Supplementary Materials

This supplementary file contains the ODEs of different sub-systems, parameters, and initial values. It also contains results of Global Sensitivity Analysis (GSA) on Iwamoto et al. (2011) cell cycle model. Further, some graphical results for the temporal dynamics of some newly added elements are also presented here to highlight their role.

In the formulae given here, dot sign indicates multiplication; i and a prefixes denote inactive and active, respectively. The heading numbering corresponds to the numbering in the article but the equation numbers may not match because we provide all the equations here while the manuscript text contains only the newly added equations.

2.1. Growth factor signalling sub-system

$$\frac{d[icMyc]}{dt} = k_1 \cdot [acMyc] - k_2 \cdot GF \cdot [icMyc], \quad (1)$$

$$\frac{d[acMyc]}{dt} = k_2 \cdot GF \cdot [icMyc] - k_1 \cdot [acMyc], \quad (2)$$

Within brackets is shown the concentration of respective proteins. We assumed cMyc to be switched between active [acMyc] and inactive [icMyc] forms (Eq. (1) and Eq. (2)) in order to simplify the model.

2.2. DNA damage signalling sub-system

2.2.1. Chk-Related module

The detailed dynamics of this module is formulated as follows (the formulae for Cdc25 phosphatases and Cyc_Cdks are represented in subsequent sections):

$$\frac{d[ATM]}{dt} = k_5 \cdot DSB(t) - k_6 \cdot [ATM], \quad (3)$$

$$\frac{d[iChk2]}{dt} = k_3 \cdot [aChk2] - k_4 \cdot [iChk2] \cdot [ATM], \quad (4)$$

$$\frac{d[aChk2]}{dt} = k_4 \cdot [iChk2] \cdot [ATM] - k_3 \cdot [aChk2], \quad (5)$$

where $DSB(t) = DDS \cdot exp(-k_7 \cdot t)$, $t\ \ is\ time$, and DDS is the DNA Damage Strength. $DSB(t)$ is the Double-Strand Break signal that can trigger the DNA damage response in both Chk-related and p53-related modules and it varies as repair progresses as shown by the formula. It is important to note that the repair process is also embedded in the model by parameter k_6 (see Table A2 for definition and value of all parameters).

2.2.2. p53-Related module

The temporal dynamics of this module can be expressed as follows (since p21, 14-3-3σ, and Gadd45α have interactions with elements in G1-S and G2-M sub-systems, the corresponding dynamics may include some elements from those systems):

$$\frac{d[p53]}{dt} = k_8 + k_9 \cdot [ATM] - k_{10} \cdot [p53] - DEG(t) \cdot [Mdm2] \cdot [p53], \quad (6)$$

$$\frac{d[Mdm2]}{dt} = k_{14} + \frac{(k_{15} \cdot [IF]^{50})}{k_{16}{}^{50} \cdot [IF]^{50}} - k_{17} \cdot [Mdm2], \quad (7)$$

$$\frac{d[IF]}{dt} = \frac{k_{18} \cdot [p53] \cdot DSB(t)}{1 + k_{19} \cdot [p53] \cdot [Mdm2]} - k_{20} \cdot [IF], \quad (8)$$

$$\frac{d[p21]}{dt} = k_{21} + k_{22} \cdot [p53] + k_{23} \cdot [p21\_CycD\_Cdk4] + k_{25} \cdot [p21\_aCycE\_Cdk2] + k_{27} \cdot [p21\_aCycA\_Cdk2] + k_{29} \cdot [p21\_aCycB\_Cdk1\_Nuc] - (k_{24} \cdot [CycD\_Cdk4] + k_{26} \cdot [aCycE\_Cdk2] + k_{28} \cdot [aCycA\_Cdk2] + k_{30} \cdot [aCycB\_Cdk1\_Nuc] + k_{31}) \cdot [p21], \quad (9)$$

$$\frac{d[14\_3\_3\sigma]}{dt} = k_{32} + k_{33} \cdot [p53] - k_{34} \cdot [14\_3\_3\sigma] - k_{35} \cdot [14\_3\_3\sigma] \cdot [iCdc25C\_Ps216], \quad (10)$$

$$\frac{d[\text{Gadd45}\alpha]}{dt} = k_{36} + k_{37} \cdot [p53] - k_{38} \cdot [\text{Gadd45}\alpha] \quad (11)$$

where $DEG(t) = k_{11} - k_{12} \cdot (DSB(t) - DDS \cdot \exp(-k_{13} \cdot DDS \cdot t))$. $DEG(t)$ is a time-dependent function that represents the degradation rate of p53 and it also depends on $DSB(t)$ and the level of DNA damage (DDS).

2.3. G1-S checkpoint signalling sub-system

2.3.1. Cdk4-Related module

The dynamics of Cdk4-Related module can be written as follows:

$$\frac{d[CycD]}{dt} = k_{39} + k_{40} \cdot [acMyc] + k_{41} \cdot [CycD\_Cdk4] - (k_{44} + k_{42} \cdot [Cdk4] + k_{43} \cdot [aSCF] + k_{147} \cdot [aAPC\_Cdc20]) \cdot [CycD], \quad (12)$$

$$\frac{d[Cdk4]}{dt} = k_{45} \cdot [CycD\_Cdk4] + k_{46} \cdot [p27\_CycD\_Cdk4] + k_{41} \cdot [CycD\_Cdk4] - k_{42} \cdot [CycD] \cdot [Cdk4], \quad (13)$$

$$\frac{d[CycD\_Cdk4]}{dt} = k_{42} \cdot [CycD] \cdot [Cdk4] + k_{23} \cdot [p21\_CycD\_Cdk4] + k_{47} \cdot [p27\_CycD\_Cdk4] - (k_{41} + k_{45} + k_{24} \cdot [p21] + k_{48} \cdot [p27]) \cdot [CycD\_Cdk4], \quad (14)$$

$$\frac{d[p27]}{dt} = k_{49} + k_{47} \cdot [p27\_CycD\_Cdk4] + k_{50} \cdot [p27\_CycE\_Cdk2] + k_{51} \cdot [p27\_aCycA\_Cdk2] - (k_{48} \cdot [CycD\_Cdk4] + k_{52} \cdot [aCycE\_Cdk2] + k_{53} \cdot [aCycE\_Cdk2] + k_{54} \cdot [aCycA\_Cdk2] + k_{55} \cdot [aCycA\_Cdk2]) \cdot [p27], \quad (15)$$

$$\frac{d[p27\_CycD\_Cdk4]}{dt} = k_{48} \cdot [CycD\_Cdk4] \cdot [p27] - (k_{46} + k_{47}) \cdot [p27\_CycD\_Cdk4], \quad (16)$$

$$\frac{d[p21\_CycD\_Cdk4]}{dt} = k_{24} \cdot [p21] \cdot [CycD\_Cdk4] - k_{23} \cdot [p21\_CycD\_Cdk4], \quad (17)$$

2.3.2. E2F-pRb module

The dynamic behaviour of elements of this module can be formulated as follows:

$$\frac{d[E2F\_pRb]}{dt} = k_{56} \cdot [E2F] \cdot [pRb] - (k_{57} \cdot [CycD\_Cdk4] + k_{58} \cdot [p27\_CycD\_Cdk4] + k_{59} \cdot [p21\_CycD\_Cdk4]) \cdot [E2F\_pRb], \quad (18)$$

$$\frac{d[iPP1]}{dt} = k_{62} \cdot [aPP1] - k_{63} \cdot [iPP1].[aCycB\_Cdk1\_Nuc], \quad (19)$$

$$\frac{d[aPP1]}{dt} = k_{63} \cdot [iPP1].[aCycB\_Cdk1\_Nuc] - k_{62} \cdot [aPP1], \quad (20)$$

$$\frac{d[pRbPPP]}{dt} = (k_{60} \cdot [aCycE\_Cdk2] + k_{61} \cdot [aCycA\_Cdk2]) \cdot [E2F\_pRbPP] - k_{64} \cdot [pRbPPP], \quad (21)$$

$$\frac{d[pRb]}{dt} = k_{65} + k_{64} \cdot [aPP1].[pRbPPP] - (k_{56} \cdot [E2F] + k_{66}) \cdot [pRb], \quad (22)$$

$$\frac{d[E2F]}{dt} = k_{67} + k_{68} \cdot [\mathrm{E2F}] + (k_{60} \cdot [aCycE\_Cdk2] + k_{61} \cdot [aCycA\_Cdk2]) \cdot [E2F\_pRbPP] - (k_{56} \cdot [pRb] + k_{146} \cdot [aCycA\_Cdk2] + k_{69}) \cdot [E2F], \quad (23)$$

2.3.3. Cdk2-Related module

The mathematical equations of this module dynamics can be expressed as follows:

$$\frac{d[CycE]}{dt} = k_{70} \cdot [E2F] + k_{72} \cdot [iCycE\_Cdk2] - (k_{73} + k_{71} \cdot [Cdk2] + k_{74} \cdot [aSCF]) \cdot [CycE], \quad (24)$$

$$\frac{d[CycA]}{dt} = k_{75} \cdot [E2F] + k_{76} \cdot [aBMyb] + k_{77} \cdot [NFY] + k_{78} \cdot [iCycA\_Cdk2] - (k_{79} + k_{80} \cdot [Cdk2] + k_{81} \cdot [aAPC\_Cdc20] + k_{82} \cdot [aAPC\_Cdh1]) \cdot CycA, \quad (25)$$

$$\frac{d[Cdk2]}{dt} = k_{72} \cdot [iCycE\_Cdk2] + k_{83} \cdot [iCycE\_Cdk2] + k_{84} \cdot [aCycE\_Cdk2] \cdot [aCycE\_Cdk2] + k_{78} \cdot [iCycA\_Cdk2] + (k_{85} \cdot [iCycA\_Cdk2] + k_{86} \cdot [aCycA\_Cdk2]) \cdot ([aAPC\_Cdc20] + [aAPC\_Cdh1]) - (k_{71} \cdot [CycE] + k_{80} \cdot [CycA]) \cdot [Cdk2], \quad (26)$$

$$\frac{d[iCycE\_Cdk2]}{dt} = k_{71} \cdot [CycE] \cdot [Cdk2] + k_{87} \cdot [aCycE\_Cdk2] - (k_{72} + k_{83} + k_{88} \cdot [aCdc25A]) \cdot [iCycE\_Cdk2], \quad (27)$$

$$\frac{d[aCycE\_Cdk2]}{dt} = k_{88} \cdot [iCycE\_Cdk2] \cdot [aCdc25A] + k_{50} \cdot [p27\_aCycE\_Cdk2] + k_{25} \cdot [p21\_aCycE\_Cdk2] - (k_{87} + k_{84} \cdot [aCycE\_Cdk2] + k_{52} \cdot [p27] + k_{26} \cdot [p21]) \cdot [aCycE\_Cdk2], \quad (28)$$

$$\frac{d[iCycA\_Cdk2]}{dt} = k_{80} \cdot [Cdk2] \cdot [CycA] + k_{89} \cdot [aCycA\_Cdk2] - (k_{78} + k_{85} \cdot ([aAPC\_Cdc20] + [aAPC\_Cdh1]) + k_{90} \cdot [aCdc25A]) \cdot [iCycA\_Cdk2], \quad (29)$$

$$\frac{d[aCycA\_Cdk2]}{dt} = k_{90} \cdot [iCycA\_Cdk2] \cdot [aCdc25A] + k_{51} \cdot [p27\_aCycE\_Cdk2] + k_{27} \cdot [p21\_aCycA\_Cdk2] - (k_{89} + k_{55} \cdot [p27] + k_{28} \cdot [p21] + k_{86} \cdot ([aAPC\_Cdc20] + [aAPC\_Cdh1])) \cdot [aCycA\_Cdk2], \quad (30)$$

$$\frac{d[p27\_aCycE\_Cdk2]}{dt} = k_{52} \cdot [p27] \cdot [aCycE\_Cdk2] - k_{50} \cdot [p27\_aCycE\_Cdk2], \quad (31)$$

$$\frac{d[p21\_aCycE\_Cdk2]}{dt} = k_{26} \cdot [p21] \cdot [aCycE\_Cdk2] - k_{25} \cdot [p21\_aCycE\_Cdk2], \quad (32)$$

$$\frac{d[p27\_aCycA\_Cdk2]}{dt} = k_{55} \cdot [p27] \cdot [aCycA\_Cdk2] - k_{51} \cdot [p27\_aCycA\_Cdk2], \quad (33)$$

$$\frac{d[p21\_aCycA\_Cdk2]}{dt} = k_{28} \cdot [p21] \cdot [aCycA\_Cdk2] - k_{27} \cdot [p21\_aCycA\_Cdk2], \quad (34)$$

$$\frac{d[iSCF]}{dt} = k_{91} \cdot [aSCF] \cdot [aAPC\_Cdh1] - k_{92} \cdot [aCycE\_Cdk2] \cdot [iSCF], \quad (35)$$

$$\frac{d[aSCF]}{dt} = k_{92} \cdot [aCycE\_Cdk2] \cdot [iSCF] - k_{91} \cdot [aSCF] \cdot [aAPC\_Cdh1], \quad (36)$$

$$\frac{d[iBMyb]}{dt} = k_{93} \cdot [E2F] - k_{94} \cdot [iBMyb] \cdot [aCycA\_Cdk2], \quad (37)$$

$$\frac{d[aBMyb]}{dt} = k_{94} \cdot [iBMyb] \cdot [aCycA\_Cdk2] - k_{95} \cdot [aBMyb], \quad (38)$$

$$\frac{d[NFY]}{dt} = k_{96} \cdot [aCycA\_Cdk2] - k_{97} \cdot [NFY], \quad (39)$$

2.3.4. Tyrosine phosphatase module

The dynamics of this module can be formulated as follows:

$$\frac{d[iCdc25A]}{dt} = k_{98} \cdot [E2F] + k_{99} \cdot [aCdc25A] - (k_{100} + k_{101} \cdot ([aCycE_{Cdk2}] + [aCycA\_Cdk2]) + k_{102} \cdot [aChk1]) \cdot [iCdc25A], \quad (40)$$

$$\frac{d[aCdc25A]}{dt} = k_{101} \cdot ([aCycE\_Cdk2] + [aCycA\_Cdk2]) \cdot [iCdc25A] - (k_{103} + k_{99} + k_{104} \cdot [aChk1]) \cdot [aCdc25A], \quad (41)$$

2.4. G2-M checkpoint signalling sub-system

2.4.1. Tyrosine kinase module

The temporal dynamics of this module can be written as follows:

$$\frac{d[iWee1]}{dt} = [aWee1] \cdot (k_{105} \cdot [aPlk1]) - (k_{106} + k_{107} \cdot [aSCF]) \cdot [iWee1], \quad (42)$$

$$\frac{d[aWee1]}{dt} = k_{108} + k_{106} \cdot [iWee1] - k_{105} \cdot [aPlk1] \cdot [aWee1], \quad (43)$$

2.4.2. Tyrosine phosphatase module

The dynamics of Tyrosine Phosphatase module can be written as follows:

$$\frac{d[iCdc25C]}{dt} = k_{109} + k_{110} \cdot [aCdc25C] - (k_{111} \cdot [aChk1] + k_{112} \cdot ([aCycB\_Cdk1\_Cyto] + [aCycB\_Cdk1\_Nuc]) + k_{113} \cdot [aPlk1]) \cdot [iCdc25C], \quad (44)$$

$$\frac{d[aCdc25C]}{dt} = k_{112} \cdot [iCdc25C] \cdot ([aCycB\_Cdk1\_Cyto] + [aCycB\_Cdk1\_Nuc]) + k_{113} \cdot [iCdc25C] \cdot [aPlk1] + k_{114} \cdot [aCdc25CP\_S216] - (k_{110} + k_{115} + k_{116} \cdot [aChk1]) \cdot [aCdc25C], \quad (45)$$

$$\frac{d[iCdc25CP\_S216]}{dt} = k_{111} \cdot [iCdc25C] \cdot [aChk1] + k_{117} \cdot [aCdc25CP\_S216] - (k_{118} \cdot ([aCycB\_Cdk1\_Cyto] + [aCycB\_Cdk1\_Nuc]) + k_{119} \cdot [aPlk1] + k_{35} \cdot [14\_3\_3\sigma]) \cdot [iCdc25CP\_S216], \quad (46)$$

$$\frac{d[aCdc25CP\_S216]}{dt} = k_{116} \cdot [aCdc25C] \cdot [aChk1] + k_{118} \cdot [iCdc25CP\_S216] \cdot ([aCycB\_Cdk1\_Cyto] + [aCycB\_Cdk1\_Nuc]) + k_{119} \cdot [iCdc25CP\_S216] \cdot [aPlk1] - (k_{114} + k_{117}) \cdot [aCdc25CP\_S216], \quad (47)$$

$$\frac{d[14\_3\_3\sigma\_iCdc25CP\_S216]}{dt} = k_{35} \cdot [iCdc25CP\_S216] \cdot [14\_3\_3\sigma] - k_{120} \cdot [14\_3\_3\sigma\_iCdc25CP\_S216], \quad (48)$$

2.4.3. Plk1-Related module

The dynamics of Plk1-Related module can be written as follows:

$$\frac{d[iPlk1]}{dt} = k_{121} \cdot [aPlk1] \cdot [aAPC\_Cdh1] - k_{122} \cdot [iPlk] \cdot [aCycB\_Cdk1\_Cyto], \quad (49)$$

$$\frac{d[aPlk1]}{dt} = k_{122} \cdot [iPlk] \cdot [aCycB\_Cdk1\_Cyto] - k_{121} \cdot [aPlk1] \cdot [aAPC\_Cdh1], \quad (50)$$

2.4.4. Cdk1-Related module

The Cdk1-Related module has the following temporal dynamics:

$$\frac{d[CycB]}{dt} = k_{123} \cdot [NFY] + [iCycB\_Cdk1\_Cyto] \cdot (k_{124} + k_{125} \cdot [Gadd45]) - (k_{126} + k_{127} \cdot [Cdk1] + (k_{128} \cdot [aAPC\_Cdc20] + k_{129} \cdot [aAPC\_Cdh1])) \cdot [CycB], \quad (51)$$

$$\frac{d[Cdk1]}{dt} = k_{130} \cdot [iCycB\_Cdk1\_Cyto] \cdot ([aAPC\_Cdc20] + [aAPC\_Cdh1]) + [aCycB\_Cdk1\_Cyto] \cdot (k_{131} \cdot [aAPC\_Cdc20] + k_{132} \cdot [aAPC\_Cdh1]) + [iCycB\_Cdk1\_Cyto] \cdot (k_{124} + k_{125} \cdot [Gadd45]) - k_{127} \cdot [CycB \cdot Cdk1], \quad (52)$$

$$\frac{d[iCycB\_Cdk1\_Cyto]}{dt} = k_{127} \cdot [CycB] \cdot [Cdk1] + k_{133} \cdot [aCycB\_Cdk1\_Cyto] - (k_{124} + k_{125} \cdot [Gadd45] + k_{134} \cdot ([aCdc25C] + [aCdc25CP\_S216]) + k_{130} \cdot ([aAPC\_Cdc20] + [aAPC\_Cdh1])) \cdot [iCycB\_Cdk1\_Cyto], \quad (53)$$

$$\frac{d[aCycB\_Cdk1\_Cyto]}{dt} = k_{135} \cdot [aCycB\_Cdk1\_Nuc] + k_{134} \cdot [iCycB\_Cdk1\_Cyto] \cdot ([aCdc25C] + [aCdc25CP\_S216]) - (k_{133} + k_{131} \cdot [aAPC\_Cdc20] + k_{132} \cdot [aAPC\_Cdh1] - k_{136} \cdot [aPlk1]) \cdot [aCycB\_Cdk1\_Nuc], \quad (54)$$

$$\frac{d[iCycB\_Cdk1\_Nuc]}{dt} = k_{137} \cdot [aCycB\_Cdk1\_Nuc] * [aWee1] - k_{138} \cdot [iCycB\_Cdk1\_Nuc] \cdot [aCdc25C] - k_{139} \cdot ([aAPC\_Cdc20] + [aAPC\_Cdh1]) \cdot [iCycB\_Cdk1\_Nuc], \quad (55)$$

$$\frac{d[aCycB\_Cdk1\_Nuc]}{dt} = k_{136} \cdot [aCycB\_Cdk1\_Cyto] \cdot [aPlk1] + k_{138} \cdot [iCycB\_Cdk1\_Nuc] \cdot [aCdc25C] + k_{29} \cdot [p21\_aCycB\_Cdk1\_Nuc] - (k_{135} + k_{137} \cdot [aWee1] + k_{140} \cdot [aAPC\_Cdc20] + k_{141} \cdot [aAPC\_Cdh1] + k_{30} \cdot p21) \cdot [aCycB\_Cdk1\_Nuc], \quad (56)$$

$$\frac{d[p21\_aCycB\_Cdk1\_Nuc]}{dt} = k_{30} \cdot [aCycB\_Cdk1\_Nuc] \cdot [p21] - k_{29} \cdot [p21\_aCycB\_Cdk1\_Nuc], \quad (57)$$

2.4.5. APC-Related module

The mathematical equations of this module are as follows:

$$\frac{d[iAPC\_Cdc20]}{dt} = k_{142} \cdot [aAPC\_Cdc20] \cdot [aAPC\_Cdh1] - (k_{143} \cdot [aCycB\_Cdk1\_Nuc] + k_{148} \cdot [aPlk1]) \cdot [iAPC\_Cdc20], \quad (58)$$

$$\frac{d[aAPC\_Cdc20]}{dt} = (k_{143} \cdot [aCycB\_Cdk1\_Nuc] + k_{148} \cdot [aPlk1]) \cdot [iAPC\_Cdc20] - k_{142} \cdot [aAPC\_Cdh1] \cdot [aAPC\_Cdc20], \quad (59)$$

$$\frac{d[iAPC\_Cdh1]}{dt} = k_{144} \cdot [aAPC\_Cdh1] \cdot ([aCycB\_Cdk1\_Nuc] + [aCycA\_Cdk2] + [aCycE\_Cdk2]) - k_{145} \cdot [iAPC\_Cdh1], \quad (60)$$

$$\frac{d[aAPC\_Cdh1]}{dt} = k_{145} \cdot [iAPC\_Cdh1] - k_{144} \cdot ([aCycB\_Cdk1\_Nuc] + [aCycA\_Cdk2] + [aCycE\_Cdk2]) \cdot [aAPC\_Cdh1], \quad (61)$$

Most sensitive parameters from Global Sensitivity Analysis (GSA) on Iwamoto et al. (2011) cell cycle model for G1/S under no DDS:

k1: synthesis of Cyclin D (through GF)

k34: rate of synthesis of p27

k24: rate of association of p27 and CycE_Cdk2

k5: synthesis of Cyclin E by E2F

k80: synthesis of Cdc25A through E2F

k82: Activation of Cdc25A through CycE_Cdk2 and CycA_Cdk2

k20: association of p27 and CycD_Cdk4

k22: Activation of CycE_Cdk2 through Cdc25A

GSA for G2/M no DDS (the above parameters plus the ones below):

k9: synthesis of Cyclin A by BMyb

K89: synthesis of NFY through CycA_Cdk2

k91: synthesis of Cyclin B by NFY

k93: association of Cyclin B and Cdk1

k105: synthesis of BMyb by E2F

k110: activation of Cdc25C through CycB_Cdk1 (Nuc and Cyt)

The results of GSA on Iwamoto et al. (2011) model show consistency between the significant parameters identified in our model and theirs. The only difference is about cMyc and PP1 which are absent in Iwamoto model (in fact, these are the most influential elements in the model).

Initial Values and Parameters

The initial values of concentration of chemical species in the proposed model are presented in Table A1. The kinetic parameters and the corresponding biochemical meaning are shown in Table A2. Initial values and parameters have been mainly taken from the mathematical model of Iwamoto et al. (2011). The software used for simulation and analysis is Matlab.

Table A1. The initial values of the concentration of chemical species used in the proposed model

Chemical Specie	Initial Value	Chemical Specie	Initial Value
Cyclin D	0.03	iCdc25C	1e-06
Cdk4	5	aCdc25C	1e-06
CycD_Cdk4	0.01	iCdc25CP_S216	0.03
p21	0	aCdc25CP_S216	0
p21_CycD_Cdk4	0	14-3-3σ	2
p27	1	14-3-3σ_iCdc25CP_S216	0.03
p27_CycD_Cdk4	0.001	Cyclin B	0
E2F_pRb	1.95	Cdk1	10
E2F_pRbPP	0.001	iCycB_Cdk1_Cyto	1e-04
pRbPP	0.01	aCycB_Cdk1_Cyto	1e-04
pRbPPP	0.01	iCycB_Cdk1_Nuc	0
pRb	0.05	aCycB_Cdk1_Nuc	0
E2F	0	p21_aCycB_Cdk1_Nuc	0
iBMyb	0	iWee1	0
aBMyb	0	aWee1	0.001
Cyclin E	0.001	iAPC_Cdc20	0.9
iCycE_Cdk2	0.001	aAPC_Cdc20	0.1
Cdk2	15	iAPC_Cdh1	0.1
iCdc25A	0.001	aAPC_Cdh1	0.9
aCdc25A	1e-04	p53	0.0265
aCycE_Cdk2	0.001	ATM	0
p27_aCycE_Cdk2	0.1	Mdm2	2.35e-04
p21_aCycE_Cdk2	0	Im	0
Cyclin A	4e-05	iChk2	0.99
iCycA_Cdk2	4e-04	aChk2	0.01
aCycA_Cdk2	1e-04	iSCF	0.9
p27_aCycA_Cdk2	1e-04	aSCF	0.1
p21_aCycA_Cdk2	0	Gaddα45	1e-04
NFY	0	acMyc	0.1
iPP1	0.1	icMyc	0.9
aPP1	0.9	aPlk1	0.1
		iPlk1	0.9

Table A2. Kinetic parameters and their definition

Kinetic Parameter	Biochemical meaning	Value
k_1	rate of ac-Myc inactivation	0.001
k_2	rate of ic-Myc activation	0.01
k_3	rate of aChk2 inactivation	1
k_4	rate of iChk2 activation through ATM	1
k_5	rate of ATM activation	0.2
k_6	rate of ATM inactivation	0.01
k_7	rate of DNA damage repair	1e-08
k_8	rate of p53 basal synthesis	1e-04
k_9	rate of p53 synthesis through ATM	0.07
k_{10}	rate of p53 degradation	0.001
k_{11}	rate of p53 degradation through Mdm2	0.0556
k_{12}	rate of suppression of p53 degradation through DSB(t)	0.772
k_{13}	rate of suppression of Mdm2-mediated degradation of p53	0.02
k_{14}	rate of Mdm2 basal synthesis	9.4e-04
k_{15}	synthesis rate of Mdm2 through IF	10
k_{16}	Hill function constant	9.5
k_{17}	rate of Mdm2 degradation	0.02
k_{18}	rate of p53 activity through binding to DNA after damage	6
k_{19}	rate of Mdm2 and p53 association	0.004
k_{20}	rate of IF degradation	0.005
k_{21}	rate of p21 basal synthesis	5e-05
k_{22}	rate of p21 synthesis through p53	0.001
k_{23}	rate of p21_CycD_Cdk4 dissociation	0.005
k_{24}	rate of p21 and CycD_Cdk4 association	5e-04
k_{25}	rate of p21_aCycE_Cdk2 dissociation	1.75e-04
k_{26}	rate of p21 and aCycE_Cdk2 association	0.0225
k_{27}	rate of p21_aCycA_Cdk2 dissociation	1.75e-04
k_{28}	rate of p21 and aCycA_Cdk2 association	0.0025
k_{29}	rate of p21_aCycB_Cdk1_Nuc dissociation	1.75e-04
k_{30}	rate of p21 and aCycB_Cdk1_Nuc association	0.0225
k_{31}	rate of p21 degradation	0.005
k_{32}	rate of 14-3-3σ basal synthesis	1
k_{33}	rate of 14-3-3σ synthesis through p53	0.01
k_{34}	rate of 14-3-3σ degradation	1
k_{35}	rate of 14-3-3σ and iCdc25CP_S216 association	100
k_{36}	rate of Gaddα45 basal synthesis	1e-05
k_{37}	rate of Gaddα45 synthesis through p53	1e-04
k_{38}	rate of Gaddα45 degradation	1e-06
k_{39}	rate of Cyclin D basal synthesis	1e-05
k_{40}	rate of Cyclin D synthesis through ac-Myc	0.003
k_{41}	rate of CycD_Cdk4 dissociation	0.0025
k_{42}	rate of Cyclin D and Cdk4 association	0.08
k_{43}	rate of Cyclin D degradation through aSCF	0.2
k_{44}	rate of Cyclin D degradation	5e-05

k_{45}	rate of CycD_Cdk4 degradation to Cdk4	8e-05
k_{46}	rate of p27_CycD_Cdk4 degradation to Cdk4	0.001
k_{47}	rate of p27_CycD_Cdk4 dissociation	5e-04
k_{48}	rate of p27 and CycD_Cdk4 association	0.009
k_{49}	rate of p27 basal synthesis	0.0015
k_{50}	rate of p27_aCycE_Cdk2 dissociation	1.75e-04
k_{51}	rate of p27_aCycA_Cdk2 dissociation	1.75e-04
k_{52}	rate of p27 and aCycE_Cdk2 association	0.0225
k_{53}	degradation rate of p27 through aCycE_Cdk2	0.05
k_{54}	degradation rate of p27 through aCycA_Cdk2	0.0015
k_{55}	rate of p27 and aCycA_Cdk2 association	0.0025
k_{56}	rate of pRb and E2F association	5e-02
k_{57}	rate of E2F_pRb phosphorylation through CycD_Cdk4	0.0025
k_{58}	rate of E2F_pRb phosphorylation through p27_CycD_Cdk4	0.0025
k_{59}	rate of E2F_pRb phosphorylation through p21_CycD_Cdk4	0.0025
k_{60}	rate of E2F_pRbPP dissociation to E2F & pRbPPP through aCycE_Cdk2	0.04
k_{61}	rate of E2F_pRbPP dissociation to E2F & pRbPPP through aCycA_Cdk2	0.0025
k_{62}	rate of inactivation of PP1	1e-03
k_{63}	rate of activation of PP1 through aCycB_Cdk1_Nuc	5e-02
k_{64}	rate of dephosphorylation of pRbPPP to pRb through PP1	5e-03
k_{65}	rate of pRb basal synthesis	5e-05
k_{66}	rate of pRb degradation	5e-05
k_{67}	rate of E2F basal synthesis	5e-04
k_{68}	rate of E2F synthesis through E2F	5e-08
k_{69}	rate of E2F degradation	5e-04
k_{70}	rate of Cyclin E synthesis through E2F	0.1
k_{71}	rate of Cyclin E and Cdk2 association	0.0025
k_{72}	rate of aCycE_Cdk2 dissociation	2.5e-05
k_{73}	rate of Cyclin E degradation	0.0025
k_{74}	rate of Cyclin E degradation through aSCF	0.01
k_{75}	rate of Cyclin A synthesis through E2F	8e-05
k_{76}	rate of Cyclin A synthesis through aBMyb	2e-04
k_{77}	rate of Cyclin A synthesis through NFY	1e-06
k_{78}	rate of iCycA_Cdk2 dissociation	2e-04
k_{79}	rate of Cyclin A degradation	5e-04
k_{80}	rate of Cyclin A and Cdk2 association	5e-04
k_{81}	rate of Cyclin A degradation through aAPC_Cdc20	0.005
k_{82}	rate of Cyclin A degradation through aAPC_Cdh1	0.005
k_{83}	rate of iCycE_Cdk2 degradation to Cdk2	0.005
k_{84}	rate of aCycE_Cdk2 degradation to Cdk2	0.05
k_{85}	rate of iCycA_Cdk2 degradation to Cdk2 through aAPC_Cdc20 & aAPC_Cdh1	0.005
k_{86}	rate of aCycA_Cdk2 degradation to Cdk2 through aAPC_Cdc20 & aAPC_Cdh1	0.0075
k_{87}	rate of aCycE_Cdk2 inactivation to form iCycE_Cdk2	0.00175
k_{88}	rate of iCycE_Cdk2 dephosphorylation and activation through aCdc25A	0.006
k_{89}	rate of aCycA_Cdk2 inactivation to form iCycA_Cdk2	5e-05
k_{90}	rate of iCycA_Cdk2 dephosphorylation and activation through aCdc25A	9e-04

k_{91}	rate of aSCF inactivation through aAPC_Cdh1	0.015
k_{92}	rate of iSCF activation through aCycE_Cdk2	0.01
k_{93}	rate of iBMyb production through E2F	0.05
k_{94}	rate of iBMyb activation through aCycA_Cdk2	0.05
k_{95}	rate of aBMyb degradation	0.002
k_{96}	rate of NFY production mediated by aCycA_Cdk2	0.001
k_{97}	rate of NFY degradation	0.005
k_{98}	rate of iCdc25A synthesis through E2F	0.04
k_{99}	rate of aCdc25A inactivation	0.005
k_{100}	rate of iCdc25A degradation	0.005
k_{101}	rate of iCdc25A degradation through aCycE_Cdk2 & aCycA_Cdk2	0.05
k_{102}	rate of iCdc25A degradation through aChk1	0.001
k_{103}	rate of aCdc25A degradation	5e-04
k_{104}	rate of aCdc25A degradation through aChk1	0.001
k_{105}	rate of aWee1 phosphorylation and inactivation through aPlk1	0.1
k_{106}	rate of iWee1 activation	1
k_{107}	rate of iWee1 degradation through aSCF	1
k_{108}	rate of aWee1 basal synthesis	2e-04
k_{109}	rate of iCdc25C basal synthesis	1e-05
k_{110}	rate of aCdc25C inactivation	0.01
k_{111}	rate of iCdc25C phosphorylation on Serine216 through aChk1	0.001
k_{112}	rate of iCdc25C activation through aCycB_Cdk1_Cyto & aCycB_Cdk1_Nuc	1
k_{113}	rate of iCdc25C activation through aPlk1	0.1
k_{114}	rate of aCdc25CP_S216 dephosphorylation to form aCdc25C	0.01
k_{115}	rate of aCdc25C degradation	1e-04
k_{116}	rate of aCdc25C phosphorylation on Serine216 through aChk1	0.001
k_{117}	rate of aCdc25CP_S216 inactivation	0.01
k_{118}	rate of iCdc25CP_S216 phosphorylation and activation through aCycB_Cdk1_Cyto & aCycB_Cdk1_Nuc	1
k_{119}	rate of iCdc25CP_S216 phosphorylation and activation through aPlk1	0.1
k_{120}	rate of 14-3-3σ_iCdc25CP_S216 degradation	1
k_{121}	rate of aPlk1 inactivation through aAPC_Cdh1	0.1
k_{122}	rate of iPlk1 activation through aCycB_Cdk1_Cyto	0.015
k_{123}	rate of Cyclin B synthesis through NFY	0.02
k_{124}	rate of iCycB_Cdk1_Cyto dissociation	1e-05
k_{125}	rate of iCycB_Cdk1_Cyto dissociation mediated by Gaddα45	2e-04
k_{126}	rate of Cyclin B degradation	0.005
k_{127}	rate of Cyclin B and Cdk1 association	0.00125
k_{128}	rate of Cyclin B degradation through aAPC_Cdc20	0.001
k_{129}	rate of Cyclin B degradation through aAPC_Cdh1	0.3
k_{130}	rate of iCycB_Cdk1_Cyto degradation to form Cdk1 through aAPC_Cdc20 & aAPC_Cdh1	0.005
k_{131}	rate of aCycB_Cdk1_Cyto degradation to form Cdk1 through aAPC_Cdc20	0.005
k_{132}	rate of aCycB_Cdk1_Cyto degradation to form Cdk1 through aAPC_Cdh1	0.05
k_{133}	rate of aCycB_Cdk1_Cyto inactivation	1e-04

k_{134}	rate of iCycB_Cdk1_Cyto activation through aCdc25C & aCdc25CP_S216	0.05
k_{135}	rate of translocation of aCycB_Cdk1 from Nucleus to Cytoplasm	5e-05
k_{136}	rate of translocation of aCycB_Cdk1 from Cytoplasm to Nucleus mediated by aPlk1	0.01
k_{137}	rate of aCycB_Cdk1_Nuc phosphorylation and inactivation through aWee1	5e-04
k_{138}	rate of iCycB_Cdk1_Nuc dephosphorylation and activation through aCdc25C	0.01
k_{139}	rate of iCycB_Cdk1_Nuc degradation through aAPC_Cdc20 & aAPC_Cdh1	0.005
k_{140}	rate of aCycB_Cdk1_Nuc degradation through aAPC_Cdc20	0.005
k_{141}	rate of aCycB_Cdk1_Nuc degradation through aAPC_Cdh1	0.03
k_{142}	rate of aAPC_Cdc20 inactivation through aAPC_Cdh1	0.05
k_{143}	rate of iAPC_Cdc20 activation through aCycB_Cdk1_Nuc	0.01
k_{144}	rate of aAPC_Cdh1 inactivation through aCycE_Cdk2 & aCycA_Cdk2 & aCycB_Cdk1_Nuc	0.1
k_{145}	rate of iAPC_Cdh1 activation	0.005
k_{146}	EF2 degradation rate through aCycA_Cdk2	0.01
k_{147}	rate of Cyclin D degradation through aAPC_Cdc20	10
k_{148}	rate of iAPC_Cdc20 activation through aPlk1	1e-04
GF	Growth Factor	1
DDS	DNA Damage Strength	0.012

The dynamics of some newly added elements and their role

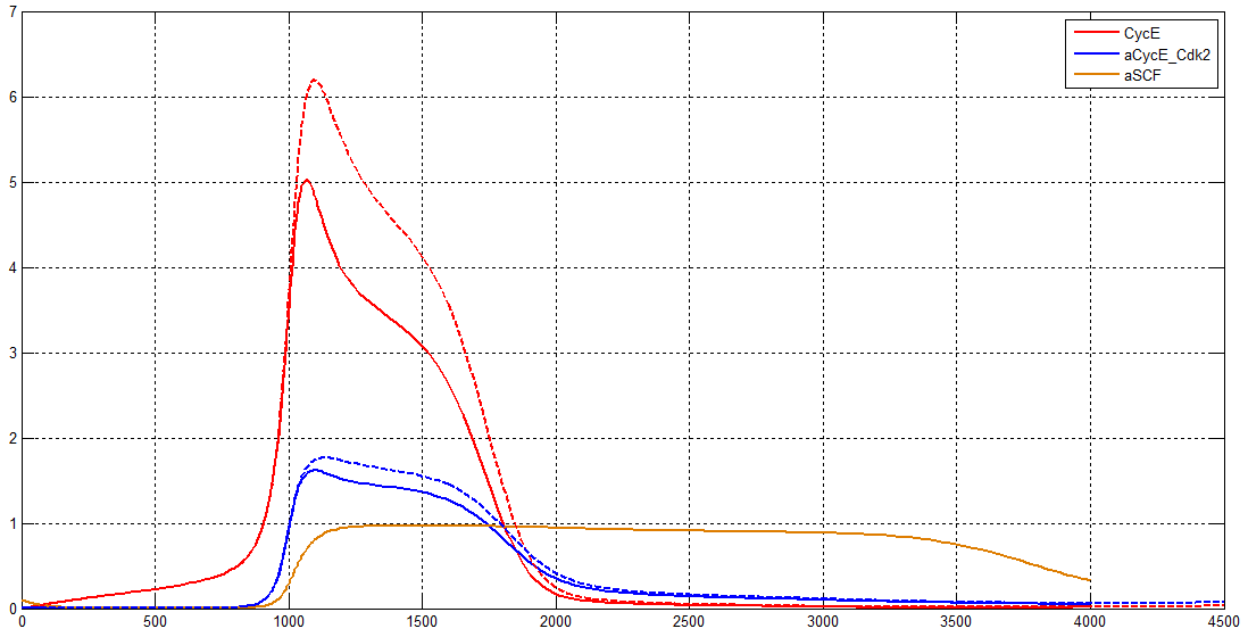

Fig. S1. Impact of newly added CycE degrader SCF on Cyclin E dynamics (solid line – with SCF and dashed line – without SCF). Figure shows that in the presence of SCF, Cyclins peak slightly sooner and degrades quicker than without SCF. Peak time (PT) of aCycE_Cdk2 indicates G1-S transition (with SCF: PT =1095, without SCF: PT= 1133; PT difference is 38) [x-axis is time; y-axis is protein concentration]

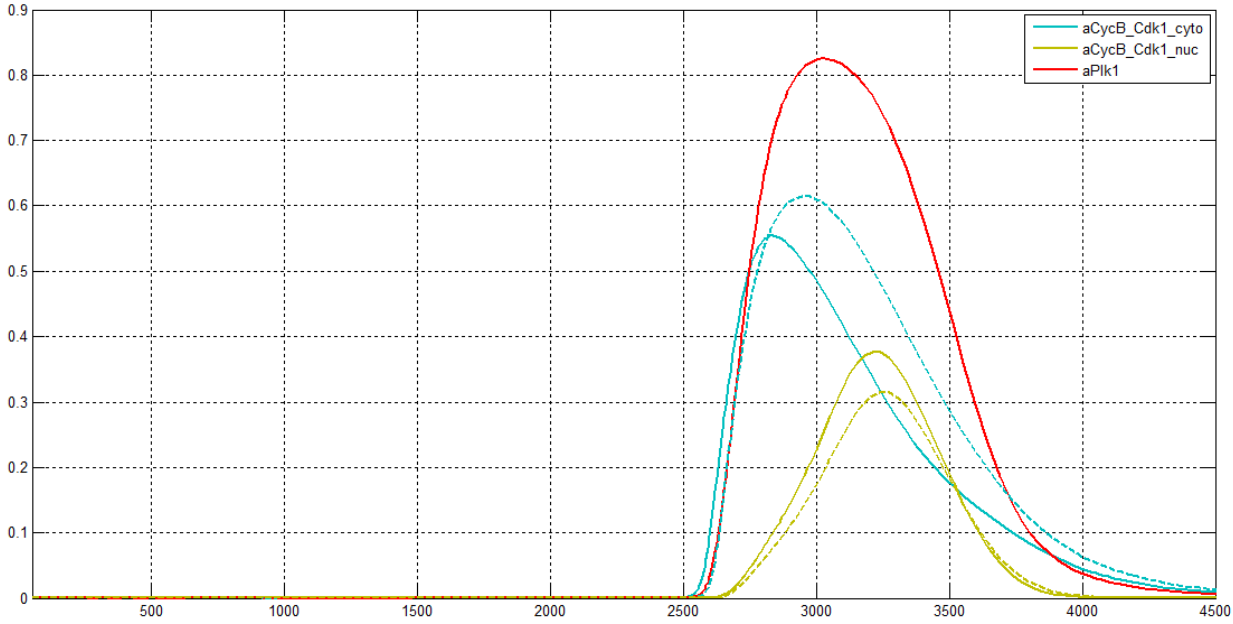

Fig. S2. Impact of newly added Plk1 on Cyclin B dynamics. (solid line – with Plk1; and dashed line – without Plk1). Figure shows that Plk1 alters the concentration and peak time of the two complexes. Peak time (PT) of CycB_Cdk1_Nuc indicates G2-M transition (PT with Plk1 is 3208 and without Plk1 is 3238; PT difference is 30). [x-axis is time; y-axis is protein concentration].