A Discrete Cell Cycle Model :
From Phase Characterization toward Observable Properties Verification

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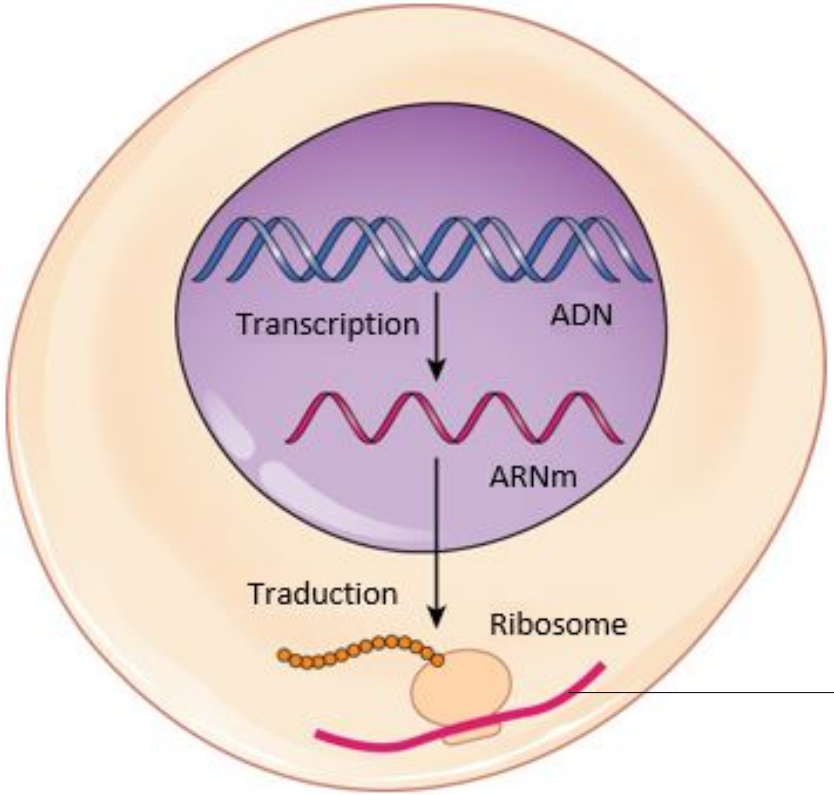
Genetic basic concepts:



[Openstax : Anatomy and Physiology]

Genetic regulatory network modeling:

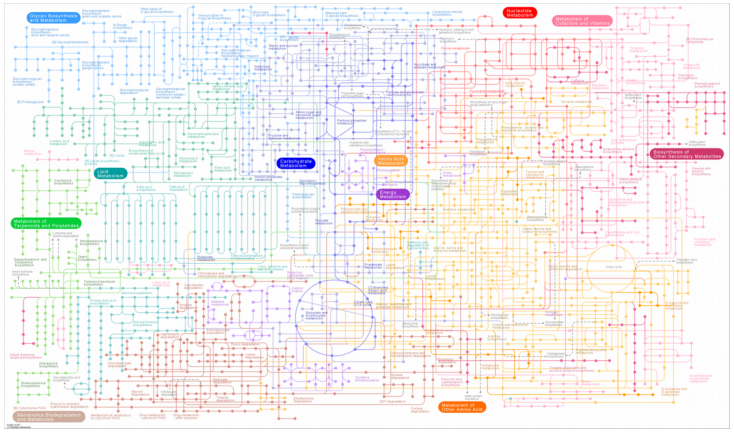
- Prior knowledge gather in an interaction graph and in dynamical parameters
- Prediction of biological behaviors
- Causality analysis

Proteins
Catalytic functions
(e.g. metabolic reactions, cell division)

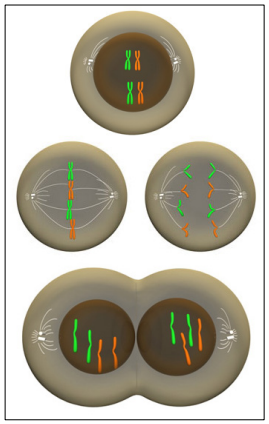
What is the Scientific Context ?

Modeling of coupled biological systems

KEGG metabolism pathways

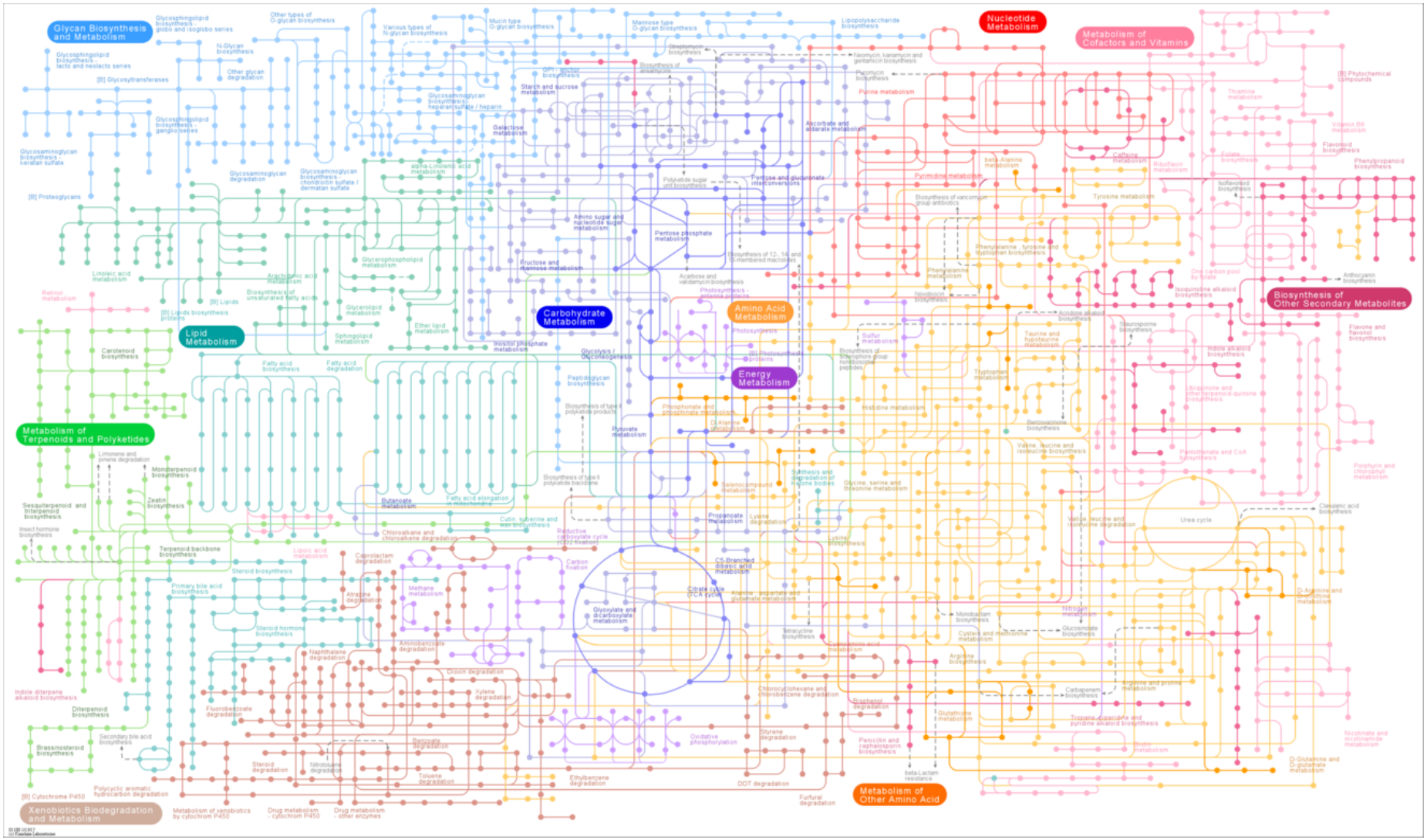


Cell cycle



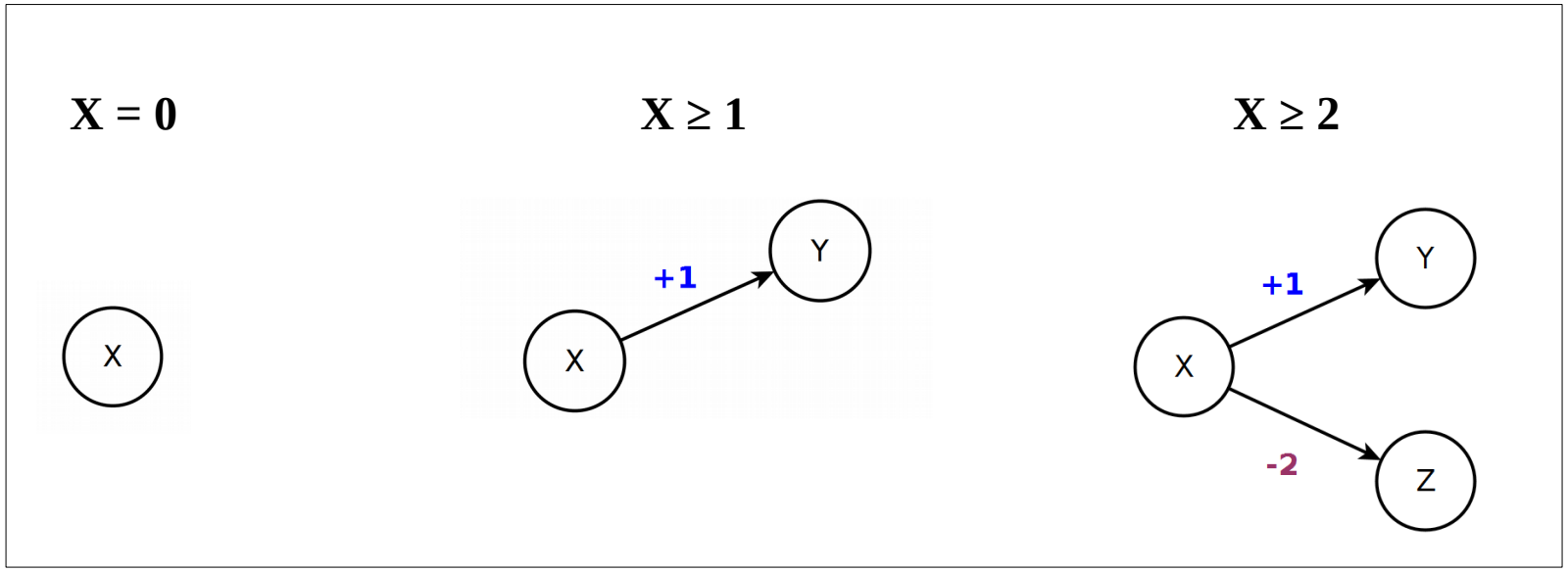
- Coupling of the metabolism and cell cycle in healthy proliferative cells
- Metabolism dynamic according to cell cycle phases and various environmental conditions
- Model consistency is verified by phase-dependent phenotypes

KEGG metabolism pathways, mus musculus



René Thomas' Formalism
Some reminders

[Activation | Inhibition] threshold:

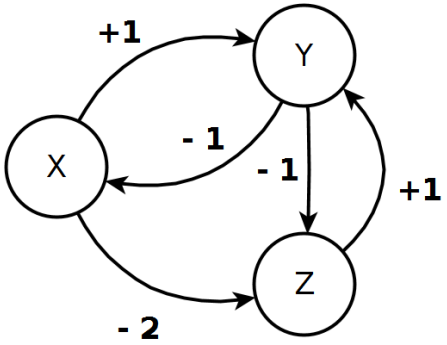


Resources:
Presence of activator(s)
Absence of inhibitor(s)

Parameters:
Discrete value
attractors

State space:
Discretized
concentration space

Interaction Graph



Parameters of Y :

$K_{Y,\{\}}$

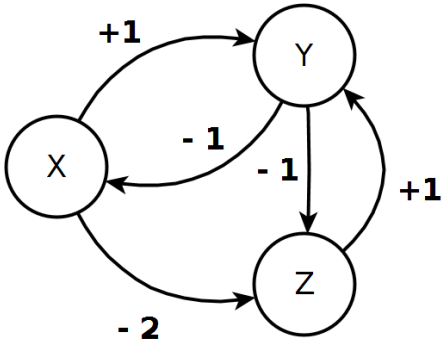
$K_{Y,\{X\}}$

$K_{Y,\{Z\}}$

$K_{Y,\{XZ\}}$

René Thomas' Formalism
An abstract discrete modeling framework

Interaction Graph



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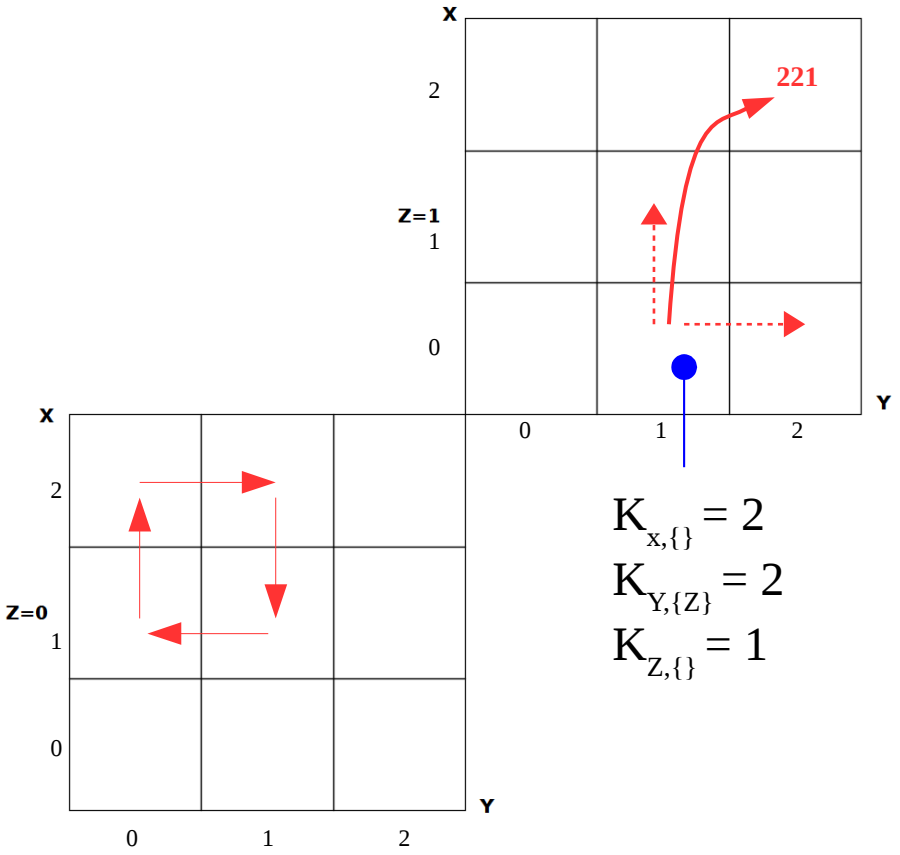
Discrete State Space:



$K_{x,\{\}} = 2$

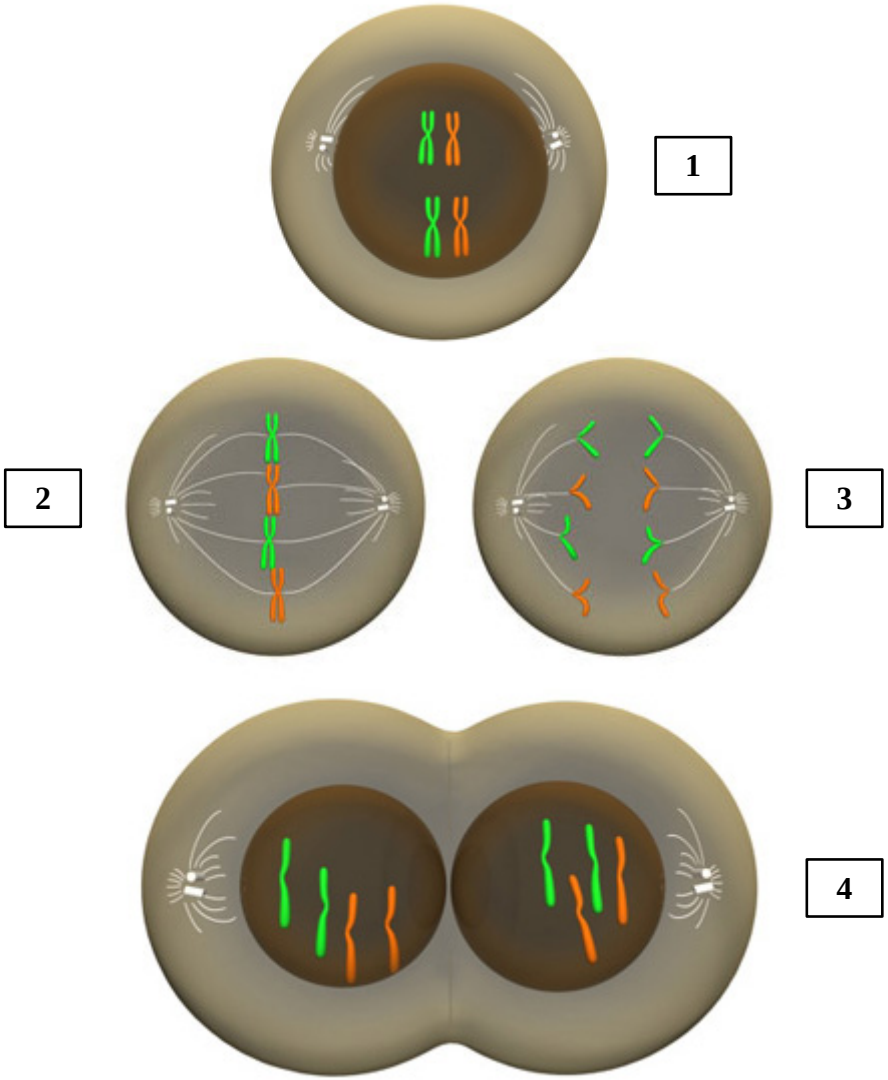
$K_{Y,\{Z\}} = 2$

$K_{Z,\{\}} = 1$

- **Biological example of state:**
  X ≥ 1: Glycolysis ON
  Y ≥ 1: Krebs ON
  Z ≥ 1: Mitosis ON

- Is a state reachable ? Stable ?

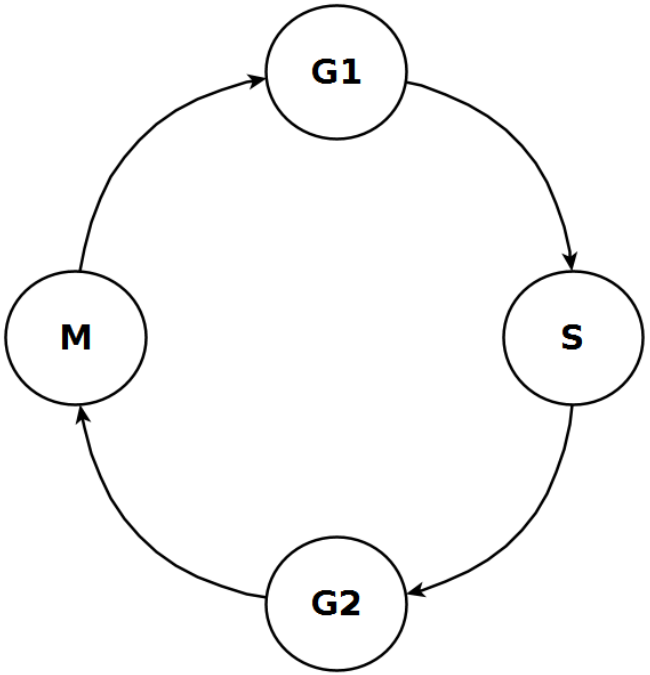
- Does a variable oscillate ?



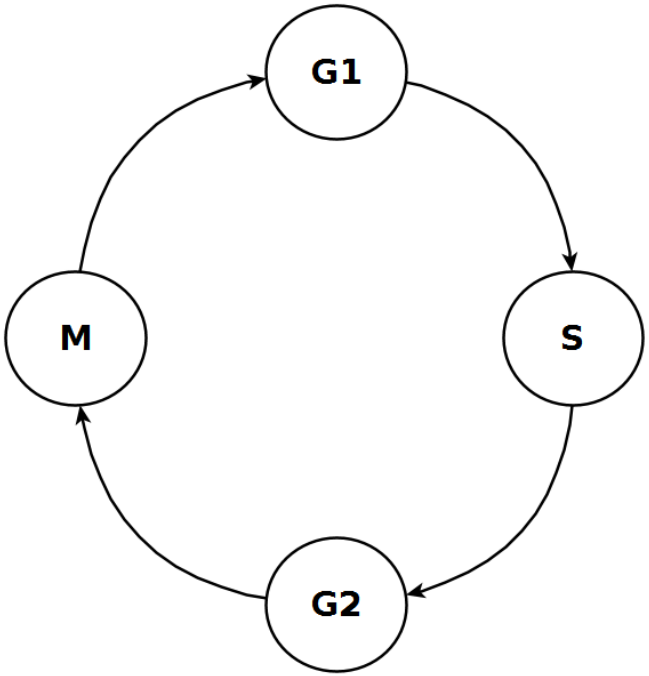
Nature Education

Cell cycle :

- DNA duplication **[1]**
- Equal DNA distribution **[2] [3]**
- Cell division **[4]**

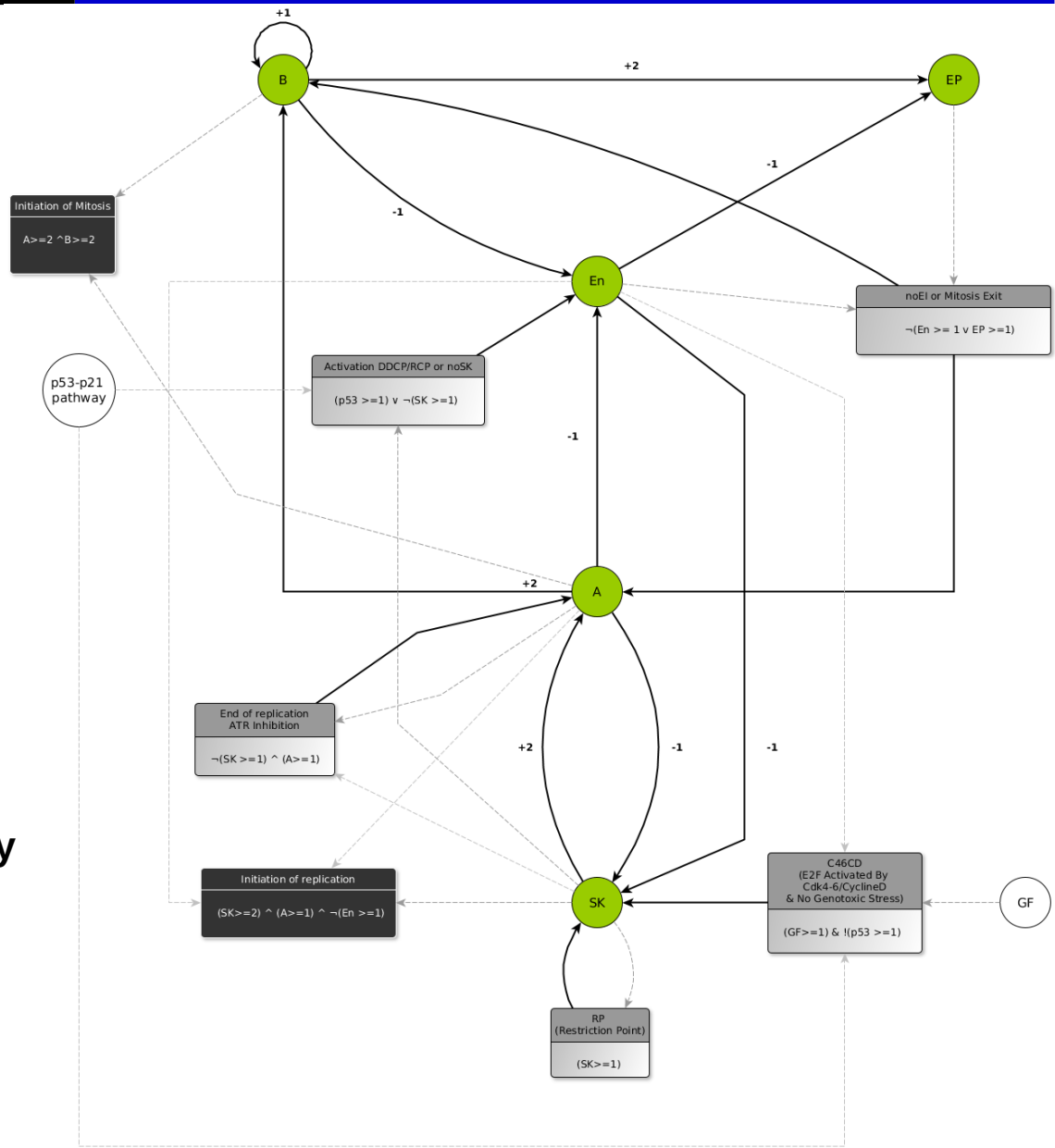


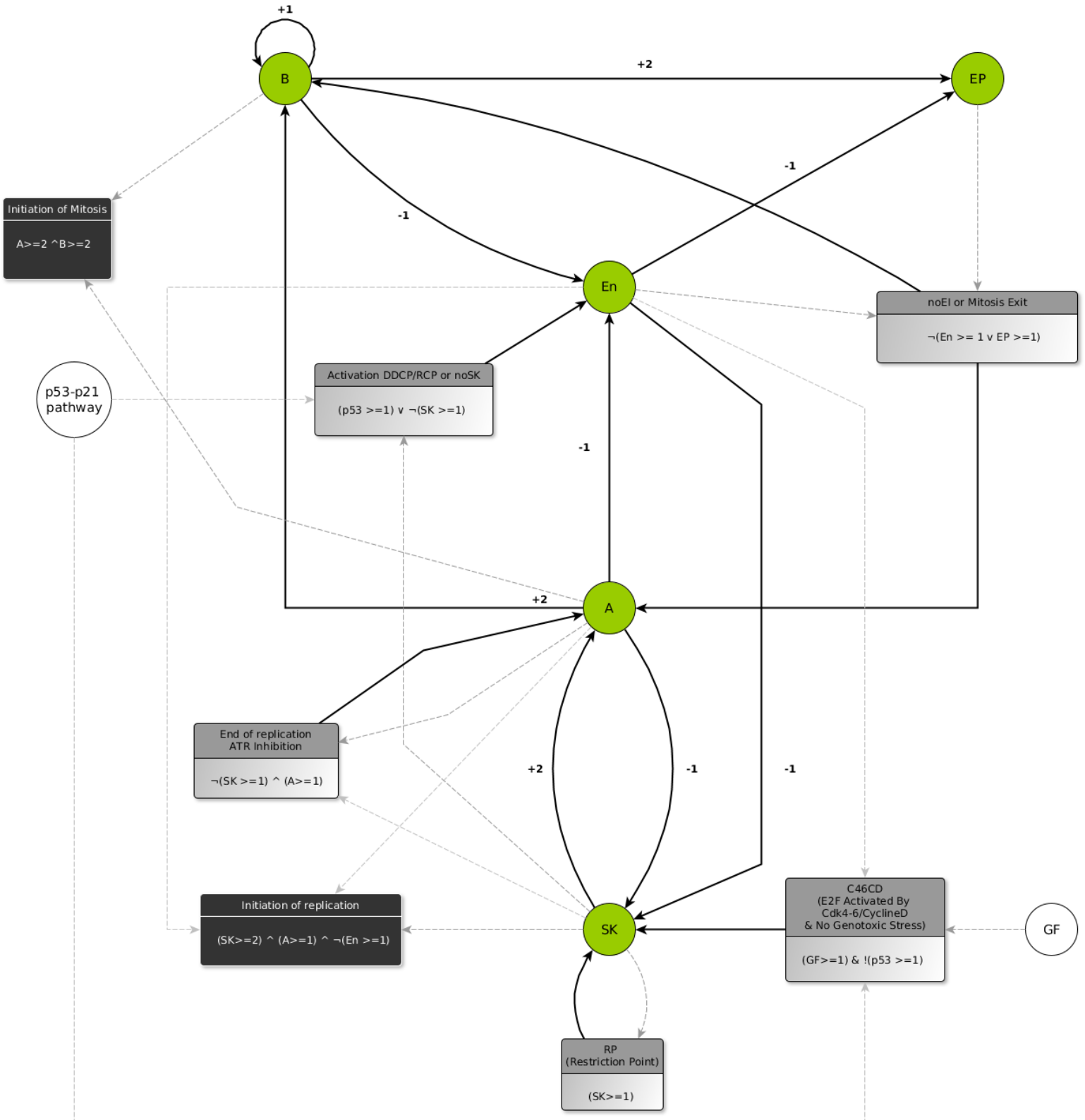
A Mammals Cell Cycle Discrete Model
The Cell Cycle and its Regulatory Network



Cell cycle progression is driven by a **regulatory networks** of:

- **Cyclins**
- **Phosphatases**




+1
B
+2
EP
-1
-1
Initiation of Mitosis
A>=2 ^B>=2
En
noEI or Mitosis Exit
¬(En >= 1 v EP >=1)
p53-p21
pathway
Activation DDCP/RCP or noSK
(p53 >=1) v ¬(SK >=1)
-1
+2
A
End of replication
ATR Inhibition
¬(SK >=1) ^ (A>=1)
+2
-1
-1
Initiation of replication
(SK>=2) ^ (A>=1) ^ ¬(En >=1)
SK
C46CD
(E2F Activated By
Cdk4-6/CyclineD
& No Genotoxic Stress)
(GF>=1) & !(p53 >=1)
GF
RP
(Restriction Point)
(SK>=1)

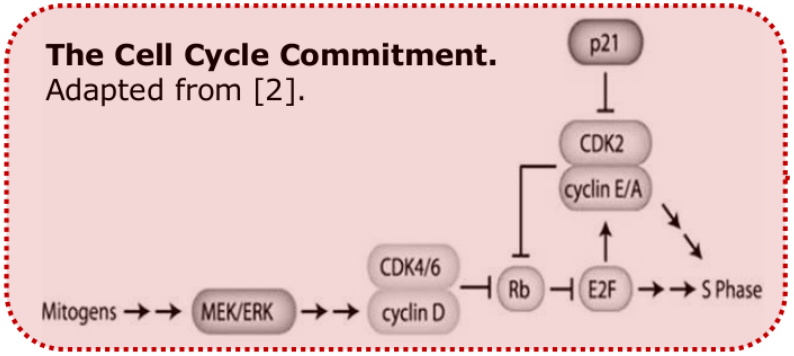
A Mammals Cell Cycle Discrete Model
Interaction Graph

5 systemic variables :

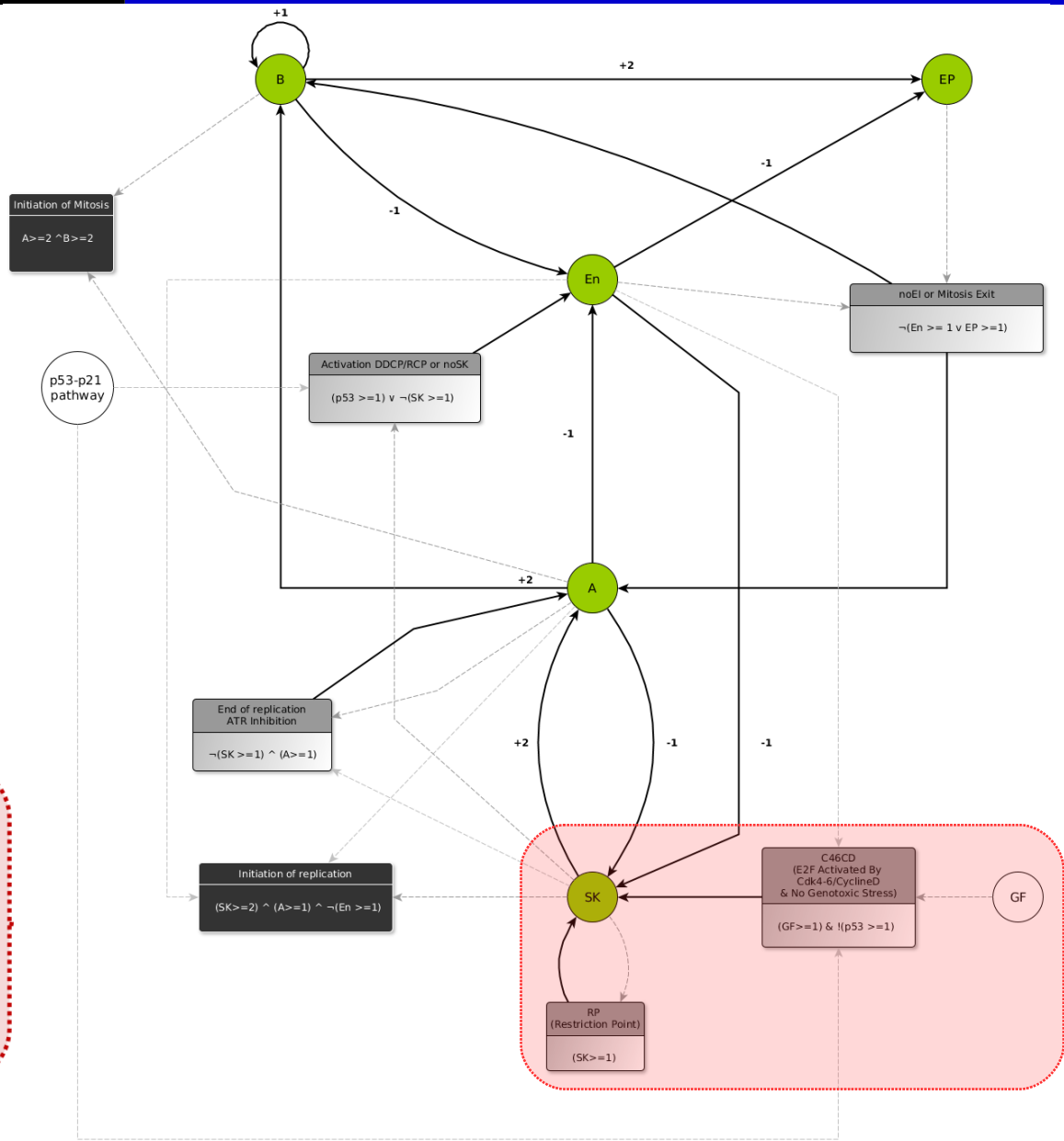
- **SK** : CycE/Cdk2
- **A** : CycA/Cdk2-1
- **B** : CycB/Cdk1
- **En** : p21, p27, APC-cdh1, Wee1, PP1A, PP2A.
- **EP** : APC-cdc20

2 environmental variables :

- GF : Growth Factors
- p53



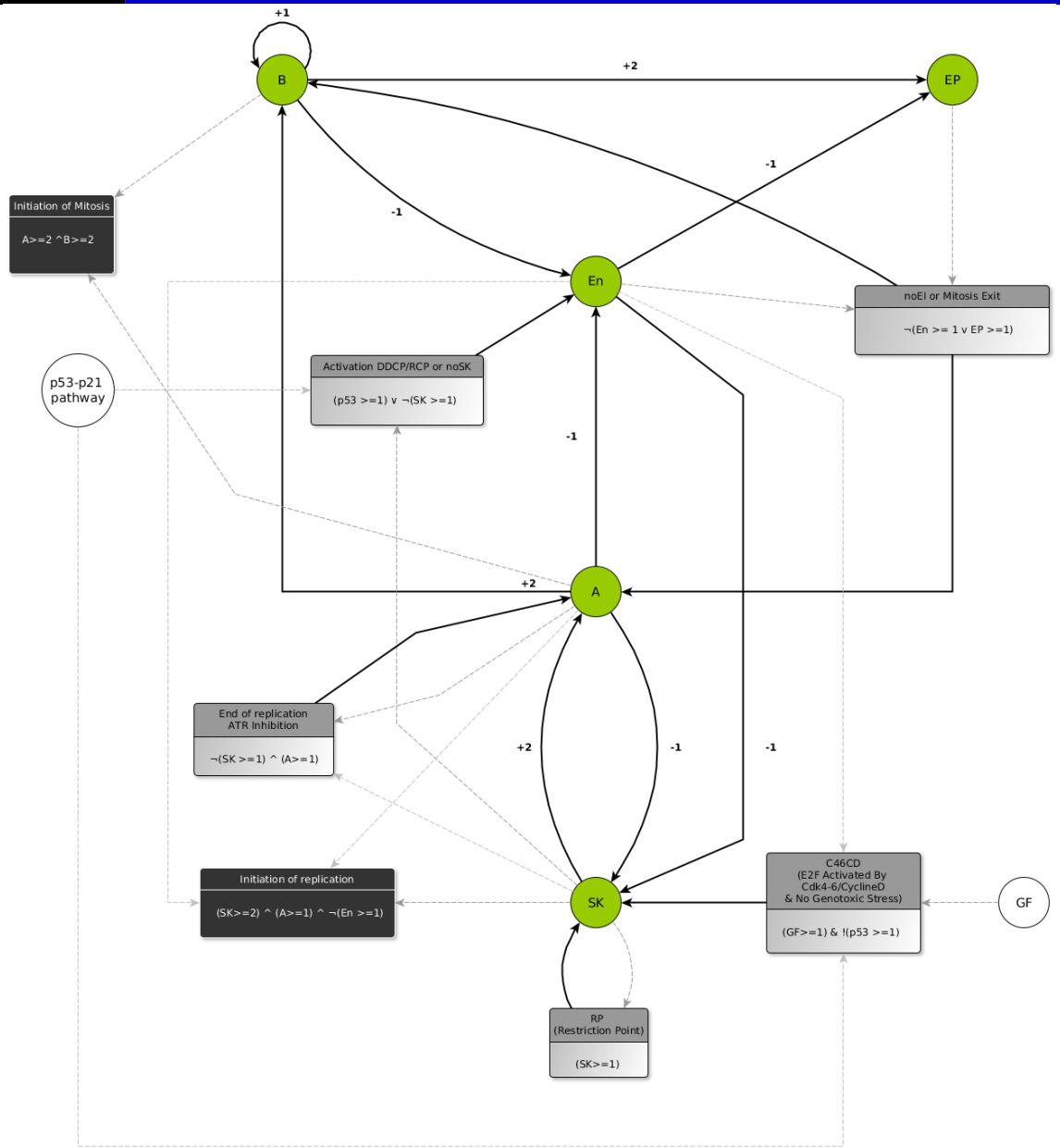
[2] Spencer SL et al. Cell 2014.



A Mammals Cell Cycle Discrete Model
Parameterization challenge

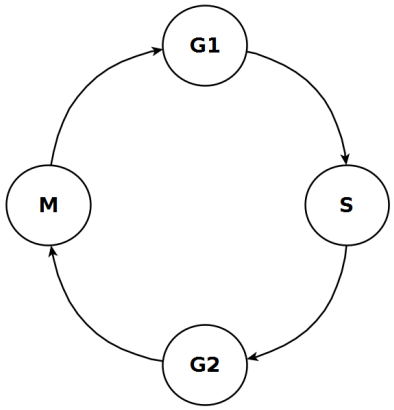
Number of parameterization :
$7.6 \times 10^9 \times 10^9$

Goal :
Identify parameterizations satisfying biological behaviors using f**ormal methods**



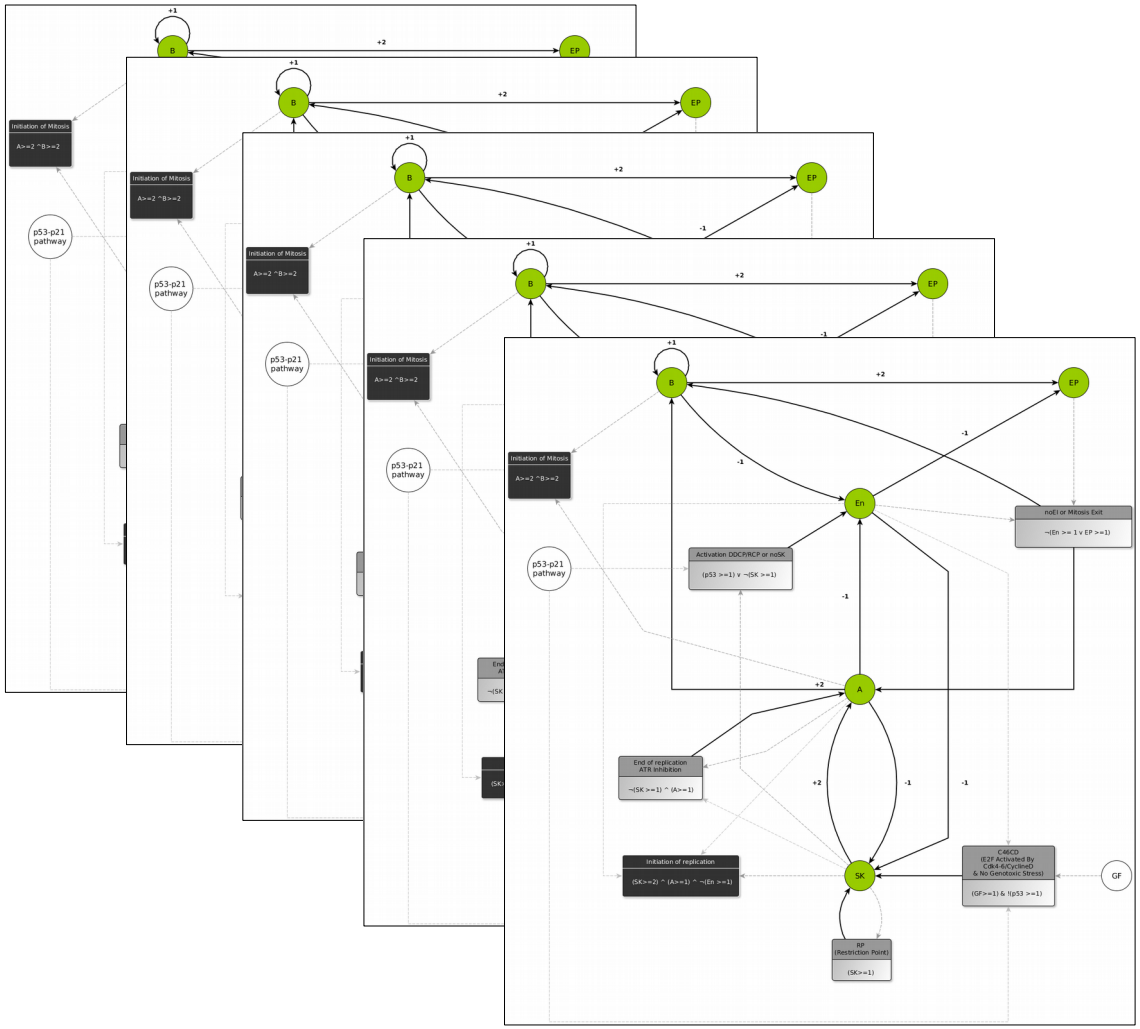
Biological behaviors verification:

- The cell cycle itself by definition



- Blocking phenotypes (*e.g.* growth factors deprivation)

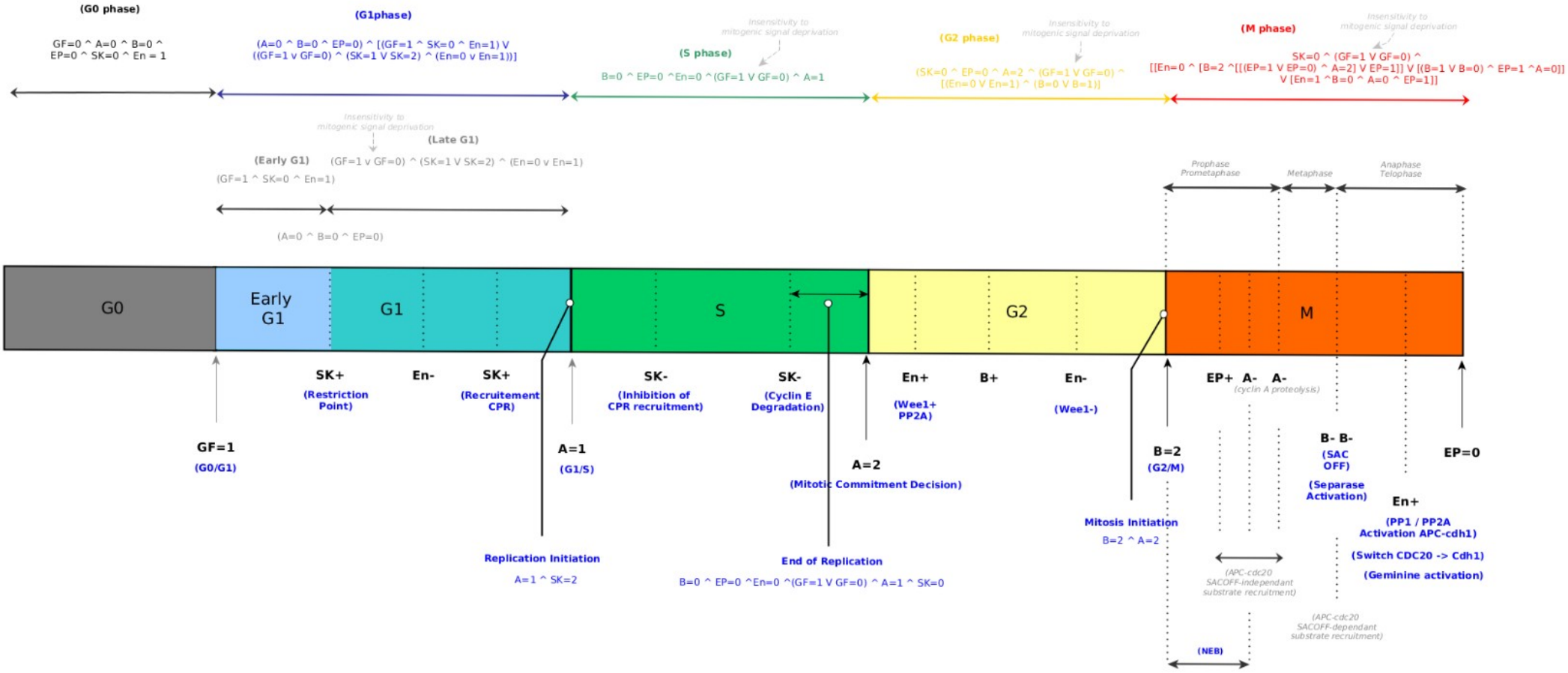
AG(GF = 0) AND (G0) ⇒ AG(G0)



Phase Observability and Model Verification

Biological trace and logical description of phases

Cell cycle verification by Hoare Logic



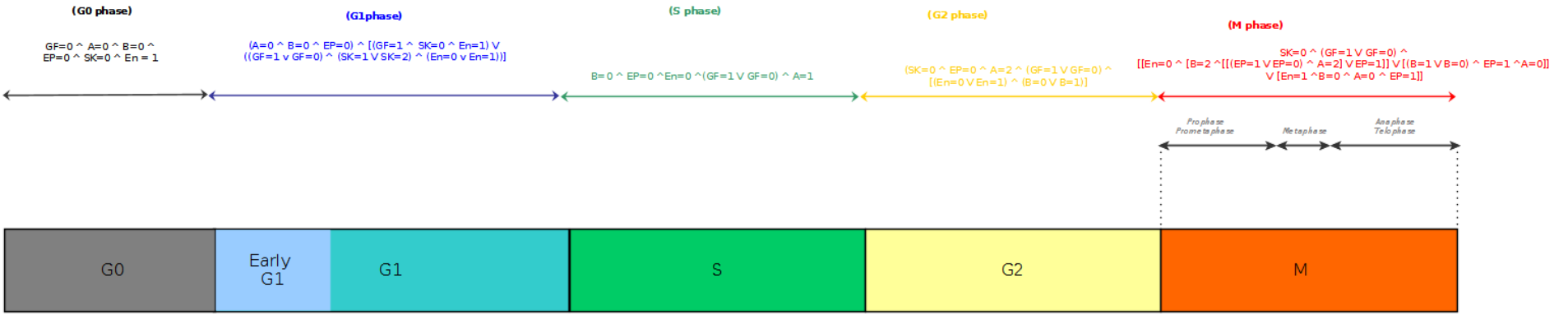
Another cell cycle model

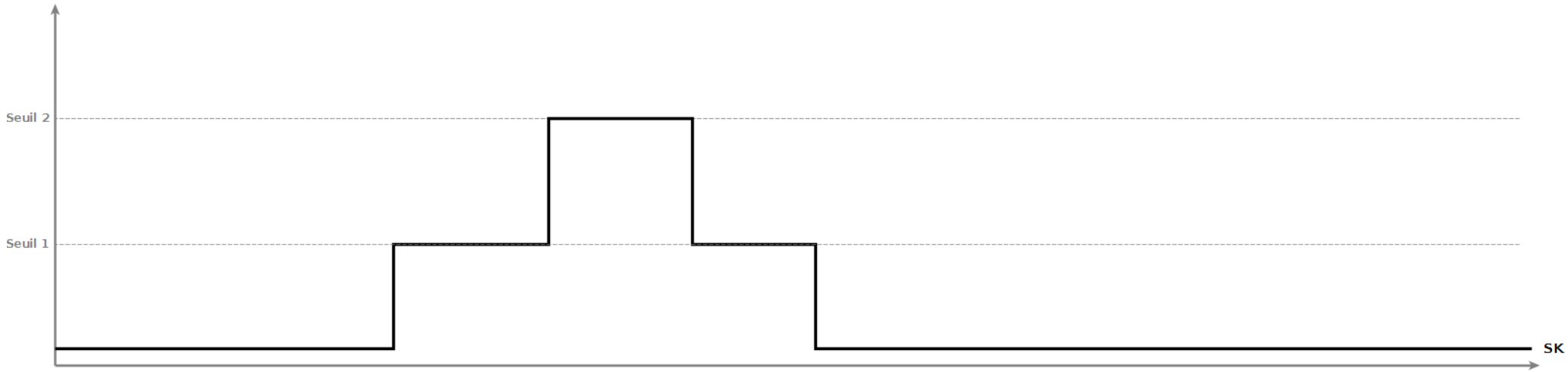
- Cell cycle **coupling** and verification of **phase dependent** phenotypes
- Exploration of reciprocal **links** between cell cycle regulatory network and energetic **metabolism** in the context of **healthy** proliferative **cells**
- Test of **various** "environmental" **conditions** (*e.g.* nutrients of medium culture, genetic variations, pharmacological inhibition)
- Study of anticancer drug **toxicity** on healthy proliferative cells

Phase Observability and Model Verification

Biological trace and Cyclins Dynamics

It exists a path that satisfies these sustained oscillations :





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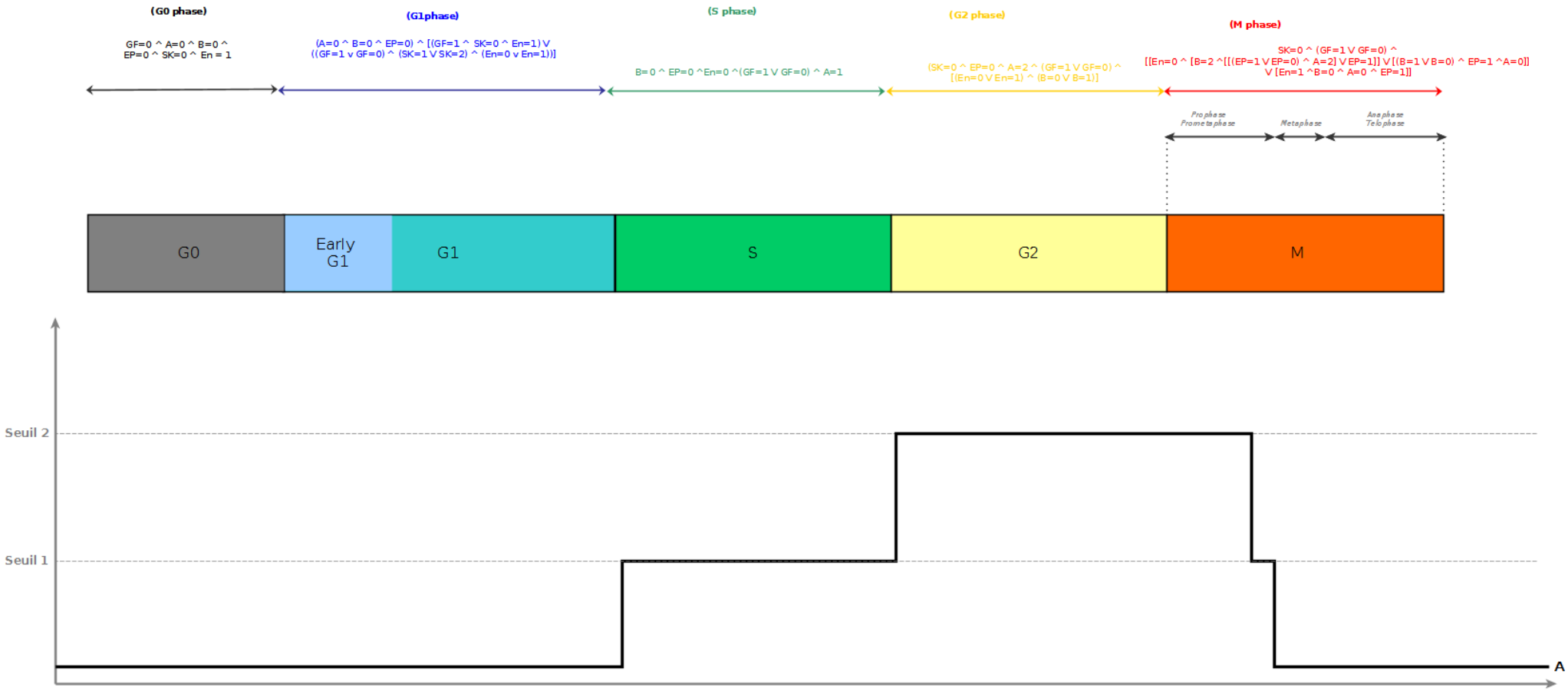

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