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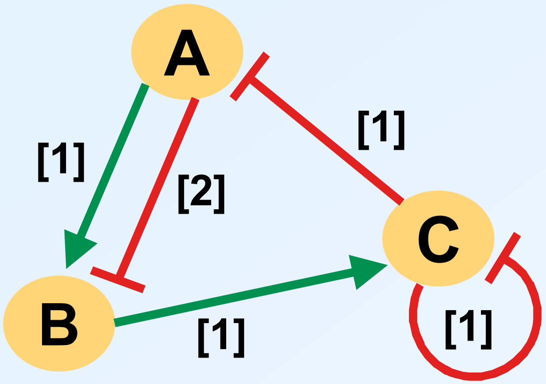
UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Dynamical analysis of logical models of genetic regulatory networks

Contents

- Logical modelling of regulatory networks
- Novel algorithms for dynamical analysis
- Application to T cell activation and differentiation
- Conclusions and prospects

Logical modelling of regulatory networks



✓ A **graph** describes the interactions between genes or regulatory products

✓ **Discrete levels** of expression associated to each gene (logical variables) and interaction

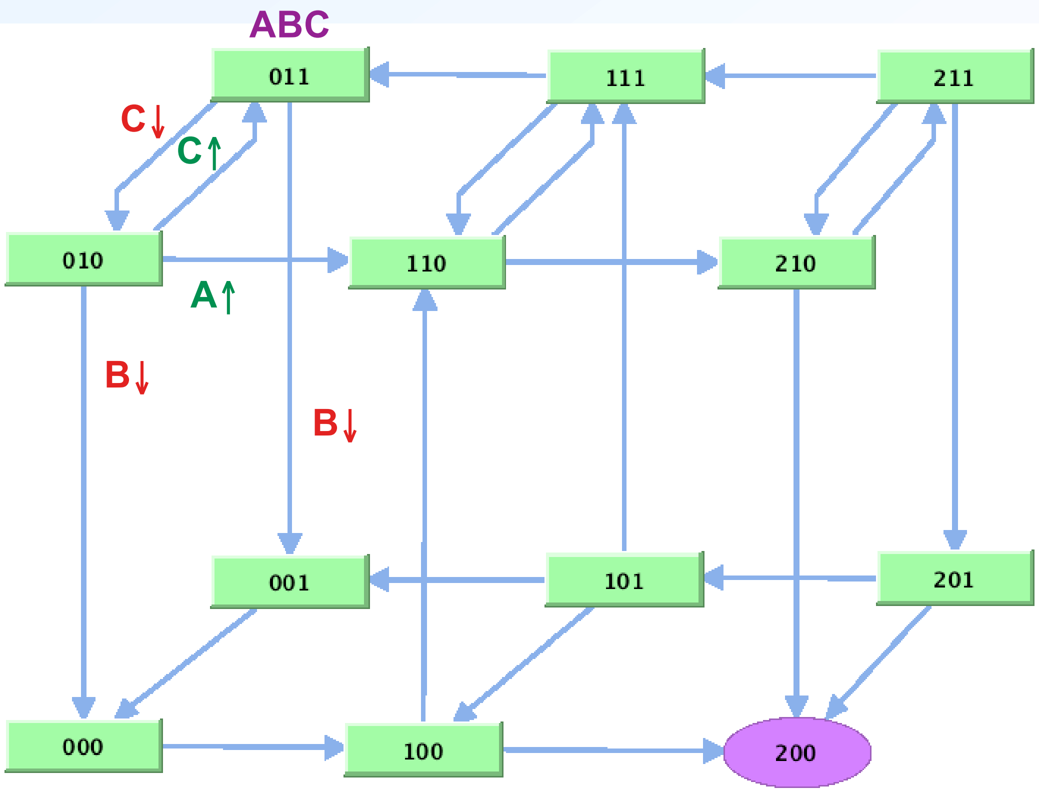
✓ **Logical parameters** define the effect of combinations of incoming interactions

$K_B(\emptyset)=0$

$K_B(\{A,1\})=1$

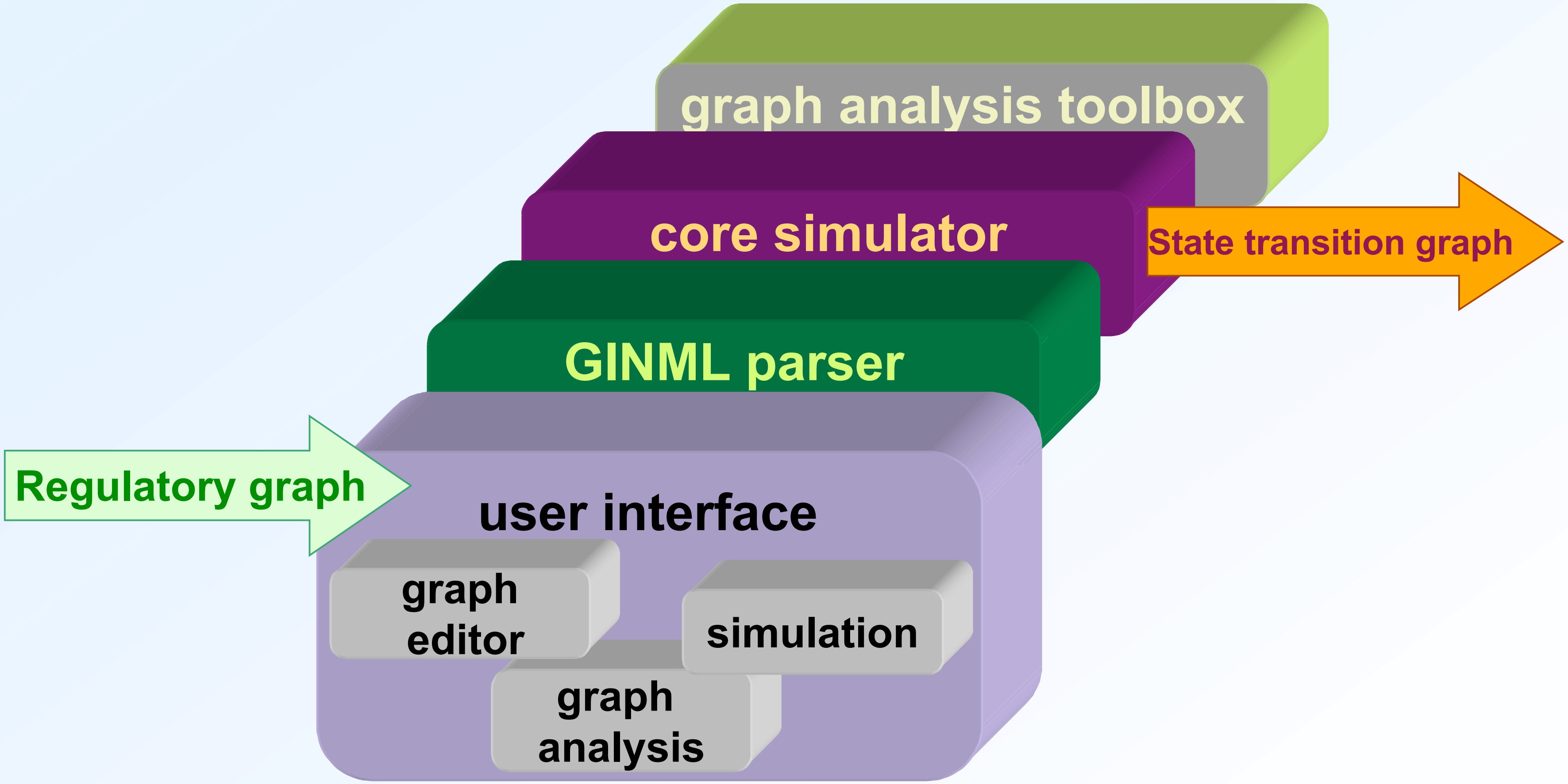
$K_B(\{A,2\})=0$

✓ The dynamics is represented by a **State Transition Graph** (here, all possible trajectories)



Chaouiya C, Remy E, Mossé B, Thieffry, D (2003). *LNCIS* **294**: 119-26.

GINsim (Gene Interaction Networks simulation)

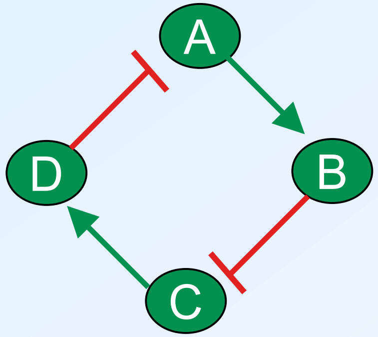


Available at http://gin.univ-mrs.fr/GINsim

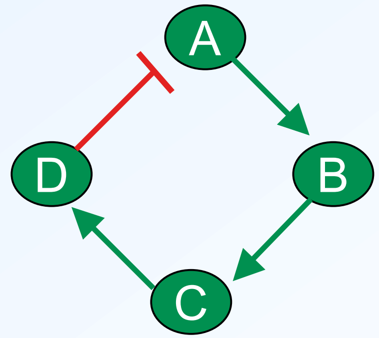
Gonzalez A, Naldi A, Sánchez L, Thieffry D, Chaouiya C (2006). *Biosystems* **84**: 91-100.

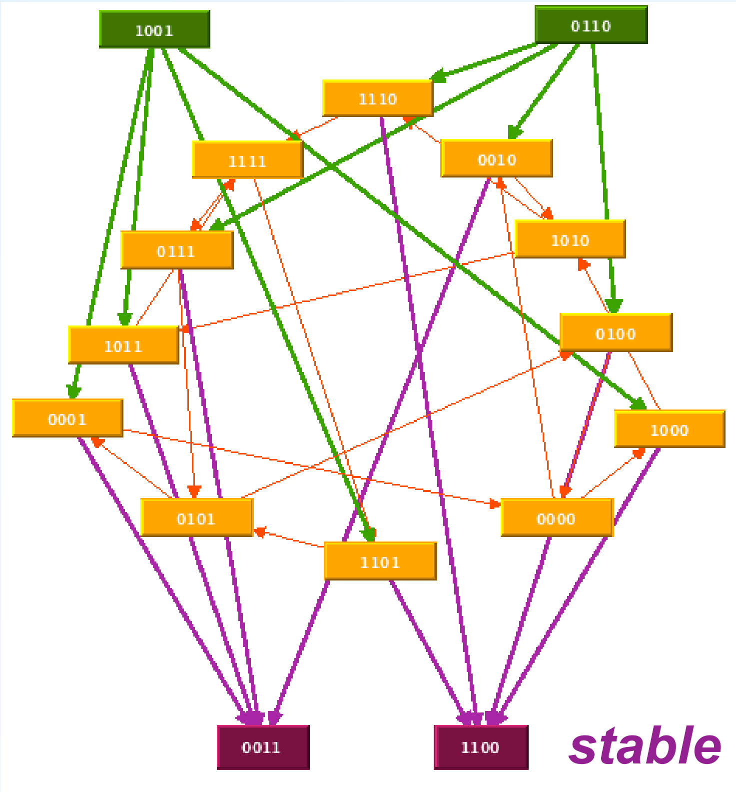
Discrete dynamics of simple feedback circuits

Positive circuit

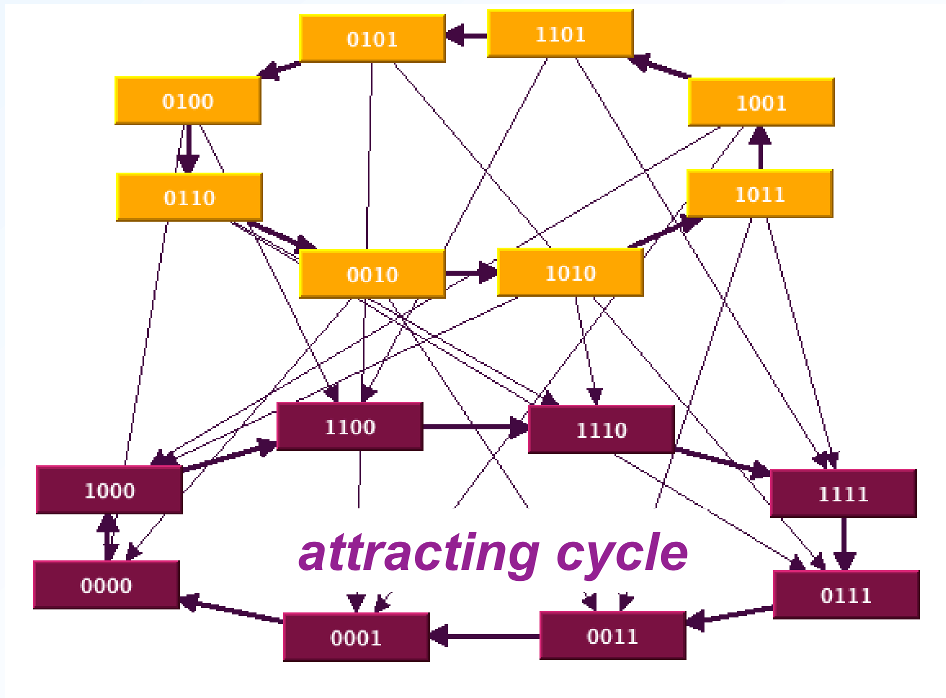


Negative circuit





stable states



Remy E, Mosse B, Chaouiya C, Thieffry D (2003). *Bioinformatics* **10**: ii172-8.

Feedback circuits & Thomas' rules

- ✓ A **positive feedback circuit** is **necessary** to generate **multiple stable states or attractors**
- ✓ A **negative feedback circuit** is **necessary** to generate **homeostasis or sustained oscillatory behaviour**

Thomas R (1988). *Springer Series in Synergics* **9**: 180-93.

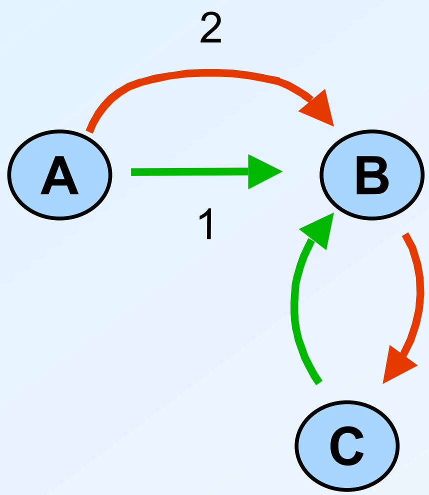
Mathematical theorems and demonstrations:

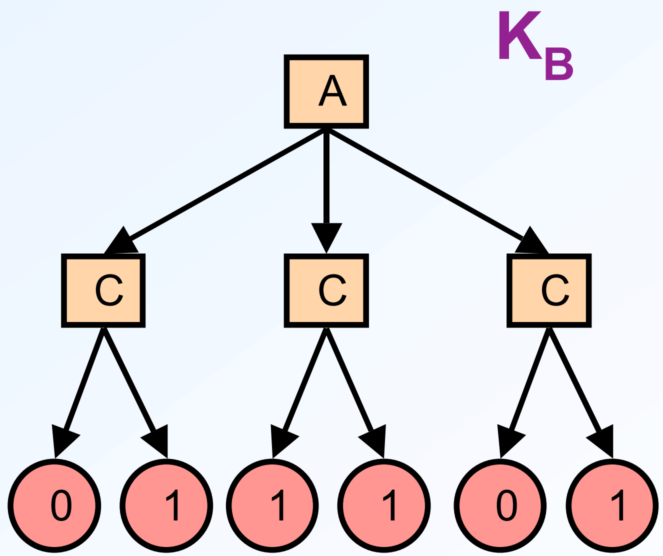
- ✓ **In the differential framework:**
  - Soulé C (2005). *ComPlexUs* **1**: 123–33.
- ✓ **In the discrete framework:**
  - Remy E, Ruet P, Thieffry D (2006). *LNCIS* **341**: 263-70.
  - Richard A (2006). *PhD thesis*, University of Evry, France.

Dynamical analysis tools

- **Priorities**
  - Mixed a/synchronous simulations
    [Fauré *et al* (2006) *Bioinformatics* **22**: e124-31]
- **Decision diagrams (Aurélien NALDI)**
  - **Stable state identification**
  - **Feedback circuit analysis**
    [Naldi *et al* (2007) *LNCS* 4695: 233-47]
- **Petri nets (Claudine CHAOUIYA)**
  - Standard Petri nets [Remy *et al* (2006). *LNCS* **4230**: 56-72]
  - Coloured Petri nets [Chaouiya *et al* (2006) *LNCS* **4220**: 95-112]
- **Logical programming**
  - Attractor identification

Logical functions as decision trees

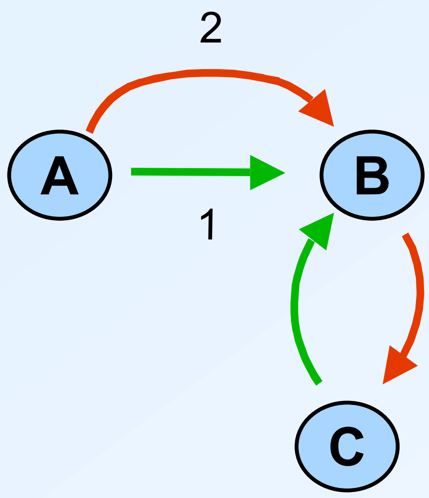


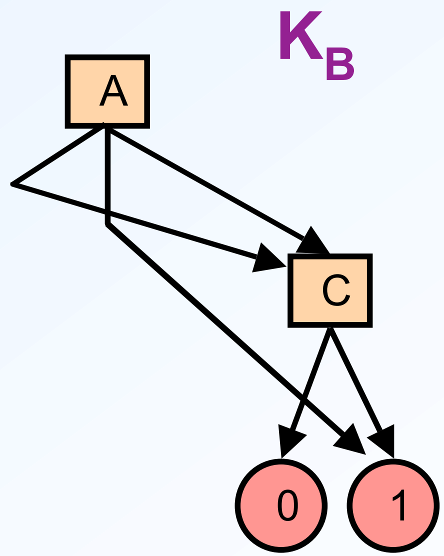


Behaviour of B given by the **logical function K_B**

$$K_B = \begin{cases} 1 & if \quad (A_1 \vee C) \\ 0 & otherwise \end{cases}$$

Logical functions as decision diagrams





Dynamics of B given by the **logical function K_B**

$$K_B = \begin{cases} 1 & if \quad (A_1 \vee C) \\ 0 & otherwise \end{cases}$$

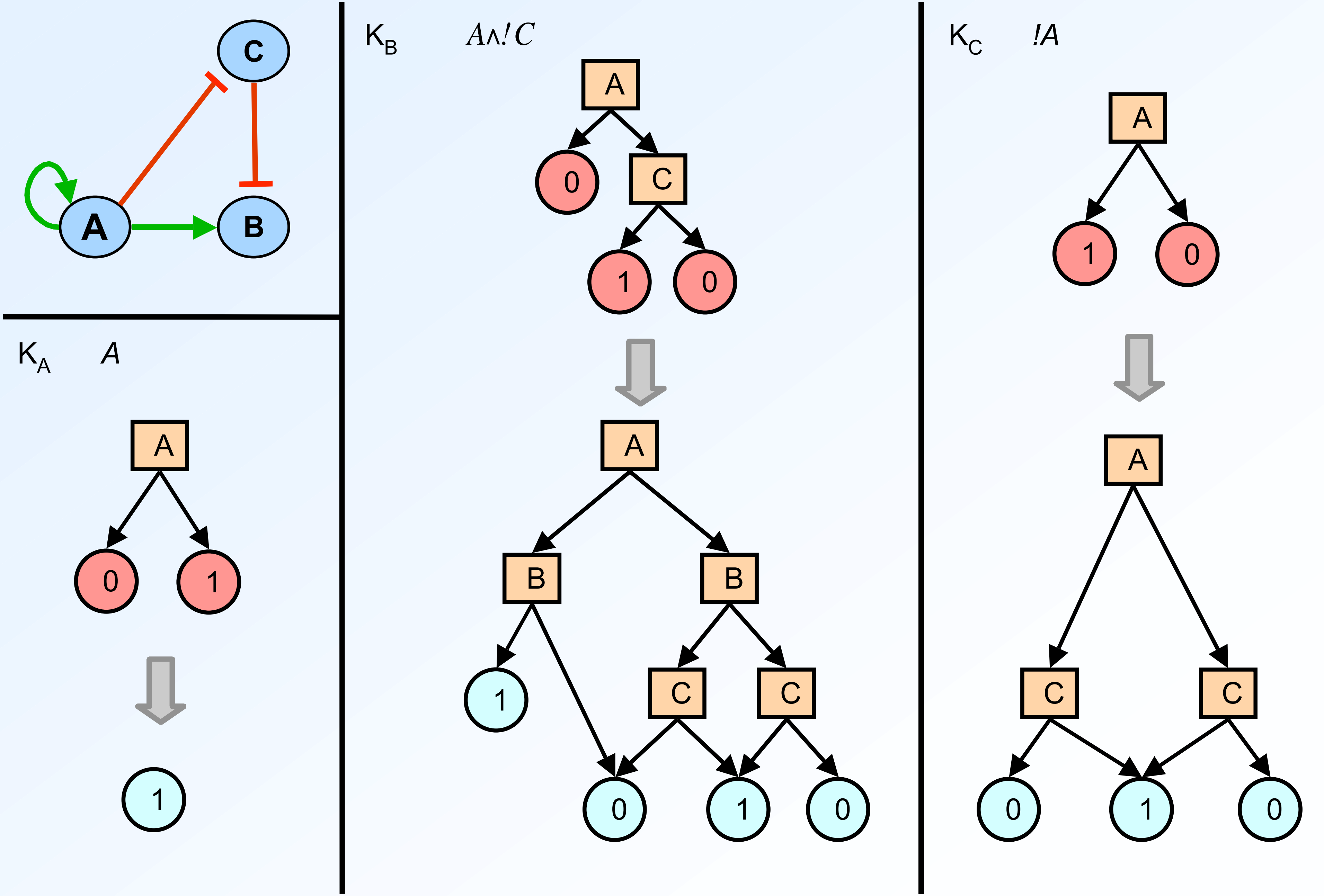
Efficient structure

Canonical representation
(for an ordering of the decision variables)

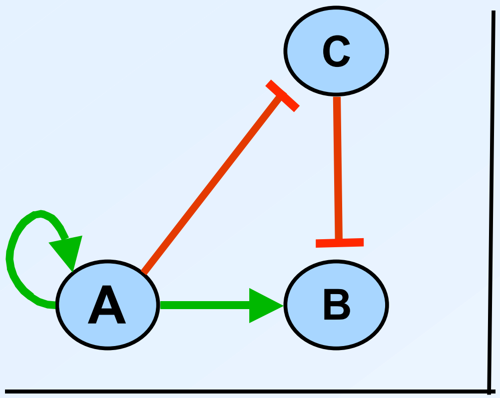
Determination of stable states

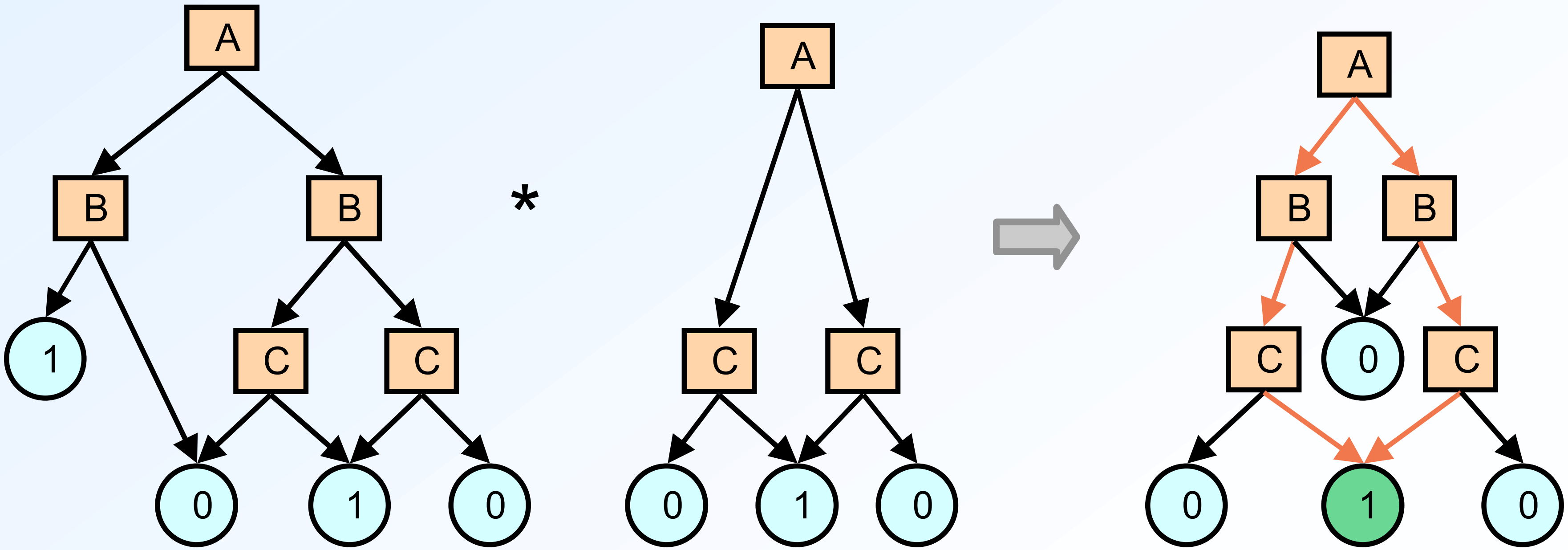
- **Stable states**: all variables are stable
- **Analytic method** to find all possible stable states
  - No simulation
  - No initial condition
- **Principle**
  - Build a stability condition for each variable
  - Combine these partial conditions

Determination of stable states



Determination of stable states

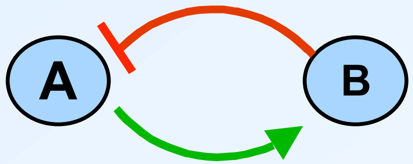


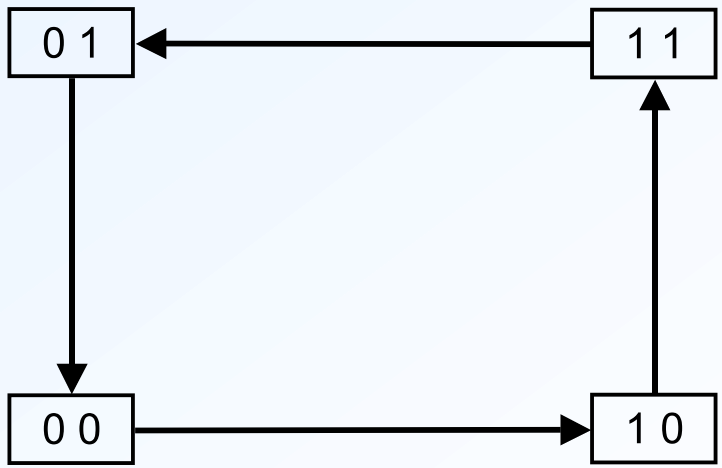


2 stable states : 001 et 110

Functionality context

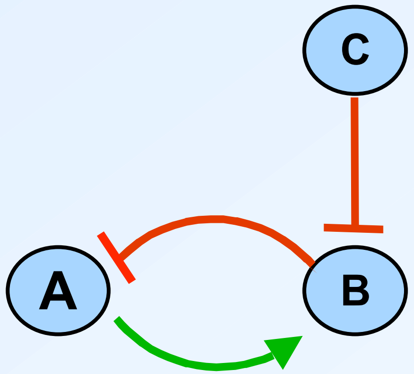
Example: **negative circuit** inducing a **cyclic behaviour**

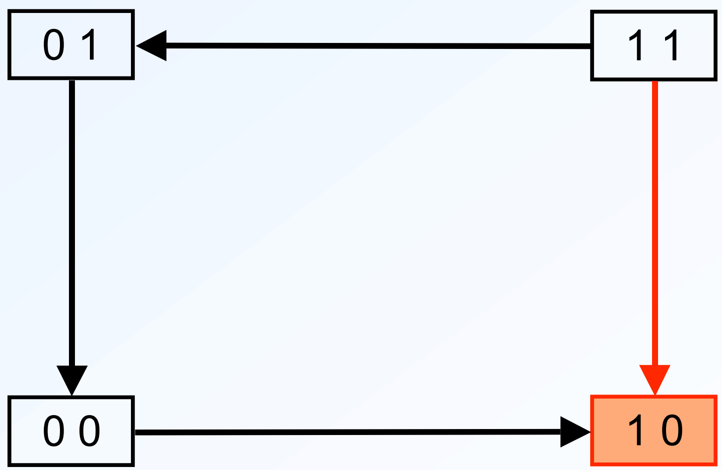




Functionality context

C prevents A from activating B





The circuit is **functional** in a given **context**:
in **absence of C**

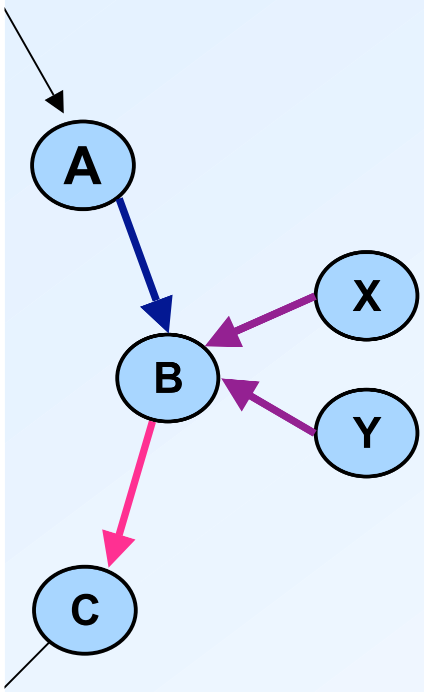
Functionality context

Functionality context: set of constraints on the expression levels of regulators

Each **interaction** has its own **context**

Context of the circuit: combination of all interaction contexts

Functionality of an interaction

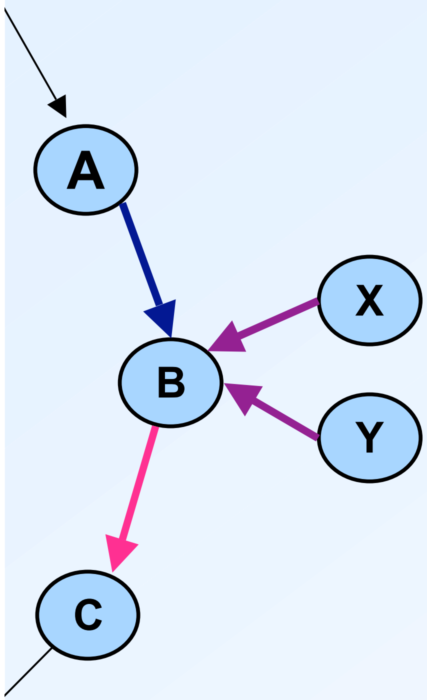


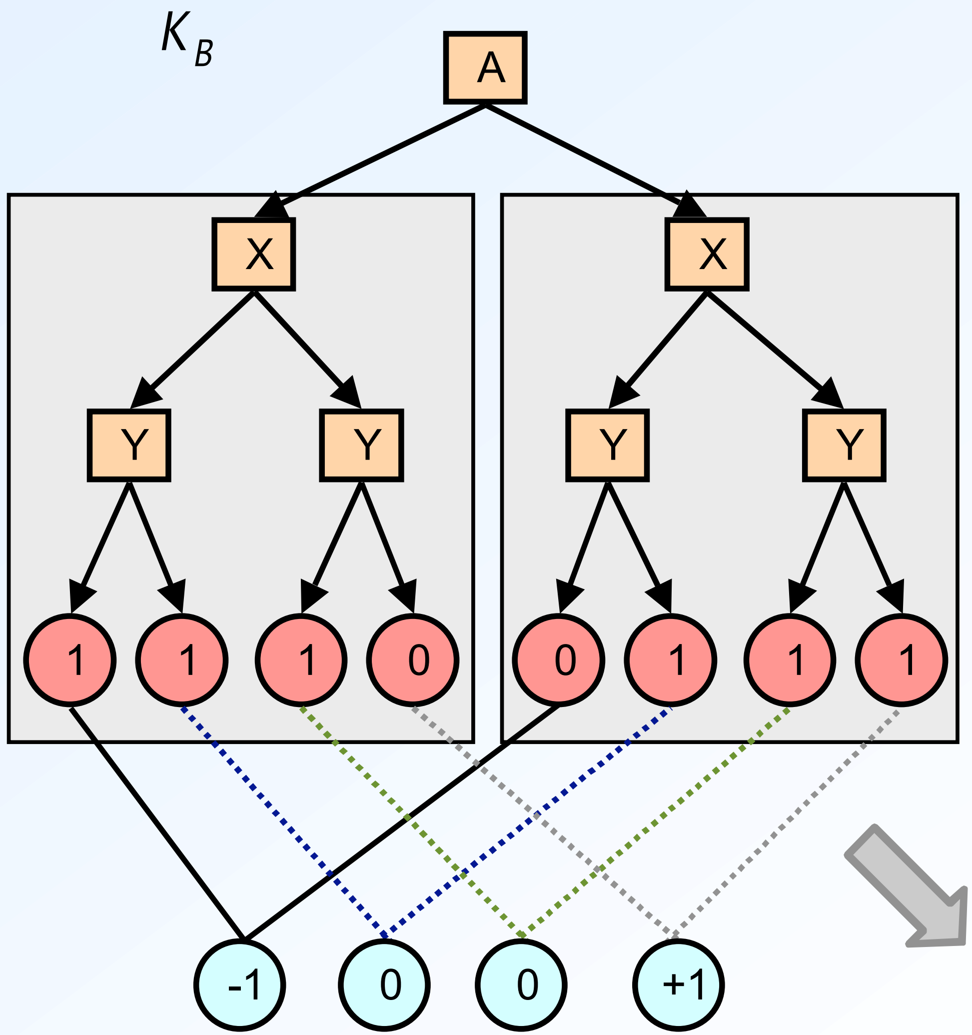
- In a circuit *(...,A,B,C,...)*, the **functionality** of the interaction *(A,B)* depends on:
  - K_B
  - the threshold of *(A,B)*
  - the threshold of *(B,C)*

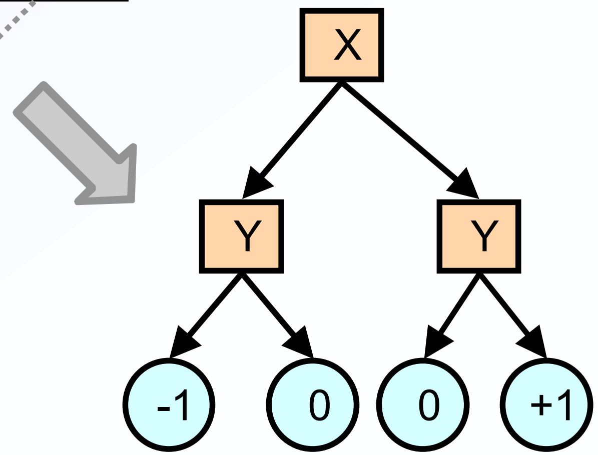
⇩

- **Functionality**: logical function depending on the **regulators of B** (represented as a decision diagram)

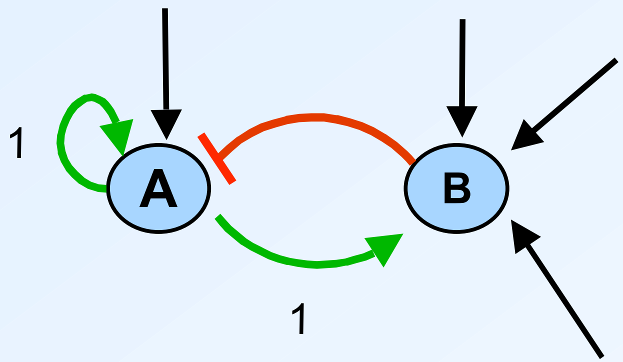
Functionality of an interaction

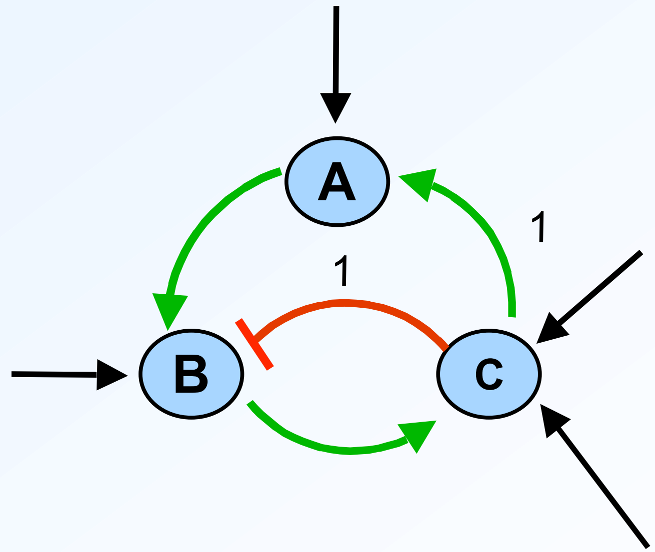






Restrictions on circuit functionality context



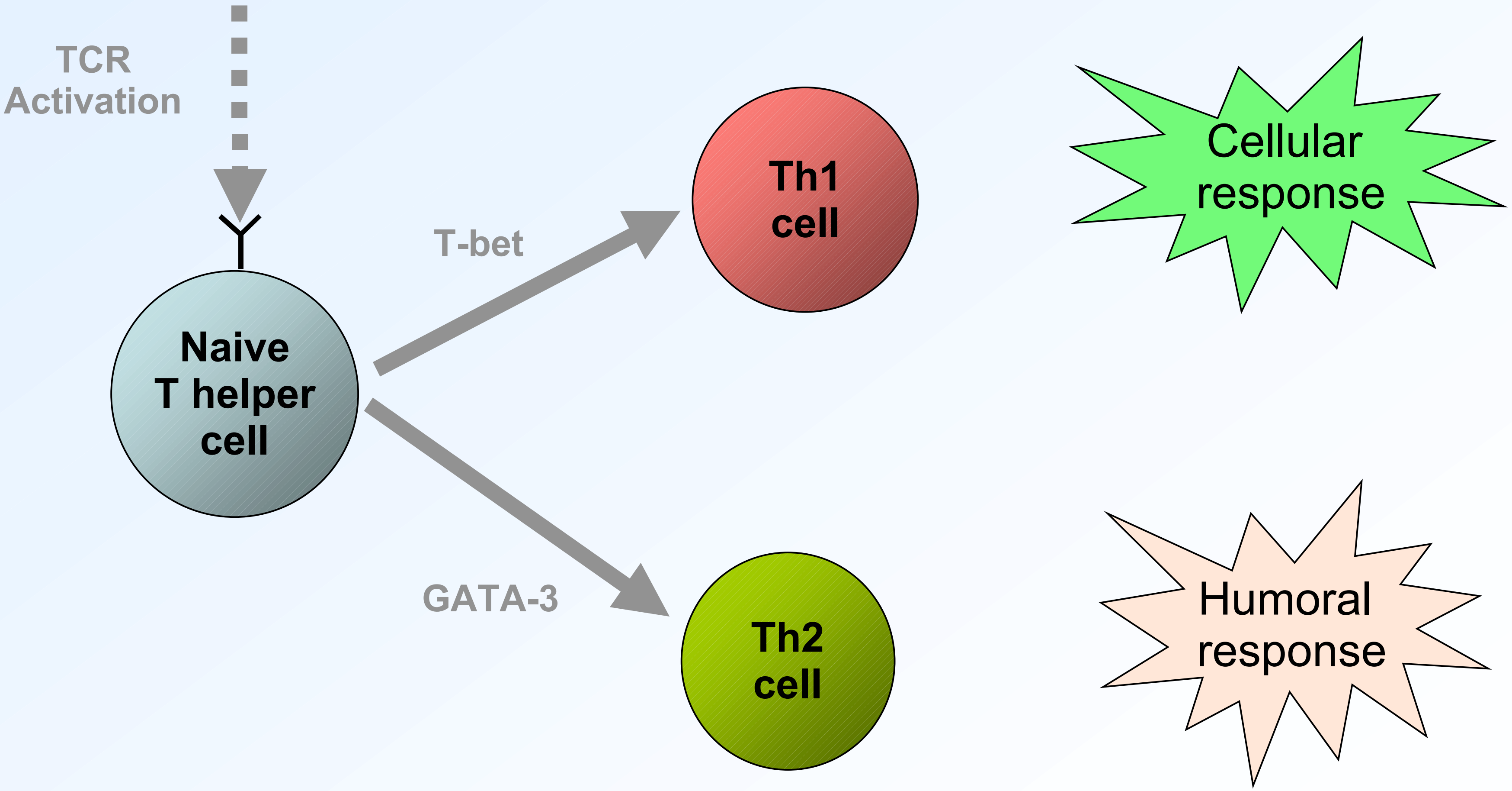


- Auto-regulation and (more generally) "**short-circuit**"
  - Circuit members appear in functionality context
  - Members of the circuit must be able to cross their threshold

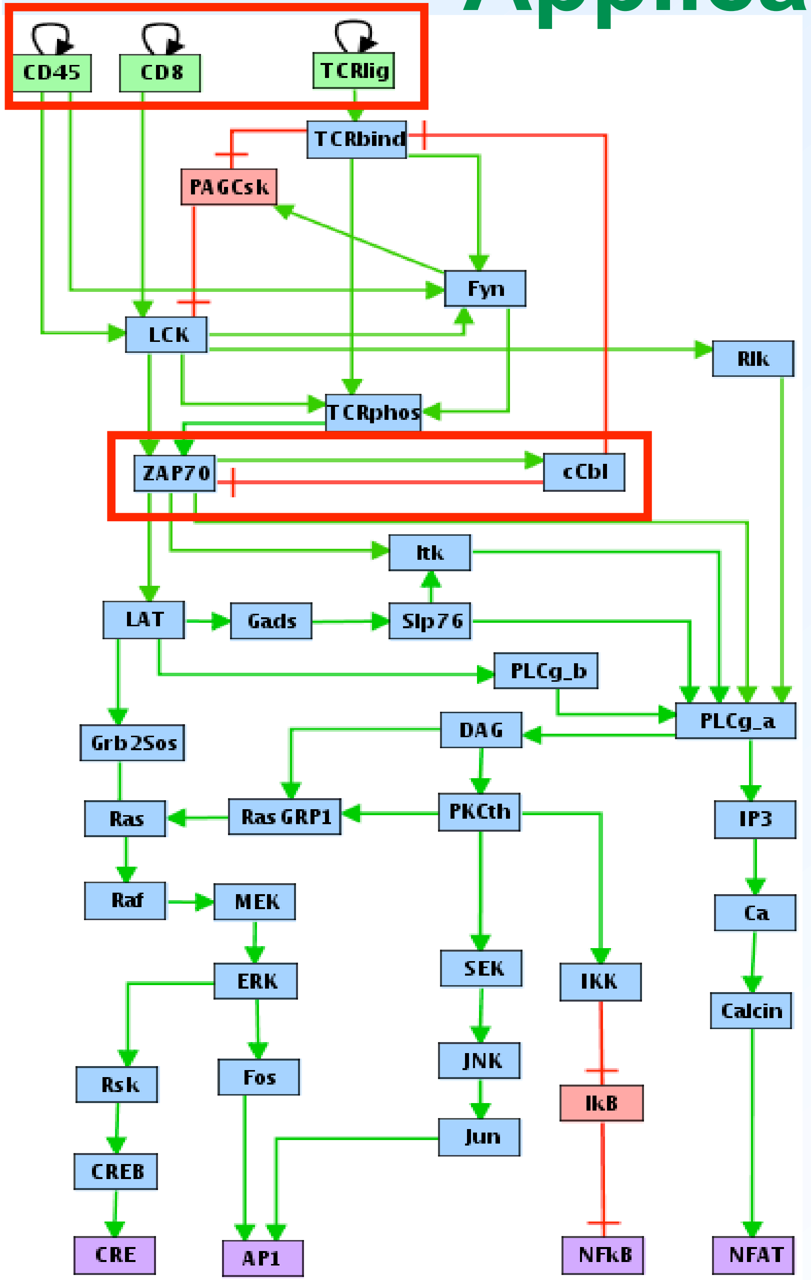
Applications

- **Cell cycle** (DIAMONDS FP6 STREP)
  - Yeast (*S. cerevisiae*)
  - Generic mammalian core
  - Drosophila (embryos)
- **T cell differentiation and activation** (ACI IMPbio & ANR BioSys)
  - **Differentiation: Th1/Th2, Regulatory T cells, lymphoid lineages**
  - **TCR signalling**
- **Drosophila development** (with **Lucas SANCHEZ**)
  - Genetic control of segmentation
  - Compartment formation in imaginal disks

T cell activation and differentiation



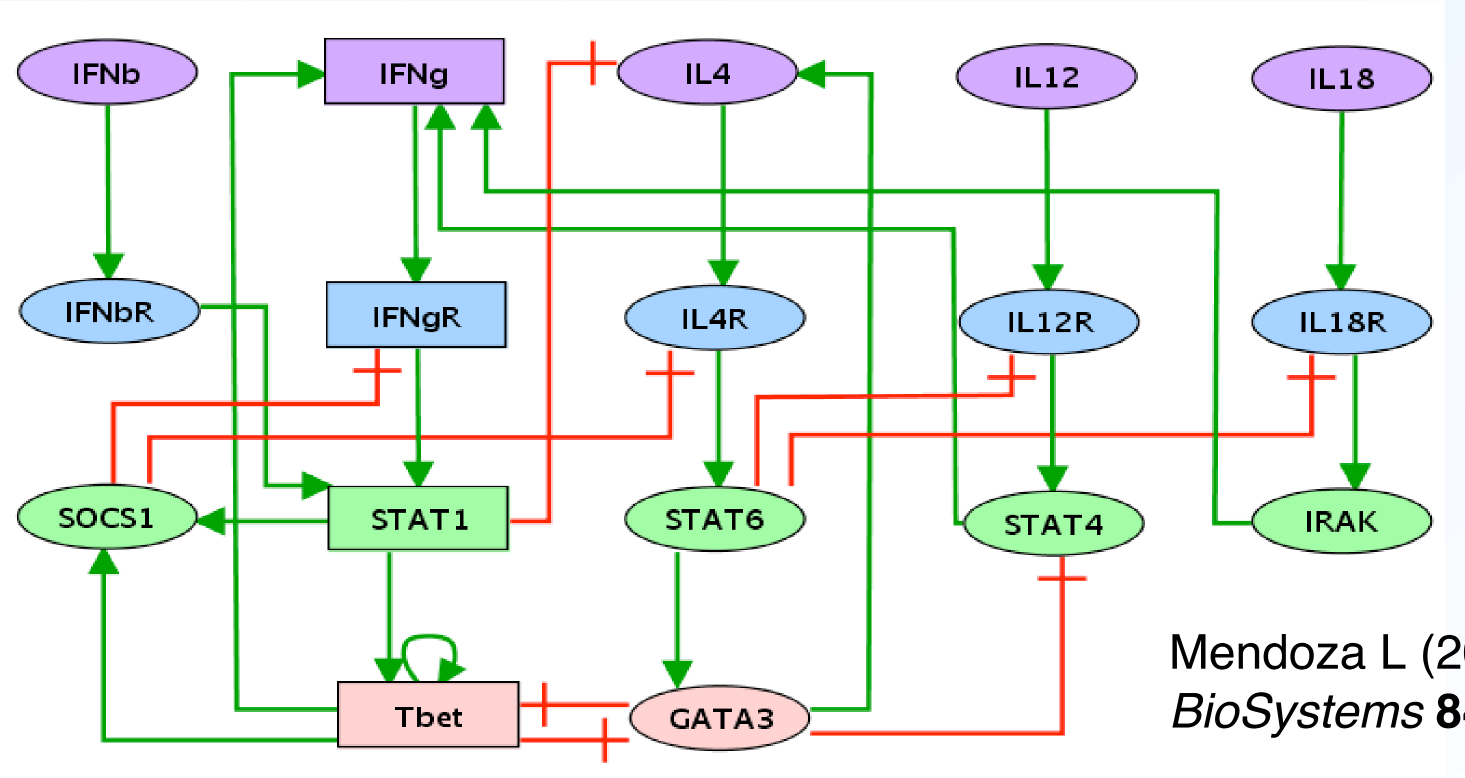
Application: TCR signalling



- **Circuit analysis:**
  4 circuits functional among 12
  - **3 positive circuits:**
    auto-regulations on inputs
    → **8 attractors:**
    one for each input combination
  - **1 negative circuit:**
    ZAP70/cCbl (functional in presence of LCK and TCRphos)
    → **cyclic attractor**
    (for 111 input)
- **Stable state analysis:**
  7 stable states

Klamt S *et al* (2006) *BMC Bioinformatics* **7**: 56.

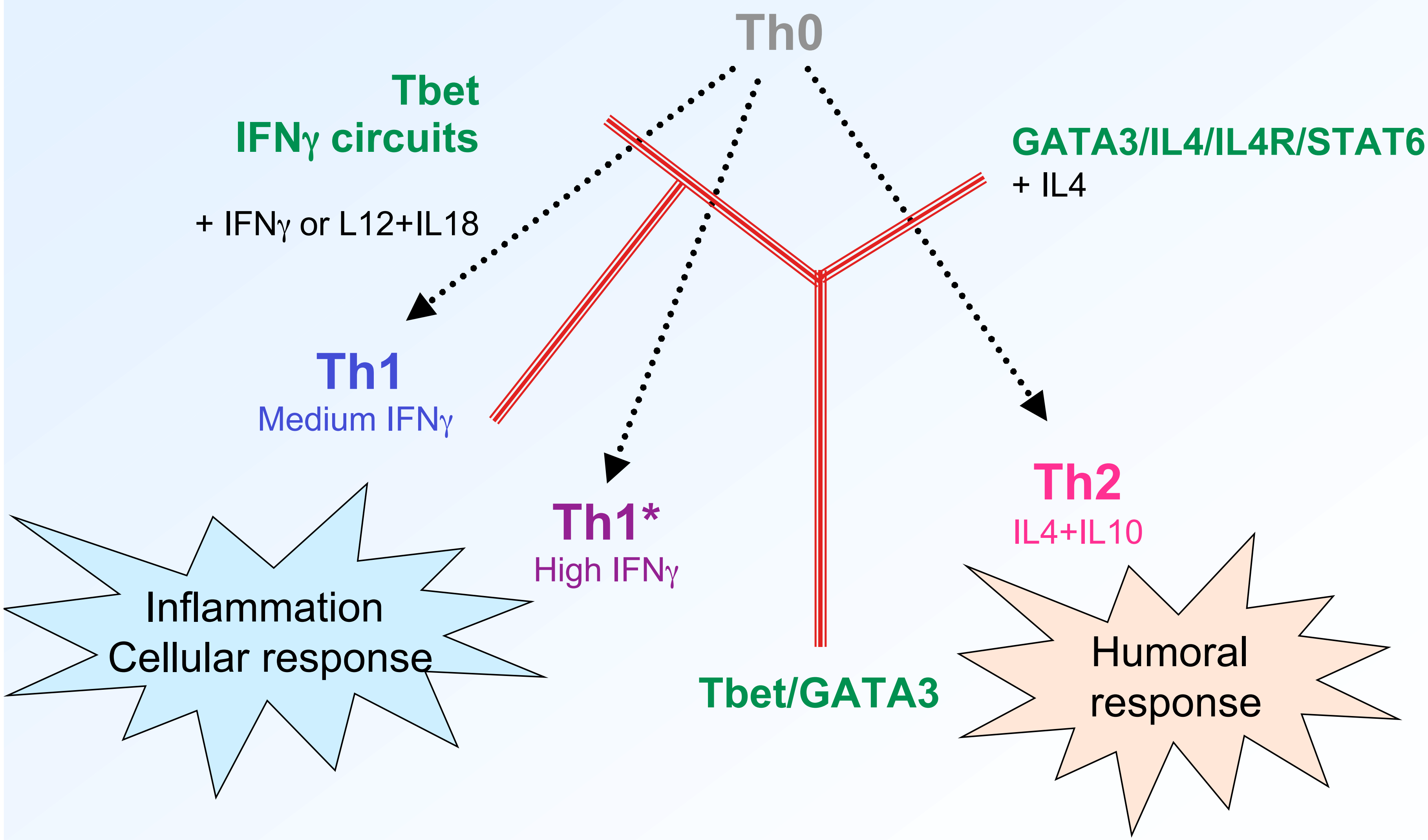
Application: Th differentiation



Mendoza L (2006)
BioSystems **84**: 101-14.

- 5 functional (positive) circuits among 22
- 4 stable states:
  - Th0 (naive)
  - Th1 and Th1* (cellular response)
  - Th2 (humoral response)

Attractors and feedback circuits



Mutant simulations

Genetic background	Predicted phenotypes	Desactivated Circuits
Wild type	Th0, Th1, Th1*, Th2	5 functional positive circuits
Tbet KO	Th0, Th2	Tbet, GATA3/Tbet
Tbet KI (high)	Th1*	Tbet, GATA3/Tbet
GATA3 KO	Th0, Th1, Th1*	GATA3/Tbet, GATA3/IL4/IL4R/STAT6
GATA3 KI	Th1 & Th1* like, Th2	GATA3/Tbet, GATA3/IL4/IL4R/STAT6
GATA3+Tbet DKO	Th0	T-bet, GATA3/Tbet, GATA3/IL4/IL4R/STAT6
GATA3+Tbet DKI	Th1* like	T-bet, GATA3/Tbet, GATA3/IL4/IL4R/STAT6
IFNγ KI (high)	Th1*	IFNγ circuits

Qualitative agreement with documented perturbations

Take-home messages

- **Flexibility** of logical/discrete modelling
- **Versatility** (gene regulation, cell cycle, differentiation...)
- **Analytical developments** (circuits functionality, stable state)
- Insights into **topology - dynamics relationships**
- **Implementation** of novel algorithms into ***GINsim***

Prospects

- **Methodological developments**
  - Determination of complex attractors
  - Further elaboration of circuit analysis

- **Th model**
  - Extension to other regulatory components (IL2)
  - Other differentiative pathways (Treg and T17)
  - Model composition (Tcell activation and differentiation)

Current supports

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