Qualitative modelling provides insights into the functioning of large biological regulatory networks

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Network Modelling

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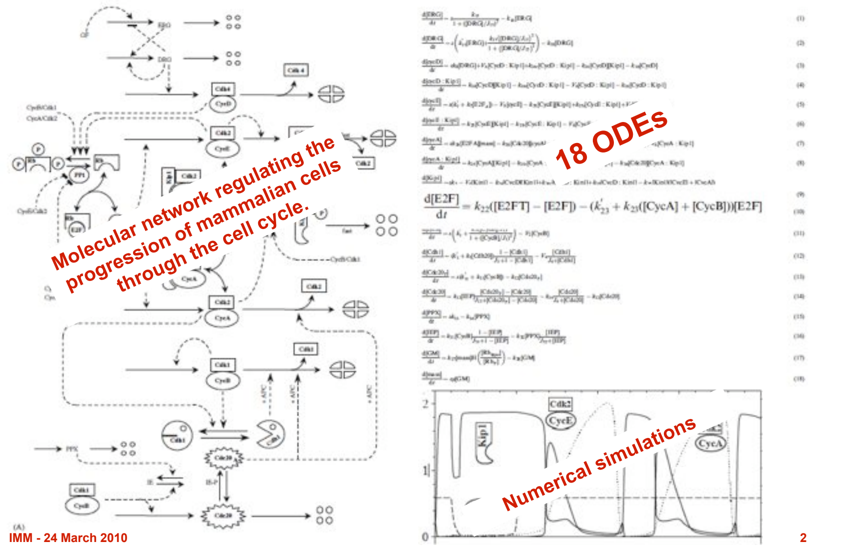
Decipher regulatory network dynamics

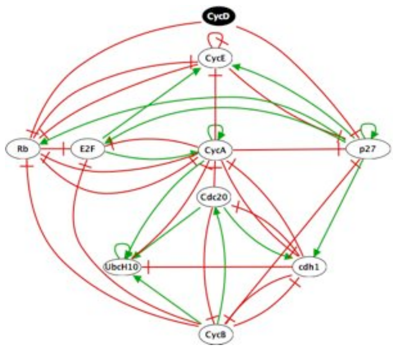
B. Novak, J.J. Tyson. (2004) A model for restriction point control of the mammalian cell cycle. J Theo Biol 230, 563–579



Decipher regulatory network dynamics

A. Fauré et al (2006) Bioinformatics, 22(14) 134-31

Regulatory graph



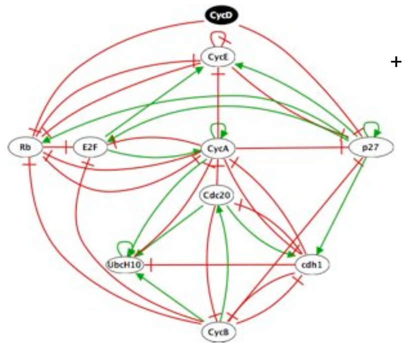
10 logical rules

CycD	$CycD$
Rb	$(\overline{CycD} \wedge \overline{CycE} \wedge \overline{CycA} \wedge \overline{CycB}) \vee (p27 \wedge \overline{CycD} \wedge \overline{CycB})$
E2F	$(\overline{Rb} \wedge \overline{CycA} \wedge \overline{CycB}) \vee (p27 \wedge \overline{Rb} \wedge \overline{CycB})$
CycE	$(E2F \wedge \overline{Rb})$
CycA	$(E2F \wedge \overline{Rb} \wedge \overline{Cdc20} \wedge \overline{(Cdh1 \wedge Ubc)}) \vee (CycA \wedge \overline{Rb} \wedge \overline{Cdc20} \wedge \overline{(Cdh1 \wedge Ubc)})$
p27	$(\overline{CycD} \wedge \overline{CycE} \wedge \overline{CycA} \wedge \overline{CycB}) \vee (p27 \wedge \overline{(CycE \wedge CycA)} \wedge \overline{CycB} \wedge \overline{CycD})$
Cdc20	$CycB$
Cdh1	$(\overline{CycA1} \wedge \overline{CycB}) \vee (Cdc20) \vee (p27 \wedge \overline{CycB})$
UbcH10	$(\overline{Cdh1}) \vee (Cdh1 \wedge Ubc \wedge (Cdc20 \vee CycA \vee CycB))$
CycB	$(\overline{Cdc20} \wedge \overline{Cdh1})$

CycB is active in the absence of both Cdc20 and Cdh1

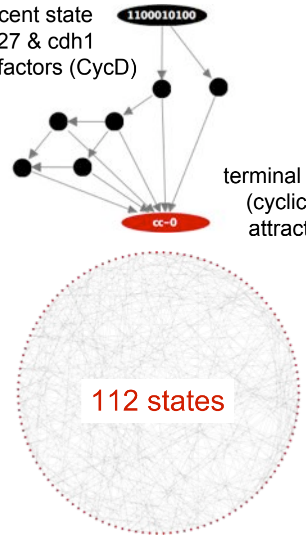
Decipher regulatory network dynamics

Regulatory graph



State transition graph

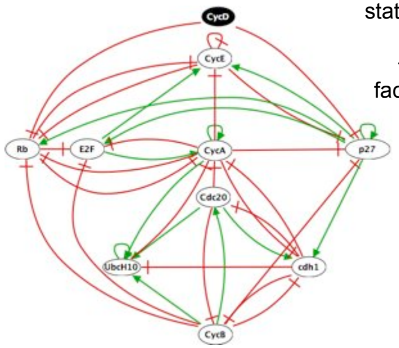
quiescent state
Rb, p27 & cdh1
+ Growth factors (CycD)



terminal SCC
(cyclical)
attractor

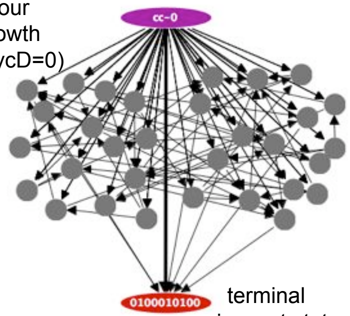
Decipher regulatory network dynamics

Regulatory graph



State transition graph

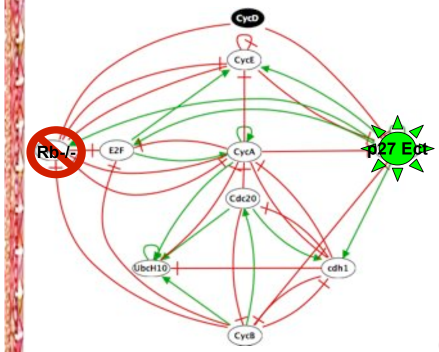
state in the cyclical behaviour + No growth factors (CycD=0)



terminal quiescent state Rb, p27 & cdh1

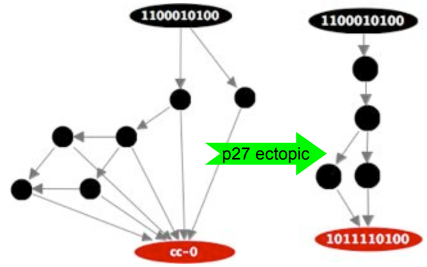
Decipher regulatory network dynamics

Regulatory graph



What about perturbations?

- Rb-/- is viable
- Ectopic expression of p27 leads to cell cycle arrest



E2F/CycE/CycA

Modelling formalisms

- Graph theory
- **Logical models**
- Piecewise Linear Differential Equations
- Nonlinear Ordinary Differential Equations
- Stochastic Equations
- Petri nets
- ...

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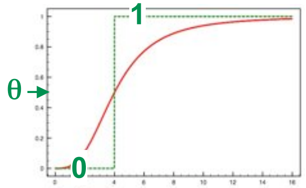
Which insights from logical models of regulatory networks?

- From the wiring, *e.g.*
  - dependency matrix
  - feedback circuit analysis
- From the dynamical properties
  - attractors (stable states, cyclical behaviours, trajectories)
  - influence of delay orders (*e.g.* fast/slow processes)
- From the analysis of perturbations
- From the confrontation of model predictions to experimental data

Overview of the logical modelling

- Lack of precise quantitative data (concentrations, kinetic parameters…)
- Threshold effects in regulation often represented as Hill or step functions

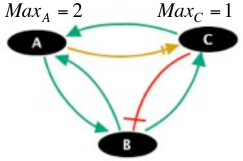


Boolean approximation

R.Thomas (1973) Boolean formalization of genetic control Circuits. JTB, 42(3):563-85.
Chaouiya C, Remy E, Mossé B, Thieffry, D (2003). *LNCIS* **294**: 119-26.

Overview of the logical modelling

Regulatory Graph (G,E,K)



$Max_A = 2$ $Max_C = 1$ $Max_B = 1$

nodes: regulatory components with discrete (activity) level (Boolean or multi-valued) $i \in G, x_i \in \{0,...,Max_i\}$

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 $K_i : \prod_{j \in Reg(i)} x_j \mapsto \{0,...,Max_i\}$

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

C present when activated by A at its medium level or by B (or both)

R.Thomas (1973) Boolean formalization of genetic control Circuits. JTB, 42(3):563-85.
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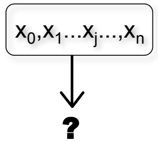
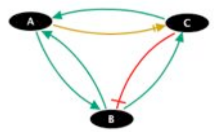
Overview of the logical modelling

State Transition Graph (S,T)

nodes: states $S = \prod_{i \in G} \{0,...,Max_i\}$

edges: transitions $T \subseteq S^2$





if $K_j(x) \neq x_j$, component g_j receives a **call for updating**

- if $K_j(\mathcal{I}_j(x)) > x_j$ then g_j is called to increase ↑
- if $K_j(\mathcal{I}_j(x)) < x_j$ then g_j is called to decrease ↓

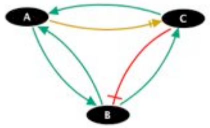
R.Thomas (1973) Boolean formalization of genetic control Circuits. JTB, 42(3):563-85.
Chaouiya C, Remy E, Mossé B, Thieffry, D (2003). *LNCIS* **294**: 119-26.

Overview of the logical modelling

State Transition Graph (S,T)

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

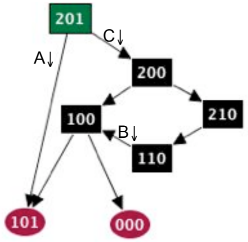
edges: transitions $T \subseteq S^2$



asynchronous

a unique call for updating executed at each step

lack of delay ⇒ all possible transitions generated



synchronous

all updating calls executed simultaneously

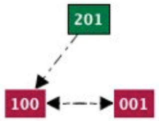


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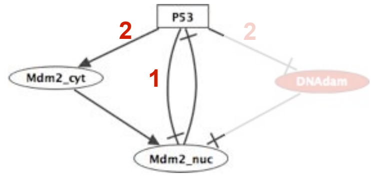
Illustration through the p53-Mdm2 network

W.Abou-Jaoude, DA.Ouattara, M.Kaufman *From structure to dynamics: frequency tuning in the p53-Mdm2 network I. Logical approach.* J Theor Biol 258(4):561-77



p53 has two targets ⇒ 3 levels

others nodes are Boolean

rule for P53? P53=2 if Mdm2_nuc=0

rule for Mdm2_cyt? Mdm2_cyt=1 if P53=2

rule for Mdm2_nuc? R1: Mdm2_nuc=1 if Mdm2_cyt=1 and P53=0

R2: Mdm2_nuc=1 if Mdm2_cyt=1

R3: Mdm2_nuc=1 if P53=0

Illustration through the p53-Mdm2 network

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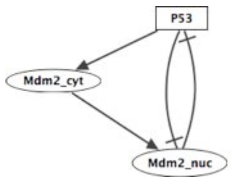
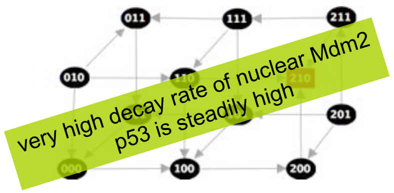
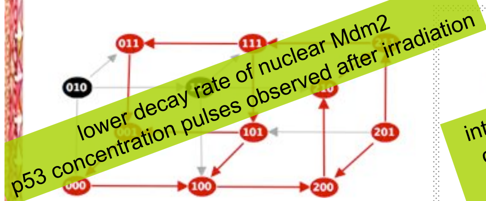
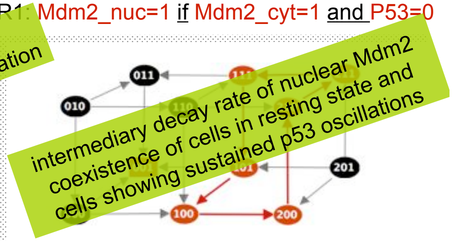




R1: Mdm2_nuc=1 if Mdm2_cyt=1 and P53=0



R2: Mdm2_nuc=1 if Mdm2_cyt=1

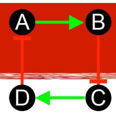


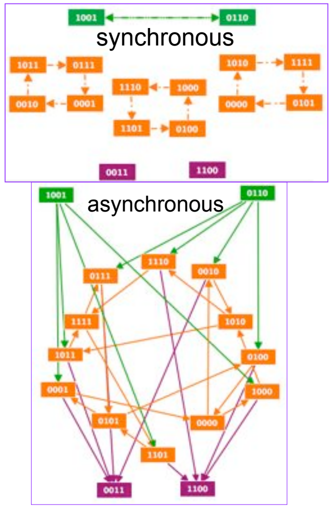
R3: Mdm2_nuc=1 if P53=0

Updating schemes

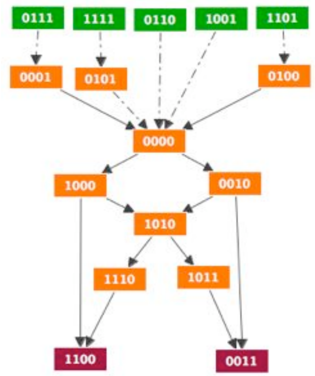
- Asynchronous
  - \+ possibly all trajectories
  - \- large state transition graphs encompassing many non-realistic trajectories
- Synchronous
  - \+ simpler state transition graphs (for any state, at most one successor)
  - \- spurious trajectories (and attractors)
- Introduction of priorities
  - \+ consideration of biological reality
  - \+ simplification of the state transition graph
  - \- loss of analytic means

Updating schemes



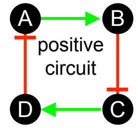


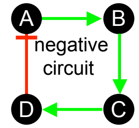
Priority classes (an example)
Degradations → **high** priority, synchronous
Syntheses → **low** priority, asynchronous



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

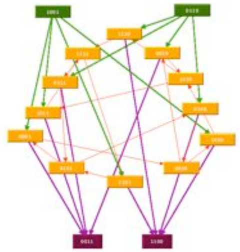
Dynamical role of regulatory circuits

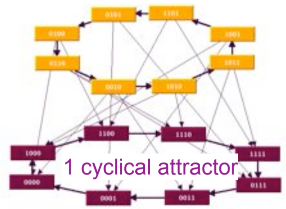




A **positive** circuit is **necessary** to generate multiple stable states or attractors
A **negative** circuit is **necessary** to generate maintained oscillations

Thomas R (1988) *Springer Series in Synergics* **9**: 180-93
Thieffry D. (2007) *Brief. Bioinform* **8**(4): 200-5



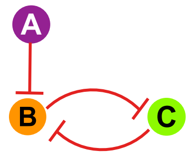


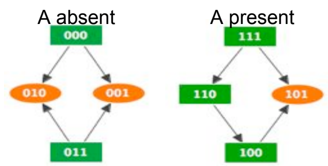
Dynamical role of regulatory circuits

- A network without positive circuit can generate at most one attractor
- A network without negative circuit cannot generate cyclic attractor
- **Necessary conditions:** the sole presence of a circuit does not imply the corresponding dynamical property

→ notion of functionality

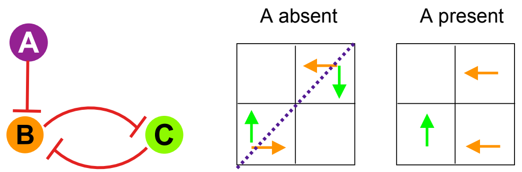
Dynamical role of regulatory circuits



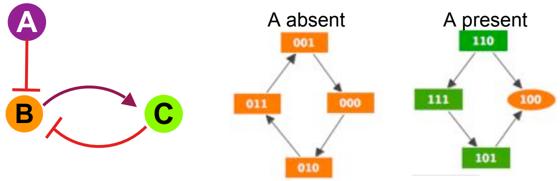


The circuit  is functional in the absence of A

Dynamical role of regulatory circuits



The circuit B–C is functional in the absence of A



The circuit B–C is functional in the absence of A

Feedback circuit analysis algorithm

Illustration through the p53-Mdm2 network

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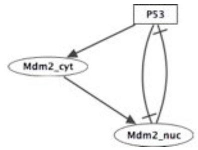
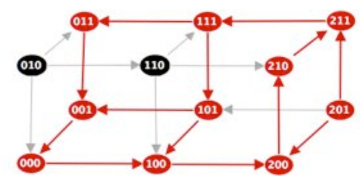


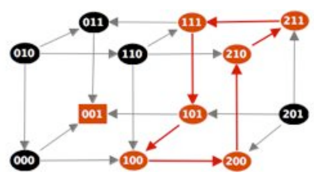
2 circuits:
- a positive circuit (cross-inhibition between p53 and nuclear Mdm2)
- a negative circuit involving the 3 components

sole the negative circuit is functional



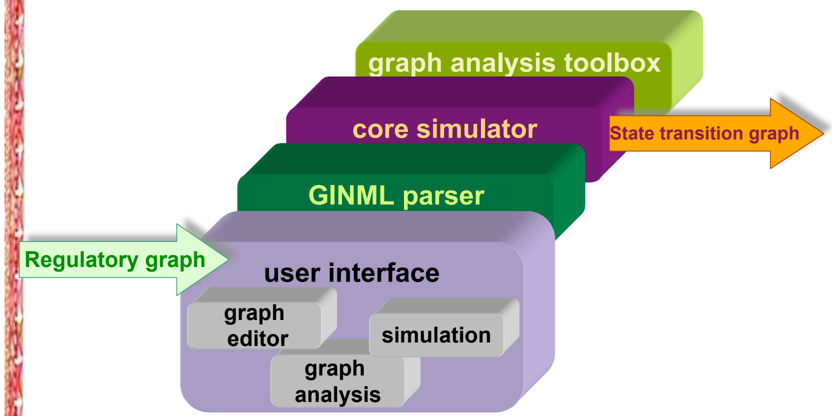
R2: Mdm2_nuc=1 if Mdm2_cyt=1

both circuits are functional



R3: Mdm2_nuc=1 if P53=0

GINsim



Available at http://gin.univ-mrs.fr/GINsim

A. Naldi, D. Berenguier, A. Fauré, F. Lopez, D. Thieffry, C. Chaouiya (2009). Biosystems, 97(2):134-9.

Specific means to handle large regulatory networks

Analysis of dynamical properties

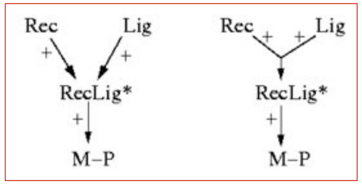
Goals: attractors, reachability, properties along trajectories

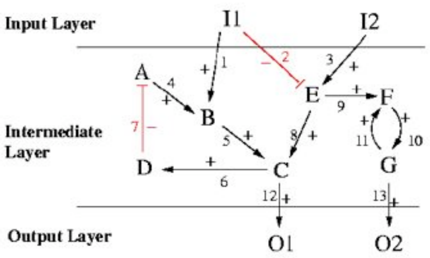
Problem: size of the state transition graph

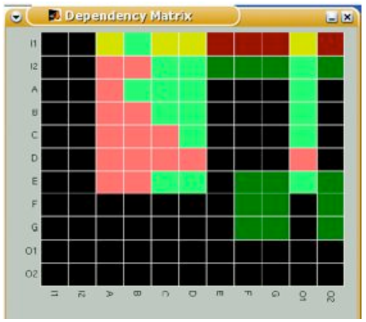
- Priority classes and mixed updating policies
- Properties derived from the structure of the model (circuit analysis)
- Hierarchical representations of STG
- Petri net representations
- Model reduction
- Model composition
- Model-checking techniques

Application to signalling networks

Samaga et al. PLoS Comput Biol (2009) 5(8)







Klamt S. et al (2006) BMC Bioinformatics, 7.

Take home message

- Qualitative versus (often illusory) quantitative modelling
- Dynamical roles of feedback circuits
- Flexibility of the (generalised) logical formalism
- Beware of the artefacts of the synchronous updating

Computational means developed in **close collaboration** with biologists