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Partial Differential Equations

An inequality for the Perron and Floquet eigenvalues of monotone differential systems and age structured equations

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Abstract

For monotone linear differential systems with periodic coefficients, the (first) Floquet eigenvalue measures the growth rate of the system. We define an appropriate arithmetico-geometric time average of the coefficients for which we can prove that the Perron eigenvalue is smaller than the Floquet eigenvalue. We apply this method to Partial Differential Equations, and we use it for an age-structured systems of equations for the cell cycle. This opposition between Floquet and Perron eigenvalues models the loss of circadian rhythms by cancer cells. ***To cite this article: J. Clairambault et al., C. R. Acad. Sci. Paris, Ser. I 345 (2007).***

Résumé

Une inégalité pour les valeurs propres de Floquet et de Perron de systèmes différentiels monotones et d'équations structurées en âge. La (première) valeur propre de Floquet décrit le taux de croissance des systèmes différentiels linéaires monotones à coefficients périodiques. Nous définissons une moyenne arithmético-géométrique en temps des coefficients, qui nous permet de démontrer que la valeur propre de Perron pour le système ainsi moyenné est plus petite que celle de Floquet. La méthode s'applique aux Équations aux Dérivées Partielles et nous l'utilisons pour un système d'équations structurées en âge qui décrit le cycle cellulaire. Cette opposition entre valeurs propres de Floquet et de Perron modélise la perte de contrôle circadien pour le cycle cellulaire des cellules cancéreuses. ***Pour citer cet article : J. Clairambault et al., C. R. Acad. Sci. Paris, Ser. I 345 (2007).***

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Les systèmes biologiques sont souvent soumis à des contrôles périodiques. Un exemple en est fourni par le rythme circadien (journalier) qui trouve son origine au niveau des noyaux suprachiasmatiques de l'hypothalamus dans un

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réseau de régulation génique à présent bien étudié [9,1]. Une question médicale reliée est de comprendre l'influence de ce rythme sur la croissance des populations de cellules tumorales, en particulier dans une perspective thérapeutique. Un cadre mathématique naturel pour étudier cette question est fourni par la théorie des équations physiologiquement structurées.

Dans cette Note, nous proposons de comparer la (première) valeur propre de Floquet, qui décrit la croissance d'un système dont les paramètres sont soumis à un contrôle périodique, et la valeur propre de Perron, qui décrit la croissance du même système, mais à coefficients moyennés. Pour parvenir à cette comparaison, nous introduisons une moyenne arithmético-géométrique appropriée, dans trois cas : Équations Différentielles Ordinaires, système dynamique discret, Équations aux Dérivées Partielles (EDP) structurées en âge.

Le premier cas concerne un système différentiel linéaire monotone périodique. Soit $t \mapsto A(t)$ une application T-périodique, à valeurs dans $\mathbb{R}^{d\times d}$, intégrable sur $[0, T]$, et considérons l'équation différentielle $\dot{X}(t) = A(t)X(t)$, où X est absolument continue et $X(0)$ est prescrit. Nous supposerons que pour $i \neq j$, on a $A_{ij}(t) \geqslant 0$ pour presque tout t, ce qui garantit que le flot en temps positif associé à cette équation différentielle préserve l'ordre partiel usuel de $\mathbb{R}^d$. Les propriétés spectrales de cette équation différentielle relèvent alors de la théorie de Perron–Frobenius. En particulier, la première valeur propre de Floquet, λ_{per}, est le plus grand réel tel qu'il existe une fonction absolument continue X, T-périodique, à valeurs dans $\mathbb{R}^d_+$ (où $\mathbb{R}_+$ désigne l'ensemble des réels positifs ou nuls), et non identiquement nulle, telle que l'équation différentielle (1) soit satisfaite. Rappelons que la moyenne arithmétique d'une fonction T-périodique $u(t)$ est donnée par (2), et définissons la matrice $\bar{A}$ par (3). Cette matrice à coefficients hors diagonaux positifs ou nuls est dotée d'une valeur propre de Perron classique λ_s, qui est le plus grand réel tel qu'il existe un vecteur non-nul $U \in \mathbb{R}^d_+$ tel que $\lambda_s U = \bar{A}U$. Le résultat suivant peut être vu comme une généralisation de celui de [3].

Théorème 1. *On a toujours* $\lambda_{\text{per}} \geqslant \lambda_s$.

Une inégalité analogue est aussi obtenue pour les deux autres cas considérés, d'un système discret en temps et du système d'EDP structurées en âge (6) qui décrit le cycle de division cellulaire.

1. Introduction

Biological systems are often subject to periodic controls. This occurs for instance with circadian rhythms, the origin of which are found in the suprachiasmatic nuclei of the hypothalamus, in a now well established gene regulatory network [9,1]. A related medical question is to understand the interactions between the cell cycle and this circadian rhythm, which is expressed in every nucleated cell, with coordinating inputs from the hypothalamus. How can these rhythms induce differentiated growth between healthy and tumoral cells? A molecular mechanism has been evidenced [9], but most importantly in laboratory experimental settings, tumour growth has been shown to be favoured by disruptions of the normal circadian rhythm [4]. From a mathematical point of view, cell population growth is well described by physiologically structured equations, see [7,2], and the first eigenvalue of the underlying differential operator is the natural quantity that accounts for the growth of the system. Our purpose is to compare the first eigenvalues in the case of constant and periodic coefficients. It is simpler to consider in the first place differential systems; with periodic and nonnegative coefficients this eigenvalue is nothing but the (first) Floquet eigenvalue; with constant coefficients it refers to the usual Perron eigenvalue. Surprisingly, it is possible to prove in great generality that the Floquet eigenvalue is larger than the Perron eigenvalue with an appropriate arithmetico-geometric average of the coefficients. Precise statements, and proofs, are given in the first subsection in the case of a differential system. The results are extended to discrete time systems (Section 3), to Partial Diff. Eq. and in a 4th section, to age structured systems. In a 5th section, we briefly comment on the relevance to physiological systems.

2. Differential systems

Let $t \mapsto A(t)$ be a T-periodic map with values in $\mathbb{R}^{d\times d}$, integrable on $[0, T]$, and let us consider the differential equation $\dot{X}(t) = A(t)X(t)$, with a prescribed initial condition $X(0) \in \mathbb{R}^d$ (when dealing with such differential equations, we will always require X to be absolutely continuous, and we understand that the equality holds for almost all t). We assume that for $i \neq j$, we have $A_{ij}(t) \geqslant 0$ for almost every t, so that the flow in positive time of this

differential equation preserves the standard partial ordering of $\mathbb{R}^d$. Hence, the spectral properties of this differential equation belong to Perron–Frobenius theory. In particular, the (first) Floquet eigenvalue, λ_{per}, can be introduced by means of the following positive Floquet problem: there exists a T-periodic function X, with values in $\mathbb{R}^d_+$ ($\mathbb{R}_+$ denotes the set of nonnegative real numbers), nonidentically zero, such that

$$\dot{X}(t) = A(t)X(t) - \lambda_{\mathrm{per}}X(t), \quad t \in \mathbb{R}. \tag{1}$$

If A satisfies some irreducibility properties, for instance if $A_{ij}(t) > 0$ for almost every t and for $i \neq j$, λ_{per} is uniquely defined by the previous property, and X is unique up to a multiplicative constant. However, the results of this note are also valid in the reducible case, in which the Floquet eigenvalue can be defined as the maximal real number λ_{per} such that there exists a function X with the above properties.

We now introduce the arithmetic mean of a T-periodic function $u(t)$ as

$$\langle u \rangle_a = \frac{1}{T}\int_0^T u(s)\,\mathrm{d}s \tag{2}$$

and we define the constant coefficient matrix $\bar{A}$ with entries:

$$\bar{A}_{ii} = \langle A_{ii} \rangle_a, \quad 1 \leqslant i \leqslant d, \qquad \bar{A}_{ij} = \exp\bigl(\bigl\langle \log(A_{ij}) \bigr\rangle_a\bigr), \quad i \neq j,\ 1 \leqslant i, j \leqslant d. \tag{3}$$

Observe that $\langle \log(A_{ij}) \rangle_a \in \mathbb{R} \cup \{-\infty\}$ is well defined for $i \neq j$, because the positive part of $\log A_{ij}(t)$ is integrable as soon as $A_{ij}(t)$ is integrable. Since the off diagonal coefficients of the matrix $\bar{A}$ are nonnegative, we can apply the Perron–Frobenius theory and consider its first (Perron) eigenvalue, λ_s, which is the maximal real number such that there is a non-zero vector $U \in \mathbb{R}^d_+$ such that $\lambda_s U = \bar{A}U$. The following result generalises that of [3]:

Theorem 2.1. *We have always* $\lambda_{\mathrm{per}} \geqslant \lambda_s$.

Proof. We first prove the inequality when $A_{ij}(t) > 0$, for almost all t and for $i \neq j$. Then, the function X in (1) is such that $X_i(t) > 0$ for all t and for all i. We set,

$$x_i(t) := \log X_i(t) \quad \text{and for } i \neq j, \quad \ell_{ij}(t) := \log A_{ij}(t).$$

From the differential system (1), we obtain

$$\dot{x}_i(t) = \sum_j X_i^{-1}(t)A_{ij}(t)X_j(t) - \lambda_{\mathrm{per}} = \sum_{j\neq i} \exp\bigl(-x_i(t) + \ell_{ij}(t) + x_j(t)\bigr) + A_{ii}(t) - \lambda_{\mathrm{per}}.$$

Taking first the arithmetic mean on $[0, T]$ componentwise, and then using Jensen's inequality, it comes for all $1 \leqslant i \leqslant d$,

$$0 = \left\langle \sum_{j\neq i} \exp\bigl(-x_i(t) + \ell_{ij}(t) + x_j(t)\bigr) \right\rangle_a + \bigl\langle A_{ii}(t) \bigr\rangle_a - \lambda_{\mathrm{per}},$$

$$0 \geqslant \sum_{j\neq i} \exp\bigl(-\bigl\langle x_i(t) \bigr\rangle_a + \bigl\langle \ell_{ij}(t) \bigr\rangle_a + \bigl\langle x_j(t) \bigr\rangle_a\bigr) + \bigl\langle A_{ii}(t) \bigr\rangle_a - \lambda_{\mathrm{per}}.$$

Setting $\bar{X}_i := \exp(\langle x_i(t) \rangle_a)$, with the definition (3) of $\bar{A}$, this inequality also reads $0 \geqslant \sum_j \bar{X}_i^{-1}\bar{A}_{ij}\bar{X}_j - \lambda_{\mathrm{per}}$, and thus, multiplying by $\bar{X}_i$, $\bar{A}\bar{X} \leqslant \lambda_{\mathrm{per}}\bar{X}$. Using the Collatz–Wielandt characterisation of the Perron eigenvalue of $\bar{A}$, $\lambda_s = \min\{r;\ \exists Y \in \operatorname{int}\mathbb{R}^d_+,\ \bar{A}Y \leqslant rY\}$, we deduce that $\lambda_s \leqslant \lambda_{\mathrm{per}}$. The general case is obtained by considering the matrix with entries $A_{ij}(t) + \epsilon$, with $\epsilon > 0$, and by applying a continuity argument, the details of which are left to the reader. □

3. Discrete systems: an inequality for the Perron eigenvalue of a geometric mean

The same proof allows us to treat discrete systems. For $k \in \mathbb{N}$, let $A(k) = A(k + p)$ be a $d \times d$, p-periodic matrix with nonnegative coefficients. We define λ_{per} to be the maximal real nonnegative number such that there exists a non-zero p-periodic solution $X(k)$ with values in $\mathbb{R}^d_+$ to

$$\lambda_{\mathrm{per}}X(k+1) = A(k)X(k), \tag{4}$$

so that $\lambda_{\mathrm{per}}^{p}$ is the Perron eigenvalue of the product $A(p-1)\cdots A(0)$. We now set $\langle u\rangle_a := p^{-1}(u(0)+\cdots+u(p-1))$ for all p-periodic functions u, and we define the constant coefficient matrix $\bar{A}$, with entries:

$$\bar{A}_{ij} = \exp\bigl(\bigl\langle \log(A_{ij})\bigr\rangle_a\bigr), \quad 1 \leqslant i, j \leqslant d \tag{5}$$

(unlike in the continuous time case, the nature of the mean is the same for diagonal and off diagonal entries). We denote by λ_s the Perron eigenvalue of the nonnegative matrix $\bar{A}$.

Theorem 3.1. *We have again* $\lambda_{\mathrm{per}} \geqslant \lambda_s$.

Proof. Since the Perron eigenvalue is a continuous function of the entries of a matrix, it suffices to show the inequality when the entries $A_{ij}(k)$ are all positive. Then, the vectors $X(k)$ above have positive entries. We set

$$x_i(k) := \log X_i(k), \quad \ell_{ij}(k) := \log A_{ij}(k), \quad \mu := \log(\lambda_{\mathrm{per}}).$$

We take componentwise the logarithm in $\lambda_{\mathrm{per}} X(k+1) = A(k)X(k)$ and arrive at

$$x_i(k+1) - x_i(k) = \log\biggl(\sum_j \exp\bigl(-x_i(k) + \ell_{ij}(k) + x_j(k)\bigr)\biggr) - \mu.$$

Taking the arithmetic mean for $k = 0, \ldots, p-1$, it becomes

$$0 = \biggl\langle \log\biggl(\sum_j \exp\bigl(-x_i(k) + \ell_{ij}(k) + x_j(k)\bigr)\biggr)\biggr\rangle_a - \mu.$$

Next, because the function $f(y_1, \ldots, y_d) = \log(\sum_j \exp(y_j))$ is convex, we apply Jensen's inequality and obtain

$$0 \geqslant \log\biggl(\sum_j \exp\bigl(-\bigl\langle x_i(k)\bigr\rangle_a + \bigl\langle \ell_{ij}(k)\bigr\rangle_a + \bigl\langle x_j(k)\bigr\rangle_a\bigr)\biggr) - \mu,$$

and, exponentiating, we get $\lambda_{\mathrm{per}}\bar{X} \geqslant \bar{A}\bar{X}$, with $\bar{X}_i := \exp(\langle x_i(k)\rangle_a)$. Using again the Collatz–Wielandt characterisation of the Perron eigenvalue of $\bar{A}$, we deduce that $\lambda_{\mathrm{per}} \geqslant \lambda_s$. □

4. An age-structured system for the cell division cycle

General references and experimental validations on the topic of structured population dynamics and cell cycle can be found in [2,7]. For a recent mathematical approach based on entropy properties, we refer to [8,10]. Here and following earlier work [3], we model our population of cells by a Partial Differential Equation for the density $n_i(t,x) \geqslant 0$ of cells with age x in the phase $i = 1, \ldots,$ at time t,

$$\begin{cases} \dfrac{\partial}{\partial t} n_i(t,x) + \dfrac{\partial}{\partial x} n_i(t,x) + \bigl[d_i(t,x) + K_{i\to i+1}(t,x)\bigr] n_i(t,x) = 0, \\ n_i(t, x=0) = \int_{x'\geqslant 0} K_{i-1\to i}(t,x') n_{i-1}(t,x')\,\mathrm{d}x', \quad 2 \leqslant i \leqslant I, \\ n_1(t, x=0) = 2\int_{x'\geqslant 0} K_{I\to 1}(t,x') n_I(t,x')\,\mathrm{d}x'. \end{cases} \tag{6}$$

Here and below we identify $I+1$ to 1. We have denoted by $d_i(t,x) \geqslant 0$ the apoptosis rate, by $K_{i\to i+1}$ 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

$$K_{i\to i+1}(t,x) \geqslant 0, \ d_i(t,x) \geqslant 0 \quad \text{are bounded,} \tag{7}$$

and, setting

$$\min_{0\leqslant t\leqslant T} K_{i\to i+1}(t,x) := k_{i\to i+1}(x), \quad \max_{0\leqslant t\leqslant T} [d_i + K_{i\to i+1}] := \mu_i(x), \quad M_i(x) = \int_0^x \mu_i(y)\,\mathrm{d}y,$$

$$\prod_{i=1}^{I} \int_0^\infty k_{i\to i+1}(y)\,\mathrm{e}^{-M_i(y)}\,\mathrm{d}y > 1/2. \tag{8}$$

With these assumptions and following [8], one can again introduce the growth rate (Floquet eigenvalue) of the system: $\lambda_{\mathrm{per}} \in \mathbb{R}$ such that there is a unique T-periodic *positive* solution to the system:

$$\begin{cases} \dfrac{\partial}{\partial t}N_i(t,x) + \dfrac{\partial}{\partial x}N_i(t,x) + \big[d_i(t,x) + \lambda_{\mathrm{per}} + K_{i\to i+1}(t,x)\big]N_i(t,x) = 0, \\ N_i(t,x=0) = \int_{x'\geqslant 0} K_{i-1\to i}(t,x')N_{i-1}(t,x')\,\mathrm{d}x', \quad 2 \leqslant i \leqslant I, \\ N_1(t,x=0) = 2\int_{x'\geqslant 0} K_{I\to 1}(t,x')N_I(t,x')\,\mathrm{d}x', \quad \sum_{i=1}^{I}\int_{x\geqslant 0} N_i(t,x)\,\mathrm{d}x = 1. \end{cases} \tag{9}$$

As in formula (3), we can define the averages

$$\begin{cases} \big\langle d_i(x)\big\rangle_a = \frac{1}{T}\int_0^T d_i(t,x)\,\mathrm{d}t, \quad \big\langle K_{i\to i+1}(t,x)\big\rangle_a = \frac{1}{T}\int_0^T K_{i\to i+1}(t,x)\,\mathrm{d}t, \\ \big\langle K_{i\to i+1}(t,x)\big\rangle_g = \exp\big(\frac{1}{T}\int_0^T \log\big(K_{i\to i+1}(t,x)\big)\,\mathrm{d}t\big). \end{cases} \tag{10}$$

These averages define the Perron eigenvalue $\lambda_s \in \mathbb{R}$, which is such that there is a unique positive solution to the system

$$\begin{cases} \dfrac{\partial}{\partial x}\bar{N}_i(x) + \big[\big\langle d_i(x)\big\rangle_a + \lambda_s + \big\langle K_{i\to i+1}(t,x)\big\rangle_a\big]\bar{N}_i = 0, \\ \bar{N}_i(x=0) = \int_{x'\geqslant 0}\big\langle K_{i-1\to i}(t,x')\big\rangle_g \bar{N}_{i-1}(x')\,\mathrm{d}x', \quad i \neq 1, \\ \bar{N}_1(x=0) = 2\int_{x'\geqslant 0}\big\langle K_{I\to 1}(t,x')\big\rangle_g \bar{N}_I(x')\,\mathrm{d}x'. \end{cases} \tag{11}$$

We have the following analogue of Theorem 2.1:

Theorem 4.1. *Under assumptions* (7)–(8)*, we still have* $\lambda_{\mathrm{per}} \geqslant \lambda_s$.

Observe that the arithmetic mean of the coefficients $K_{i\to i+1}$ is taken in the PDEs, whereas their geometric mean is taken in the integral equations. Hence, an artificial loss rate of cells $\langle K_{i\to i+1}\rangle_a - \langle K_{i\to i+1}\rangle_g$ from phase i to phase $i+1$ arises in the averaged model.

Proof. The proof differs slightly from that of Theorem 2.1 because, working with $x \in \mathbb{R}_+$ the corresponding quantities cannot always be normalised as measures. Therefore, following [3], we define $q_i(x) = \langle \log N_i(t,x) - \log \bar{N}_i(x)\rangle_a$ and we have, up to the insertion of a factor 2 when $i = 1$,

$$q_i(x=0) = \left\langle \log\left(\frac{N_i(t,0)}{\bar{N}_i(0)}\right)\right\rangle_a = \left\langle \log \int \big\langle K_{i-1\to i}(x)\big\rangle_g \frac{\bar{N}_{i-1}(x)}{\bar{N}_i(0)}\frac{N_{i-1}(t,x)}{\bar{N}_{i-1}(x)}\frac{K_{i-1\to i}(t,x)}{\langle K_{i-1\to i}(x)\rangle_g}\,\mathrm{d}x\right\rangle_a.$$

We can now define the probability measures

$$\mathrm{d}\mu_i(x) = \big\langle K_{i-1\to i}(x)\big\rangle_g \frac{\bar{N}_{i-1}(x)}{\bar{N}_i(0)} \quad \text{for } i \neq 1, \qquad \mathrm{d}\mu_1(x) = 2\big\langle K_{I\to 1}(x)\big\rangle_g \frac{\bar{N}_I(x)}{\bar{N}_1(0)}.$$

Using Jensen's inequality, we obtain

$$\begin{aligned} q_i(x=0) &\geqslant \left\langle \int \log\left(\frac{N_{i-1}(t,x)}{\bar{N}_{i-1}(x)}\frac{K_{i-1\to i}(t,x)}{\langle K_{i-1\to i}(x)\rangle_g}\right)\mathrm{d}\mu_i(x)\right\rangle_a \\ &= \left\langle \int \log\left(\frac{N_{i-1}(t,x)}{\bar{N}_{i-1}(x)}\right)\mathrm{d}\mu_i(x)\right\rangle_a + \left\langle \int \log\left(\frac{K_{i-1\to i}(t,x)}{\langle K_{i-1\to i}(x)\rangle_g}\right)\mathrm{d}\mu_i(x)\right\rangle_a = \int q_{i-1}(x)\,\mathrm{d}\mu_i(x), \end{aligned}$$

since by definition of $\langle K_{i-1\to i}(x)\rangle_g$ we have $\int \langle \log(\frac{K_{i-1\to i}(t,x)}{\langle K_{i-1\to i}(x)\rangle_g})\rangle_a\,\mathrm{d}\mu_i(x) = 0$. Because q_i satisfies $\frac{\partial}{\partial x}q_i + \lambda_{\mathrm{per}} - \lambda_s = 0$, we arrive at

$$q_i(x=0) \geqslant \int q_{i-1}(x)\,\mathrm{d}\mu_i(x) = \int \big[q_{i-1}(0) + (\lambda_s - \lambda_{\mathrm{per}})x\big]\,\mathrm{d}\mu_i(x).$$

Therefore, summing over i from 1 to I, we have obtained the result since $0 \geqslant (\lambda_s - \lambda_{\mathrm{per}})\sum_{i=1}^{I}\int x\,\mathrm{d}\mu_i(x)$. □

5. Physiological relevance of the model to the question of circadian control on tumour growth

In [3], with different averaging of transition rates $K_{i\to i+1}$, we had found no natural hierarchy between λ_{per} and λ_s, whereas periodic control exerted on the sole apoptosis rates d_i produced a Floquet eigenvalue which was shown to be always higher than the corresponding Perron eigenvalue obtained by arithmetic averaging of the d_i. The present note gives natural hypotheses that are needed to compare the eigenvalues and conclude that $\lambda_{\mathrm{per}} > \lambda_s$ when the coefficients $K_{i\to i+1}$ also vary. From these results a question arises: if $\lambda_{\mathrm{per}} > \lambda_s$, then how come that experimental results [4] show faster tumour growth when the normal circadian rhythm is disrupted by irregular light inputs? Experimental tumour growth curves with and without jet-lag-like circadian clock disruption [4] essentially differ at the beginning of proliferation, when it shows almost pure exponential behaviour, so that possible discrepancies between theoretical and experimental results are most likely not due to not taking into account nonlinear feedback. Clearly, setting at a constant value (instead of periodic) the coefficients d_i or $K_{i\to i+1}$ is not sufficient to take into account the complexity involved in the disruption of circadian control. To this purpose, it may be necessary to represent more complex control mechanisms involving, e.g., the inhibition of cyclin dependent kinases by clock-controlled genes such as Wee1 [5] together with elaborate models of the molecular circadian clock [6] and its disruptions.

References

[1] S. Bernard, D. Gonze, B. Čajavec, H. Herzel, A. Kramer, Synchronization-induced rhythmicity of circadian oscillators in the suprachiasmatic nucleus, PLoS Computational Biology 3 (4) (2007) e68, doi:10.1371/juornal.pcbi.0030068.
[2] G. Chiorino, J.A.J. Metz, D. Tomasoni, P. Ubezio, Desynchronization rate in cell populations: mathematical modeling and experimental data, J. Theor. Biol. 208 (2001) 185–199.
[3] J. Clairambault, P. Michel, B. Perthame, Circadian rhythm and tumour growth, C. R. Acad. Sci. Paris, Ser. I 342 (1) (2006) 17–22.
[4] E. Filipski, P.F. Innominato, M.W. Wu, X.M. Li, S. Iacobelli, L.J. Xian, F. Lévi, Effect of light and food schedules on liver and tumor molecular clocks in mice, J. Nat. Cancer Inst. 97 (7) (2005) 507–517.
[5] A. Goldbeter, A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase, Proc. Nat. Acad. Sci. USA 88 (1991) 9107–9111.
[6] J.-C. Leloup, A. Goldbeter, Modeling the mammalian circadian clock: Sensitivity analysis and multiplicity of oscillatory mechanisms, J. Theor. Biol. 230 (2004) 541–562.
[7] J.A.J. Metz, O. Diekmann, The Dynamics of Physiologically Structured Populations, Lecture Notes in Biomathematics, vol. 68, Springer-Verlag, 1986.
[8] P. Michel, S. Mischler, B. Perthame, General relative entropy inequality: an illustration on growth models, J. Math. Pures Appl. 84 (9) (2005) 1235–1260.
[9] E. Nagoshi, C. Saini, C. Bauer, T. Laroche, F. Naef, U. Schibler, Circadian gene expression in individual fibroblasts: cell-autonomous and self-sustained oscillators pass time to daughter cells, Cell 119 (2004) 693–705.
[10] B. Perthame, Transport Equations in Biology, Frontiers in Mathematics, Birkhäuser, Basel, 2007.