Supporting Information

The balance between cell cycle arrest and cell proliferation: Control by the extracellular matrix and by contact inhibition

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The kinetic equations of the detailed model for the cyclin/Cdk network driving the mammalian cell cycle are described below. Equations [S5] to [S42] are the same as equations [2] to [39] listed in the Supporting Information of our previous publication (Gérard and Goldbeter, 2009) (http://www.pnas.org/content/106/51/21643.long?tab=ds). However, some equations must be slightly modified to take into account the present extensions of the model. Thus, equations [1] and [9] in (Gérard and Goldbeter, 2009), describing the time evolution of AP1 and cyclin D, are replaced, respectively, by the new Eqs. [S1] and [S12], while Eq. [16], describing the time evolution of Skp2, is replaced by the new Eq. [S19]. Moreover, 3 new kinetic equations, Eqs [S2], [S3] and [S4] have been added to account for the time evolution of the active forms of the kinase FAK, Hippo and YAP, respectively.

Table S1 below defines the different variables of the model, while Table S2 gives the definition of the parameters of the model, together with their values used in numerical simulations.

The initial conditions used to reach the stable steady state in the bifurcation diagrams of Figs. 2 and 6 are as follows (concentrations are tentatively expressed in μM):
AP1 = 0.57 ; *FAK* = 0.726 ; *pRB* = 23.42 ; *pRBc1* = 41.9195 ; *pRBp* = 9.429 ; *pRBc2* = 8.438 ; *pRBpp* = 0.000737 ; *E2F* = 17.897 ; *E2Fp* = 0.1038 ; *Cd* = 0.0348 ; *Mdi* = 0.01946 ; *Md* = 0.4397 ; *Mdp27* = 0.72198 ; *Ce* = 0.00150 ; *Mei* = 0.00529 ; *Me* = 0.0148 ; *Skp2* = 0.1900 ; *Mep27* = 0.0162 ; *Pei* = 0.1787 ; *Pe* = 1.3759 ; *Ca* = 0.0384 ; *Mai* = 0.1353 ; *Ma* = 0.0414 ; *Map27* = 0.0272 ; *p27* = 0.547 ; *p27p* = 0.0306 ; *Cdh1i* = 0.00439 ; *Cdh1a* = 1.0912 ; *Pai* = 0.51979 ; *Pa* = 0.3604 ; *Cb* = 0.0344 ; *Mbi* = 0.039 ; *Mb* = 0.0068 ; *Mbp27* = 0.0022 ; *Cdc20i* = 0.712 ; *Cdc20a* = 0.0073 ; *Pbi* = 0.559 ; *Pb* = 0.0943 ; *Wee1* = 0.2652 ; *Wee1p* = 0.1674.

<u>Kinetic equations of the model :</u>

1. Cell cycle entry regulated by growth factors (GF), and by the extracellular matrix (ECM) via FAK

$$\frac{dAP1}{dt} = \left(v_{\mathrm{SAP1}} \cdot \left(\frac{GF}{K_{\mathrm{AGF}} + GF} \right) + v_{\mathrm{S2AP1}} \cdot \left(\frac{FAK}{K_{\mathrm{AFAK}} + FAK} \right) - k_{\mathrm{DAP1}} \cdot AP1 \right) \cdot eps \quad \textbf{[S1]}$$

$$\frac{dFAK}{dt} = \left(V_{\mathrm{1FAK}} \cdot \left(ECM + GF \right) \cdot \left(\frac{FAK_{\mathrm{T}} - FAK}{K_{\mathrm{1FAK}} + \left(FAK_{\mathrm{T}} - FAK \right)} \right) - V_{\mathrm{2FAK}} \cdot \left(\frac{FAK}{K_{\mathrm{2FAK}} + FAK} \right) \right) \cdot eps \quad \textbf{[S2]}$$

2. *Cell cycle entry controlled by cell contact inhibition via Hippo and YAP*

$$\frac{dHippo}{dt} = \left(V_{\mathrm{1HIPPO}} \cdot CI \cdot \left(\frac{Hippo_{\mathrm{T}} - Hippo}{K_{\mathrm{1HIPPO}} + \left(Hippo_{\mathrm{T}} - Hippo \right)} \right) - V_{\mathrm{2HIPPO}} \cdot \left(\frac{Hippo}{K_{\mathrm{2HIPPO}} + Hippo} \right) \right) \cdot eps \quad \textbf{[S3]}$$

$$\frac{dYAP}{dt} = \left(V_{\mathrm{1YAP}} \cdot \left(\frac{YAP_{\mathrm{T}} - YAP}{K_{\mathrm{1YAP}} + \left(YAP_{\mathrm{T}} - YAP \right)} \right) - V_{\mathrm{2YAP}} \cdot \left(ahip + Hippo \right) \cdot \left(\frac{YAP}{K_{\mathrm{2YAP}} + YAP} \right) \right) \cdot eps \quad \textbf{[S4]}$$

3. *Antagonistic regulation exerted by pRB and E2F*

$$\frac{dpRB}{dt} = (v_{sprb} - k_{pc1} \cdot pRB \cdot E2F + k_{pc2} \cdot pRbc1 - V_1 \cdot (\frac{pRB}{K_1 + pRB}) \cdot (Md + Mdp27) + V_2 \cdot (\frac{pRBp}{K_2 + pRBp}) - k_{dprb} \cdot pRB) \cdot eps \quad \textbf{[S5]}$$

$$\frac{dpRBc1}{dt} = (k_{pc1} \cdot pRB \cdot E2F - k_{pc2} \cdot pRbc1) \cdot eps \quad \textbf{[S6]}$$

$$\frac{dpRBp}{dt} = (V_1 \cdot (\frac{pRB}{K_1 + pRB}) \cdot (Md + Mdp27) - V_2 \cdot (\frac{pRBp}{K_2 + pRBp}) - V_3 \cdot (\frac{pRBp}{K_3 + pRBp}) \cdot Me + V_4 \cdot (\frac{pRBpp}{K_4 + pRBpp}) - k_{pc3} \cdot pRBp \cdot E2F + k_{pc4} \cdot pRBc2 - k_{dpRBp} \cdot pRBp) \cdot eps \quad \textbf{[S7]}$$

$$\frac{dpRBc2}{dt} = (k_{pc3} \cdot pRBp \cdot E2F - k_{pc4} \cdot pRBc2) \cdot eps \quad \textbf{[S8]}$$

$$\frac{dpRBpp}{dt} = (V_3 \cdot (\frac{pRBp}{K_3 + pRBp}) \cdot Me - V_4 \cdot (\frac{pRBpp}{K_4 + pRBpp}) - k_{dpRBpp} \cdot pRBpp) \cdot eps \quad \textbf{[S9]}$$

$$\frac{dE2F}{dt} = (v_{se2f} - k_{pc1} \cdot pRB \cdot E2F + k_{pc2} \cdot pRBc1 - k_{pc3} \cdot pRBp \cdot E2F + k_{pc4} \cdot pRBc2$$
$$- V_{1e2f} \cdot Ma \cdot (\frac{E2F}{K_{1e2f} + E2F}) + V_{2e2f} \cdot (\frac{E2Fp}{K_{2e2f} + E2Fp}) - k_{de2f} \cdot E2F) \cdot eps \quad \textbf{[S10]}$$

$$\frac{dE2Fp}{dt} = (V_{1e2f} \cdot Ma \cdot (\frac{E2F}{K_{1e2f} + E2F}) - V_{2e2f} \cdot (\frac{E2Fp}{K_{2e2f} + E2Fp})$$
$$- k_{de2fp} \cdot E2Fp) \cdot eps \quad \textbf{[S11]}$$

4. Module Cyclin D/Cdk4-6: G1 phase

$$\frac{dCd}{dt} = (k_{cd1} \cdot AP1 + k_{cd2} \cdot E2F \cdot (\frac{K_{i7}}{K_{i7} + pRB}) \cdot (\frac{K_{i8}}{K_{i8} + pRBp}) + k_{cd3} \cdot FAK + k_{cd4} \cdot YAP$$
$$- k_{com1} \cdot Cd \cdot (Cdk4_{tot} - (Mdi + Md + Mdp27)) + k_{decom1} \cdot Mdi \quad \textbf{[S12]}$$
$$- V_{dd} \cdot (\frac{Cd}{K_{dd} + Cd}) - k_{ddd} \cdot Cd) \cdot eps$$

$$\frac{dMdi}{dt} = (k_{com1} \cdot Cd \cdot (Cdk4_{tot} - (Mdi + Md + Mdp27))$$
$$- k_{decom1} \cdot Mdi + V_{m2d} \cdot (\frac{Md}{K_{2d} + Md}) - V_{m1d} \cdot (\frac{Mdi}{K_{1d} + Mdi})) \cdot eps \quad \textbf{[S13]}$$

$$\frac{dMd}{dt} = (V_{m1d} \cdot (\frac{Mdi}{K_{1d} + Mdi}) - V_{m2d} \cdot (\frac{Md}{K_{2d} + Md}) - k_{c1} \cdot Md \cdot p27 + k_{c2} \cdot Mdp27) \cdot eps \quad \textbf{[S14]}$$

$$\frac{dMdp27}{dt} = (k_{c1} \cdot Md \cdot p27 - k_{c2} \cdot Mdp27) \cdot eps \quad \textbf{[S15]}$$

5. Module Cyclin E/Cdk2: G1 phase and G1/S transition

$$\frac{dCe}{dt} = (k_{ce} \cdot E2F \cdot (\frac{K_{i9}}{K_{i9} + pRB}) \cdot (\frac{K_{i10}}{K_{i10} + pRBp})$$
$$- k_{com2} \cdot Ce \cdot (Cdk2_{tot} - (Mei + Me + Mep27 + Mai + Ma + Map27)) \quad \textbf{[S16]}$$
$$+ k_{decom2} \cdot Mei - V_{de} \cdot (\frac{Skp2}{K_{dceskp2} + Skp2}) \cdot (\frac{Ce}{K_{de} + Ce}) - k_{dde} \cdot Ce) \cdot eps$$

$$\frac{dMei}{dt} = (k_{com2} \cdot Ce \cdot (Cdk2_{tot} - (Mei + Me + Mep27 + Mai + Ma + Map27)) - k_{decom2} \cdot Mei + Vm2e \cdot (Wee1 + i_{b1}) \cdot (\frac{Me}{K_{2e} + Me}) - V_{m1e} \cdot Pe \cdot (\frac{Mei}{K_{1e} + Mei})) \cdot eps \quad \textbf{[S17]}$$

$$\frac{dMe}{dt} = (V_{m1e} \cdot Pe \cdot (\frac{Mei}{K_{1e} + Mei}) - V_{m2e} \cdot (Wee1 + i_{b1}) \cdot (\frac{Me}{K_{2e} + Me}) - k_{c3} \cdot Me \cdot p27 + k_{c4} \cdot Mep27) \cdot eps \quad \textbf{[S18]}$$

$$\frac{dSkp2}{dt} = (V_{sskp2} + V_{s2skp2} \cdot FAK - V_{dskp2} \cdot (\frac{Skp2}{K_{dskp2} + Skp2}) \cdot (\frac{Cdh1a}{K_{cdh1} + Cdh1a}) - k_{ddskp2} \cdot Skp2) \cdot eps \quad \textbf{[S19]}$$

$$\frac{dMep27}{dt} = (k_{c3} \cdot Me \cdot p27 - k_{c4} \cdot Mep27) \cdot eps \quad \textbf{[S20]}$$

$$\frac{dPei}{dt} = (v_{spei} + V_{6e} \cdot (\frac{Pe}{K_{6e} + Pe}) - V_{m5e} \cdot (Me + a_e) \cdot (\frac{Pei}{K_{5e} + Pei}) - k_{dpei} \cdot Pei) \cdot eps \quad \textbf{[S21]}$$

$$\frac{dPe}{dt} = (V_{m5e} \cdot (Me + a_e) \cdot (\frac{Pei}{K_{5e} + Pei}) - V_{6e} \cdot (\frac{Pe}{K_{6e} + Pe}) - k_{dpe} \cdot Pe) \cdot eps \quad \textbf{[S22]}$$

6. Module Cyclin A/Cdk2: S phase and S/G2 transition

$$\frac{dCa}{dt} = (k_{ca} \cdot E2F \cdot (\frac{K_{i11}}{K_{i11} + pRB}) \cdot (\frac{K_{i12}}{K_{i12} + pRBp}) - k_{com3} \cdot Ca \cdot (Cdk2_{tot} - (Mei + Me + Mep27 + Mai + Ma + Map27)) + k_{decom3} \cdot Mai - V_{da} \cdot (\frac{Ca}{K_{da} + Ca}) \cdot (\frac{Cdc20a}{K_{acdc20} + Cdc20a}) - k_{dda} \cdot Ca) \cdot eps \quad \textbf{[S23]}$$

$$\frac{dMai}{dt} = (k_{com3} \cdot Ca \cdot (Cdk2_{tot} - (Mei + Me + Mep27 + Mai + Ma + Map27)) - k_{decom3} \cdot Mai + V_{m2a} \cdot (Wee1 + i_{b2}) \cdot (\frac{Ma}{K_{2a} + Ma}) - V_{m1a} \cdot Pa \cdot (\frac{Mai}{K_{1a} + Mai})) \cdot eps \quad \textbf{[S24]}$$

$$\frac{dMa}{dt} = (V_{m1a} \cdot Pa \cdot (\frac{Mai}{K_{1a} + Mai}) - V_{m2a} \cdot (Wee1 + i_{b2}) \cdot (\frac{Ma}{K_{2a} + Ma}) - k_{c5} \cdot Ma \cdot p27 + k_{c6} \cdot Map27) \cdot eps \qquad \textbf{[S25]}$$

$$\frac{dMap27}{dt} = (k_{c5} \cdot Ma \cdot p27 - k_{c6} \cdot Map27) \cdot eps \qquad \textbf{[S26]}$$

$$\frac{dp27}{dt} = (v_{s1p27} + v_{s2p27} \cdot E2F \cdot (\frac{K_{i13}}{K_{i13} + pRB}) \cdot (\frac{K_{i14}}{K_{i14} + pRBp}) - k_{c1} \cdot Md \cdot p27 + k_{c2} \cdot Mdp27 - k_{c3} \cdot Me \cdot p27 + k_{c4} \cdot Mep27 - k_{c5} \cdot Ma \cdot p27 + k_{c6} \cdot Map27 - k_{c7} \cdot Mb \cdot p27 + k_{c8} \cdot Mbp27 - V_{1p27} \cdot Me \cdot (\frac{p27}{K_{1p27} + p27}) + V_{2p27} \cdot (\frac{p27p}{K_{2p27} + p27p}) - k_{ddp27} \cdot p27) \cdot eps \qquad \textbf{[S27]}$$

$$\frac{dp27p}{dt} = (V_{1p27} \cdot Me \cdot (\frac{p27}{K_{1p27} + p27}) - V_{2p27} \cdot (\frac{p27p}{K_{2p27} + p27p}) - V_{dp27p} \cdot (\frac{Skp2}{K_{dp27skp2} + Skp2}) \cdot (\frac{p27p}{K_{dp27p} + p27p}) - k_{ddp27p} \cdot p27p) \cdot eps \qquad \textbf{[S28]}$$

$$\frac{dCdh1i}{dt} = (V_{2cdh1} \cdot (\frac{Cdh1a}{K_{2cdh1} + Cdh1a}) \cdot (Ma + Mb) - V_{1cdh1} \cdot (\frac{Cdh1i}{K_{1cdh1} + Cdh1i}) - k_{dcdh1i} \cdot Cdh1i) \cdot eps \qquad \textbf{[S29]}$$

$$\frac{dCdh1a}{dt} = (v_{scdh1a} + V_{1cdh1} \cdot (\frac{Cdh1i}{K_{1cdh1} + Cdh1i}) - V_{2cdh1} \cdot (\frac{Cdh1a}{K_{2cdh1} + Cdh1a}) \cdot (Ma + Mb) - k_{dcdh1a} \cdot Cdh1a) \cdot eps \qquad \textbf{[S30]}$$

$$\frac{dPai}{dt} = (v_{spai} + V_{6a} \cdot (\frac{Pa}{K_{6a} + Pa}) - V_{m5a} \cdot (Ma + a_a) \cdot (\frac{Pai}{K_{5a} + Pai}) - k_{dpai} \cdot Pai) \cdot eps \qquad \textbf{[S31]}$$

$$\frac{dPa}{dt} = (V_{m5a} \cdot (Ma + a_a) \cdot (\frac{Pai}{K_{5a} + Pai}) - V_{6a} \cdot (\frac{Pa}{K_{6a} + Pa}) - k_{dpa} \cdot Pa) \cdot eps \qquad \textbf{[S32]}$$

7. Module Cyclin B/Cdk1: G2 phase and G2/M transition

$$\frac{dCb}{dt} = (v_{cb} - k_{com4} \cdot Cb \cdot (Cdk1_{tot} - (Mbi + Mb + Mbp27)) + k_{decom4} \cdot Mbi$$
$$-V_{db} \cdot (\frac{Cb}{K_{db} + Cb}) \cdot ((\frac{Cdc20a}{K_{dbcdc20} + Cdc20a}) + (\frac{Cdh1a}{K_{dbcdh1} + Cdh1a})) - k_{ddb} \cdot Cb) \cdot eps \quad \textbf{[S33]}$$

$$\frac{dMbi}{dt} = (k_{com4} \cdot Cb \cdot (Cdk1_{tot} - (Mbi + Mb + Mbp27)) - k_{decom4} \cdot Mbi$$
$$+V_{m2b} \cdot (Wee1 + i_{b3}) \cdot (\frac{Mb}{K_{2b} + Mb}) - V_{m1b} \cdot Pb \cdot (\frac{Mbi}{K_{1b} + Mbi})) \cdot eps \quad \textbf{[S34]}$$

$$\frac{dMb}{dt} = (V_{m1b} \cdot Pb \cdot (\frac{Mbi}{K_{1b} + Mbi}) - V_{m2b} \cdot (Wee1 + i_{b3}) \cdot (\frac{Mb}{K_{2b} + Mb})$$
$$-k_{c7} \cdot Mb \cdot p27 + k_{c8} \cdot Mbp27) \cdot eps \quad \textbf{[S35]}$$

$$\frac{dMbp27}{dt} = (k_{c7} \cdot Mb \cdot p27 - k_{c8} \cdot Mbp27) \cdot eps \quad \textbf{[S36]}$$

$$\frac{dCdc20i}{dt} = (v_{scdc20i} - V_{m3b} \cdot Mb \cdot (\frac{Cdc20i}{K_{3b} + Cdc20i}) + V_{m4b} \cdot (\frac{Cdc20a}{K_{4b} + Cdc20a})$$
$$-k_{dcdc20i} \cdot Cdc20i) \cdot eps \quad \textbf{[S37]}$$

$$\frac{dCdc20a}{dt} = (V_{m3b} \cdot Mb \cdot (\frac{Cdc20i}{K_{3b} + Cdc20i}) - V_{m4b} \cdot (\frac{Cdc20a}{K_{4b} + Cdc20a})$$
$$-k_{dcdc20a} \cdot Cdc20a) \cdot eps \quad \textbf{[S38]}$$

$$\frac{dPbi}{dt} = (v_{spbi} + V_{6b} \cdot (\frac{Pb}{K_{6b} + Pb}) - V_{m5b} \cdot (Mb + a_b) \cdot (\frac{Pbi}{K_{5b} + Pbi}) - k_{dpbi} \cdot Pbi) \cdot eps \quad \textbf{[S39]}$$

$$\frac{dPb}{dt} = (V_{m5b} \cdot (Mb + a_b) \cdot (\frac{Pbi}{K_{5b} + Pbi}) - V_{6b} \cdot (\frac{Pb}{K_{6b} + Pb}) - k_{dpb} \cdot Pb) \cdot eps \quad \textbf{[S40]}$$

$$\frac{dWee1}{dt} = (v_{swee1} - V_{m7b} \cdot (Mb + i_b) \cdot (\frac{Wee1}{K_{7b} + Wee1}) + V_{m8b} \cdot (\frac{Wee1p}{K_{8b} + Wee1p}) - k_{dwee1} \cdot Wee1) \cdot eps \quad \textbf{[S41]}$$

$$\frac{dWee1p}{dt} = (V_{m7b} \cdot (Mb + i_b) \cdot (\frac{Wee1}{K_{7b} + Wee1}) - V_{m8b} \cdot (\frac{Wee1p}{K_{8b} + Wee1p})$$
$$-k_{dwee1p} \cdot Wee1p) \cdot eps \quad \textbf{[S42]}$$

The original model (see Ref. [11]) contained 5 additional equations to describe the DNA replication checkpoint, which, for reasons of simplicity, was not retained in the present numerical analysis. For a complete list of the original equations of the model for the Cdk network, see supporting information in [11] at the address: http://www.pnas.org/content/suppl/2009/12/09/0903827106.DCSupplemental/0903827106SI.