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A mathematical model of the cell cycle and its control

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Abstract: We consider mathematical models for the cell cycle, i.e. the sequence of events that leads to mitosis, at the level of a population of cells. These are structured population Partial Differential Equations that describe the evolution of the population along each phase of the cycle and the transition to the next phase. These models allow several types of controls such as therapeutic control in case of cancer therapy (some chemotherapies are known to act on specific phases of the cycle or on the transitions between phases) or circadian control by the central nervous system (in the suprachiasmatic nuclei). We study the long time behaviour of this system of PDEs using an entropy method and exhibit, by numerical simulations, the action of the circadian control

Key-words: Structured population dynamics, cell cycle, cicardian and therapeutic control, entropy methods, cancer modelling

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Un modèle mathématique pour le cycle cellulaire et son contrôle

Résumé : Nous considérons un modèle mathématique pour le cycle cellulaire, c'est-à-dire la série d'événements menant à la mitose, au niveau d'une population de cellules. Ce sont des Équations aux Dérivées Partielles qui décrivent l'évolution d'une population durant chaque phase du cycle et la transition à la phase suivante. Ces modèles permettent divers types de contrôles comme le contrôle thérapeutique (certaines chimiothérapies sont connues pour agir sur des phases spécifiques du cycle cellulaire ou sur les transitions entre phases) ou le contrôle circadien par le système nerveux central (au niveau des noyaux suprachiasmatiques). Nous étudions le comportement asymptotique en temps long pour ce système d'EDP en utilisant une méthode d'entropie et nous montrons, grâce à des tests numériques, l'action du contrôle circadien.

Mots-clés : Dynamique de populations structurées, cycle cellulaire, contrôle circadien et thérapeutique, méthode d'entropie, modélisation du cancer.

1 Introduction

Even though each type of cancer is unique because of the complexity in factors of development such as the variety of tissues, the numerous combinations of genetic alterations, the succession of events as vasculogenesis and angiogenesis ([2], [17]), several critical events are however common to the evolution of each cancer which are targets for potential therapeutic actions. Among them is the suppression of apoptosis (programmed cellular death) and deregulation of cell proliferation, we refer to [11] for a review of this aspect. This leads to try to understand the tumour development at the level of a population of cells while 'macroscopic' models for the neoplastic progression have been widely proposed and validated ([7] and the references therein). One can hope that a better understanding and control of the cell cycle can be used practically in cancer therapy. Our aim is to include in our model two key features of several anti-cancer drugs. The first one is that they act on specific phases of the cell cycle, for instance by promoting or inhibiting transition from a given phase to another, or to apoptosis. The second one is that drugs efficiency and/or toxicity seems to be strongly related to a 24 hour rhythm imposed by the circadian central clock [16].

Several mathematical approaches are proposed to model the cell cycle depending on the expected output one wishes to achieve. Description of a single cell by a system of Ordinary Differential Equations modelling the sequence of biomolecular events has been proposed by several authors and specifically the circadian rhythm is treated in [24]. When a population of cells is considered one is lead to structure the population by 'age' in the phase and this is the point of view we use here. The mathematical formalism for this purpose enters the class of Partial Differential Equations. The simplest way to do so is related to the famous McKendrick-Von Foerster model, also called renewal equation (see [3], [18] for instance)

$$\frac{\partial}{\partial t}\, n(t,a) + \frac{\partial}{\partial a}\, n(t,a) + d(a)\, n(t,a) = 0, \quad t \geq 0,\, a \geq 0, \tag{1.1}$$

$$n(t, a=0) = \int_{a\geq 0} b(a) n(t,a) da, \tag{1.2}$$

$$n(t=0,a) = n_0(a). \tag{1.3}$$

Here $n(t,a)$ denotes the density of cells at time t and age a, $d(a)$ the death rate, and $b(a)$ the birth rate. This general model may be specialized to the case

$$b(a) = 2\delta(a = A_b),$$

thus expressing that mitosis (doubling of the cell) arises at given age $a = A_b$. This type of model has been used broadly and compared to *in vitro* experiments in [23], [8] and the references therein. The model we propose below is a generalization of this kind of description. Let us point out that the simplicity of the biological description in such a model led several authors to improvements and variants. For instance different individual cells, under constant environmental conditions, have been proved to exhibit highly variable intermitotic intervals (Lebowitz and Rubinow [15] and the references therein) and this observation led

those authors to postulate an improved mathematical model where the population is also structured in terms of a generation time τ, thus leading to the evolution for the cell density $n(t,a,\tau)$

$$\begin{aligned} &\frac{\partial}{\partial t}\, n(t,a,\tau) + \frac{\partial}{\partial a}\, n(t,a,\tau) + D(a,\tau)\, n(t,a,\tau) = 0, \quad t \geq 0,\ a \geq 0,\ \tau \geq 0, \\ &n(t,a=0,\tau) = \int b(a,\tau,\tau')n(t,a,\tau')da\ d\tau' \\ &n(t=0,a,\tau) = n_0(a,\tau). \end{aligned} \tag{1.4}$$

A somewhat related but more general model is that of Rotenberg [21]. Then, the biological hidden variable is a maturation velocity $\mu \in [0,1]$, and the observable state a is the biological age, more relevant than the physical age, in other words, the degree of maturity (and then a/μ is the physical age in the previous models). Then, the density of population $n(t,a,\mu)$ satisfies the transport equation

$$\frac{\partial}{\partial t}\, n(t,a,\mu) + \mu \frac{\partial}{\partial a}\, n(t,a,\mu) + D(a,\mu)n(t,a,\mu) = \int K(a,\mu,\mu')n(t,a,\mu')d\mu', \tag{1.5}$$

with again boundary conditions at $a=0$, and initial data at $t=0$,

$$n(t,a=0,\mu) = \int b(a',\mu',\mu)n(t,a',\mu')d\mu' da',$$

$$n(t=0,a,\mu) = n_0(a,\mu).$$

This model enhances the stochasticity in the time evolution of the population thanks to the kernel K which allows a random change of the maturation velocity, and also, as in the previous models, in the birth process. We also refer to [10] for other models with the notion of maturity. More recently fragmentation models have been proposed to measure cells in terms of their DNA content x leading to 'size strucutred' models ([4]). This is related to the recent availability of flow cytometry which allows on-line measurements of DNA content. The model then is based on the equation

$$\frac{\partial}{\partial t}\, n(t,x) + \frac{\partial}{\partial x}\, n(t,x) + d(x)n(t,x) = 4n(t,2x) - n(tx). \tag{1.6}$$

The right hand side expresses that after mitosis, the DNA content $2x$ is split in twice x-DNA content for each cell.

In this paper we keep the renewal model for cell cycle and we first present a model which allows to keep more biologically based assumptions than the mere equation (1.1)-(1.2). We refer specifically to the notion of phases in the cycle which allow to introduce controls such as the effect of a circadian clock which blocks periodically the phase transition. We give some mathematical results concerning the solutions and especially the existence of a (Malthus) parameter for the total growth of the population. Then we propose numerical tests to measure the effect of the circadian clock on the total growth.

2 A model for the cell cycle

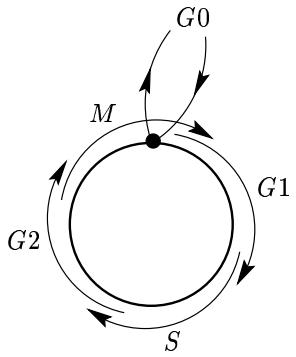

Figure 1: Principle of the cell cycle and its phases.

The cell division (mitosis) is the result of a full cycle that a cell should undergo successfully ([14]). It is usually accepted that the cycle consists in four phases, (i) a growth phase, denoted G1, where mostly the cell doubles its size, (ii) a synthesis phase, denoted by S, where the DNA is duplicated, (iii) a rest phase, denoted by G2, which is used to check and repair the errors in S phase, (iv) the mitosis, phase M, itself where the two DNA folds separate (anaphase) and the cell divides finally. The important feature for our purpose is that the cell cycle progression is controlled by proteins (Cyclin Dependent Kinases, CDK in short, see [22]) and thus we wish to keep this notion in the mathematical model. Also much of the cells stay at rest in a quiescent phase called G0, typically, skin cells are constantly in the cycle, endothelial cells are known to stay at rest and may be activated by Vascular Endothelial Growth Factors when angiogenesis occurs. On the other hand, the cell cycle duration is also extremely variable for human cells, from several minutes to several days (up to several years for cells with low renewal rates), depending on the cells [14], [13].

Our cell population model uses the density of cells in the phase i, denoted by $n_i(t,a)$,at time t and with age a in the cell, and say $i = 0$ for the rest phase G0, and $i = 1, 2 \ldots, I$ with $I = 4$ in the above scenario. We call $K_{i\to i+1}(a) \geq 0$ the transition rate from phase i to phase $i+1$ depending on the age a in the phase i ($K_{I\to I+1}$ stands sometimes for $K_{I\to 1}$ in order to simplify some notations). As a simple model we can have in mind is

$$K_{i\to i+1}(a) = \psi_i \ \mathbf{1}_{\{a\geq a_i\}}, \qquad \psi_i > 0, \tag{2.1}$$

a constant rate after some age a_i is attained. These transition rates could be controlled by drugs or by the circadian clock as mentioned in the introduction, thus leading to a variant

$$K_{i\to i+1}(t,a) = \psi(t) \ \mathbf{1}_{\{a\geq a_i\}}, \tag{2.2}$$

then $\psi(t)$ is a switch activated periodically at certain times in the circadian control, by a therapy in case of therapeutic control.

Then the evolution of the density in the phase is modelled via a McKendrick-Von Foerster equation as presented in the introduction. Variable $d_i > 0$ is the death rate in the phase i : as mentioned in our introduction, it could also be controlled by drugs with a circadian rhythm; $v_i(a) > 0$ is the evolution speed in the phase which could also be controlled by some nutrients for instance in phase G1. Hence, for $1 \leq i \leq I$, $t \geq 0$ and $a \geq 0$, we have

$$\begin{cases} \dfrac{\partial}{\partial t}\, n_i(t,a) + \dfrac{\partial}{\partial a}\left[v_i(a) n_i(t,a)\right] + d_i(a) n_i(t,a) + K_{i\to i+1}(a) n_i(t,a) = 0, \\ \\ v_i(0) n_i(t,a=0) = \displaystyle\int_{a'\geq 0} K_{i-1\to i}(a')\; n_{i-1}(t,a')\; da'. \end{cases} \tag{2.3}$$

For $i = 1$, the renewal condition does not make sense because the phase $i-1$ does not exist and we replace it by

$$v_1(0) n_1(t,a=0) = 2\tau_M \int_{a'\geq 0} K_{I\to 1}(a')\; n_I(t,a')\; da', \tag{2.4}$$

where $0 < \tau_M \leq 1$ is the rate of cells which continue the cycle after mitosis. For the sake of simplicity we have not described the phase $G0$ which receives the extra cells after mitosis and possibly can introduce new cells in the cycle. Of course our model is completed by a Cauchy data set

$$n_i(t=0,a) = n_i^0(a) \geq 0, \qquad \forall i = 1,\dots,I, \quad \forall a > 0. \tag{2.5}$$

This model thus retains some aspects of Rotenberg [21] model (see the introduction) with a discrete set of maturation states (μ in (1.5) corresponds to i in (2.3)) while keeping the main feature that enough phase progression is needed for transition to the next phase. It also has the advantage of indicating clearly possible control points for further modelling. This kind of system can either create exponential growth or exponential decay of the total population size depending on the death and transition parameters and of course the control parameters. This feature is analysed in the next section.

3 Mathematical results

The above system of transport equations is endowed with a natural maximum principle which preserves the nonnegativity of n_i and of a natural L^1 theory which reflects the conservation of densities by the drift term. These are usual properties that can be handled by various well understood mathematical methods and we state an existence result for completeness. More interesting is the large time asymptotic analysis which can hardly be performed here by standard methods based on Laplace transform. We rather use entropy methods introduced

in this context in [20], see also [19], [25].

We always assume below that all the (nonnegative) coefficients $(d_i,\ v_i,\ K_{i\to i+1})$ are continuous and

$$\infty > \overline{v} \geq v_i(a) \geq \underline{v} > 0, \qquad v_i(\cdot) \text{ is Lipschitz continuous.} \tag{3.1}$$

$$K_{i\to i+1}(a) \leq \overline{K} < \infty, \tag{3.2}$$

$$\frac{d_i(a)}{a} \to \infty, \quad K_{i\to i+1}(a) > 0 \qquad \text{for } a \text{ large.} \tag{3.3}$$

Theorem 3.1 *(Existence) With the assumptions (3.1)-(3.3) and*

$$n_i^0 \in L^1(\mathbb{R}^+),$$

there exists a unique distributional solution $n_i \in C(\mathbb{R}^+; L^1(\mathbb{R}^+))$, $n_i \geq 0$, to the system (2.3)-(2.5). It satisfies the a priori bound

$$\sum_{i=1,\dots,I} \int_0^\infty n_i(t,a)\,da \leq e^{t\,(2\tau_M - 1)\|K_{I\to 1}\|_{L^\infty}}. \tag{3.4}$$

The a priori bound here is very crude and does not use the precise structure of the operators involved in the dynamics. It is aimed to show why L^1 theory is natural through its simplicity. Concerning the time behaviour, it turns out that the population grows with an exponential rate of parameter λ. A more accurate result is indeed

Theorem 3.2 *(Long time behaviour) With the assumptions of Theorem 3.1, there exists a unique parameter $\lambda \in \mathbb{R}$ and unique (up to a multiplicative constant) C^1 functions $\phi_i(a) > 0$, $\phi_i(a) \to 0$ as $a \to \infty$ such that*

$$\sum_{i=1,\dots,I} \int_0^\infty n_i(t,a)\phi_i(a)\,da = e^{\lambda\, t} \sum_{i=1,\dots,I} \int_0^\infty n_i^0(a)\phi_i(a)\,da \qquad \forall t \geq 0. \tag{3.5}$$

An explicit formula for the Malthus parameter λ is given below, equation (3.9), that allows to check whether there is extinction i.e. $\lambda < 0$ or growth i.e. $\lambda > 0$. It can be seen as the first eigenvalue for the underlying operator the existence of which follows by the Krein-Rutman theorem ([9]), but below we give a direct and constructive proof. We can also go further and make more precise the long time asymptotics as follows

Theorem 3.3 *(Time asymptotics) With the assumptions and notations of Theorem 3.2, there exists a unique positive solution (up to a multiplicative constant) to*

$$\begin{cases} \dfrac{\partial}{\partial a}\left[v_i(a)N_i(a)\right] + \left[d_i(a) + K_{i\to i+1}(a) + \lambda\right]N_i(a) = 0, \\ \\ v_i(0)N_i(a=0) = \displaystyle\int_{a'\geq 0} K_{i-1\to i}(a')\, N_{i-1}(a')\, da', \end{cases} \tag{3.6}$$

and one has

$$\int_{a=0}^{\infty} |n_i(t,a)e^{\lambda t} - M_0 N_i(a)| da \to 0, \qquad as \quad t\to\infty, \tag{3.7}$$

with M_0 the constant such that

$$\sum_{i=1,\dots,I} \int_0^\infty n_i^0(a)\, da = M_0 \sum_{i=1,\dots,I} \int_0^\infty N_i(a)\, da.$$

These theorems follow from classical methods which where extended to the Rotenberg model in [20]. Notice that the convergence rate in (3.7) can be proved to be exponential in simple situations, but we do not know of simple formulas involving the coefficients of the equation itself (d_i, $K_{i-1\to i}$, ...). Their proofs are thus simple variants of the arguments that can be found in a more sophisticated form in [20] and we only sketch the main arguments.

Proof of Theorem 3.1. We do not give a proof of this very classical result which is based on the Banach-Picard fixed point theorem, and we only mention briefly the derivation of the a priori bound (3.4). The positivity of the solution is obvious because $(n_i)_-$ (the negative part is defined by $a_- = max(0,-a)$) is a subsolution with a vanishing initial data and thus remains negative (therefore zero) for all times. The L^1 bound is obtained by integration in age, using the positivity of the d_i

$$\frac{d}{dt}\sum_{i=1,\dots,I}\int_0^\infty n_i(t,a)\, da + \sum_{i=1,\dots,I}\int_0^\infty K_{i\to i+1}(a)n_i(t,a)da \leq \sum_{i=1,\dots,I} v_i(0)n_i(t,0),$$

therefore, the boundary fluxes exactly compensate (as expected in the model) the transition rates and it remains

$$\begin{aligned} \frac{d}{dt}\sum_{i=1,\dots,I}\int_0^\infty n_i(t,a)\, da &\leq (2\tau_M - 1)\int_0^\infty K_{I\to 1}(a)n_I(t,a)da \\ &\leq (2\tau_M - 1)\|K_{I\to 1}\|_{L^\infty}\int_0^\infty n_I(t,a)\, da \\ &\leq (2\tau_M - 1)\|K_{I\to 1}\|_{L^\infty}\sum_{i=1,\dots,I}\int_0^\infty n_i(t,a)\, da, \end{aligned}$$

and the result follows.

Proof of Theorem 3.2. The stationary dual problem to (3.1)–(3.2) is given by an eigenvalue problem: find λ such that there is a solution to

$$\begin{cases} v_i(a)\dfrac{\partial}{\partial a}\,\phi_i(a) - [d_i(a) + K_{i\to i+1}(a) + \lambda]\phi_i(a) = -\phi_{i+1}(0)\bar{K}_{i\to i+1}(a), \\ \\ \phi_i(a) \to 0 \qquad as \quad a \to \infty. \end{cases} \tag{3.8}$$

Here we have used $\bar{K}_{i\to i+1}(a) = K_{i\to i+1}(a)$ for $i = 1, \dots, I-1$ and $\bar{K}_{I\to 1}(a) = 2\tau_M K_{I\to 1}(a)$.

In other words, multiplying (3.1)–(3.2) by $\phi_i(a)$, multiplying equation (3.8) by $n_i(t,a)$ and integrating da and summing up in i, we arrive at

$$\frac{d}{dt}\left[e^{-\lambda t}\sum_{i=1,\dots,I}\int_0^\infty \phi_i(a)n_i(t,a)\,da\right] - e^{-\lambda t}\sum_{i=1,\dots,I} v_i(a=0)n_i(t,a=0)\phi_i(a=0)$$

$$= -e^{-\lambda t}\sum_{i=1,\dots,I}\phi_{i+1}(0)\int_0^\infty \bar{K}_{i\to i+1}(a)n_i(t,a)\,da,$$

(this uses the condition at infinity for the dual problem!). After rearranging the sum on the right and taking into account the renewal condition (3.2), the above equation reduces to

$$\frac{d}{dt}\left[e^{-\lambda t}\sum_{i=1,\dots,I}\int_0^\infty \phi(a)n_i(t,a)\,da\right] = 0.$$

Therefore the result of Theorem 3.2 is reduced to proving the existence of a solution to the dual problem with the announced properties. To do so, we write the solution when λ is given and show that a single λ is possible in order to satisfy the condition at infinity. We have

$$\phi_i(a) = e^{D_i(a)+\frac{\lambda}{v_i(a)}a}[\phi_i(0) - \phi_{i+1}(0)\int_0^a \frac{\bar{K}_{i\to i+1}(\sigma)}{v_i(a)}\,e^{-(D_i(\sigma)+\frac{\lambda}{v_i(a)}\sigma)}\,d\sigma,$$

with

$$D_i(a) = \int_0^a \frac{d_i(\sigma) + K_{i\to i+1}(\sigma)}{v_i(a)}\,d\sigma.$$

Because the problem is defined up to a multiplicative constant (we look for the first eigenvalue of a positive operator) we may choose $\phi_1(0) = 1$. Then, the vanishing condition at infinity for ϕ_1 gives

$$\phi_2(0) = \left[\int_0^\infty \frac{\bar{K}_{1\to 2}(\sigma)}{v_i(a)}\,e^{-(D_1(\sigma)+\frac{\lambda}{v_i(a)}\sigma)}\,d\sigma\right]^{-1}.$$

Notice that our assumptions show that this integral is well defined for $\lambda > \underline{d}/\overline{v}$ at least. The vanishing condition at infinity for ϕ_2 then gives

$$\phi_3(0) = \phi_2(0) \left[\int_0^\infty \frac{\bar{K}_{2\to 3}(\sigma)}{v_i(a)} \, e^{-(D_2(\sigma) + \frac{\lambda}{v_i(a)}\sigma)} \, d\sigma \right]^{-1}.$$

After a complete cycle, we arrive at the condition

$$1 = \phi_1(0) = \phi_I(0) \left[\int_0^\infty \frac{\bar{K}_{I\to 1}(\sigma)}{v_i(a)} \, e^{-(D_I(\sigma) + \frac{\lambda}{v_i(a)}\sigma)} \, d\sigma \right]^{-1},$$

in other words the value of λ is given by the formula

$$1 = \prod_{i=1}^{I} \int_0^\infty \frac{\bar{K}_{i\to i+1}(\sigma)}{v_i(a)} \, e^{-(D_i(\sigma) + \frac{\lambda}{v_i(a)}\sigma)} \, d\sigma. \tag{3.9}$$

A condition that is fullfilled by a single value of λ because this product defines a decreasing and C^1 function, it vanishes for $\lambda \to \infty$ and it tends to ∞ for $\lambda \to -\infty$. This concludes the proof of the existence of a solution ϕ_i to the dual problem (notice that all the required properties are indeed satisfied) and thus the Theorem 3.2 is proved.

Proof of Theorem 3.3. We refer to [20] for a proof and we just indicate briefly the very reason behind this convergence. First of all, notice that the existence of solutions to equation (3.6) for N_i follows (by exact formulas) from the same choice as above of the parameter λ (in other words the primal and dual problems have the same first eigenvalue associated to a positive eigenvector!). Next, we have

$$\begin{cases} \dfrac{\partial}{\partial t}\left(e^{-\lambda t} n_i(t,a)\right) + \dfrac{\partial}{\partial a}\left[e^{-\lambda t} v_i(a) n_i(t,a)\right] + \left[d_i(a) + K_{i\to i+1}(a) + \lambda\right] n_i(t,a) = 0, \\ v_i(0) e^{-\lambda t} n_i(t, a=0) = \displaystyle\int_{a'\geq 0} K_{i-1\to i}(a') \, e^{-\lambda t} n_{i-1}(t,a') \, da'. \end{cases}$$

Substracting equation (3.6) for N_i, and multiplying by $\mathrm{sgn}(e^{-\lambda t} n_i(t,a) - N_i)$ (this is well justified even though the sgn function is not smooth) we arrive at

$$\begin{cases} \dfrac{\partial}{\partial t} |e^{-\lambda t} n_i(t,a) - N_i(a)| + \dfrac{\partial}{\partial a}\left[v_i(a) |e^{-\lambda t} n_i(t,a) - N_i(a)|\right] \\ \qquad\qquad + \left[d_i(a) + K_{i\to i+1}(a) + \lambda\right] |n_i(t,a) - N_i(a)| = 0, \\ v_i(0) |e^{-\lambda t} n_i(t, a=0) - N_i(a=0)| \leq \left| \displaystyle\int_{a'\geq 0} \left[K_{i-1\to i}(a') \, e^{-\lambda t} n_{i-1}(t,a') - N_i(a')\right] da' \right|. \end{cases}$$

Therefore, after integration against the dual solution $\phi_i(a)$, and summation of these equations we arrive at

$$\begin{aligned}\frac{d}{dt}\sum_{i=1,\dots,I} & \int_{a\geq 0} |e^{-\lambda t}n_i(t,a) - N_i(a)da|\phi_i(a) \\ & \leq \sum_{i=1,\dots,I} \phi_i(0)\left[|\int_{a\geq 0} K_{i-1\to i}(a)[e^{-\lambda t}n_i(t,a) - N_i(a)]da| \right. \\ & \qquad \left. - \int_{a\geq 0} K_{i-1\to i}(a)|e^{-\lambda t}n_i(t,a) - N_i(a)|da\right] \\ & \leq 0.\end{aligned}$$

This proves that the quantity decays but also that the quantity in the right hand side is integrable, that is

$$\int_{t=0}^{\infty} |\int_{a\geq 0} K_{i-1\to i}(a)[e^{-\lambda t}n_i(t,a) - N_i(a)]da| - \int_{a\geq 0} |K_{i-1\to i}(a)e^{-\lambda t}n_i(t,a) - N_i(a)|da < \infty,$$

which implies that

$$e^{-\lambda t}n_i(t,a) - N_i(a) \to 0, \qquad as \quad t\to\infty,$$

on the support of $K_{i-1\to i}(\cdot)$. Then, one can obtain that the full quantity vanishes in using the PDE again and compactness arguments that are detailed in [20].

4 Numerical method: one phase

Before we consider the effect of an outside control on one of the phases, we present the numerical method used here. It is based on an upwind scheme for the transport equation ([12]) in the finite volume spirit. These methods are known to be inaccurate except when an optimal time step can be used: we therefore consider here this optimal situation (CFL=1), this is possible under the restriction that

$$v_i(a) = Cst, \qquad \forall i = 1,\dots,I,$$

a condition that we assume from now on with $v_i(a) = 1$, i.e. $\Delta t = \Delta a$ where these are the (uniform) discretization parameters in the two variables t and a. Below we denote by $n_j^n(i)$ the average value of $n_i(t^n, a)$ on the $j-th$ cell in the age variable, at time $t^n = n\Delta t$.

In order to avoid further time restriction, we also consider an implicit scheme for the death rates and transition rates. We arrive at the algorithm:

$$n_1^{n+1}(i) = \Delta t \sum_{j=2,\dots,J} K_{i-1\to i}(j)n_j^{n+1}(i-1),$$

$$n_j^{n+1}(i)[1 + \Delta t * (d(j) + K_{i\to i+1}(j)] = n_{j-1}^n(i), \qquad j = 2, \dots, J,$$

(except for $i = 1$ where the cell division factor $2\tau_M$ is added). Here we have in mind that the first point in a represents the flux on the boundary and not an average in a cell. Therefore the point $n_1^n(i)$ is excluded from the discrete renewal kernel.

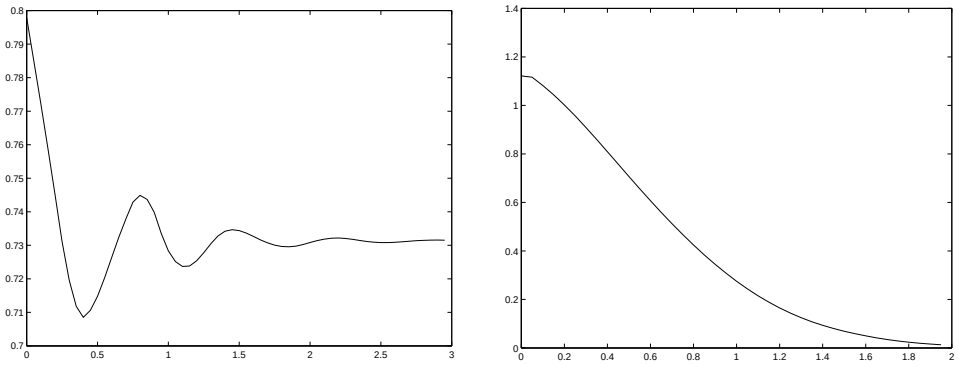

Figure 2: Solution of the renewal equation (one phase) in case 1 (peaked renewal kernel). Left:the total population density as a function of time. Right: the steady state $N(a)$.

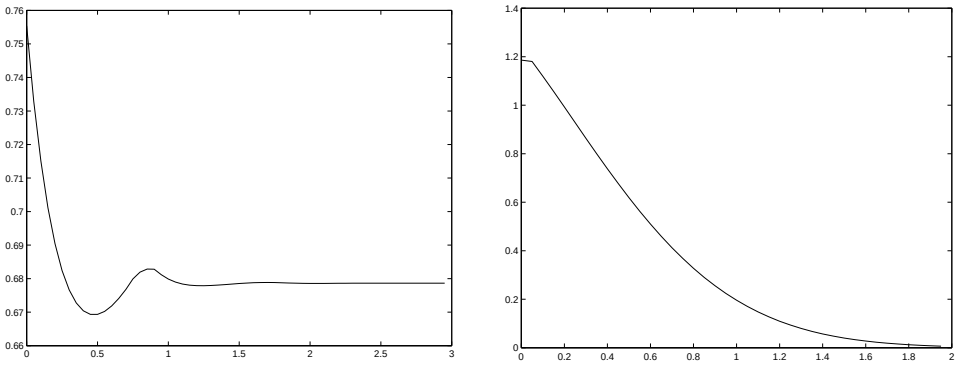

Figure 3: Solution of the renewal equation (one phase) in case 2 (uniform renewal kernel). Left: the total population density as a function of time. Right: the steady state $N(a)$.

For the sake of completeness, we now present results for the case of one phase (McKendrick-Von Foerster equation). They are obtained with $J = 2*20$ (20 is the number of discretization points for a unit age time which is the maximal age for renewal in the choice we make below for K i.e. $a_M = 1$ in the two cases below). In other words our simulations are conducted

for $0 \leq a \leq 2 * a_M$ and up to the final time $t_{final} = 3 * a_M$. Also we use a death rate $d(a) = 2. * a/a_M$. As expressed in Theorem 3.3, after multiplication by the factor $e^{-\lambda t}$, the solution converges to a steady state but with an oscillatory behaviour. We exhibit this phenomenon in the numerical tests below and relate it to the form of the kernel $K(a)$ used for the renewal term. We consider in this case a renewal kernel K with bounded support. We show that the more 'peaked' is the kernel K, the more oscillations the solution exhibits. To do so, we consider two cases

- First case. $K(a) = 4 * \mathbf{1}_{\{a_M/2 \leq a \leq a_M\}}$, see Figure 2.
- Second case. $K(a) = 2 * \mathbf{1}_{\{0 \leq a \leq a_M\}}$, see Figure 3.

This kind of behaviour has been confirmed and matched to experiments on various type of cells including cancerous cells (see [23], [8], [4]). Especially the importance of transition times has been well reported in the above references and more experimental works ([6]).

5 Numerical results on the circadian control (two phases)

We now come to the case of two phases in the model (2.3)–(2.5) for the cell cycle. The motivation for keeping only two phases is simplicity, this still allows a reduced number of parameters in the model while dealing with a more realistic structure. Still assuming that the cycle speeds are constant in the two phases (of equal length even though G1 phase is usually reported as the longest and the most fluctuating), it can be discretized exactly as explained previously in §4 and we do not give additional details.

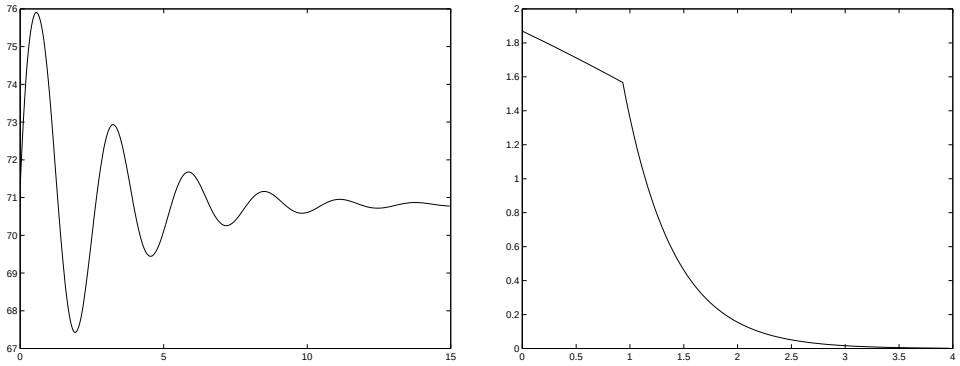

Figure 4: Solution of the cell cycle equation (two phases) without periodic control. Left: the total population density in the first phase as a function of time. Right: the steady state $N_1(a)$.

We first consider the uncontrolled case, we are in the situation of transition rates given by (2.1), see Figure 4 and compare with Figures 2 and 3. Again, the results are shown

after normalizing the solution by the growth factor $e^{\lambda t}$, with λ the first eigenvalue (Malthus parameter) which has been analysed in §3.

Next, we have investigated the effect of a circadian control that can affect the transitions as motivated in the introduction. It is known that healthy cells are highly affected by the circadian rhythm ([16], [5] for instance). It may act in various ways: on each of the two transitions, and either stopping the transitions during a certain time of the day or, on the contrary, in allowing phase transitions during a certain time interval. In each of these cases, as long as this circadian control is of small amplitude, we have observed that it creates (after some transition) a circadian period in the cell dynamics. In Figure 5, we show an example where the circadian control blocks the transition from phase 1 to phase 2 periodically, as proposed in (2.2). The function $\psi_1(t)$ is taken equal to one except that is drops to $1/2$ on periodic intervals of length $(k * 1.2, k * 1.2 + .2)$ in cell cycle units. The oscillations that can be seen in Figure 5 exhibit variable pseudoperiod; (i) the double of the cell cycle period at the beginning, (ii) the period of the circadian control at the end (see Figure 6).

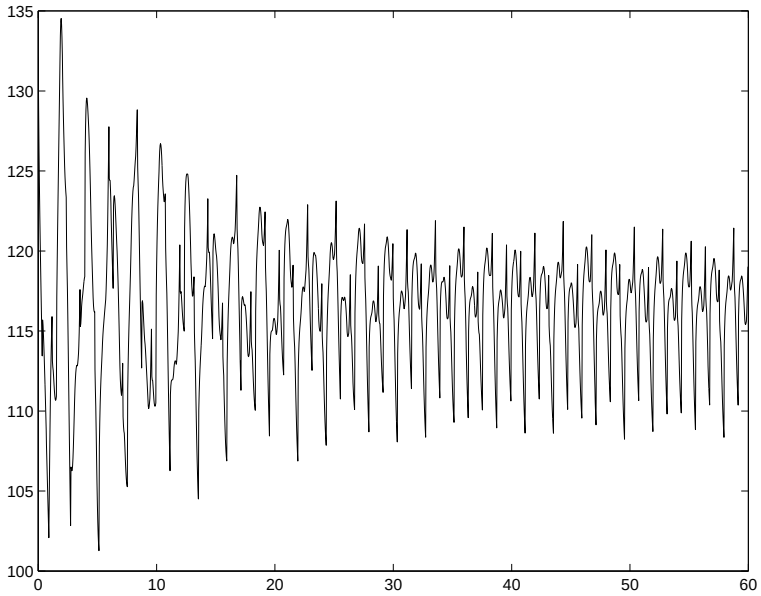

Figure 5: Solution of the cell cycle equation (two phases) with periodic blocking. The total population density in the first phase as a function of time (unit=cell cycle).

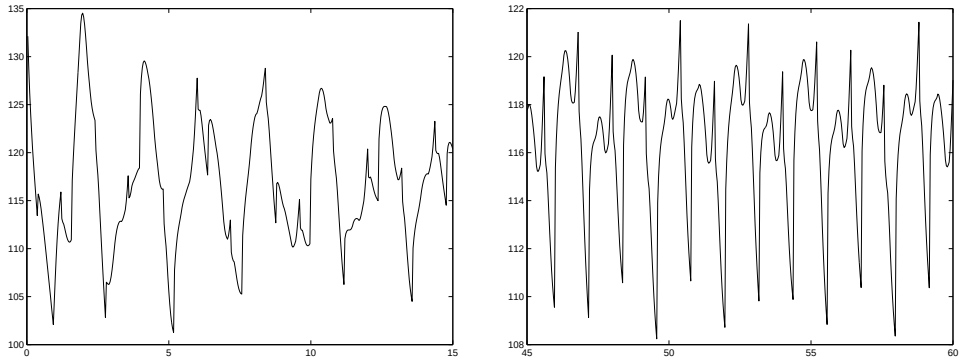

Figure 6: Zoom in Figure 5. Left: at the beginning, the pseudoperiod is half the cell cycle time. Right: after some time, the pseudoperiod is the circadian clock.

6 Conclusion

Motivated by understanding the role of cell cycle in tumour developments we have considered a mathematical model to describe a cell population structured by its age in each phase. This model is especially designed to incorporate control parameters at several, biologically based, points (death rate, transition rates) in order to take into account therapy or circadian clock. A mathematical theory for existence and long time asymptotics has been developed which uses an entropy method introduced recently in this subject. The numerical tests are in accordance with this theory and with several previous comparisons with experiments. Numerical results are also given on the effect of a circadian control showing, again, as reported in experimental works, that it imposes a circadian rhythm to the cell cycle.

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References

[1] M. Adimy and L. Pujo-Menjouet, *Asymptotic behaviour of a singular transport equation modelling cell division*, DCDS(B) Vol. 3, No. 3 (2003) 439–456.

[2] A. R. A. Anderson and M. A. J. Chaplain, *A mathematical model for capillary network formation in the absence of endothelial cell proliferation*, Appl. Math. Lett., 11(3) 109–114, 1998.

[3] O. Arino, *A survey of structured cell population dynamics*, Acta Biotheor. 43, 3–25 (1995).

[4] B. Basse, B. C. Bagulay, E. S. Marshall, W. R. Joseph, B. van Brunt, G. Wake, D. J. N. Wall, *A mathematical model for analysis of the cell cycle in cell lines derived from human tumors*, J. Math. Biol. (2003).

[5] G. A. Bjarnason, R. Jordan, *Circadian variation of cell proliferation and cell cycle protein expression in man: clinical implications.* In Progress in cell cycle research, Vol. 4, 193–206, L. Meijer, A. Jézéquel, B. Ducommun Editors. Kluwer Academic, Plenum publisher, New-York (2000).

[6] R. F. Brooks, D. C. Bennett, J. A. Smith, *Mammalian cell cycles need two random transitions*, Cell, 19:493–504 (1980).

[7] H. M. Byrne, J. R. King, D. L. S. McElwain and L. Presiozi, *A two-phase model of solid tumor growth.* Preprint 2001.

[8] G. Chiorino, J. A. J. Metz, D. Tomasoni and P. Ubezio, *Desynchronization rate in cell populations: mathematical modeling and experimental data*, J. Theor. Biol. (2001) 208, 185-199.

[9] R. Dautray and J.-L. Lions, *Analyse Mathématique et cacul numérique pour les sciences et les techniques*, Masson, 1988.

[10] J. Dyson, R. Villella-Bressan and G. Webb, *A nonlinear age and maturity structured model of population dynamics, II. Chaos*, J. Math. Anal. Appl. 242 (2000) No. 2, 255–270.

[11] G. I. Evan and K. H. Vousden, *Proliferation, cell cycle and apoptosis in cancer*, Nature, Vol. 411 (may 2001), 342–348.

[12] E. Godlewski and P.-A. Raviart, *Numerical Approximation of Hyperbolic Systems of Conservation Laws*, Appl. Math. Series 118. Springer-Verlag (1996).

[13] A. Goldbeter, *Biochemical oscillators and cellular rhythms*, Cambridge University Press 1997.

[14] J. Keener and J. Sneyd, *Mathematical physiology*, Ch. 13.

[15] J.L. Lebowitz and S.I. Rubinow, *A theory for the age and generation time distribution of a microbial population*, J. Math. Biology, 1 (1977) 17–36.

[16] F. Lévi, *Cancer chronotherapeutics*, Special issue of Chronobiology international, Vol. 19, No. 1, 2002.

[17] D. Manoussaki, *A mechanochemical model of angiogenesis and vasculogenesis*, ESAIM: Math. Model. Num. Anal., to appear.

[18] J. A. J. Metz and O. Diekmann, *The dynamics of physiologically structured populations*, LN in biomath. Vol. 68, Berlin, Springer-Verlag, 1986.

[19] S. Mischler and B. Wennberg, *On the spatially homogeneous Boltzmann equation*, Ann. Inst. H. Poincaré Anal. Non Linéaire 16 (1999), no. 4, 467–501.

[20] S. Mischler, B. Perthame and L. Ryzhik, *Stability in a Nonlinear Population Maturation Model*, Math. Models Meth. Appl. Sci., Vol. 12, No. 12 (2002) 1751–1772.

[21] M. Rotenberg, *Transport theory for growing cell populations*, J. Theor. Biol. (1983) 103, 181–199.

[22] E. A. Sausville, *Complexities in the development of cyclin-dependent kinase inhibitor drugs*, Trends in Molecular Medicine vol. 8 No. 4 (Suppl.) 2002.

[23] J. J. Tyson and O. Diekmann, *Sloppy size control of the cell division cycle*, J. Theor. Biol. (1986) 118, 405–426.

[24] J. J. Tyson, C. I. Wong, C. D. Thron and B. Novak, *A simple model of circadian rhythms based on dimerization and proteolysis of PER and TIM*, Biophys. J. 77, 2411–2417 (1999).

[25] C. Villani, *A review of mathematical topics in collisional kinetic theory*, in Handbook of mathematical fluid dynamics, S. Friedlander and D. Serre, Eds. Tome I, chapitre 2. North-Holland, Amsterdam (2002).

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