

Logical modelling of the cell cycle in yeast and mammals

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Cell cycle

GINsim

Priorities

Work in
progress

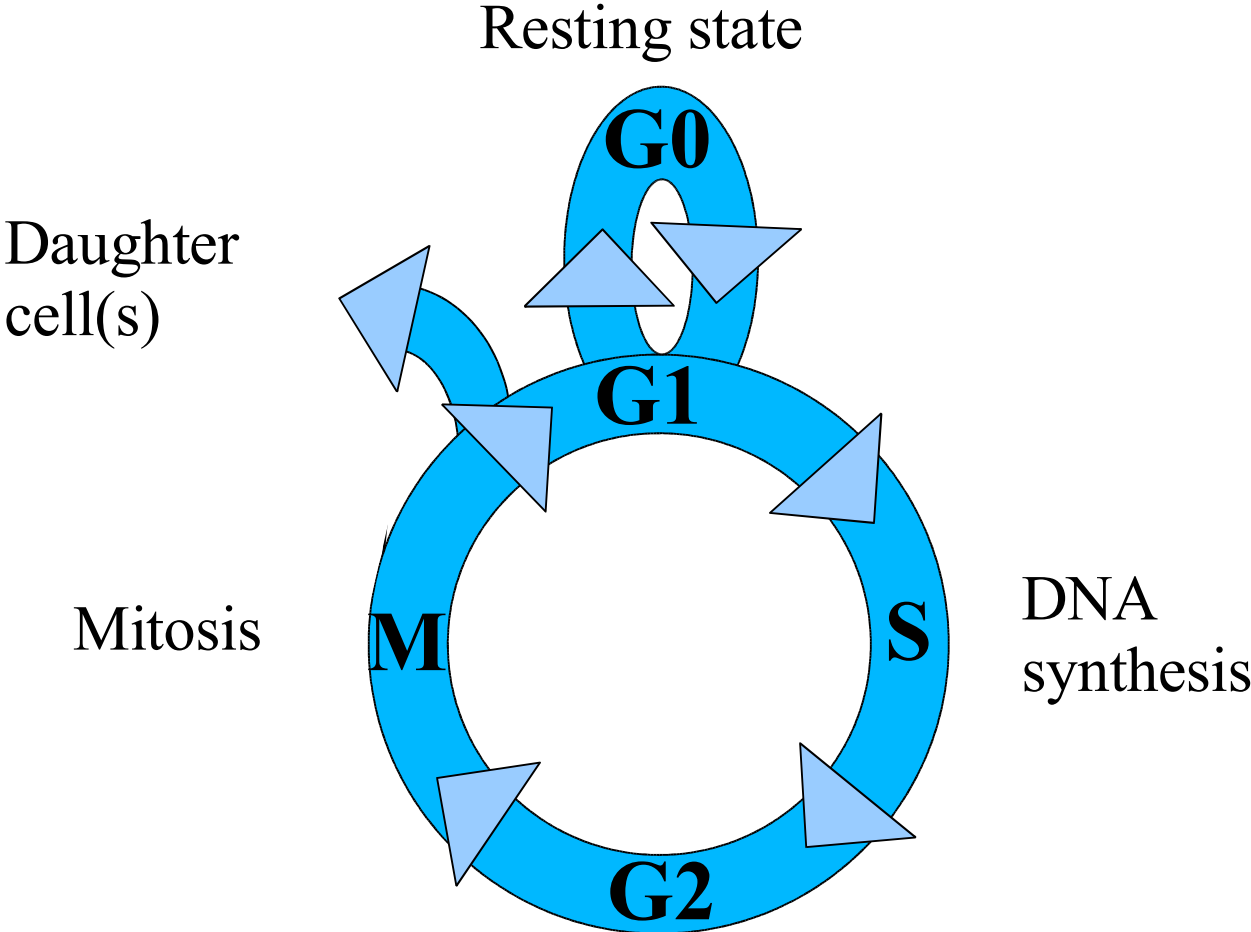
Conclusion

Introduction

The **cell cycle** is at the center of many different research problematics:
cancer, development, differentiation, ageing, cloning...

It is thus crucial to develop our **understanding** of the system, and a **model** is a **necessary** step, given the **complexity**.

The cell cycle



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Checkpoints

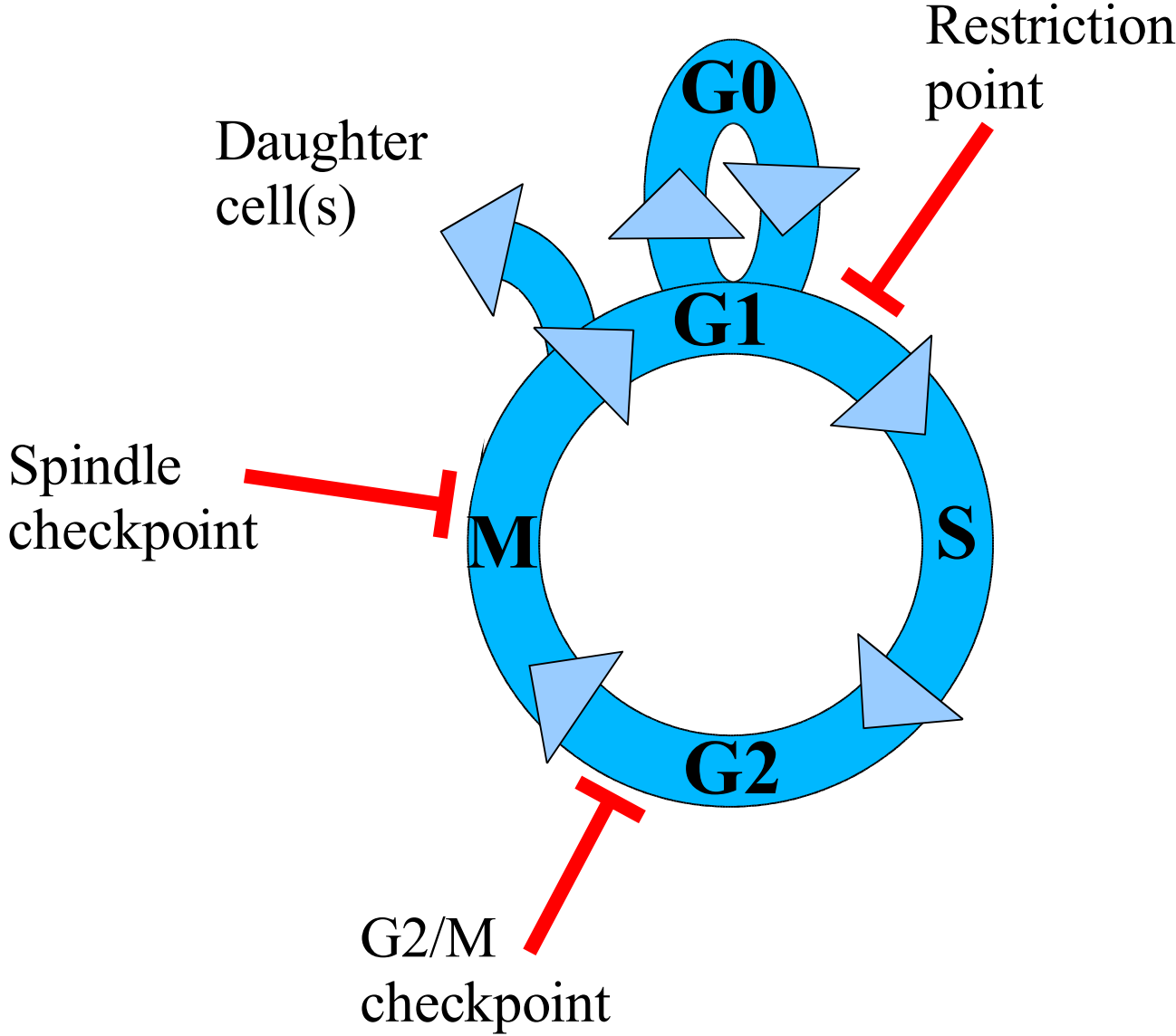
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Molecular actors

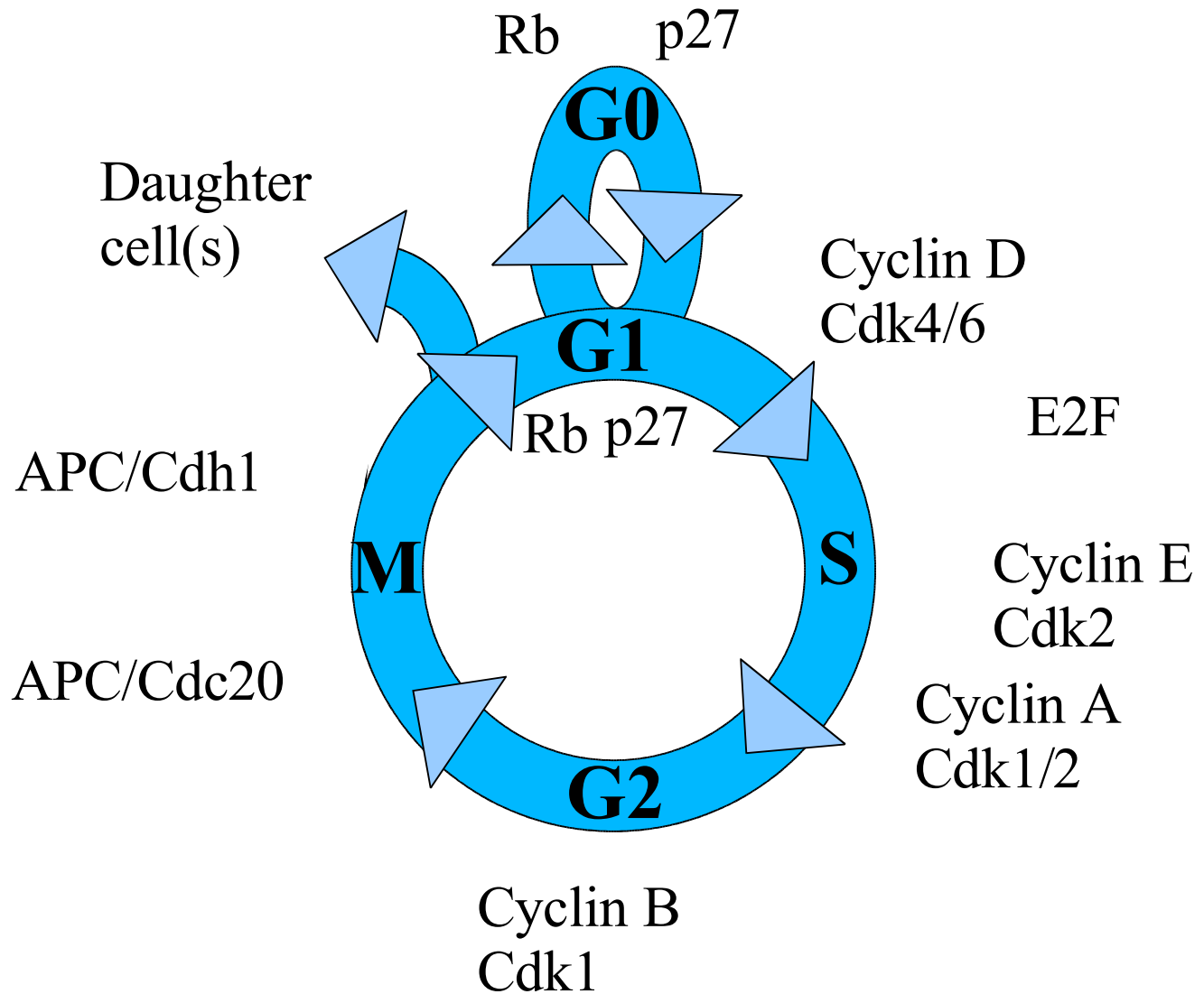
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Kohn's map

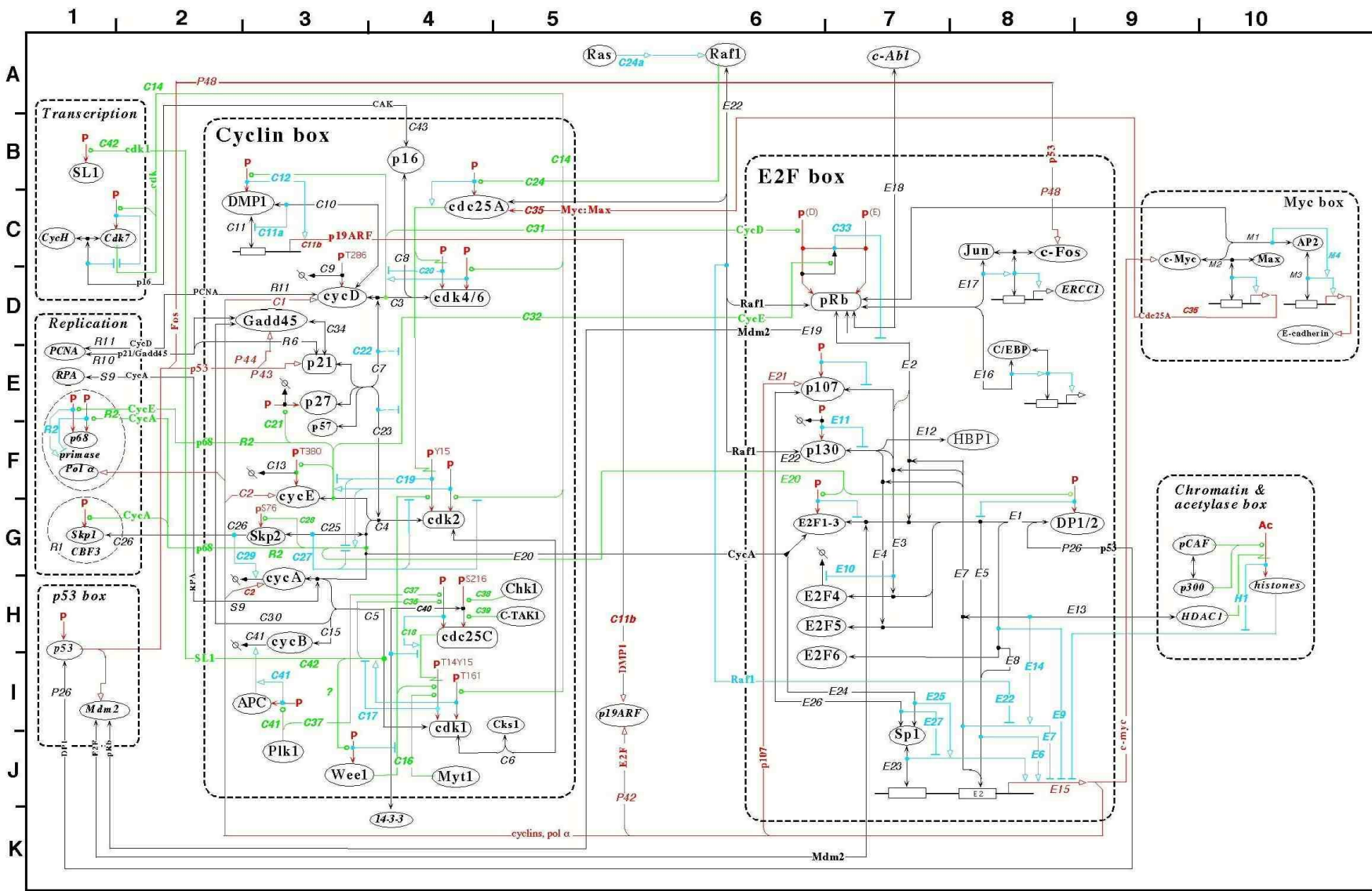
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Kohn (1999), Molecular Biology of the Cell 10, 2703-2734

The core oscillator

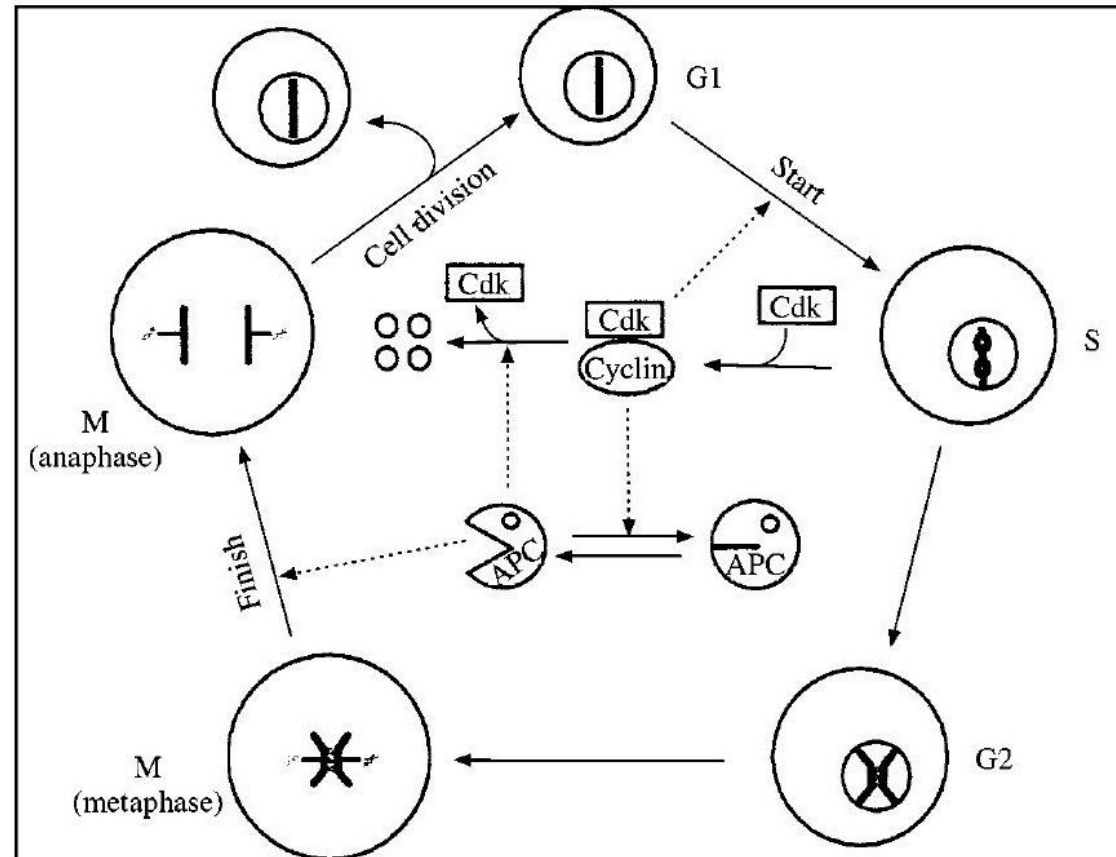
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Tyson, J.J. and Novak, B. (2001). J. Theor. Biol. 210:249-263.

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Logical modelling

- **Qualitative**

- ◆ Coarse-grained
- ◆ But **good approximation**
- ◆ **Intuitive**

- **Simple**

- ◆ Limited discrete **parameter** space
- ◆ **Extension** relatively **easy**
- ◆ **Modular** approach

- **Analytical tools**

- ◆ Stable states, cyclic **attractors**
- ◆ **circuit** analysis

Cell cycle

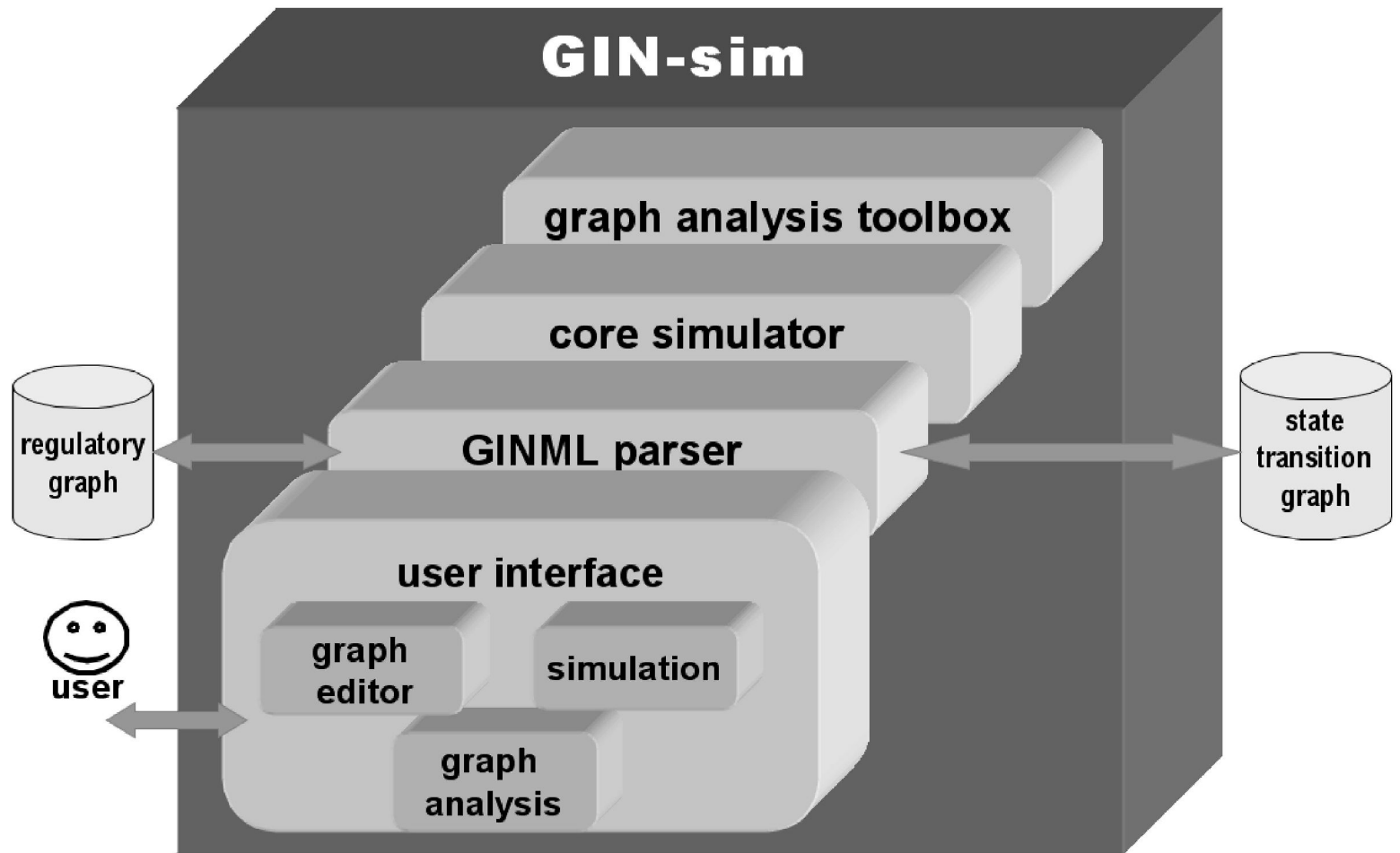
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<http://gin.univ-mrs.fr/GINsim/>

Regulatory graph

- **Nodes**

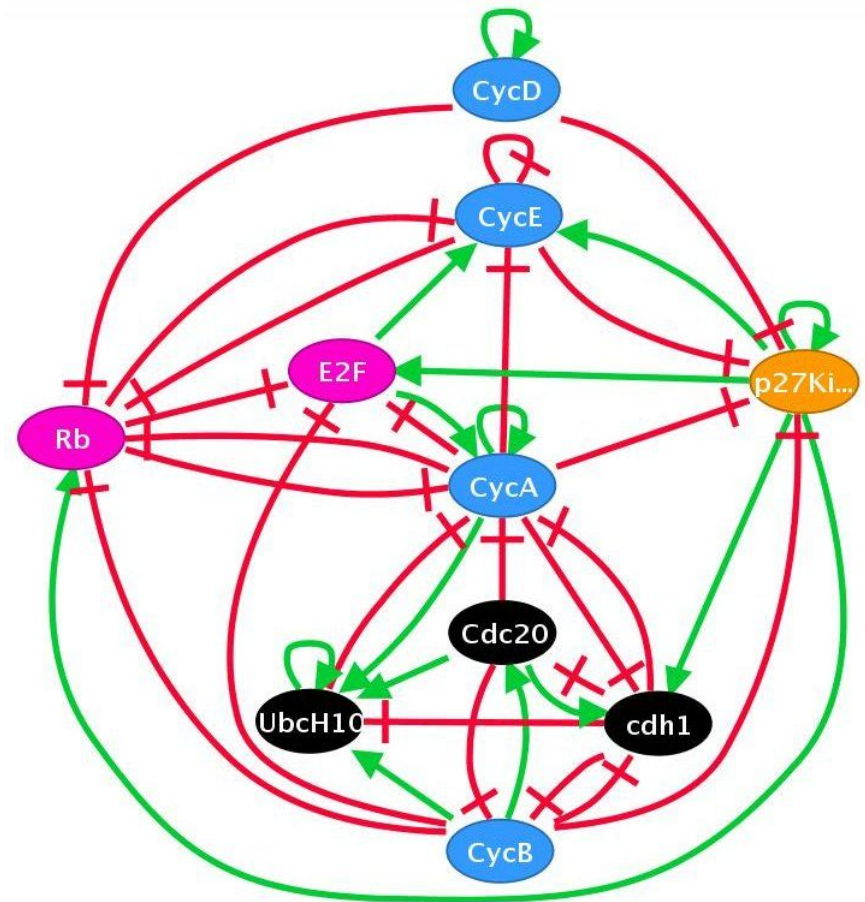
- ◆ regulators (proteins...)
- ◆ discrete levels of expression

- **Arcs**

- ◆ directed interactions

- **Logical parameters**

- ◆ Rules directing the dynamics of the system



attributs de modelisation		attributs graphiques		attributs du graphe	
nom		valeur	interactions actives	<<	cdh1 0 [1,Max] -
id	CycA	1	E2F_0	X	Cdc20 0 [1,Max] -
max	1	1	E2F_0 CycA_0	▲	CycA 0 [1,Max] +
basale	0	1	E2F_0 cdh1_0	▼	E2F 0 [1,Max] +
notes	parametres	1	CycA_0 E2F_0 cdh1_0		UbcH10 0 [1,Max] -
			1 E2F_0 UbcH10_0		Rb 0 [1,Max] -
			1 CycA_0 UbcH10_0		

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Updating assumptions

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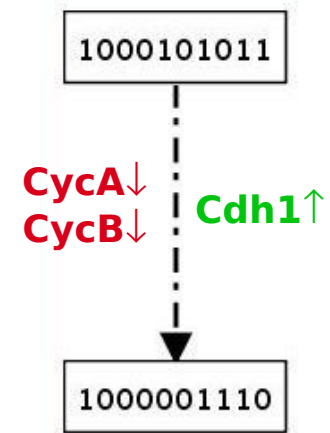
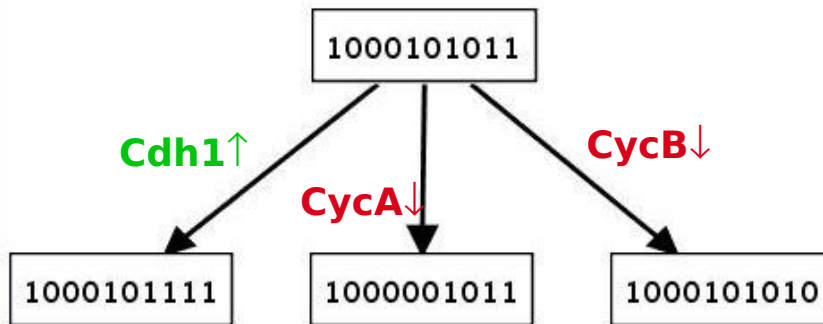
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Asynchronous

Synchronous

CycD Rb E2F CycE **CycA** p27 **Cdc20** Cdh1 **UbcH10** **CycB**



Asynchronous state transition graph

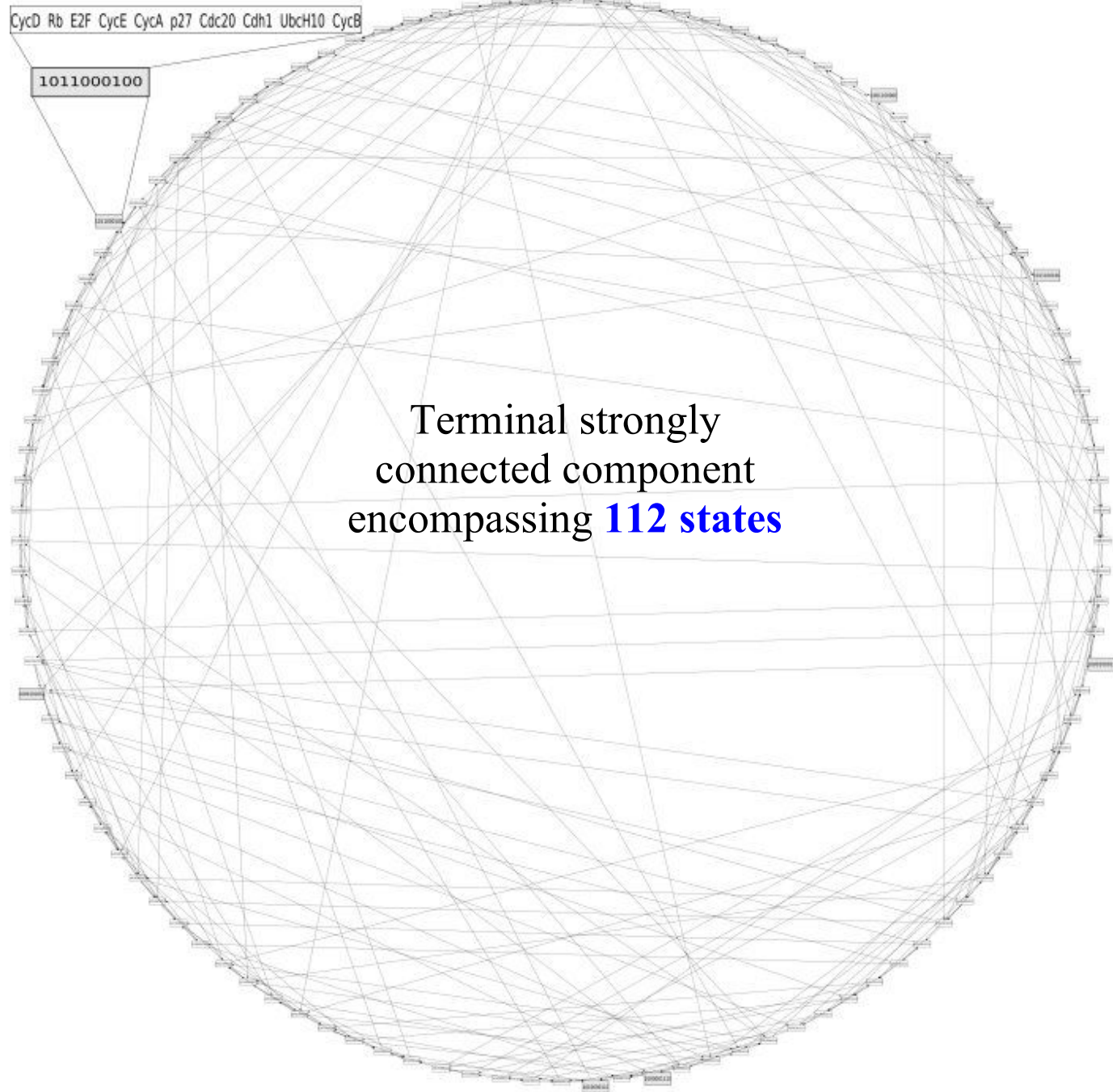
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Synchronous state transition graph

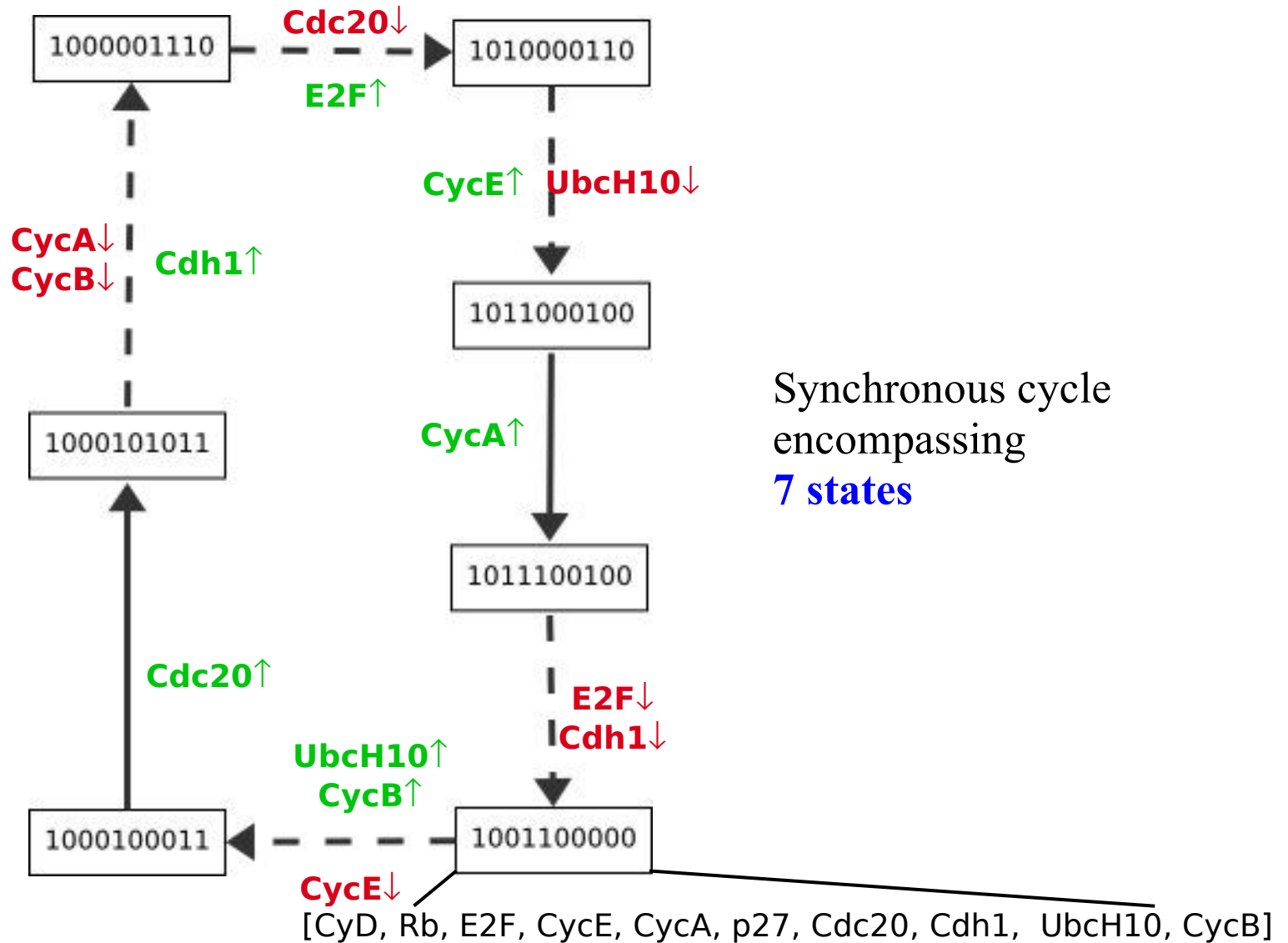
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Defining transition priorities

Both **synchronous** and **asynchronous** assumptions may generate **artifacts**:

- synchronous: **independent** processes are **coupled**
 - **artificial** transitions
 - **lack of precision.**
- asynchronous: **temporal undetermination**
 - **artefactual** pathways
 - **cyclic attractor** gets **very large**

Hence the need for an **intermediate** assumption.

Mixed (a)synchronous assumption and priorities

Use of two **assumptions** to build 2 x 2 priority classes:

1) synthesis rates **slower** than **degradation** rates

➤ 2 different priority classes

2) components regulated by the **same mechanism** are grouped in **synchronous classes**

➤ synchronous versus asynchronous gene sets for each priority level

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Mixed (a)synchronous assumption and priorities

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Rank	Type	Transitions
1	Asynch.	CycD↓↑, Rb↓↑, p27↓↑, Cdh1↓, E2F↓, CycE↓
1	Synch.	CycA↓, Cdc20↓, UbcH10↓, CycB↓
2	Asynch.	E2F↑, CycE↑, CycA↑, Cdc20↑
2	Synch.	UbcH10↑, CycB↑

Mixed state transition graph

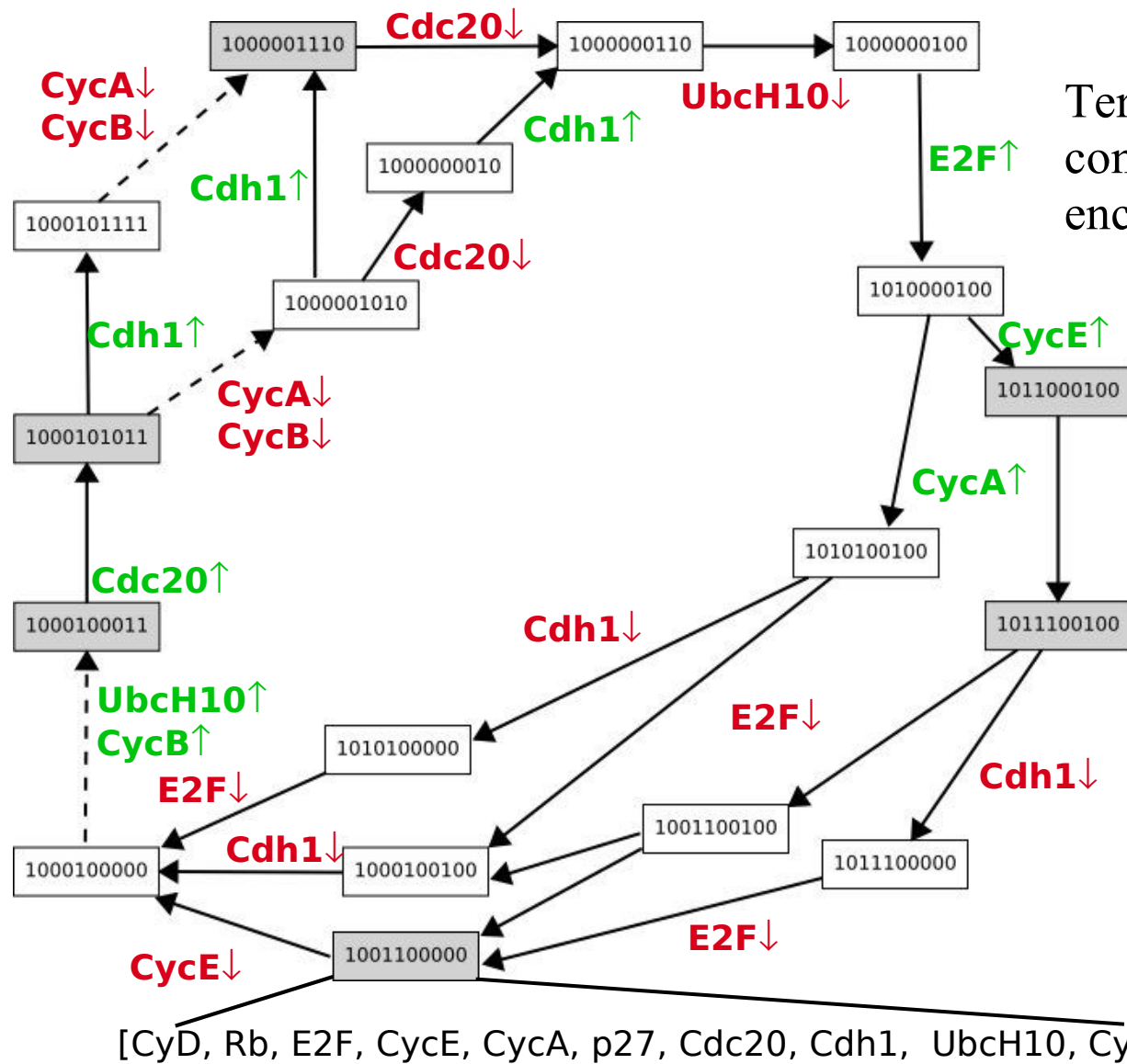
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Work in Progress

Development of a logical model of the **budding yeast** cell cycle (in collaboration with **Andrea Ciliberto**)

- **Well-known** system
- Large number of characterised **mutants**
- Existing ODE models focusing on **specific parts** of the cycle

Goal :

- **one single logical model** integrating all different **modules**.



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Though still very **simple**, our current models grasp the **main aspects** of the system – including **mass** in the yeast model.

The **priority system** allows us to reach the **appropriate temporal precision**, and thus develop more **detailed** and **expanded** models.

Prospects

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- Models

- **Yeast** model
- **Mammalian** model
- **Coupling** of cell cycle with **differentiation**

- Analysis

- **Functionality** of the **regulatory loops**
- **Model-checking**
- **Comparative** analysis of different systems



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Acknowledgements

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