Logical model specification assisted with model checking: application to mammalian cell cycle

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Supplementary tables

Table S1. Comparison of the results of perturbation simulations for the original model of Fauré et al (2006) and the revised

version (cf. Figure 1 and Table 1). All perturbations are encoded in the model available in the repository associated with GINsim.

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p27 KO (early kinetics) Viable cell cycle in presence or OK Rb E1 p27 KO E2F [Rb@0] CycE [Rb@0] CycA[Rb@0] Viable cell cycle in presence or OK p27 KO (cell dependent) Cycle in absence of growth factors Disagreement	SKp2 EI RD E2 E2F [RD(@U] CycE [RD(@U] CycA [RD(@U])]	absence of growth factors	model	
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	p27 KO (cell dependent)	Cycle in absence of growth factors	Disagreement	Disagreement
Kivard et al., 1996; Kotosniba et al., 2014	Rivard et al., 1996; Kotoshiba et al., 2014		- sugi comont	

Table S2. Verification of dynamical biological properties with model-checking. The initial state G1 is represented by

CycE=0 & CycA=0 & CycB=0 & Cdh1=1 in the initial model, and by CycE=0 & CycA=0 & CycB=0 & Cdh1=1 & Rb=1 & p27=1 in the updated model. The initial state G2 is represented by Rb=0 & Cdh1=0 & p27=0 & CycE=0.

Biological property	Sequences of events verified by model-checking	Original model	Updated model
Dbserved sequence for eyclins only	1. Correct sequence starting from G1: CycE=0 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=0 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=0 -> CycE=0 & CycA=0 & CycB=1 -> CycE=0 & CycA=0 & CycB=1 -> CycE=0 & CycA=0 & CycB=0	ОК	OK
Observed sequence for Ill species	2. Correct sequence defined in Figure 2 (with p27, Rb and Skp2 OFF) and Figure 3.	OK but with p27, Rb and Skp2 OFF	OK
rreversibility of CycE nactivation	3. Incorrect sequence starting from G1: CycE=0 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=1 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=0 -> CycE=1 & CycA=1 & CycB=0	OK	OK
reversibility of CycA nactivation	4. Incorrect sequence starting from G1: CycE=0 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=1 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=1 -> CycE=0 & CycA=0 & CycB=1 -> CycE=0 & CycA=1 & CycB=1	OK	ОК
rreversibility of CycB nactivation	5. Incorrect sequence starting from G1: CycE=0 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=1 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=1 -> CycE=0 & CycA=0 & CycB=1 -> CycE=0 & CycA=0 & CycB=0 -> CycE=0 & CycA=0 & CycB=1	No	No
equential activation of CycE and CycA	6. Incorrect sequence starting from G1 (activation of CycA before CycE): CycE=0 & CycA=0 -> CycE=0 & CycA=1 -> CycE=1 & CycA=1	No	OK
Degradation of CycE n S phase, activation f CycB in G2 phase	7. Incorrect sequence starting from G1 (CycB activation before CycE inactivation): CycE=0 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=1 & CycA=1 & CycB=0 -> CycE=1 & CycA=1 & CycB=1 -> CycE=0 & CycA=1 & CycB=1 -> CycE=0 & CycA=0 & CycB=1 -> CycE=0 & CycA=0 & CycB=0	No	No
ynthesis of CycA in arly S phase, ctivation of CycB in 32 phase	8. Incorrect sequence starting from G1 (CycB activation before CycA activation): CycE=0 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=1 -> CycE=1 & CycA=1 & CycB=1	OK	OK
Degradation of CycA n early mitosis, legradation of CycB in ate mitosis	9. Incorrect sequence starting from G1 (CycB inactivation before CycA inactivation): CycE=0 & CycA=0 & CycB=0 -> CycE=1 & CycA=0 & CycB=0 -> CycE=1 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=0 -> CycE=0 & CycA=1 & CycB=1 -> CycE=0 & CycA=1 & CycB=0 -> CycE=0 & CycA=0 & CycB=0	No	No
Complete removal of CycB is essential to orevent spindle theckpoint after sister thromatid disjunction	10. Incorrect sequence starting from G1 (CycE activation before CycB inactivation): CycE=0 & CycA=0 & CycB=0 ->CycE=1 & CycA=0 & CycB=0 ->CycE=1 & CycA=1 & CycB=0 ->CycE=0 & CycA=1 & CycB=0 ->CycE=0 & CycA=1 & CycB=1 ->CycE=0 & CycA=0 & CycB=1 ->CycE=1 & CycA=0 & CycB=1	OK	OK
Feedforward loop that nsures that cells dvance to S-phase	11. Correct sequence starting from G1: CycE=0 & CycA=0 & p27=1 -> CycE=1 & CycA=0 & p27=1 -> CycE=1 & CycA=0 & p27=0 -> CycE=1 & CycA=1 & p27=0 -> CycE=0 & CycA=1 & p27=0	No	OK
rreversibly: hosphorylation of Rb by CycE to release E2F	12. Incorrect sequence starting from G1 (p27 inhibited without CycE): CycE=0 & CycA=0 & p27=1 -> CycE=0 & CycA=0 & p27=0 -> CycE=1 & CycA=0 & p27=0 -> CycE=1 & CycA=0 & p27=0 -> CycE=0 & CycA=1 & p27=0 & p27	No	OK
nd increase the ynthesis of CycE, long with the hosphorylation of p27	13. Incorrect sequence starting from G1 (CycA activated before p27 inhibition): CycE=0 & CycA=0 & p27=1 -> CycE=1 & CycA=0 & p27=1 -> CycE=1 & CycA=1 & p27=1	No	ОК
Degradation of B yclins by the APC/C omplex is required for nitosis to take place	14. Correct sequence from G2: CycA=1 & CycB=0 & Cdc20=0 -> CycA=1 & CycB=1 & Cdc20=0 -> CycA=1 & cycB=1 & Cdc20=1 -> CycA=0 & CycB=1 & Cdc20=1 -> CycA=0 & CycB=0 & cdc20=1 -> CycA=0 & CycB=0 & Cdc20=0 15. Incorrect sequence from G2 (inactivation of CycB without Cdc20):	ОК	OK
CycA=1 & CycB=1 & Cdc20=0 16. Incorr CycA=1 &	CycA=1 & CycB=0 & Cdc20=0 -> CycA=1 & CycB=1 & Cdc20=0 -> CycA=1 & CycB=1 & Cdc20=1 -> CycA=0 & CycB=1 & Cdc20=1 -> CycA=0 & CycB=1 & Cdc20=0 -> CycA=0 & CycB=0 & Cdc20=0 16. Incorrect sequence from G2 (inactivation of CycA without Cdc20): CycA=1 & CycB=0 & Cdc20=0 -> CycA=1 & CycB=1 & Cdc20=0 ->CycA=0 &	_	
2dh1 is not required or mitotic exit	CycB=1 & Cdc20=0 ->CycA=0 & CycB=0 & Cdc20=0 17. Correct sequence from G2 (mitosis exit without Cdh1): CycA=1 & CycB=0 & Cdc20=0 & Cdh1=0 -> CycA=1 & CycB=1 & Cdc20=0 & Cdh1=0 -> CycA=1 & CycB=1 & Cdc20=1 & Cdh1=0 -> CycA=0 & CycB=1 & Cdc20=1 & Cdh1=0 -> CycA=0 & CycB=0 & Cdc20=1 & Cdh1=0 -> CycA=0 & CycB=0 & Cdc20=0 & Cdh1=0	ОК	OK
JbcH10 is required for he destruction of nitotic cyclins and ther mitosis-related ubstrates	18. Incorrect sequence from G2 (mitosis exit without UbcH10) : CycA=1 & CycB=0 & Cdc20=0 & UbcH10=0 -> CycA=1 & CycB=1 & Cdc20=0 & UbcH10=0 -> CycA=1 & CycB=1 & Cdc20=1 & UbcH10=0 -> CycA=0 & CycB=1 & Cdc20=1 & UbcH10=0 -> CycA=0 & CycB=0 & Cdc20=0 & UbcH10=0 & Cdc20=0 & UbcH10=0 & Cdc20=0 & UbcH10=0 & Cdc20=0 & UbcH10=0 &	No	OK