biology

MDPI

Supplementary information

Modeling the circadian control of the cell cycle and its consequences for cancer chronotherapy

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Table S1. Parameters values.

Symbol	Definition	Value
$Cdc20_{tot}$	Total concentration of protein Cdc20	1 μM
$E2F_{tot}$	Total concentration of transcription factor E2F	1 μM
GF	Growth factor	1 μM
Me_{tot}	Total concentration of cyclin E/Cdk2	1 μM
Ma_{tot}	Total concentration of cyclin A/Cdk1	1 μM
Mb_{tot}	Total concentration of cyclin B/Cdk1	1 μM
K_{ib}	Inhibition constant for Wee1 inactivation by cyclin B/Cdk1	0.5 μM
v_{sd}	Maximum rate of synthesis of cyclin D/Cdk4-6 induced by growth factor	0.175 μM·h^{-1}
K_{gf}	Michaelis constant for synthesis of cyclin D/Cdk4-6 complex induced by growth factor	0.1 μM
V_{dd}	Maximum degradation rate of cyclin D/Cdk4-6 complex	0.245 μM·h^{-1}
K_{dd}	Michaelis constant for degradation of cyclin D/Cdk4-6 complex	0.1 μM
V_{1e2f}	Rate constant for activation of E2F by cyclin D/Cdk4-6 and cyclin E/Cdk2 complexes	0.4 h^{-1}
K_{1e2f}	Michaelis constant for E2F activation by cyclin D/Cdk4-6 and cyclin E/Cdk2 complexes	0.005 μM
V_{2e2f}	Rate constant for inactivation of E2F by cyclin A/Cdk2 complex	0.7 h^{-1}
K_{2e2f}	Michaelis constant for E2F inactivation by cyclin A/Cdk2 complex	0.005 μM
V_{1Me}	Rate for activation of cyclin E/Cdk2 by E2F	1.1 μM·h^{-1}
K_{1Me}	Michaelis constant for cyclin E/Cdk2 activation by E2F	0.005 μM
V_{2Me}	Rate constant for inactivation of cyclin E/Cdk2 by cyclin A/Cdk2	1.6 h^{-1}
K_{2Me}	Michaelis constant for cyclin E/Cdk2 inactivation by cyclin A/Cdk2	0.005 μM
V_{1Ma}	Rate constant for activation of cyclin A/Cdk2 by E2F	0.6 h^{-1}
K_{1Ma}	Michaelis constant for cyclin A/Cdk2 activation by E2F	0.005 μM
V_{2Ma}	Rate constant for inactivation of cyclin A/Cdk2 by Cdc20	0.6 h^{-1}
K_{2Ma}	Michaelis constant for cyclin A/Cdk2 inactivation by Cdc20	0.005 μM
V_{1Mb}	Rate for activation of cyclin B/Cdk1 by cyclin A/Cdk2	1 μM·h^{-1}
K_{1Mb}	Michaelis constant for cyclin B/Cdk1 activation by cyclin A/Cdk2	0.005 μM
V_{2Mb}	Rate for inactivation of cyclin B/Cdk1 by Cdc20	0.8 h^{-1}
K_{2Mb}	Michaelis constant for cyclin B/Cdk1 inactivation by Cdc20	0.005 μM
V_{1Cdc20}	Rate constant for activation of Cdc20 through phosphorylation by cyclin B/Cdk1	1.8 h^{-1}
K_{1Cdc20}	Michaelis constant for Cdc20 activation through phosphorylation by cyclin B/Cdk1	0.005 μM
V_{2Cdc20}	Rate of inactivation of Cdc20 through dephosphorylation	0.6 μM·h^{-1}
K_{2Cdc20}	Michaelis constant for Cdc20 inactivation through dephosphorylation	0.005 μM
K_{ie}	Michaelis constant for cyclin B/Cdk1 inactivation by cyclin E/Cdk2	0.2 μM
a_1	Basal term for activation of cyclin E/Cdk2	1
a_2	Basal term for activation of cyclin B/Cdk1	1
a_3	Basal term for inactivation of cyclin B/Cdk1	1
b_1	Term representing self-activation of cyclin E/Cdk2 through mutual activation between cyclin E/Cdk2 and phosphatase Cdc25	1
b_2	Term representing self-activation of cyclin B/Cdk1 through mutual activation between cyclin B/Cdk1 and phosphatase Cdc25	1
b_3	Term representing deactivation of cyclin B/Cdk1 enhanced by Wee1	20

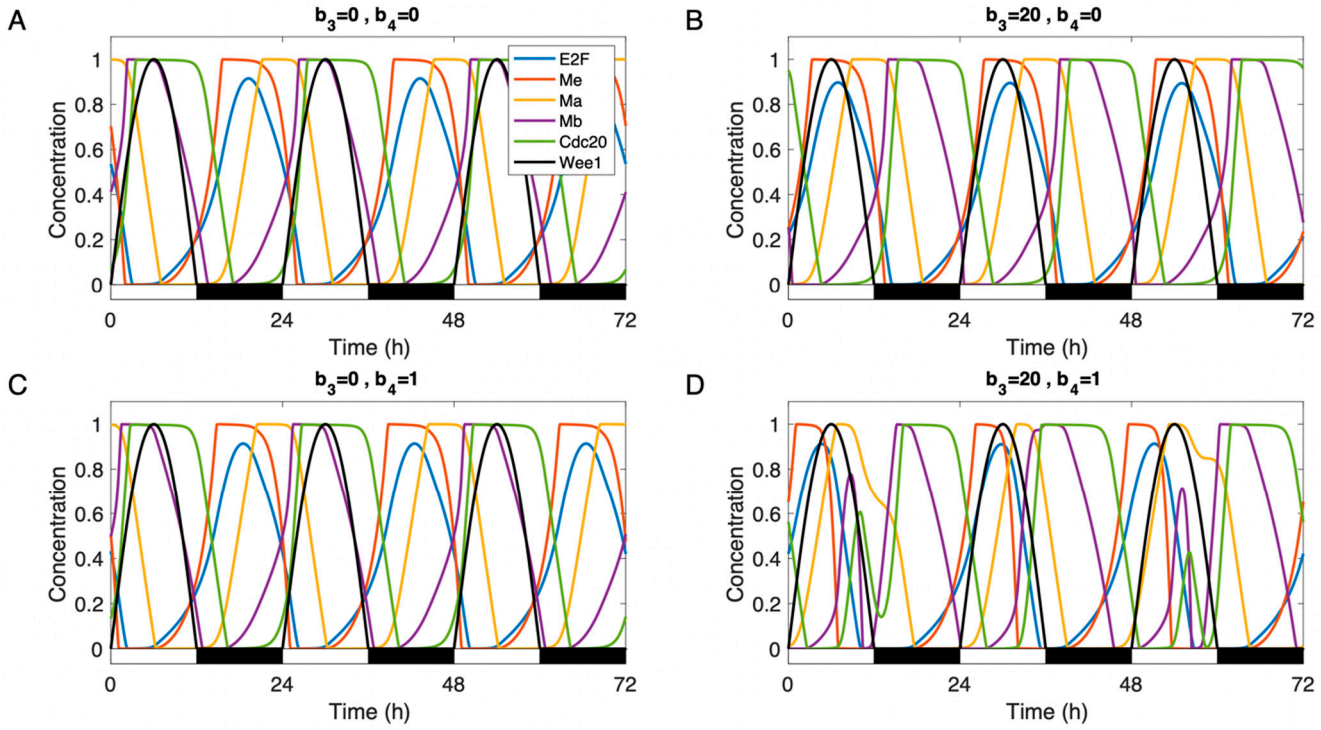

Figure S1. Dynamics of the cell cycle network (A) in absence of circadian signal, and (B-D) in presence of a circadian signal (Wee1). Three coupling scenarios are considered: Wee1 acting only on cyclin B/Cdk1 (B), only on cyclin E/Cdk2 (C), or both on cyclin B/Cdk1 and on cyclin E/Cdk2 (D). To account for the effect of Wee1 on Cyclin E/Cdk2, the term V_{2Me} in Eq. (3) has been replaced by $V_{2Me}\,(a_4 + b_4\,.\,Wee1)$ with $a_4 = 1$. The values of b_3 and b_4, which quantify the strength of circadian coupling, are indicated on the top of each panel. Note that the results are not qualitatively changed if we would take $b_4 = 20$ (not shown).

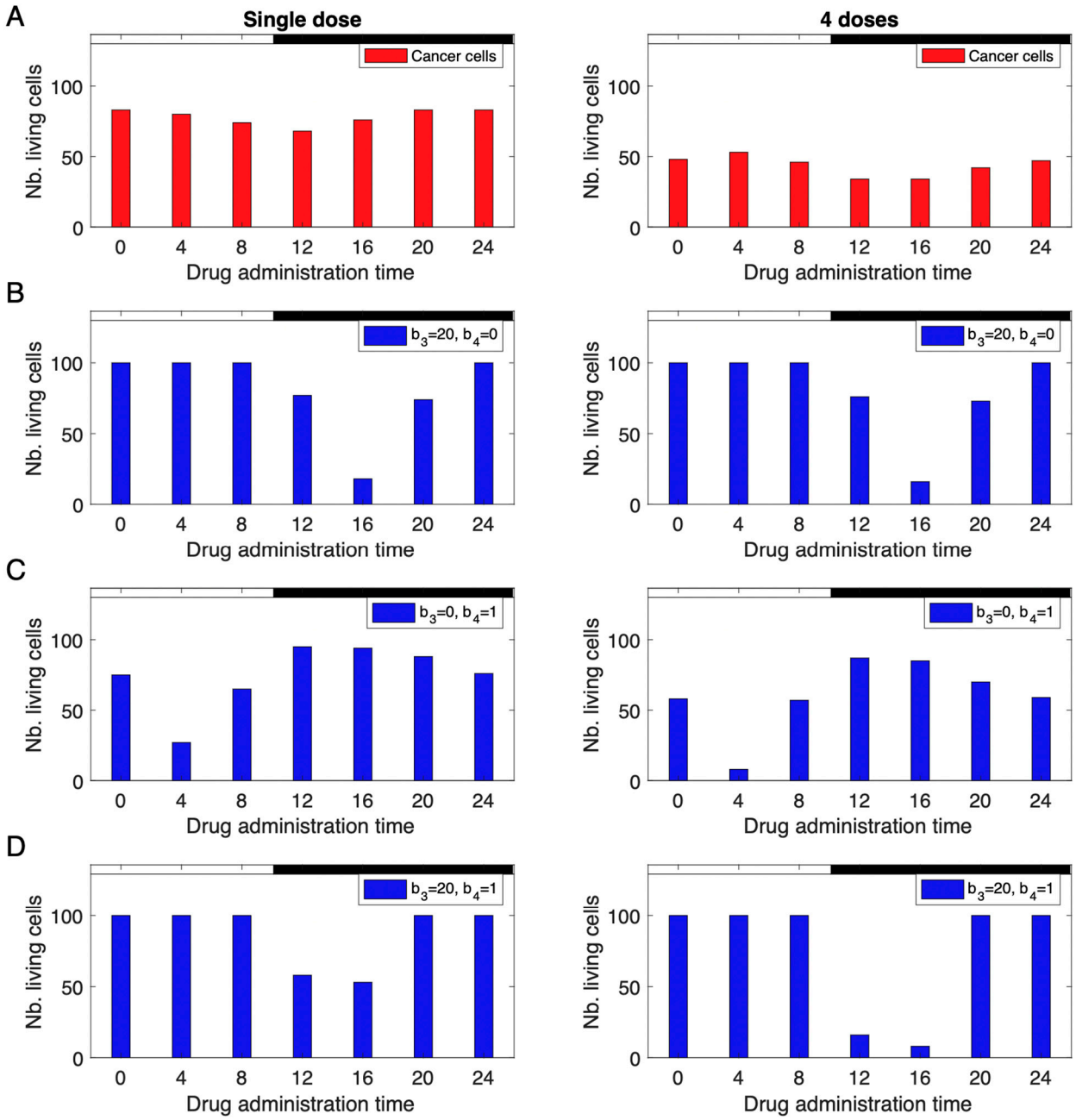

Figure S2. Effect of the schedule of the treatment. The different histograms give the number of living entrained/healthy (blue) vs non-entrained/cancer cells (red) remaining after the application of an anti-*Mb* drug, when a single dose (left panels) or 4 doses at interval of 5 days (right panels) are administrated. The following cases are considered: (A) no entrainment. (B) Wee1 acts only on cyclin B/Cdk1. (C) Wee1 acts only on cyclin E/Cdk2. (D) Wee1 acts both on cyclin B/Cdk1 and on cyclin E/Cdk2. To account for the inhibition of cyclin E / Cdk2 by Wee1, Eq. (3) has been modified as described in the legend of Figure S1. The initial number of cells is 100. The drug targets cells with a level of *Mb* larger than 0.95 and the duration of the application of the drug is 0.5h. ZT 0 represents the beginning of the L phase (i.e. start of expression of Wee1).