Table S1. List of biochemical reactions and related reaction rate in the computational model[(a)].

No.[(b)]	Mechanism[(c)]	Reaction rate law/rule[(d)]
r01	CyclinB + CDK1 <-> [CDK1:CyclinB]	kb_CyclinB_CDK1*CyclinB*CDK1 - kub*[CDK1:CyclinB]
r02	CyclinB + CDK1_pY15 <-> [CDK1_pY15:CyclinB]	kb_CyclinB_CDK1*CyclinB*CDK1_pY15 - kub*[CDK1_pY15:CyclinB]
r03	[CDK1:CyclinB] -> [CDK1_pT161:CyclinB]	Vm_CAK_CDK1B*[CDK1:CyclinB]/(km_CAK_CDK1B +[CDK1:CyclinB])
r04	[CDK1_pY15:CyclinB] -> [CDK1_pY15_pT161:CyclinB]	Vm_CAK_CDK1B*[CDK1_pY15:CyclinB]/(km_CAK_CDK1B+ [CDK1_pY15:CyclinB])
r05	[CDK1_pT161:CyclinB] -> [CDK1:CyclinB]	kdp*[CDK1_pT161:CyclinB]
r06	[CDK1_pY15_pT161:CyclinB] -> [CDK1_pY15:CyclinB]	kdp*[CDK1_pY15_pT161:CyclinB]
r07	Wee1 + [CDK1:CyclinB] <-> [Wee1:(CDK1:CyclinB)]	kb_Wee1_CDK1B*Wee1*[CDK1:CyclinB] - kub*[Wee1:(CDK1:CyclinB)]
r08	[Wee1:(CDK1:CyclinB)] -> Wee1 + [CDK1_pY15:CyclinB]	kcat_Wee1_CDK1B*[Wee1:(CDK1:CyclinB)]
r09	Wee1 + [CDK1_pT161:CyclinB] <-> [Wee1:(CDK1_pT161:CyclinB)]	kb_Wee1_CDK1B*Wee1*[CDK1_pT161:CyclinB] - kub*[Wee1:(CDK1_pT161:CyclinB)]
r10	[Wee1:(CDK1_pT161:CyclinB)] -> Wee1 + [CDK1_pY15_pT161:CyclinB]	kcat_Wee1_CDK1B*[Wee1:(CDK1_pT161:CyclinB)]
r11	[CDK1_pT161:CyclinB] + Wee1 <-> [(CDK1_pT161:CyclinB):Wee1]	kb_CDK1B_Wee1*[CDK1_pT161:CyclinB]*Wee1 - kub*[(CDK1_pT161:CyclinB):Wee1]
r12	[(CDK1_pT161:CyclinB):Wee1] -> [CDK1_pT161:CyclinB] + Wee1_pT123	kcat_CDK1B_Wee1*[(CDK1_pT161:CyclinB):Wee1]
r13	Wee1_pT123 -> Wee1	kdp*Wee1_pT123
r14	PLK1_pT210 + Wee1_pT123 <-> [PLK1_pT210:Wee1_pT123]	kb_PLK1P_Wee1*PLK1_pT210*Wee1_pT123 - kub*[PLK1_pT210:Wee1_pT123]
r15	[PLK1_pT210:Wee1_pT123] -> PLK1_pT210	kcat_PLK1P_Wee1*[PLK1_pT210:Wee1_pT123]
r16	AuroraA_pT288 + CDC25 <-> [AuroraA_pT288:CDC25]	kb_AuroraAP_CDC25*AuroraA_pT288*CDC25 - kub*[AuroraA_pT288:CDC25]
r17	[AuroraA_pT288:CDC25] -> AuroraA_pT288 + CDC25_pS	kcat_AuroraAP_CDC25*[AuroraA_pT288:CDC25]
r18	PLK1_pT210 + CDC25 <-> [PLK1_pT210:CDC25]	kb_PLK1P_CDC25*PLK1_pT210*CDC25-kub*[PLK1_pT210:CDC25]
r19	[PLK1_pT210:CDC25] -> PLK1_pT210 + CDC25_pS	kcat_PLK1P_CDC25*[PLK1_pT210:CDC25]
r20	[CDK1_pT161:CyclinB] + CDC25 <-> [(CDK1_pT161:CyclinB):CDC25]	kb_CDK1B_CDC25*[CDK1_pT161:CyclinB]*CDC25-kub*[(CDK1_pT161:CyclinB):CDC25]
r21	[(CDK1_pT161:CyclinB):CDC25] -> [CDK1_pT161:CyclinB] + CDC25_pS	kcat_CDK1B_CDC25*[(CDK1_pT161:CyclinB):CDC25]

r22	CDC25_pS -> CDC25	kdp*CDC25_pS
r23	CDC25_pS + [CDK1_pY15:CyclinB] <-> [CDC25_pS:(CDK1_pY15:CyclinB)]	kb_CDC25_CDK1B*CDC25_pS*[CDK1_pY15:CyclinB]-kub*[CDC25_pS:(CDK1_pY15:CyclinB)]
r24	[CDC25_pS:(CDK1_pY15:CyclinB)] -> CDC25_pS + [CDK1:CyclinB]	kcat_CDC25_CDK1B*[CDC25_pS:(CDK1_pY15:CyclinB)]
r25	CDC25_pS + [CDK1_pY15_pT161:CyclinB] <-> [CDC25_pS:(CDK1_pY15_pT161:CyclinB)]	kb_CDC25_CDK1B*CDC25_pS*[CDK1_pY15_pT161:CyclinB] - kub*[CDC25_pS:(CDK1_pY15_pT161:CyclinB)]
r26	[CDC25_pS:(CDK1_pY15_pT161:CyclinB)] -> CDC25_pS + [CDK1_pT161:CyclinB]	kcat_CDC25_CDK1B*[CDC25_pS:(CDK1_pY15_pT161:CyclinB)]
r27	AuroraA + AuroraA <-> [AuroraA:AuroraA]	kb_AuroraA_AuroraA*AuroraA*AuroraA - kub*[AuroraA:AuroraA]
r28	[AuroraA:AuroraA] -> AuroraA_pT288 + AuroraA	kcat_AuroraA_AuroraA*[AuroraA:AuroraA]
r29	AuroraA_pT288 + AuroraA <-> [AuroraA_pT288:AuroraA]	kb_AuroraAP_AuroraA*AuroraA_pT288*AuroraA - kub*[AuroraA_pT288:AuroraA]
r30	[AuroraA_pT288:AuroraA] -> AuroraA_pT288 + AuroraA_pT288	kcat_AuroraAP_AuroraA*[AuroraA_pT288:AuroraA]
r31	AuroraA_pT288 + PLK1 <-> [AuroraA_pT288:PLK1]	kb_AuroraAP_PLK1*AuroraA_pT288*PLK1 - kub*[AuroraA_pT288:PLK1]
r32	[AuroraA_pT288:PLK1] -> AuroraA_pT288 + PLK1_pT210	kcat_AuroraAP_PLK1*[AuroraA_pT288:PLK1]
r33	Bora + PLK1 <-> [Bora:PLK1]	kb_Bora_PLK1*Bora*PLK1 - kub*[Bora:PLK1]
r34	AuroraA_pT288 + [Bora:PLK1] -> [AuroraA_pT288:(Bora:PLK1)]	kb_AuroraAP_BoraPLK1*AuroraA_pT288*[Bora:PLK1]
r35	[AuroraA_pT288:(Bora:PLK1)] -> AuroraA_pT288 + Bora + PLK1_pT210	kcat_AuroraAP_BoraPLK1*[AuroraA_pT288:(Bora:PLK1)]
r36	PLK1_pT210 -> PLK1	kdp*PLK1_pT210
r37	PLK1_pT210 + Bora <-> [PLK1_pT210:Bora]	kb_PLK1P_Bora*PLK1_pT210*Bora - kub*[PLK1_pT210:Bora]
r38	[PLK1_pT210:Bora] -> PLK1_pT210	kcat_PLK1P_Bora*[PLK1_pT210:Bora]
r39	ATR -> ATR_active	kcat_damage*ATR
r40	Claspin + CHK1 <-> [Claspin:CHK1]	kb_Claspin_CHK1*Claspin*CHK1 - kub*[Claspin:CHK1]
r41	ATR_active + [Claspin:CHK1] -> [ATR_active:(Claspin:CHK1)]	kb_ATR_ClaspinCHK1*ATR_active*[Claspin:CHK1]
r42	[ATR_active:(Claspin:CHK1)] -> ATR_active + Claspin + CHK1_pS	kcat_ATR_ClaspinCHK1*[ATR_active:(Claspin:CHK1)]
r43	CHK1_pS -> CHK1	kdp*CHK1_pS

r44	CHK1_pS + CDC25 <-> [CHK1_pS:CDC25]	kb_CHK1_CDC25*CHK1_pS*CDC25 - kub*[CHK1_pS:CDC25]
r45	[CHK1_pS:CDC25] -> CHK1_pS + CDC25_ppp	kcat_CHK1_CDC25*[CHK1_pS:CDC25]
r46	[14-3-3] + CDC25_ppp <-> [14-3-3:CDC25_ppp]	kb_1433_CDC25*[14-3-3]*CDC25_ppp - kub*[14-3-3:CDC25_ppp]
r47	CDC25_ppp -> CDC25	kdp*CDC25_ppp
r48	PLK1_pT210 + Claspin <-> [PLK1_pT210:Claspin]	kb_PLK1P_Claspin*PLK1_pT210*Claspin - kub*[PLK1_pT210:Claspin]
r49	[PLK1_pT210:Claspin] -> PLK1_pT210	kcat_PLK1P_Claspin*[PLK1_pT210:Claspin]
r50	null -> CyclinB	ks_CyclinB*(CyclinB_max-CyclinB_total)/(CyclinB_max*CyclinB_total)
r51	null -> AuroraA	ks_AuroraA*(AuroraA_max-AuroraA_total)/(AuroraA_max*AuroraA_total)
r52	null -> Bora	ks_Bora*(Bora_max-Bora_total)/(Bora_max*Bora_total)
r53	null -> PLK1	ks_PLK1*(PLK1_max-PLK1_total)/(PLK1_max*PLK1_total)
r54	AuroraA + VX680 <-> [Aurora-A:VX680]	kb_ AuroraA _VX*AuroraA* VX680 - kub*[Aurora-A:VX680]
r55	AuroraA_pT288 + VX680 <-> [AuroraA_pT288:VX680]	kb_ AuroraA _VX*AuroraA_pT288* VX680 - kub*[AuroraA_pT288: VX680]
r56	PLK1 + BI2536 <-> [PLK1:BI2536]	kb_PLK1_BI*PLK1*BI2536 - kub*[PLK1:BI2536]
r57	PLK1_pT210 + BI2536 <-> [PLK1_pT210:BI2536]	kb_PLK1_BI*PLK1_pT210*BI2536 - kub*[PLK1_pT210:BI2536]

(a) An idealized cell may be considered as a sphere with a diameter of 1.25×10^{-5} m, resulting in a cell volume of roughly 2×10^{-12} L. Given a typical concentration of a specific protein to be 1 nM, we calculate the total protein number of 1.2×10^{3} molecules/cell. For a reaction volume containing 1.2×10^{3} molecules, we are justified in using ordinary differential equations to describe changes in a continuous concentration of molecular species. The concentration of molecular species was in units of molecules/cell. Quantitative analysis of the experimental time series data of the protein levels of molecular species was performed with QuantityOne software (Bio-Rad) as described[1-3]. Biochemical reactions between species of the same proteins (e.g. with different phosphorylation states) were assumed to have the same reaction rate parameters.

(b) Description of biochemical reactions:

r01 and **r02**: Cyclin B and cyclin-dependent kinase 1 (Cdk1) form cyclin B/Cdk1, which is the key regulator of cell cycle progression[4, 5]. $[CDK1]_{t=0} = 2 \times 10^{5}$ molecules/cell[6].

r03 and **r04**: Phosphorylation of Cdk1 on Thr161 by Cdk-activating kinase (CAK) is required for the complete activation of cyclin B/Cdk1[7, 8]. The process is mathematically expressed as Michaelis-Menten equations, in which the Michaelis constant $k_{m\_CAK\_CDK1B}$ is 7.08×10^5 molecule, and the maximal reaction rate $V_{m\_CAK\_CDK1B}$ is 1.93×10^{11} (molecule $\cdot$min^{-1}) [7].

r05 and **r06**: Dephosphorylation of Cdk1-pT161.

r07 – **r10**: Cdk1 is held inactive by the phosphorylation on Thr14 and Tyr15 by kinase Wee1 during the S and G2 phases prior to mitosis[9, 10]. $[\text{Wee1}]_{t=0} = 2.5 \times 10^4$ (molecules/cell) [11].

r11 and **r12**: Activated cyclin B-Cdk1 phosphorylates Wee1 on Ser123, thereby creating a binding site for kinase Plk1[11-14].

r13: Dephosphorylation of Wee1-pT123.

r14 and **r15**: Phosphorylation on Ser123 of Wee1 creates the binding site for the Plk1 PBD domain and accelerates the further phosphorylation of Wee1 by Plk1, which induces the degradation of Wee1 by β-TrCP ubiquitin-proteasome system[12, 14].

r16 – **r19**: Activated Aurora-A and Plk1 will directly phosphorylate Cdc25 and thereby stimulate its phosphatase activity[15-18]. $[\text{Cdc25}]_{t=0} = 1 \times 10^4$ (molecules/cell) [11, 19].

r20 and **r21**: Following activation, cyclin B-Cdk1 phosphorylates and activates Cdc25[20, 21].

r22: Dephosphorylation of Cdc25.

r23 – **r26**: The dual specificity phosphatase Cdc25 dephosphorylates Thr14 and Tyr15 of Cdk1, thereby activating cyclin B-Cdk1[21-23].

r27 – **r30**: During mitotic entry, the kinase activity of Aurora-A depends on the auto-phosphorylation of Thr288 in its T loop[24-26].

r31 and **r32**: Activated Aurora-A will phosphorylate Thr210 of Plk1 and thereby promote its activation[27, 28].

r33 – **r35**: Bora directly binds to Plk1 and controls the accessibility of its activation loop for phosphorylation, which greatly enhances the activation effect by Aurora-A[27, 28].

r36: Dephosphorylation of Plk1-pT210.

r37 and **r38**: The degradation of Bora depends on Plk1 mediated phosphorylation[29].

r39: In response to G2 DNA damage, the activity of ataxia–telangiectasia and rad3-related ATR kinase is triggered[30, 31]. $[\text{ATR}]_{t=0} = 2.4 \times 10^3$ (molecules/cell) [32]. To mimic the DNA-damage response, the parameter k_{cat_damage} representing ATR activation was set to 0.8; and during checkpoint recovery, k_{cat_damage} was reset to zero. These settings give model simulations that are consistent with previous experimental observations[32].

r40 – **r42**: Activated ATR will phosphorylate and activate checkpoint kinase Chk1, in the assistance of Claspin[33-35]. $[\text{Chk1}]_{t=0} = 2.4 \times 10^4$ (molecules/cell) [32].

r43: Dephosphorylation of Chk1.

r44 – **r46**: Once activated, Chk1 will inhibit the phosphatase activity of Cdc25 by phosphorylating and promoting its association with decoy protein 14-3-3 [33, 36, 37].

r47: Dephosphorylation of Cdc25.

r48 and **r49**: Plk1-mediated degradation of Claspin by ubiquitin and proteasome system during checkpoint recovery[38-41].

r50 – **r53**: **Definition of protein synthesis**. The synthesis of cyclin B, Aurora-A, Plk1 and Bora were formulated as sigmoid functions. The initial values of the corresponding reaction rate parameters (i.e. *ks1_ProteinName*, *ks2_ProteinName*) were estimated by fitting to the experimental data. The protein maximum levels (i.e. *ProteinName_max*) were obtained from previous experimental measurements. It is found that the sigmoid functions give simulation results that are absolutely consistent with experimental values (i.e. the protein expression pattern). Whereas, using a simple method considering only constant rate of protein synthesis and linear protein degradation gives disappointing simulation results that are inconsistent with the experimental values (data not shown).

r50: The synthesis of cyclin B[28, 42].

$[CyclinB\_max]_{t=0} = 8 \times 10^3$ (molecules/cell) [6].

[CyclinB_total] = [(CDK1_pT161:CyclinB):Wee1] + [(CDK1_pT161:CyclinB):CDC25] + [CDC25_pS:(CDK1_pY15:CyclinB)] + [CDC25_pS:(CDK1_pY15_pT161:CyclinB)] + [CDK1:CyclinB] + [CDK1_pT161:CyclinB] + [CDK1_pY15:CyclinB] + [CDK1_pY15_pT161:CyclinB] + [CyclinB] + [Wee1:(CDK1:CyclinB)] + [Wee1:(CDK1_pT161:CyclinB)].

$ks\_CyclinB = 100.57e^{0.0126\boldsymbol{T}}$. (Note: *T* is simulation time)

r51: The synthesis of Aurora-A[28, 29].

$[AuroraA\_max]_{t=0} = 7.2 \times 10^3$ (molecules/cell) [24, 43].

[AuroraA_total] = [AuroraA] + 2*[AuroraA:AuroraA] + [AuroraA_pT288] + [AuroraA_pT288:(Bora:PLK1)] + 2*[AuroraA_pT288:AuroraA] + [AuroraA_pT288:CDC25] + [AuroraA_pT288:PLK1].

$ks\_AuroraA = 180.38e^{0.0172\boldsymbol{T}}$.

r52: The synthesis of Bora[28, 29].

$[Bora\_max]_{t=0} = 4.5 \times 10^3$ (molecules/cell) [28].

[Bora_total] = [AuroraA_pT288:(Bora:PLK1)] + [Bora] + [Bora:PLK1] + [PLK1_pT210:Bora].

$ks\_Bora = 221.95e^{0.0141\boldsymbol{T}}$.

r53: The synthesis of Plk1[28, 29, 44].

$[PLK1\_max]_{t=0} = 9.6 \times 10^3$ (molecules/cell) [43, 45].

[PLK1_total] = [AuroraA_pT288:(Bora:PLK1)] + [AuroraA_pT288:PLK1] + [Bora:PLK1] + [PLK1] + [PLK1_pT210] +

[PLK1_pT210:Bora] + [PLK1_pT210:CDC25] + [PLK1_pT210:Claspin] + [PLK1_pT210:Wee1_pT123].

ks_PLK1 = $155.73e^{0.0160T}$.

r54 and **r55**: The Aurora-A inhibitor VX-680 can bind with both the unphosphorylated form (*Aurora-A*) and the phosphorylated form (*AuroraA_pT288*) of Aurora-A. kb_ AuroraA _VX = 1.3×10^{-7} (molecule^{-1} min^{-1}) [46].

r56 and **r57**: The PLK1 inhibitor BI-2536 can bind with both the unphosphorylated form (*PLK1*) and the phosphorylated form (*PLK1_pT210*) of PLK1. kb_PLK1_BI = 6.8×10^{-7} (molecule^{-1} min^{-1}) [47, 48].

(c) Definition of abbreviations used:

:	indicates a protein complex;
_p**	indicates that a protein is phosphorylated;
<->	indicates a reversible reaction;
->	indicates an irreversible reaction;
null ->	indicates that a species is synthesized;
-> null	indicates that a species is degraded.

(d) The simulation time was in units of minute. Protein unbinding rates k_{ub} were set to 0.1 min^{-1}, which is of the same order of magnitude as in other mathematical models[2, 3]. The dephosphorylation rates k_{dp} were set to 0.008 (min^{-1}) [49].

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