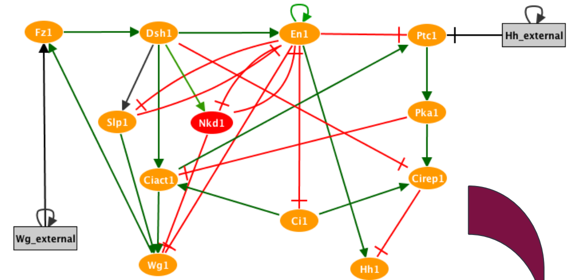


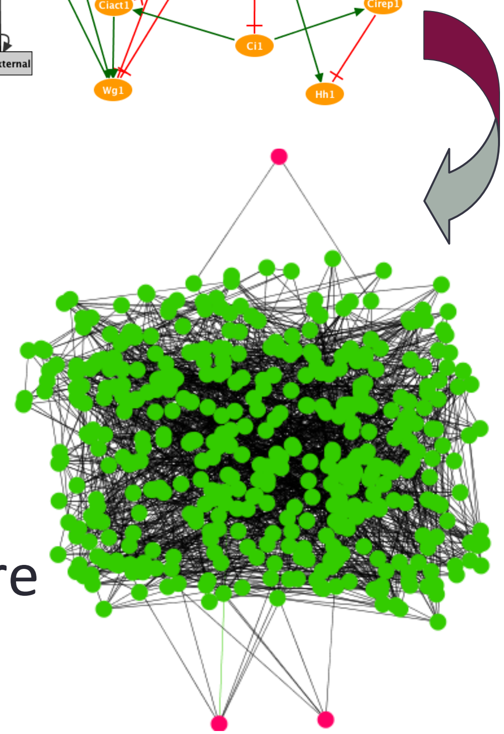
n	2^n
1	2
2	4
3	8
4	16
5	32
6	64
7	128
8	256
9	512
10	1,024
11	2,048
12	4,096
13	8,192
14	16,384
15	32,768
16	65,536
17	131,072
18	262,144
19	524,288
20	1,048,576
21	2,097,152
22	4,194,304
23	8,388,608
24	16,777,216
25	33,554,432
26	67,108,864
27	134,217,728
28	268,435,456
29	536,870,912
30	1,073,741,824

Means to handle large logical models

Goals: attractors, reachability, properties along trajectories, …

Problem: size of the state transition graph

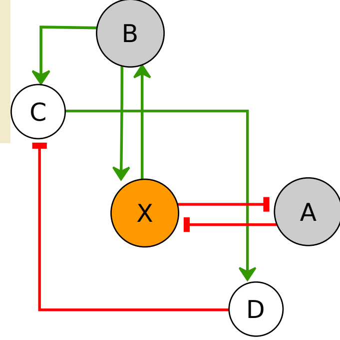




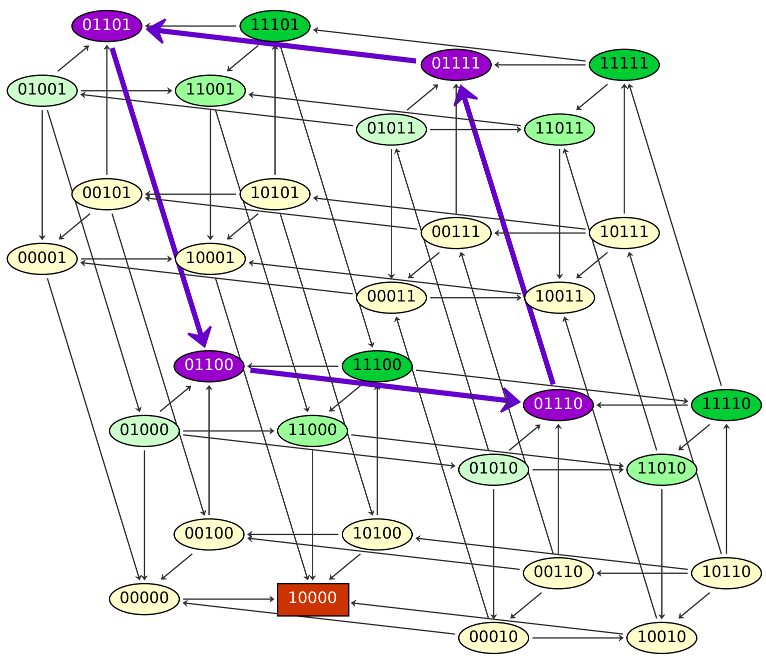
- **Hierarchical representations of STG**
- **Efficient STG exploration**
- Monte Carlo simulations
- **Model-checking techniques**

- Properties derived from the model structure (e.g. attractors & circuit analysis)
- **Model reduction**

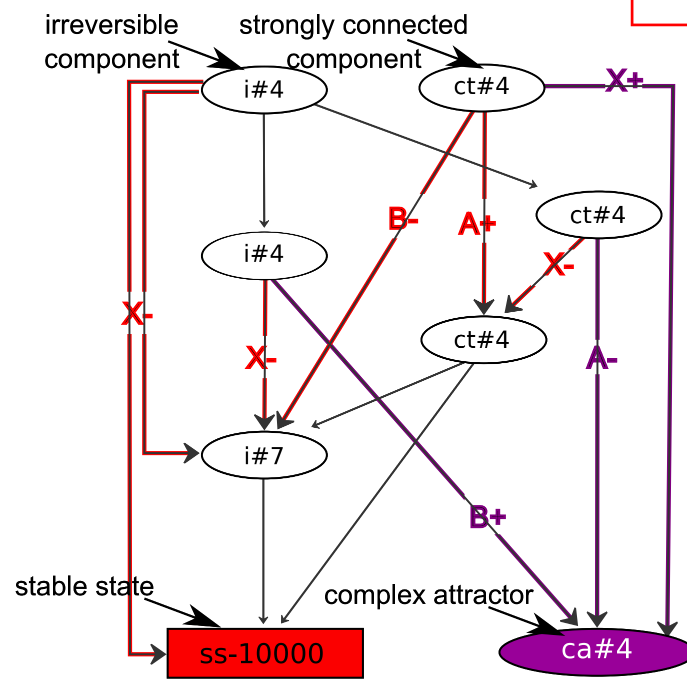
Representations of the dynamics



Revealing the structure of the dynamics (basins of attraction)



State Transition Graph



Hierarchical transition graph

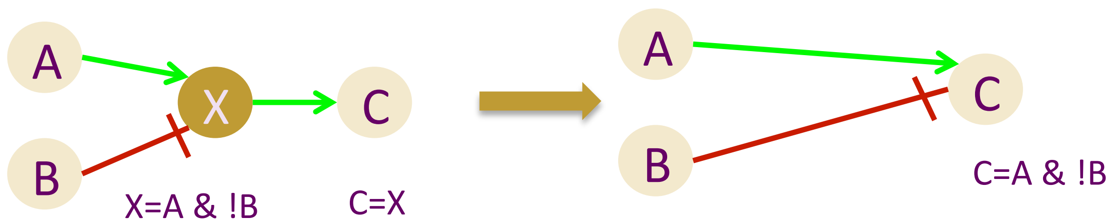
Bérenguier et al.(2013) Chaos 23

Each complex SCC of the STG contracted to a single node

All trivial SCCs sharing the same **σ-image** gathered into a single node

To each SCC X, σ(X) is the set of SCCs reachable from X, including X itself if it is complex or terminal

Model reduction



In the rules of its targets, replace X by its own rule

- Cannot apply to self-regulated nodes
- X is faster than the other nodes…

This reduction does not generate new trajectories (it can only prevent some)

- Stable states and elementary cyclical attractors are preserved
- Complex attractors originate from CA and transient SCC of the original model
- Reachability may be not conserved

- Reduction of (pseudo) input nodes preserves the attractors
- **Reduction of (pseudo) output nodes preserves the attractors and their reachability**

A. Naldi, *et al* (2011)Theoretical Computer Science 412(21):2207-18

Mapping multi-valued to Boolean models

WHY???

A number of methods and tools restricted to Boolean models

HOW???

Three decades ago, a multivalued to Boolean variable mapping was proposed by P. Van Ham

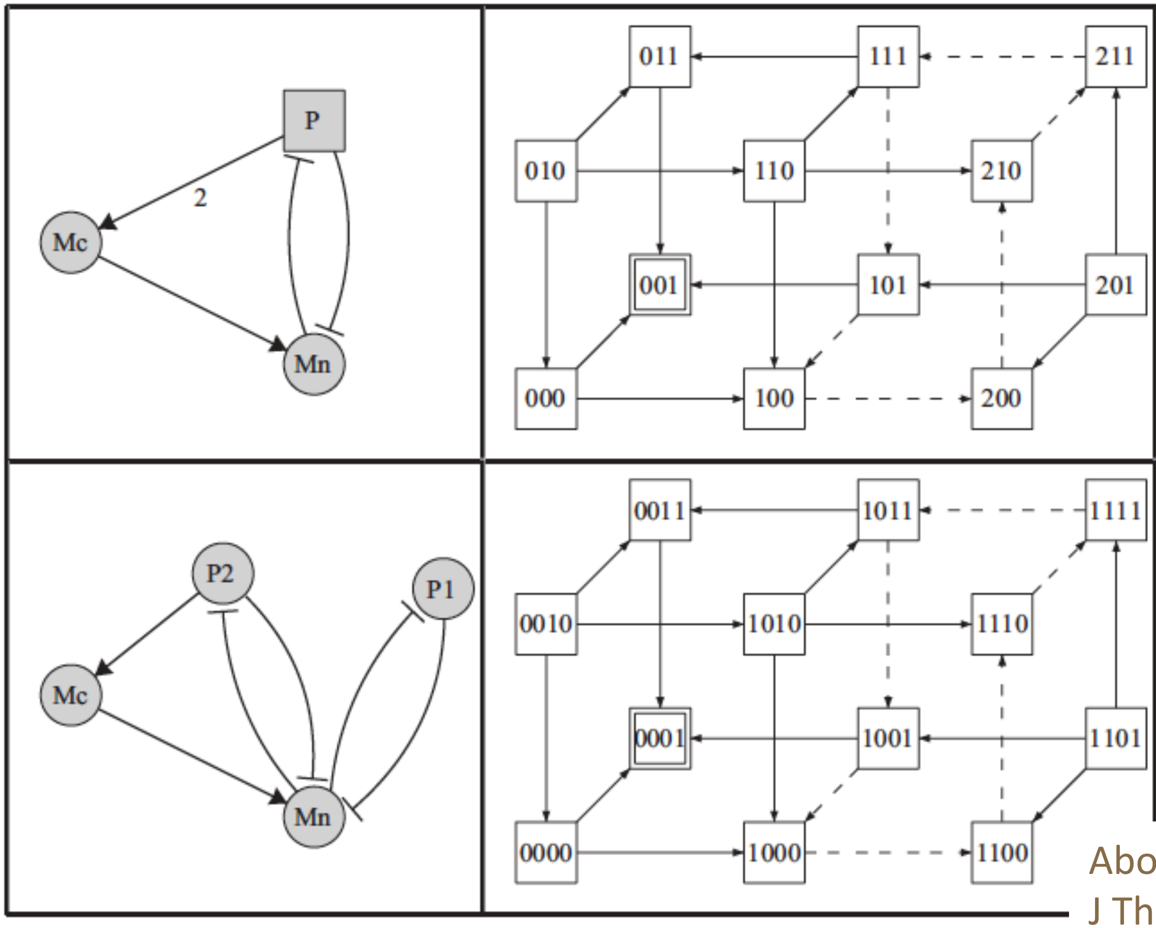
Formalisation of this mapping & proof that it is the sole mapping preserving the regulatory structure of the underlying graph plus its dynamical behaviour

A in {0,1,2} → A_1 in {0,1} A_2 in {0,1}

A	**A_2**	**A_1**
0	0	0
1	0	1
2	1	0
Not admissible!!	1	1

G. Didier, E. Remy, C. Chaouiya (2011) Journal of Theoretical Biology, 270:177–184

Mapping multi-valued to Boolean models



p53/Mdm2 network

Abou-Jaoudé W, Ouattara DA, Kaufman M. J Theor Biol. 2009 21;258(4):561-77.

G. Didier, E. Remy, C. Chaouiya (2011) Journal of Theoretical Biology, 270:177–184

Mapping Boolean to ODE models

WHY???

enrich Boolean models built up from coarse information by features of quantitative models, such as

- Intermediate expression levels,
- Continuous transitions,
- Transient perturbations
- Different time-scales.

Mapping Boolean to ODE models

Theoretical Biology and Medical Modelling

BioMed Central

Research

Open Access

A method for the generation of standardized qualitative dynamical systems of regulatory networks

Luis Mendoza* and Ioannis Xenarios

BMC Bioinformatics

Software

Dynamic simulation of regulatory networks using SQUAD

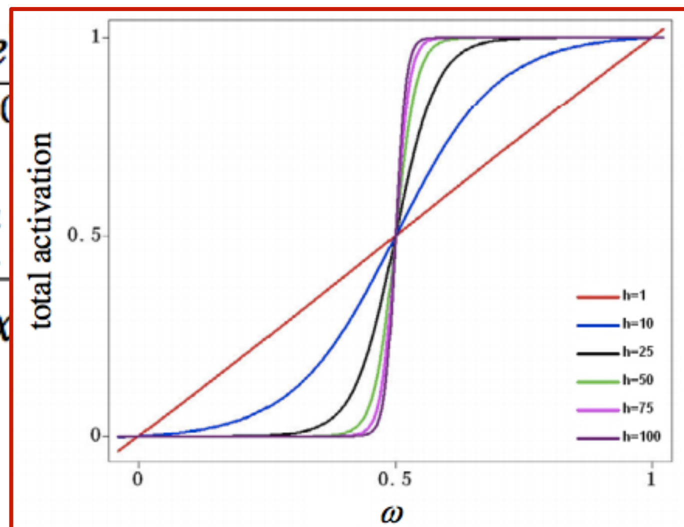
Alessandro Di Cara[1], Abhishek Garg[2], Giovanni De Micheli[2], Ioannis Xenarios*[3] and Luis Mendoza*[4]

Boolean models

A node is ON in the presence of at least one of its activators and none of its inhibitors

$$\frac{dx_i}{dt} = \frac{-e \ldots}{(1-e \ldots}$$

$$\omega_i = \left(\frac{1+\sum\alpha_n}{\sum\alpha_n}\right)\left(\frac{\sum\alpha_n x_n^a}{1+\sum\alpha_n x \ldots}\right) \ldots \frac{\ldots n}{\ldots x_m^i}\Bigg)\Bigg)$$



$$0 \le x_i \le 1$$

$$0 \le \omega_i \le 1$$

$$h, \alpha_n, \beta_m, \gamma_i > 0$$

Mapping Boolean to ODE models

Krumsiek *et al. BMC Bioinformatics* 2010, **11**:233
http://www.biomedcentral.com/1471-2105/11/233

BMC Bioinformatics

SOFTWARE **Open Access**

Odefy – From discrete to continuous models

Jan Krumsiek[1], Sebastian Pölsterl[1], Dominik M Wittmann[1,2], Fabian J Theis[1,2*]

Boolean models transformed to systems of ODEs by multivariate polynomial interpolation and optional application of sigmoidal Hill functions

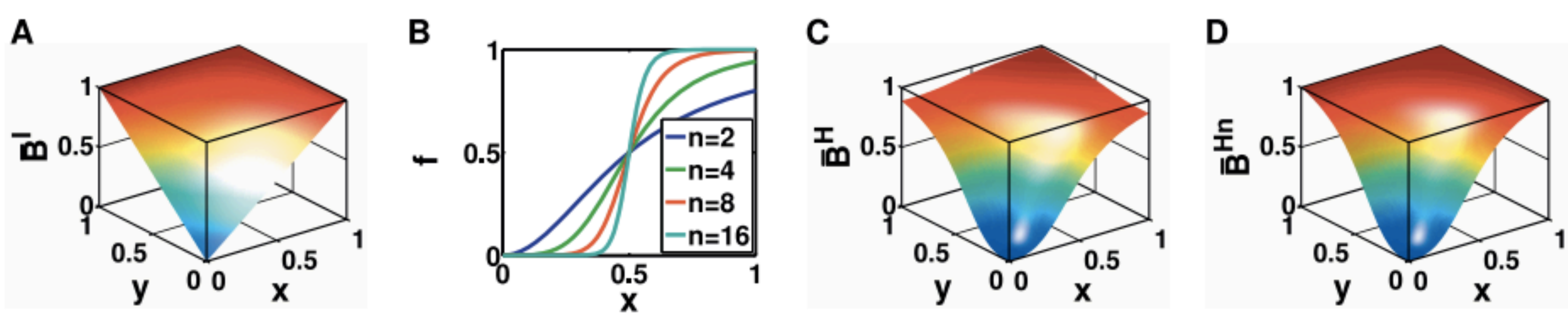


Figure 2 Continuous homologues of Boolean functions. Continuous homologues of Boolean functions. **A** Multilinear interpolation of a two-variable OR gate (Boole-Cube). **B** Hill functions with Hill coefficients n = 2, 4, 8, 16 and k = 0.5 as continuous relaxation of a Boolean step function. **C** Composition of BooleCube from (A) with Hill functions (HillCube). **D** normalized HillCube from (C).

Conclusions

- Within the logical framework, there is a range of
  - Forms / extensions
  - Methods for analysis
  - Tools
- The framework is useful and widely used!
- As the **field** is growing (models, methods, tools), a community effort for standardization has been launched

  CoLoMoTo http://colomoto.org
  - SBML qual
  - *LogicalModel* library
  - Web site

    Repositories for models, methods and tools

    Standards (model, simulation settings, model annotations, vocabularies...)

    Directory of groups