A mathematical model of the cell cycle and its circadian control

Jean Clairambault [a,d], Philippe Michel [b,c], Benoît Perthame [a,b]

[a] **INRIA, projet BANG, Domaine de Voluceau, BP 105, F78153 Le Chesnay Cedex, E-mail: jean.clairambault@inria.fr**

[b] **Département de Mathématiques et Applications, UMR 8553, École Normale Supérieure, 45, rue d'Ulm, F75230 Paris Cedex 05, tel. 01 44 27 20 36, fax 01 44 32 20 80 E-mail: Michel@dma.ens.fr, Benoit.Perthame@ens.fr**

[c] **CEREMADE, Université Paris 9 Dauphine, Place du Maréchal de Lattre de Tassigny, F75775 Paris cedex 16**

[d] **INSERM E 0354 "Rythmes biologiques et cancer", Hôpital Paul-Brousse, 14, Av. Paul-Vaillant-Couturier, F94807 Villejuif cedex**

Abstract

We address the following question: Can one sustain, on the basis of mathematical models, that for cancer cells, the loss of control by circadian rhythm favours a faster growth? This question, which comes from the observation that tumour growth in mice is enhanced by experimental disruption of the circadian rhythm, may be tackled by mathematical modelling of the cell cycle. For this purpose we consider an age-structured population model with control of death (apoptosis) rates and phase transitions, and two eigenvalues: one for periodic control coefficients (via a variant of Floquet theory in infinite dimension) and one for constant coefficients (taken as the time average of the periodic case). We show by a direct proof that, surprisingly enough considering the abovementioned observation, the periodic eigenvalue is always greater than the steady state eigenvalue when the sole apoptosis rate is concerned. We also show by numerical simulations when transition rates between the phases of the cell cycle are concerned, that, without further hypotheses, no natural hierarchy between the two eigenvalues exists. This at least shows that, if such models are to take account of the abovementioned observation, control of death rates inside phases is not sufficient, and that transition rates between phases are a key target in proliferation control.

1 Cell cycle and circadian rhythm

The goal of this Note is to address by means of mathematical and numerical models the following idea underlying chronotherapy [12, 17]: circadian rhythms influence cell proliferation. In particular, tumour growth has been showed to be favoured by disruptions of the normal circadian rhythm, as assessed e.g. by central body temperature or rest-activity recordings [6, 7]. Also several epidemiological studies have shown that workers exposed to prolonged shift work are significantly more exposed to the risk of developing colorectal cancer than others with regular work time schedules [7]. It is thus suspected that a loss of circadian control on the cell cycle dynamics may account for an acceleration in tumour progression. This idea is now sustained by a better understanding of the mechanisms underlying apoptosis and cell cycle phase transitions through proteins such as p53 and cyclins. Indeed, some of these mechanisms, such as phosphorylation of the dimer CycB-Cdc2 by the kinase Wee1 are directly controlled by circadian genes as Bmal1, see [13, 18, 20].
Our approach relies on mathematical equations for the cell cycle which are well settled nowadays. We introduce circadian control through periodic coefficients and assess the hypothesis according to which periodicity diminishes the system growth as compared to constant coefficients (with the same average), i.e., we want to decide if a loss of circadian control theoretically favours tumour growth.
General references and experimental validations of the topic of structured population dynamics and cell-cycle can be found in [1, 2, 3, 11, 14, 19]. For a more recent approach based on entropy properties, we refer to [15, 16]. Here and following earlier work [4], we model our population of cells by a Partial Differential Equation for the density $n_i(t,x) \geq 0$ of cells with age x in the phase $i = 1, ...I$, at time t.

$$\begin{cases} \frac{\partial}{\partial t} n_i(t,x) + \frac{\partial}{\partial x} n_i(t,x) + [d_i(t,x) + K_{i\to i+1}(t,x)] n_i(t,x) = 0, \\ n_i(t, x=0) = \displaystyle\int_{x'\geq 0} K_{i-1\to i}(t,x')\, n_{i-1}(t,x')\, dx', \quad 2 \leq i \leq I, \\ n_1(t,x=0) = 2 \displaystyle\int_{x'\geq 0} K_{I\to 1}(t,x')\, n_I(t,x')\, dx'. \end{cases} \tag{1}$$

Here and below we identify $I+1$ to 1. We denote by $d_i(t,x) \geq 0$ the apoptosis rate, $K_{i\to i+1}$ the transition rates from one phase to the next, and the last one ($i = I$) is mitosis where the two cells separate. These coefficients can be constant in time (no circadian control) or time T-periodic in order to take into account the circadian rhythm. Our assumptions are

$$K_{i\to i+1}(t,x) \geq 0, \; d_i(t,x) \geq 0 \qquad \text{are bounded,} \tag{2}$$

and, setting $\min_{0\leq t\leq T} K_{i\to i+1}(t,x) := k_{i\to i+1}(x)$, $\max_{0\leq t\leq T} [d_i + K_{i\to i+1}] := \mu_i(x)$, $M_i(x) = \int_0^x \mu_i(y) dy$,

$$\prod_{i=1}^{I} \int_0^\infty k_{i\to i+1}(y) e^{-M_i(y)} dy > 1/2. \tag{3}$$

Classically, one can introduce the growth rate of the system λ_{per} (Malthus parameter, first eigenvalue) such that there is a unique T-periodic **positive** solution to

$$\begin{cases} \frac{\partial}{\partial t}N_i(t,x) + \frac{\partial}{\partial x}N_i(t,x) + [d_i(t,x) + \lambda_{per} + K_{i\to i+1}(t,x)]N_i(t,x) = 0, \\ N_i(t,x=0) = \int_{x'\geq 0} K_{i-1\to i}(t,x')\; N_{i-1}(t,x')\; dx', \quad 2 \leq i \leq I, \\ N_1(t,x=0) = 2\int_{x'\geq 0} K_{I\to 1}(t,x')\; N_I(t,x')\; dx' \qquad \sum_{i=1}^{I}\int N_i(t,x)dx = 1. \end{cases} \tag{4}$$

Under our assumptions (2)–(3), the existence of a solution to (4), with $\lambda_{per} > 0$, follows from an infinite dimensional version of Floquet theory and one has (see for instance [15])

$$\sum_i \int \left| n_i(t,x)e^{-\lambda_{per}t} - \rho N_i(t,x)\right| \varphi_i(t,x)dx \to 0 \qquad \text{as } t \to \infty,$$

where $\varphi_i(t,x)$ denotes the periodic positive solution to the adjoint problem to (4) normalised by $\sum_i \int N_i(t,x)\varphi_i(t,x)dx = 1$, and $\rho = \sum_{i=1}^{N}\int n_i(t=0,x)\varphi_i(t=0,x)dx$. In other words, the periodic solution is the observed stable state after renormalisation by the growth rate λ_{per}.

One can also introduce the coefficients averaged in time

$$\langle K_{i\to i+1}(x)\rangle := \frac{1}{T}\int_0^T K_{i\to i+1}(t,x)dt, \qquad \langle d_i(t,x)\rangle := \frac{1}{T}\int_0^T d_i(t,x)dt,$$

and consider the associated steady state solution. This allows us to define another growth rate λ_s, and a steady state solution $\bar{N}_i$ to

$$\begin{cases} \frac{\partial}{\partial x}\bar{N}_i(x) + [\langle d_i(x)\rangle + \lambda_s + \langle K_{i\to i+1}(x)\rangle]\bar{N}_i(x) = 0, \\ \bar{N}_i(x=0) = \int_{x'\geq 0} \langle K_{i-1\to i}(x')\rangle\; \bar{N}_{i-1}(x')\; dx', \quad 2 \leq i \leq I, \\ \bar{N}_1(x=0) = 2\int_{x'\geq 0} \langle K_{I\to 1}(x')\rangle\; \bar{N}_I(x')\; dx', \qquad \sum_{i=1}^{I}\int \bar{N}_i(x)dx = 1. \end{cases} \tag{5}$$

For these problems, we address the hypothesis that circadian control reduces the system growth, i.e., $\lambda_{per} \leq \lambda_s$ (index *per* standing for "periodic" and s for "stationary"). In section 3, we prove that, surprisingly enough, the opposite is true, i.e., $\lambda_{per} \geq \lambda_s$ when the circadian control acts only on the apoptosis rate. In section 4, we show by numerical experiments that no hierarchy exists between the two eigenvalues when the circadian control acts on the transition rate $K_{1\to 2}$ in a reduced 2-phase model. These results give hints towards designing physiologically based models of the cell cycle for cancer therapeutics which are summarised in section 5.

2 Analysis of local variation by small oscillations

In this section, we prove that the local variation, with respect to a circadian control, of the growth rate λ is related to the solution $(N_i, \lambda, \varphi_i)$ of a normalised eigenproblem. First, we define the oscillating part of $K_{i-1\to i}$, d_i for all i:

$$\tilde{K}_{i-1\to i}(t,x) := K_{i-1\to i}(t,x) - \langle K_{i-1\to i}(x)\rangle,$$
$$\tilde{K}_{I\to 1}(t,x) := K_{I\to 1}(t,x) - \langle K_{I\to 1}(x)\rangle,$$
$$\tilde{d}_i(t,x) := d_i(t,x) - \langle d_i(x)\rangle,$$

and we set, for all $\varepsilon \geq 0$,

$$K^{\varepsilon}_{i-1\to i}(t,y) := \varepsilon\tilde{K}_{i-1\to i}(t,y) + \langle K_{i-1\to i}(.,y)\rangle,$$
$$K^{\varepsilon}_{I\to 1}(t,x) := \varepsilon\tilde{K}_{I\to 1}(t,x) - \langle K_{I\to 1}(x)\rangle,$$
$$d^{\varepsilon}_i(t,x) := \varepsilon\tilde{d}_i(t,x) + \langle d_i(x)\rangle,$$

and $n^{\varepsilon}_i(t,y)$ solution to

$$\begin{cases} \frac{\partial}{\partial t}n^{\varepsilon}_i(t,x) + \frac{\partial}{\partial x}n^{\varepsilon}_i(t,x) + [d^{\varepsilon}_i(t,x) + K_{i\to i+1}(t,x)]n^{\varepsilon}_i(t,x) = 0, \\ n^{\varepsilon}_i(t,0) = \displaystyle\int_{x'\geq 0} K^{\varepsilon}_{i-1\to i}(t,x')n^{\varepsilon}_{i-1}(t,x')dx', \quad 2 \leq i \leq I, \\ n^{\varepsilon}_1(t,x=0) = 2\displaystyle\int_{x'\geq 0} K^{\varepsilon}_{I\to 1}(t,x')\, n_I(t,x')\, dx'. \end{cases} \tag{6}$$

Now, using the results recalled in section 1, we have, for all $\varepsilon \in [0,1]$, the existence of $(N^{\varepsilon}_i, \lambda_{\varepsilon}, \varphi^{\varepsilon}_i)$ solution to

$$\begin{cases} \frac{\partial}{\partial t}N^{\varepsilon}_i(t,x) + \frac{\partial}{\partial x}N^{\varepsilon}_i(t,x) + [d^{\varepsilon}_i(t,x) + \lambda_{\varepsilon} + K^{\varepsilon}_{i\to i+1}(t,x)]N^{\varepsilon}_i(t,x) = 0, \\ N^{\varepsilon}_i(t,x=0) = \displaystyle\int_{x'\geq 0} K^{\varepsilon}_{i-1\to i}(t,x')\, N^{\varepsilon}_{i-1}(t,x')\, dx', \quad 2 \leq i \leq I, \\ N^{\varepsilon}_1(t,x=0) = 2\displaystyle\int_{x'\geq 0} K^{\varepsilon}_{I\to 1}(t,x')\, N^{\varepsilon}_I(t,x')\, dx' \qquad \sum_{i=1}^{I}\int N^{\varepsilon}_i(t,x)dx = 1. \end{cases} \tag{7}$$

$$-\frac{\partial}{\partial t}\varphi^{\varepsilon}_i(t,x) - \frac{\partial}{\partial x}\varphi^{\varepsilon}_i(t,x) + [d^{\varepsilon}_i(t,x) + \lambda_{\varepsilon} + K^{\varepsilon}_{i\to i+1}(t,x)]\varphi^{\varepsilon}_i(t,x) = \varphi^{\varepsilon}_{i+1}(t,0)K^{\varepsilon}_{i\to i+1}(t,x), \quad 1 \leq i \leq I-1, \tag{8}$$

$$-\frac{\partial}{\partial t}\varphi^{\varepsilon}_I(t,x) - \frac{\partial}{\partial x}\varphi^{\varepsilon}_I(t,x) + [d^{\varepsilon}_I(t,x) + \lambda_{\varepsilon} + K^{\varepsilon}_{I\to 1}(t,x)]\varphi^{\varepsilon}_I(t,x) = 2\varphi^{\varepsilon}_1(t,0)K^{\varepsilon}_{I\to 1}(t,x), \tag{9}$$

with

$$\int_0^\infty \sum_{i=1}^I N_i^\varepsilon(t,x)\varphi_i^\varepsilon(t,x)dx = 1, \quad \forall t \geq 0. \tag{10}$$

Moreover, we have $\lambda_0 = \lambda_s$, $\lambda_1 = \lambda_{per}$ and

Theorem 2.1 *The function $\lambda \mapsto \lambda_\varepsilon$ is differentiable for all $\varepsilon \in]0,1[$, and*

$$\frac{d\lambda_\varepsilon}{d\varepsilon} = \frac{1}{T}\int_0^T \int_0^\infty N_I^\varepsilon(t,x)\Big[2\tilde{K}_{I\to 1}(t,x)\varphi_1^\varepsilon(t,0) - \big(\tilde{d}_I(t,x) + \tilde{K}_{I\to 1}(t,x)\big)\varphi_I^\varepsilon(t,x)\Big]dxdt$$
$$+ \frac{1}{T}\int_0^T \int_0^\infty \sum_{i=1}^{I-1} N_i^\varepsilon(t,x)\Big[\tilde{K}_{i\to i+1}(t,x)\varphi_{i+1}^\varepsilon(t,0) - \big(\tilde{d}_i(t,x) + \tilde{K}_{i\to i+1}(t,x)\big)\varphi_i^\varepsilon(t,x)\Big]dxdt. \tag{11}$$

Proof. First we define $(N^\varepsilon, \lambda^\varepsilon, \varphi^\varepsilon)$ by

$$\forall (t,y) \in [0,\infty[^2, \quad N^\varepsilon(t,y) \in [0,\infty[^I, \quad N^\varepsilon(t,y)|_i := N_i^\varepsilon(t,y),$$
$$\forall (t,y) \in [0,\infty[^2, \quad \varphi^\varepsilon(t,y) \in [0,\infty[^I, \quad \varphi^\varepsilon(t,y)|_i := \varphi_i^\varepsilon(t,y),$$
$$\lambda^\varepsilon := \lambda_\varepsilon,$$

thus we define the operator $\mathcal{L}_\varepsilon^*$ such that $\mathcal{L}_\varepsilon^*\varphi^\varepsilon = \lambda^\varepsilon\varphi^\varepsilon$,

$$\mathcal{L}_\varepsilon^*(g)|_i := \frac{\partial}{\partial t}g_i(t,x) + \frac{\partial}{\partial x}g_i(t,x) - [d_i^\varepsilon(t,x) + K_{i\to i+1}^\varepsilon(t,x)]g_i(t,x) +$$
$$g_{i+1}(t,0)K_{i\to i+1}^\varepsilon(t,x), \quad 1 \leq i \leq I-1,$$

$$\mathcal{L}_\varepsilon^*(g)|_I := \frac{\partial}{\partial t}g_I(t,x) + \frac{\partial}{\partial x}g_I(t,x) - [d_I^\varepsilon(t,x) + K_{I\to 1}^\varepsilon(t,x)]g_I(t,x) + 2g_1(t,0)K_{I\to 1}^\varepsilon(t,x),$$

and its dual satisfying $\mathcal{L}^\varepsilon N^\varepsilon = \lambda^\varepsilon N^\varepsilon$. Thus, for all ε and ε' such that ε and $\varepsilon - \varepsilon' \in]0,1[$, we have :

$$\lambda^\varepsilon = \int_0^\infty \mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y)N^\varepsilon(y)dy.$$

Therefore, we find

$$\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'} = \int_0^\infty \mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y)N^\varepsilon(y)dy - \int_0^\infty \mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^{\varepsilon-\varepsilon'})(y)N^{\varepsilon-\varepsilon'}(y)dy.$$

But, the normalisation gives

$$\int_0^\infty \varphi^\varepsilon(y)N^\varepsilon(y)dy = \int_0^\infty \varphi^{\varepsilon-\varepsilon'}(y)N^{\varepsilon-\varepsilon'}(y)dy = 1, \tag{12}$$

and so, we have

$$\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'} = \int_0^\infty \Big(\mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y) - \mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^\varepsilon)(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy$$
$$+ \int_0^\infty \mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y)\Big(N^\varepsilon(y) - N^{\varepsilon-\varepsilon'}(y)\Big)dy$$
$$- \int_0^\infty \Big(\mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^{\varepsilon-\varepsilon'})(y) - \mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^\varepsilon)(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy.$$

Using the definition of $\mathcal{L}^*$, $\mathcal{L}$ and their duality, we find :

$$\begin{aligned}\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'} = \int_0^\infty \Big(\mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y) - \mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^\varepsilon)(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy \\ + \lambda^\varepsilon \int_0^\infty \varphi^\varepsilon(y)\Big(N^\varepsilon(y) - N^{\varepsilon-\varepsilon'}(y)\Big)dy \\ - \lambda^{\varepsilon-\varepsilon'} \int_0^\infty \Big(\varphi^{\varepsilon-\varepsilon'}(y) - \varphi^\varepsilon(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy.\end{aligned}$$

Thus, using the normalisation (12), we have

$$\begin{aligned}\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'} = \int_0^\infty \Big(\mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y) - \mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^\varepsilon)(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy \\ + \lambda^\varepsilon \int_0^\infty \varphi^\varepsilon(y)\Big(N^\varepsilon(y) - N^{\varepsilon-\varepsilon'}(y)\Big)dy \\ - \lambda^{\varepsilon-\varepsilon'} \int_0^\infty \varphi^\varepsilon(y)\Big(N^\varepsilon(y) - N^{\varepsilon-\varepsilon'}(y)\Big)dy,\end{aligned}$$

and

$$\begin{aligned}\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'} = \int_0^\infty \Big(\mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y) - \mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^\varepsilon)(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy \\ + \lambda^\varepsilon \int_0^\infty \Big(\varphi^{\varepsilon-\varepsilon'}(y) - \varphi^\varepsilon(y)\Big)N^{\varepsilon-\varepsilon'}(y) \\ - \lambda^{\varepsilon-\varepsilon'} \int_0^\infty \Big(\varphi^{\varepsilon-\varepsilon'}(y) - \varphi^\varepsilon(y)\Big)N^{\varepsilon-\varepsilon'}(y).\end{aligned}$$

And so, we have

$$\begin{aligned}(\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'})[1 - \int_0^\infty \Big(\varphi^{\varepsilon-\varepsilon'}(y) - \varphi^\varepsilon(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy] = \\ \int_0^\infty \Big(\mathcal{L}_\varepsilon^*(\varphi^\varepsilon)(y) - \mathcal{L}_{\varepsilon-\varepsilon'}^*(\varphi^\varepsilon)(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy.\end{aligned}$$

Using that

$$(\mathcal{L}_*^\varepsilon - \mathcal{L}_*^{\varepsilon-\varepsilon'})(g) = \varepsilon'\big(- [\tilde{d}_i + \tilde{K}_{i\to i+1}]g_i + g_{i+1}(0)\tilde{K}_{i\to i+1}\big),$$

we find that

$$\begin{aligned}(\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'})[1 - \int_0^\infty \Big(\varphi^{\varepsilon-\varepsilon'}(y) - \varphi^\varepsilon(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy] = \\ \varepsilon' \int_0^\infty \Big(- [\tilde{d}_i + \tilde{K}_{i\to i+1}]\varphi_i^\varepsilon + \varphi_{i+1}^\varepsilon(0)\tilde{K}_{i\to i+1}\Big)N^{\varepsilon-\varepsilon'}dy,\end{aligned}$$

And finally, we find

$$\frac{\lambda^\varepsilon - \lambda^{\varepsilon-\varepsilon'}}{\varepsilon'} = \frac{\int_0^\infty \Big(- [\tilde{d}_i + \tilde{K}_{i\to i+1}]\varphi_i^\varepsilon + \varphi_{i+1}^\varepsilon(0)\tilde{K}_{i\to i+1}\Big)N^{\varepsilon-\varepsilon'}dy}{(1 - \int_0^\infty \Big(\varphi^{\varepsilon-\varepsilon'}(y) - \varphi^\varepsilon(y)\Big)N^{\varepsilon-\varepsilon'}(y)dy)}. \tag{13}$$

Using the Lebesgue dominated convergence theorem, we can pass to the limit and find that the function $\varepsilon \mapsto \lambda^{\varepsilon}$ (i.e., λ_ε) is differentiable and (11) is satisfied. $\square$

Then, we find directly that, in the particular case when $K_{i\to i+1}$ is independent of time and d_i is independent of age, we cannot control the growth rate λ. Indeed, we have

Corollary 2.2 *Assume* $\tilde{d}_i(t,x) = \rho_i(t)$, $\tilde{K}_{i\to i+1}(t,x) = 0$ *then*

$$\frac{d\lambda_\varepsilon}{d\varepsilon} = 0, \tag{14}$$

and $\lambda_s = \lambda_{per}$.

Proof. Using (11), we find

$$\frac{d\lambda_\varepsilon}{d\varepsilon} = -\frac{1}{T}\int_0^T \int_0^\infty \sum_{i=1}^{I} N_i^\varepsilon(t,x)\varphi_i^\varepsilon(t,x)dx\rho_i(t)dt,$$

but we have $\displaystyle\int_0^T \rho_i(t)dt = 0$ and (10), thus we find (14) and

$$\lambda_{per} - \lambda_s = \int_0^1 \frac{d\lambda_\varepsilon}{d\varepsilon} = 0. \quad \square$$

To summarise this section, direct computation in the most general case, when $K_{i\to i+1}$ and d_i are time dependent leads to hardly tractable formulae; the local variation of the first eigenvalue is not easily found theoretically and usually may be computed only numerically (see section 4). Nevertheless, in some cases, using the equations for N_i and $\bar{N}_i$, we can find its global variation(see section 3).

3 Control by apoptosis

In this section we consider the case when the circadian control only acts on apoptosis, i.e., $K_{i\to i+1}$ depends only upon x.

Theorem 3.1 *Assume that* $d_i(t,x) \geq 0$, $K_{i\to i+1}(x) \geq 0$ *are bounded and that (3) holds, then the eigenvalue problems (4), (5) have unique solutions* $(\lambda_{per}, N(t,x))$, $(\lambda_s, \bar{N}(x))$, *and*

$$\lambda_{per} \geq \lambda_s. \tag{15}$$

Proof. The existence part for the two problems is standard and we do not prove it again (see [4, 15]). For the ordering of eigenvalues, consider the function $q_i(x) =< \log\left(\frac{N_i(t,x)}{\bar{N}_i(x)}\right) >$. It satisfies

$$\frac{\partial}{\partial x} q_i + \lambda_{per} - \lambda_s = 0,$$

$$q_i(x=0) =< \log\left[\int K_{i-1\to i}(x)\frac{\bar{N}_{i-1}(x)}{\bar{N}_i(0)}\,\frac{N_{i-1}(t,x)}{\bar{N}_{i-1}(x)}\,dx\right] > .$$

Since $d\mu_i(x) = K_{i-1\to i}(x)\frac{\bar N_{i-1}(x)}{\bar N_i(0)}dx$ is a probability measure thanks to the condition $\bar N_i(0)$ (a factor 2 should be included for $i=1$), we also have

$$
\begin{aligned}
q_i(x=0) \quad &\geq \quad < \int \log \frac{N_{i-1}(t,x)}{\bar N_{i-1}(x)}\, d\mu_i(x) > \qquad\qquad \text{(by Jensen's inequality)} \\
&= \quad \int q_{i-1}(x)\, d\mu_i(x) \qquad\qquad = \int [q_{i-1}(0) + (\lambda_s - \lambda_{per})x]\, d\mu_i(x)\ .
\end{aligned}
$$

Therefore, summing over i from 1 to I,

$$0 \geq (\lambda_s - \lambda_{per}) \sum_{i=1}^{I} \int_{x=0}^{\infty} x\, d\mu_i(x),$$

and the result follows. $\square$

Notice that the same question has been addressed for positive matrices, in [5]. Of course a discrete version of equations (4), (5) based, say on an upwind scheme, leads to study the same inequalities for matrices with positive coefficients and our method applies to matrices with periodic diagonal terms.

4 Control by phase transition

We have performed numerical tests for the cell cycle systems (4), (5) based on a classical upwind scheme with $CFL = 1$ which gives the exact transport solver (see [4] for details). We have taken a simplified version of the cell cycle with two phases ($I = 2$): G1-S-G2 and M. In other words, in the full cell-cycle (G1, synthesis, G2, mitosis) we only retain as a major event the transition from G2 to M. The apoptosis rate has been taken constant and the transition rates are

$$K_{1\to 2}(t,x) = \psi(t)\mathbb{1}_{\{x\geq x_*\}}, \qquad K_{2\to 1}(t,x) = \mathbb{1}_{\{x\geq x_{**}\}}.$$

We have in mind the following order of magnitudes for several animal tumour cells: total cycle duration is 21 h, 8 h for G1, 8 h for S, 4h for G2, 1 h for M (therefore in this case $x_* = 20$ h and $x_{**} = 1$ h). But we will also consider different duration ratios x_*/x_{**} between the 2 phases G1-S-G2 and M, from 1 to 20. The reason for this is that although the G2/M transition is known to be a circadian control target with an identified mechanism (Bmal1→Wee1→cdc2 -the cyclin dependent kinase cdc2 being rather known as cdk1 in mammals), another control target, with as yet unidentified mechanism (though the genes *per* and $cMyc$ have been shown to be involved [8, 9]), could take place at the G1/S transition, and the G1 phase may have a very variable duration. So that while in principle testing here the G2/M transition, we may also be testing the G1/S gate control, by an unknown 24 h-rhythmic cdc2-like factor. The function $\psi(t)$ has 24h period. We have tested for ψ several shapes (*cosine* and square wave functions), but eventually kept only 2 square waves, a brief one with 4 hours at value 1 and the remaining 20 hours at 0, the other one with 12 hours at 1 and 12 hours at 0. The first one mimics the shape of the cdc2 kinase behaviour, with entrainment by 24 h-rhythmic Wee1, according to A. Goldbeter's model of the mitotic oscillator [10], the other a version of the same cdc2 model, with no entrainment, but fixed coefficients yielding also a 24 h period.

In the following tables, we show a comparison between the two eigenvalues (periodic and stationary), for the two tested ψ periodic transition functions. For reading convenience, the greater of the two eigenvalues is underlined.

G1-S-G2/M, brief sq. w.	λ_{per}	λ_s
1	$\underline{0.2385}$	0.2350
2	0.2260	$\underline{0.2923}$
3	0.2395	$\underline{0.3189}$
4	0.2722	$\underline{0.3331}$
5	0.3065	$\underline{0.3427}$
6	0.3305	$\underline{0.3479}$
7	0.3472	$\underline{0.3517}$
8	$\underline{0.3622}$	0.3546
10	$\underline{0.3808}$	0.3588
20	$\underline{0.4125}$	0.3675

G1-S-G2/M, 12-12 sq. w.	λ_{per}	λ_s
1	0.2623	$\underline{0.2821}$
2	0.3265	$\underline{0.3448}$
3	...	...
4	...	...
5	...	...
6	...	...
7	0.4500	$\underline{0.4529}$
8	$\underline{0.4588}$	0.4575
10	$\underline{0.4713}$	0.4641
20	$\underline{0.5006}$	0.4818

Table 1. The periodic and stationary eigenvalues for 2 periodic phase transition functions and different duration ratios between the first and second phases. See text for details.

Thus no clear hierarchy can be seen between the two eigenvalues, even if some regularity may be suspected, and these simulations show cases favorable to our initial hypothesis in the interval 2≤G1-S-G2/M≤7. It is likely that 2 phases only in the model may not be sufficient to account for the physiopathological observation which guided us for this modelling work, and that, as it is, this model aggregates in an inaccurate way physiological effects of the G1/S and G2/M transition controls. Future work on the basis of this experimental observation should encompass 3 phases: G1, S-G2 and M, and better knowledge of circadian control both at the G1/S and G2/M transitions, and synchronisation between these transitions.

5 Conclusion

To summarise these results:

1/ This model allows to study the interactions in proliferating tissues between the cell cycle and physiological control systems such as the circadian clock.

2/ More than 2 phases and better knowledge of other mechanisms (cortisol, Cyclin E on G1/S) might be necessary to account for the physiopathological facts reported from animal experimentation and human clinical observations which guided us in this investigation of the first eigenvalues of the periodic and stationary problems.

3/ The unexpected result $\lambda_{per} \geq \lambda_s$ for apoptosis control suggests that the sole control of death rate inside cell cycle phases might be unable to describe control of proliferation by cytotoxic drugs in cancer treatment. Transition rates should be considered in a therapeutic perspective.

Acknowledgments

We are gratefully indebted to Stéphane Gaubert for helpful discussions on theoretical and numerical aspects of this work, and to Béatrice Laroche and Stéphane Mischler for the derivation of the model.

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