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

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The **cell cycle** is series of events that lead to correct duplication of a cell DNA (S-phase) and its equal distribution into two daughter cells (M-phase). Progression through cell cycle is driven by a **regulatory network** of cyclin-dependent kinases (CDKs) and phosphatases. Recent studies highlight non-canonical function of CDKs and phosphatases notably in regulation of carbon and energy **metabolism** according to **cell cycle phases** : G1, S, G2 and M phases. Based on a **qualitative** modeling framework, a discrete model of the regulation of cell cycle has been designed. Using **formal methods**, model parameterization is constrained notably by a **biological trace**, describing the complete sequence of regulatory events during cell cycle phases. This model will underlie coupling between cell cycle and metabolism in order to explain metabolic reprogramming across cell cycle phases.

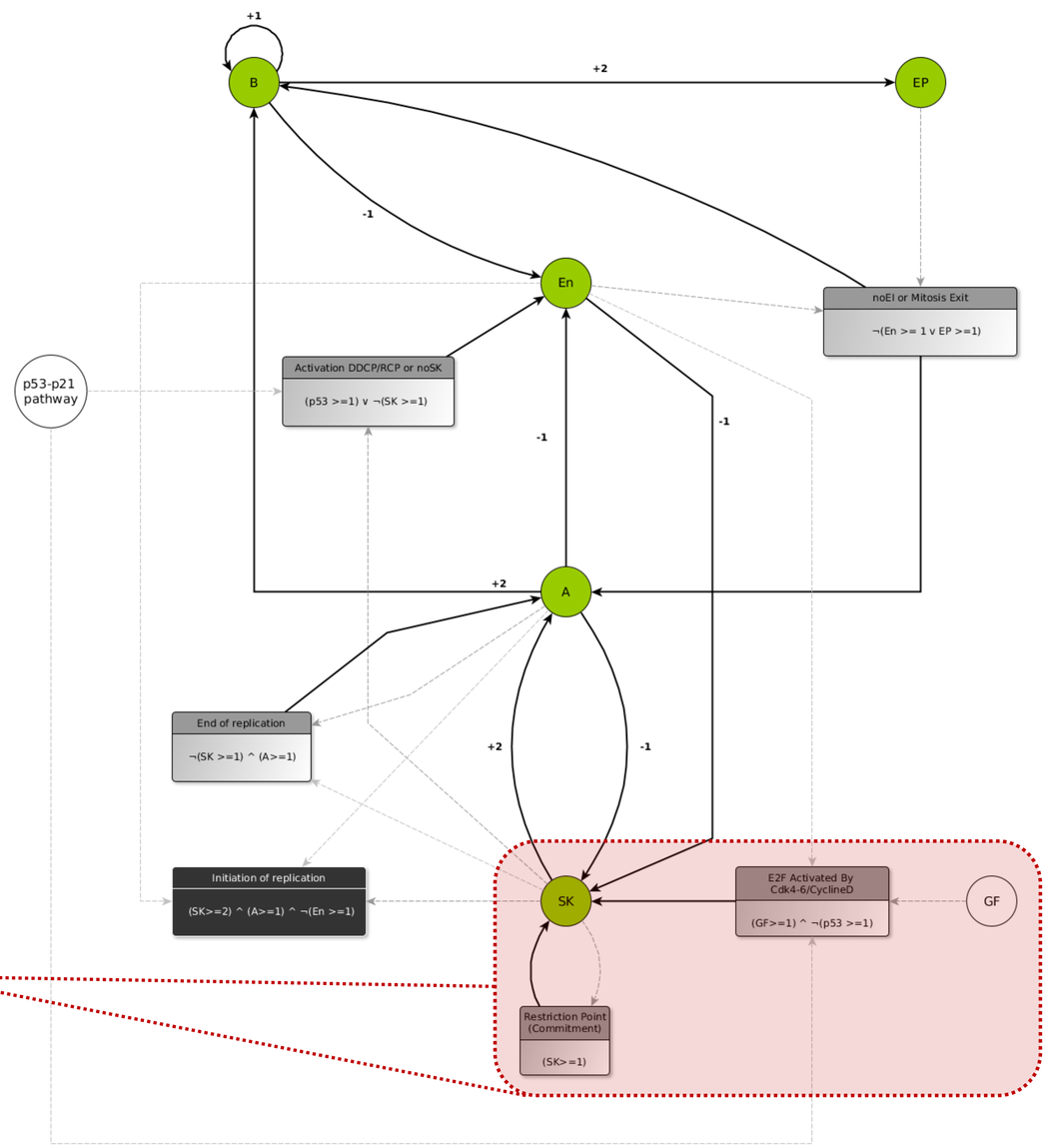
1 The Thomas' Modeling Framework

Discrete Thomas' modeling framework represents qualitative dynamic of **abstract** biological entities (*e.g.* mRNAs, proteins or pathways). Concentration space is divided into hypercubes (interval products) called discrete **states** separated by thresholds. A threshold represents a mandatory concentration above which an entity is active on one of its target.

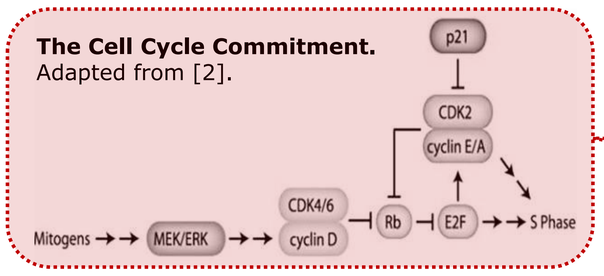
GF	SK	A	B	En	EP
Growth Factors (*e.g.* FGFs)	*Starting Kinase :* Cdk2/CycE	Cdk2/CycA Cdk1/CycA	Cdk1/CycB	*Ennemies :* p21, p27, APC-cdh1, Wee1, PP1,PP2	*Exit Protein :* APC-cdc20

Static knowledge are represented by an **interaction graph** where nodes (circles) are biological entities, edges are either an inhibition (-) or activation (+). The network **global dynamics** is governed by a set of parameters *K*. **Parameter identification** is a crucial step in modeling process.

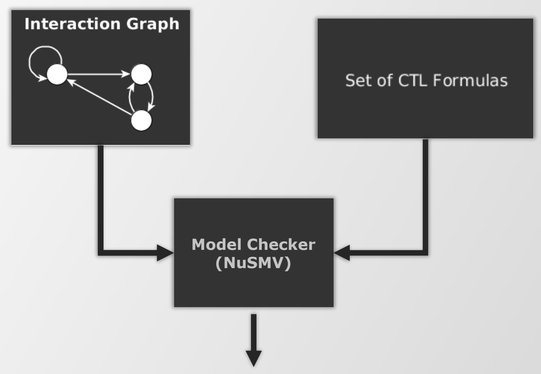
Discrete Interaction Graph of Mammalian Cell Cycle Regulation



The Cell Cycle Commitment.
Adapted from [2].



2 Model-Checking



{Set of models that satisfy CTL formulas}

Model checking is a formal method that tests if a model (interaction graph + a parameterization) satisfies CTL formulas that encode biological behavioural properties by exploring the space of states in an exhaustive manner. An intensive use of Model Checking allows the selection of coherent models.

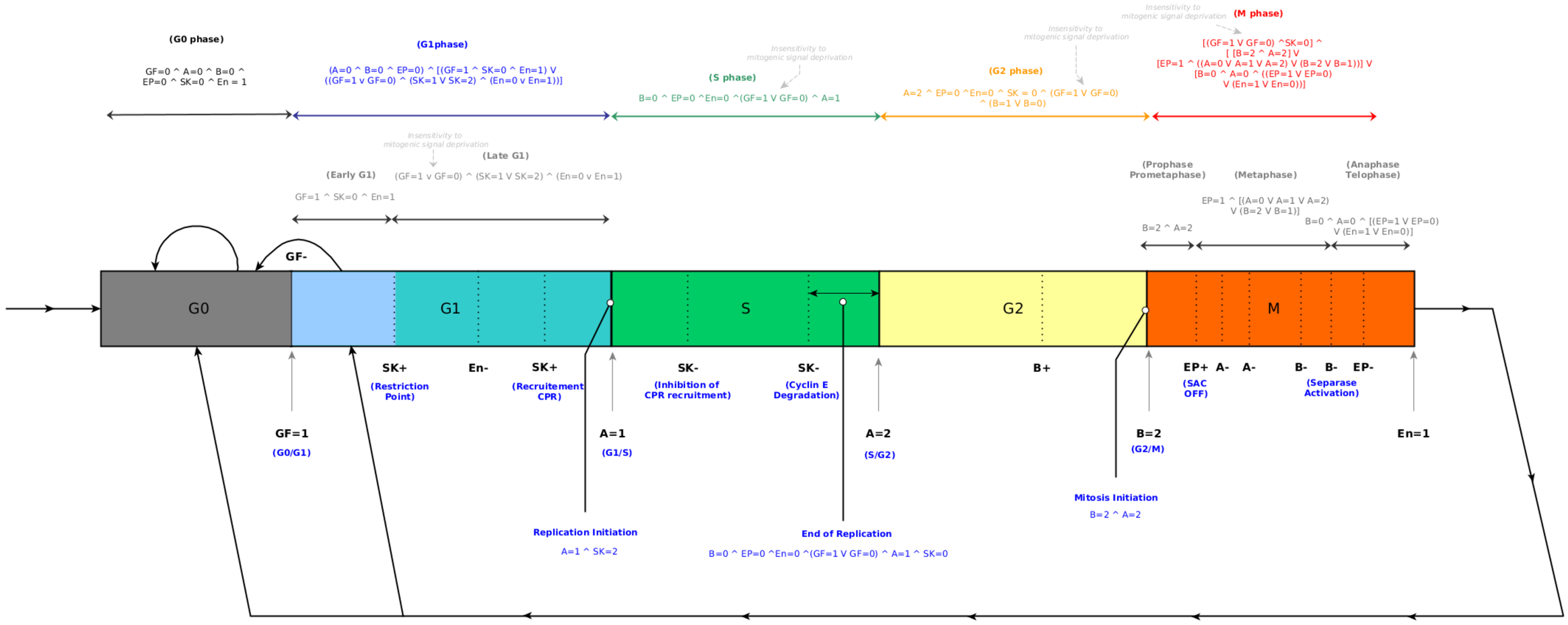
Given the interaction graph of cell cycle regulation and that the quiescence (G0) is described by: GF=*0* ∧ A=0 ∧ B=0 ∧ SK=0 ∧ EP=0 ∧ En=1, the formula (***GF=0 ∧ G0) ⇒ AG (G0)*** means that a constant growth factor deprivation implies a quiescence state stability.

3 Discrete Hoare Logic

Hoare logic is a formal method used to constrain parameter values of discrete regulatory network so that the dynamic of an interaction graph is compatible with a **biological trace**. The cell cycle can be seen as a biological trace determined from experimental observations of the sequence of regulatory events from G0 or G1 to mitosis, see below.

4 Modeling Prospects

A consistent parameterized interaction graph of mammalian cell cycle regulation must presents that series of events. It can be used to elucidate **causal relation** between the cell cycle coupled with other biological systems (*e.g.* the metabolism or circadian clock) and **phase-dependent** phenotypes experimentally observed. One prospect is the understanding of metabolic reprogramming in healthy and cancer cells.



Biological Trace and Logical Description of Cell Cycle Phases

[1] Salazar-Roa M and Malumbres M. Fueling the cell division cycle. *Trends in Cell Biology.* 2017. Vol.27, No. 1. [PubMed: 27746095]
[2] Spencer SL et al. The proliferation-quiescence decision is controlled by a bifurcation in CDK2 activity at mitotic exit. *Cell*. 2014. 155(2): 369 – 383. [PubMed: 24075009]
[3] Bernot G., Comet JP., Richard A. and Guespin J. Application of formal methods to biological regulatory networks : Extending Thomas's asynchronous logical approach with temporal logic. *J.T.B.. 2004.* 229(3): 339-347.