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An age-and-cyclin-structured cell population model with proliferation and quiescence for healthy and tumoral tissues

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Abstract: We present a nonlinear model of the dynamics of a cell population divided in a proliferative and a quiescent compartments. The proliferative phase represents the complete cell division cycle (G_1-S-G_2-M) of a population committed to divide at its end. The model is structured by the time spent by a cell in the proliferative phase, and by the amount of *cyclin D/(CDK4 or 6)* complexes. Cells can transit from one compartment to the other, following transition rules which differ according to the tissue state: healthy or tumoral. The asymptotic behaviour of solutions of the nonlinear model is analysed in

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both cases, exhibiting tissue homeostasis or tumour exponential growth. The model is simulated by numerical solutions which confirm its theoretical predictions.

Key-words: Cell cycle, Population dynamics, Partial Differential Equations, Cyclins, Tumour growth, Cancer.

Un modèle de populations cellulaires structuré en âge et en cycline avec prolifération et quiescence pour des tissus sains et tumoraux

Résumé : Nous présentons un modèle non linéaire de la dynamique d'une population cellulaire divisée en un compartiment proliférant et un compartiment quiescent. La phase de prolifération représente l'ensemble du cycle de division cellulaire ($G_1 - S - G_2 - M$) d'une population de cellules appelées à se diviser en fin de cycle. Le modèle est structuré par le temps passé par une cellule dans la phase de prolifération et par la quantité de complexes *cycline D/(CDK4 ou 6)*. Les cellules peuvent passer d'un compartiment à l'autre, en suivant des lois de transition qui diffèrent suivant que le tissu qu'elles constituent est de nature saine ou tumorale. Le comportement asymptotique des solutions du modèle non linéaire est analysé dans les deux cas, et montre une homéostasie tissulaire dans le premier, et une croissance exponentielle (tumorale) dans le second. Des simulations numériques du modèle confirment ses prédictions théoriques.

Mots-clés : Cycle cellulaire, Dynamique des populations, Équations aux dérivées partielles, Cyclines, Croissance tumorale, Cancer.

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1 Introduction

Living tissues, subject to renewal, are constituted of two different categories of cells: the proliferating cells (p) and the quiescent cells (q). Proliferating cells grow and divide, giving birth at the end of the cell cycle to new cells, or else transit to the quiescent compartment (often referred to as the G_0 phase), whereas quiescent cells do not grow nor divide but either transit to the proliferative compartment or else stay in G_0 and eventually differentiate according to the tissue type.

In a tumour cell population the number of proliferating cells increases continuously as long as it is malignant and active, whereas in a normal (healthy) cell population, the size of the proliferative compartment remains bounded since the total number of cells, proliferating and quiescent, remains constant (at least in the mean, e.g. by averaging over 24 hours) so as to maintain tissue homeostasis.

During the first phase (often referred to as G_1) of the proliferating cell cycle, until the restriction point (R) in late G_1 has been reached, proliferating cells may enter the quiescent G_0 phase and stop proliferation. Indeed, experiments by Zetterberg and Larsson [10, 34] showed that the restriction point (R) divides the G_1 phase into two parts: before R, cells may enter the quiescent phase, but once it has been passed, they are committed to proceed along the other phases (S, G_2, M, which will not be considered here as such) until cell division.

The switching of cells between quiescence and proliferation depends on extracellular environmental conditions such as growth and antigrowth factors, and is regulated differently in normal and tumour cells, due to differences in the expression of the involved genes.

Cell population models with proliferative and quiescent compartments have been investigated by authors who studied the asynchronous exponential growth property [3, 14, 15, 28]. Our goal here is to design a generic cell population model applicable to both cancer and normal tissue growth.

Unlimited tumour growth, by opposition to healthy tissue homeostasis, can be seen in particular as a deregulation of transitions between proliferative and quiescent compartments. Furthermore, recent measurements [16] indicate that cyclins are the most determinant control molecules for phase transitions.

For these reasons, and since we are interested in studying in parallel the behaviour of healthy and tumour cells, we structure our cell population model in age and cyclin content, a process which we describe step by step in sections 2 and 3. In section 4, we analyse the theoretical properties of the model, which we illustrate by numerical simulations in section 5. Finally, some comments and future prospects are briefly developed in section 6.

2 Molecular mechanisms involved in the G_1 phase

A variety of proteins are produced during the proliferative cell cycle. The progression of a cell through the cycle is controlled by complexes composed of two proteins: a cyclin (structural protein) and a cyclin dependent kinase (or CDK), an enzyme which is needed for the cyclin to activate. Each phase of the cell cycle has specific *cyclin/CDK* complexes. In particular, *cyclin D/(CDK4 or 6)* and *cyclin E/CDK2* activate during the G_1 phase. Cyclin D is the first cyclin which is synthesized at the beginning of the cell cycle. The level of cyclin D is controlled by the extracellular environment. Thus, cyclin D synthesis is induced by specific growth factors (GFs) [5], and its level decays when cells are deprived of GFs. GFs bind to specific receptors on the external cytoplasmic membrane, stimulating an intracellular signalling pathway (*Ras/Raf/Map kinase)* by means of which cyclin D is eventually synthesized (see [2, 4, 30], for more details). Experiments reported in [17, 35] show the important role of cyclin D as a regulator of the transition between G_1 and G_0. They show that a reduced exit from G_1 to G_0 occurs when cyclin D is overexpressed, whereas non overexpressing cells remain in G_0. Progression through the restriction point (R) is essentially related to cyclin D level inasmuch as when there is a sufficient amount of cyclin D, cells pass the restriction point and are committed to proceed through the rest of the cell cycle. Moreover, cyclin D makes complexes with either CDK4 or CDK6 kinases and these complexes are able to phosphorylate other proteins which are important for cell progression in the G_1 phase through the restriction point and further for the rest of the cell division cycle: DNA replication, mitosis and cell division.

In this paper, we are interested in the molecular interactions that are related to the activity of the *cyclin D/(CDK4 or 6)* complexes. Several authors [24, 25, 26, 32] have described and simulated, under specific assumptions, part of these complex reactions. Here, we give a simple model to describe the activity of *cyclin D/(CDK4 or 6)* induced by growth factors.

Let x be the amount of the complexes *cyclin D/(CDK4 or 6)* and w an aggregated variable representing the amount of the various molecules involved in the synthesis of cyclin D such as *Ras/Raf*. We consider x and w as regulating variables in a simple nonlinear system of ordinary differential equations (ODEs) with respect to age a in the G_1 phase. Synthesis of x occurs at a rate c_1 and its degradation at a rate c_2; we assume that the synthesis of w is induced by

growth factors (GFs) at a constant rate c_3, its degradation occurring at a rate c_4. The ODE model can thus be written as follows:

$$\begin{cases} \dfrac{dx}{da} = c_1 \dfrac{x}{1+x} w - c_2 x, \quad x(0) = x_0 > 0, \\ \dfrac{dw}{da} = c_3 - c_4 w, \quad w(0) = w_0 > 0. \end{cases} \tag{1}$$

The only nonlinearity of the model is located in the term $c_1 \dfrac{x}{1+x}$ representing a positively autoregulating coefficient with saturation for x under the linear influence of the lumped variable w. Substituting the solution of the second equation of (1), we can reduce (1) to one equation in x:

$$\frac{dx}{da} = c_1 \frac{x}{1+x} \left(\frac{c_3}{c_4} + e^{-c_4 a} (w_0 - \frac{c_3}{c_4}) \right) - c_2 x, \quad x(0) = x_0. \tag{2}$$

This holds only for the G_1 phase since we assume that cyclin amount x and age a remain constant in G_0 phase. A natural quantity arises in the qualitative analysis of (2), the x-nullcline:

$$X(a) = \frac{c_1}{c_2} \left(\frac{c_3}{c_4} + e^{-c_4 a} (w_0 - \frac{c_3}{c_4}) \right) - 1.$$

We assume that $w_0 \leq \dfrac{c_3}{c_4}$ and $c_1 c_3 > c_2 c_4$ which is a way to express that the lumped variable w is increasing from its initial to its asymptotic value, and that in the early G_1 phase the overall synthesis of the chemicals involved in the progression of the G_1 phase overcomes their degradation. Therefore, a fundamental property of equation (2) is that the cyclin concentration x is limited by:

$$x_{\max} = \frac{c_1 c_3}{c_2 c_4} - 1 > 0. \tag{3}$$

We keep this simple model for our next purpose which is to describe a population of cells, in proliferative or quiescent state.

3 Physiologically structured model

We consider here only two phases: a quiescent one (physiologically G_0) and a proliferative one (physiologically $G_1 - S - G_2 - M$). The cell populations we study are firstly structured by the time spent inside the proliferative phase. This phase represents here the complete cell division cycle since cell birth, and this time in the phase will hereafter be referred to as a, for physiological age in the cycle. As proposed in [6, 33], we also structure the model by the amount of *cyclin D/(CDK4 or 6)* complexes, denoted by variable x. Indeed, as mentioned earlier, this biological quantity is the most important determinant of

progression up to the restriction point R in the late G_1 phase.

Let $p\,(t,a,x)$and $q\,(t,a,x)$ be respectively the densities of proliferating and quiescent cells with age a and content x in *cyclin D/(CDK4 or 6)* complexes at time t.
We also consider a "total weighted population", i.e., an effective population density, N defined by:

$$N\,(t) = \int_0^{+\infty}\int_0^{+\infty} \Big(\varphi^*(a,x)p\,(t,a,x) + \psi^*(a,x)q\,(t,a,x)\Big)\,dadx. \tag{4}$$

Here the weights φ^* and ψ^* represent environmental factors such as growth and anti-growth factors acting on the populations of proliferating and quiescent cells, respectively. N is the density of the fraction of the total population consisting in the cells that are sensitive to these factors and are thus qualified to influence, e.g. by a mechanism apparented to density inhibition, the G_0/G_1 transition. This excludes for instance apoptotic or pre-apoptotic cells.

Exits from the quiescent compartment are due either to apoptosis (physiological cell death) at a rate d or to transition to the proliferative phase according to a "recruitment" or "getting in" function G, which is assumed to depend on the total weighted population N. We also assume that cells may leave the proliferative compartment for the quiescent one according to a "demobilisation" or "leak" function $L\,(a,x)$. These functions L and G, which represent the core mechanism of exchange between proliferation and quiescence in our model, will be described in section 3.2. The model may thus be written as:

$$\begin{cases} \dfrac{\partial}{\partial t}p\,(t,a,x) + \dfrac{\partial}{\partial a}\left(\Gamma_0 p\,(t,a,x)\right) + \dfrac{\partial}{\partial x}\left(\Gamma_1\,(a,x)\,p\,(t,a,x)\right) = \\ -\left(L\,(a,x) + F(a,x) + d_1\right)p\,(t,a,x) + G\,(N\,(t))\,q\,(t,a,x)\,, \\ \dfrac{\partial}{\partial t}q\,(t,a,x) = L\,(a,x)\,p\,(t,a,x) - \left(G\,(N\,(t)) + d_2\right)q\,(t,a,x)\,. \end{cases} \tag{5}$$

Quiescent cells are assumed to be halted in their individual physiological evolution, in the sense that once a cell becomes quiescent, its age and cyclin content are fixed at their last values as belonging to a proliferative cell. In this way, quiescent cells do not age and do not change their cyclin content.

The parameter Γ_0 denotes the evolution speed of physiological age a with respect to time t, which is assumed to be constant in this model; if for example $\Gamma_0 = 0.5$, it means that physiological age a evolves twice as slowly as real time t. Similarly, the function Γ_1 represents the evolution speed of *cyclin D/(CDK4*

or 6) with respect to time, i.e., Γ_0 times the speed $\dfrac{dx}{da}$ of x with respect to physiological age a, which is given by equation (2), with $w_1 = w_0 - \dfrac{c_3}{c_4} < 0$:

$$\frac{dx}{da} = \frac{\Gamma_1(a,x)}{\Gamma_0} = c_1 \frac{x}{1+x}\left(\frac{c_3}{c_4} + e^{-c_4 a} w_1\right) - c_2 x.$$

The parameters d_1, d_2 are apoptosis rates for proliferating and quiescent cells respectively, and $F(a,x)$ is the fraction of cells which leave the proliferative population to divide according to a process which will be described later.

To complete the description of the model (5), we specify initial conditions:

$$p(0,a,x) = p_i(a,x), \quad a \geq 0, \; x \geq 0, \tag{6}$$

and

$$q(0,a,x) = q_i(a,x), \quad a \geq 0, \; x \geq 0, \tag{7}$$

where p_i and q_i are nonnegative functions.

In the following section, we describe a condition for entering the proliferating phase (physiologically in G_1) at age $a = 0$, but note that no such condition is needed at $x = 0$, since cyclin level $x = 0$ is never reached in the process described by (2) because Γ_1 vanishes at $x = 0$.

3.1 Unequal division

The distribution of the cellular material between daughter cells is assumed to be unequal. Due to variability in cyclin content between the two daughter cells when division occurs (see [18], and [31] for a relation with ageing), some cells may inherit a bigger amount of certain proteins as cyclins, whereas others start the cycle with a smaller amount of the same proteins. We consider that the distribution of the amount of *cyclin D/(CDK4 or 6)* between the two daughter cells is given by a conditional density $f(a,x,y)$ such that the probability for a daughter cell, born from a mother cell with content y in *cyclin D/(CDK4 or 6)* with $x_1 \leq y \leq x_2$, to have itself content x in *cyclin D* is:

$$\frac{\displaystyle\int_{x_1}^{x_2} f(a,y,x)\,dy}{\displaystyle\int_0^{+\infty} f(a,y,x)\,dy}.$$

We also consider that all newborn cells are at birth in the proliferative compartment. Then we have the following condition at the boundary $a = 0$,

$$p\left(t,0,x\right) = \frac{2}{\Gamma_0}\int\limits_0^{+\infty}\int\limits_0^{+\infty} f\left(a,x,y\right)p\left(t,a,y\right)dady. \tag{8}$$

The following conditions follow from the above interpretation:
(1) The cyclin amount of a daughter cell is smaller than that of its mother cell at the time of division:

$$f(a,x,y) = 0 \text{ if } x > y.$$

(2) The cyclin amount y of the mother cell is exactly conserved and shared by the two daughters

$$f(a,x,y) = f(a,y-x,y)$$

and

$$\int_0^{+\infty} f(a,x,y)dx = F\left(a,y\right),$$

where $F(a,y)$ is the fraction of cells which at age a and cyclin content y leave the proliferating phase to undergo cell division. These cells disappear and are replaced by two daughter cells which immediately restart in the proliferative phase for their own part.

We choose for F a standard Hill function:

$$F\left(a,y\right) = \frac{k_1 y^{\gamma_1}}{k_2^{\gamma_1} + y^{\gamma_1}}\mathbb{1}_{[A^*,+\infty[}(a),$$

where k_1 is the maximum effect of cyclin D on cell division , k_2 is the cyclin content yielding its half-maximum effect, γ_1 is the Hill coefficient tuning the steepness of the switch at $y = k_2$ between 0 and k_1 for the effect, and A^* is the minimal cell cycle duration; we also consider that cyclin repartition is uniform after division:

$$f\left(a,x,y\right) = \frac{F\left(a,y\right)}{y}\mathbb{1}_{[0,y]}(x).$$

3.2 Transition control between proliferation and quiescence

Lynch [19] has studied the effect of a transcription factor that inhibits the proliferation of human colon cancer cells by reducing cyclin D gene expression and hence inducing an accumulation of cells in G_0. Deprivation of growth factors (GFs) in the early G_1 phase also leads to a low cyclin D level in cells, when *cyclin D/CDK4* is the only cyclin/CDK complex present, and the low level of cyclin D is such that cells exit G_1 to enter the G_0 phase.

We firstly assume that transition from proliferation to quiescence depends on age and cyclin content of the cell. At the beginning of the cell cycle, the cell remains in the proliferative phase but from a certain age on, if its content in *cyclin D/(CDK4 or 6)* is not high enough, the cell passes to the quiescent phase.

We set the "demobilisation" function from proliferation to quiescence as:

$$L\left(a,x\right)=A_1\frac{A_2^{\gamma_2}}{A_2^{\gamma_2}+x^{\gamma_2}}\mathbb{1}_{[\bar{A},+\infty[}(a).$$

In this setting, if the Hill exponent γ_2 is high enough (e.g. between 5 and 10), A_2 is the "switching" cyclin content value x beyond which, the "leak" function L becomes close to zero, preventing escape to quiescence. At this point, the cell population is irreversibly committed to proceed into the proliferating phase until division. The value A_2 may thus be interpreted as the *cyclin D/(CDK4 or 6)* level determining the restriction point, in the sense of Zetterberg and Larsson [34]. The steep switch in function L represents the fact that transition from G_1 to G_0 is preceded by a rapid increase in physiological cyclin-dependent kinase inhibitors (CDKIs), such as p15, p21, p27, significantly reducing the activities of the G_1 CDKs [29].

Secondly, as regards the reverse transition from quiescence to proliferation (the "recruitment" function), it may be assumed to depend on the total population of cells (see e.g. [20]). In the present model, as stated above, we assume that the recruitment depends on those cells (subpopulation N of the total population) that are qualified to be sensitive to growth or anti-growth factors. Two cases are studied in this paper, since we assume healthy tissues and tumours to behave differently with respect to the transition from G_0 to G_1:

1) For a healthy tissue, the fraction of the quiescent cells that reenter the proliferative phase decreases when the total population grows; in this case we define the recruitment function G as a monotone Hill function of N decreasing to zero, representing density inhibition:

$$G\left(N\right)=\frac{\alpha_1\theta^n}{\theta^n+N^n}, \tag{9}$$

where parameters α_1, θ and n have the same meaning as k_1, k_2 and γ_1 for function $F(a,x)$, see above, except that the switch is from α_1 to zero instead of zero to k_1.

2) For a tumour, the fraction of the quiescent cells that enter the proliferative phase is also decreasing with the total population, but asymptotically tends towards a non zero value when the population is very large, representing a

population density inhibition less complete than in healthy tissues. So that, in the tumoral case, we take G as follows:

$$G(N) = \frac{\alpha_1 \theta^n + \alpha_2 N^n}{\theta^n + N^n}, \qquad \text{with } \alpha_2 < \alpha_1 \text{ to ensure decay.} \tag{10}$$

We then analyse the qualitative behaviour of the model, which enables us to distinguish a healthy tissue from a tumour by the asymptotic behaviour of their cell densities.

4 Analysis and qualitative behaviour

We now perform the analysis of the model developed above. We use for that purpose the method of Generalised Relative Entropy (GRE), which was recently introduced in [21, 22, 23]. It allows us to deal with the model in its full generality. The GRE method is based on the study of eigenproblems for linearised systems and relies on the Krein-Rutman theorem for compact positive operators (see [11]). The use of other methods is possible, for instance methods based on the theory of abstract semigroups with structural conditions as described below or, in special cases, reduction to differential equations with delay (see [1] for instance).

4.1 Linear problem

The linear problem associated with (5) assumes that the transition rate from the quiescent to the proliferative state is a constant $\tilde{G}$, such that:

$$\begin{cases} \dfrac{\partial p}{\partial t} + \dfrac{\partial (\Gamma_0 p)}{\partial a} + \dfrac{\partial (\Gamma_1 (a,x)\, p)}{\partial x} = -\left(L(a,x) + F(a,x) + d_1\right) p(t,a,x) + \tilde{G} q(t,a,x), \\ \dfrac{\partial q}{\partial t} = L(a,x)\, p(t,a,x) - (\tilde{G} + d_2) q(t,a,x), \\ p(t,0,x) = \dfrac{2}{\Gamma_0} \displaystyle\int_0^{+\infty}\int_0^{+\infty} f(a,x,y)\, p(t,a,y)\, da\, dy. \end{cases} \tag{11}$$

Gyllenberg and Webb, studying a similar linear problem by methods relying on the theory of continuous semigroups, proved the existence and uniqueness of a positive solution for the system, and also proved that it has the property of asynchronous exponential growth [14] (note that this results in fact from variants of the Krein-Rutman theorem [11]). It means the following: the growth rate associated with (11) -the so-called Malthus parameter- i.e., the first eigenvalue of the problem, also referred to as the Perron eigenvalue in the

finite-dimensional case, is defined as the only λ yielding a nonnegative steady state (P, Q) solution of:

$$\begin{cases} \lambda P + \dfrac{\partial\left(\Gamma_0 P\right)}{\partial a} + \dfrac{\partial\left(\Gamma_1\left(a,x\right)P\right)}{\partial x} = -\left(L\left(a,x\right) + F(a,x) + d_1\right)P + \tilde{G}Q, \\ (\lambda + \tilde{G} + d_2)Q = L\left(a,x\right)P, \\ P(0,x) = \dfrac{2}{\Gamma_0}\displaystyle\int_0^{+\infty}\int_0^{+\infty} f\left(a,x,y\right)P\left(a,y\right)dady. \end{cases} \tag{12}$$

Of course this system can be reduced to a single equation on P, and λ depends continuously upon $\tilde{G}$. For an age-structured model it can be solved by the method of characteristics.
For further purposes, it is also useful to introduce the adjoint system, following the theory developed in [21]. Here, there is an additional difficulty coming from the boundary condition at $a = 0$. The adjoint problem reads:

$$\begin{cases} \lambda\varphi - \Gamma_0\dfrac{\partial\varphi}{\partial a} - \Gamma_1\left(a,x\right)\dfrac{\partial\varphi}{\partial x} - 2\displaystyle\int_0^{+\infty}\varphi\left(0,y\right)f\left(a,y,x\right)dy \\ = -\left(L\left(a,x\right) + F(a,x) + d_1\right)\varphi + L\left(a,x\right)\psi, \\ (\lambda + \tilde{G} + d_2)\psi = \tilde{G}\varphi, \end{cases} \tag{13}$$

with $\varphi \geq 0$, $\psi \geq 0$, and normalisation by the condition:

$$\int_0^{+\infty}\int_0^{+\infty}\Big(\varphi(a,x)P\left(a,x\right) + \psi(a,x)Q\left(a,x\right)\Big)dadx = 1.$$

These equations imply that solutions of (11) satisfy:

$$\begin{aligned} &\int_0^{+\infty}\int_0^{+\infty}\Big(\varphi(a,x)p\left(t,a,x\right) + \psi(a,x)q\left(t,a,x\right)\Big)dadx \\ &= e^{\lambda t}\int_0^{+\infty}\int_0^{+\infty}\Big(\varphi(a,x)p_i\left(a,x\right) + \psi(a,x)q_i\left(a,x\right)\Big)dadx\,, \end{aligned} \tag{14}$$

a condition that clearly expresses exponential growth with rate λ.

In the following, we explain why these growth rates can allow to qualitatively distinguish between healthy and tumoral tissues. This will be done

according to the behaviour of the first eigenvalue λ for the system linearised at the extreme values of the recruitment function G, $G(0) = \alpha_1$ and $G_\infty = \alpha_2$. We then present the main features of the nonlinear problem using a method introduced in [8] enforcing conditions on the linearised problem.

4.2 Healthy tissue: Non-extinction (a priori bound from below)

Coming back to the nonlinear problem, we first state conditions enforcing non-extinction. For this purpose, we need to investigate the linearised problem around $N(t) = 0$ and its first eigenvalue.
We assume that the coefficients are such that the following qualitative properties hold true:

(H1) For $\tilde{G} = G(0) = \alpha_1$, the first eigenvalue, denoted here as λ_0, of system (12) and its adjoint (13), is positive ($\lambda_0 > 0$).
(H2) For the corresponding solutions to (12) and (13) obtained for $\tilde{G} = G(0)$, (p_0, q_0) and (φ_0, ψ_0), there exists a constant C_0, such as $\varphi^* \leq C_0\varphi_0$ and $\psi^* \leq C_0\psi_0$ (φ^*, ψ^* being as defined in (4)).

These assumptions express that even if there are very few cells in the healthy tissue, the population can be regenerated spontaneously. Note that if we a priori assume the existence of a maximum possible age, then the positivity of φ_0 and ψ_0 implies that (H2) is automatically satisfied for any pair of bounded functions (φ^*, ψ^*).

Lemma 1 *Under hypotheses (H1) and (H2) there exists a number m_0 such that:*

$$\int_0^{+\infty}\int_0^{+\infty}\Big(\varphi_0(a,x)p(t,a,x) + \psi_0(a,x)q(t,a,x)\Big)\,dadx \geq m_0 > 0 \qquad \forall t \geq 0.$$

Proof of Lemma 1 Indeed, setting:

$$S_0(t) = \int_0^{+\infty}\int_0^{+\infty}\Big(\varphi_0(a,x)p(t,a,x) + \psi_0(a,x)q(t,a,x)\Big)\,dadx,$$

and using (5) and (13), we have, by the same duality principle used for deriving (14):

$$\frac{dS_0}{dt}(t) = \lambda_0 S_0(t) - \frac{\lambda_0 + d_2}{G(0)}(G(0) - G(N(t)))\int_0^{+\infty}\int_0^{+\infty} \psi_0(a,x)q(t,a,x)dadx\,,$$

whence, because $p \geq 0$:

$$\frac{dS_0}{dt}(t) \geq \left(\frac{\lambda_0 + d_2}{G(0)}G(N(t)) - d_2\right) S_0(t).$$

Therefore, firstly:

$$S_0(t) \geq S_0(0)\exp\left\{\int_0^t \left(\frac{\lambda_0 + d_2}{G(0)}G(N(u)) - d_2\right) du\right\} > 0.$$

Now, if the minimum of $S_0\,(t)$ is attained at $t = 0$, then $S_0(t) \geq S_0(0) > 0$; otherwise it is attained at some point t_0 (possibly at infinity), where $\frac{dS_0}{dt}(t_0) = 0$, which yields:

$$G(N(t_0)))\frac{\lambda_0 + d_2}{G(0)} - d_2 \leq 0,$$

or equivalently:

$$G(N(t_0)) \leq \frac{d_2}{\lambda_0 + d_2}G(0).$$

Since G is continuous and decreasing to 0, there exists a number $N_0 > 0$ such that:

$$G(N_0) = \frac{d_2}{\lambda_0 + d_2}G(0).$$

Thus $G(N(t_0)) \leq G(N_0)$, which implies that $N(t_0) \geq N_0 > 0$ and by (H2), for all t, $S_0(t) \geq S_0(t_0)\frac{N_0}{C_0}$. Therefore we have proved the result with

$$m_0 = \min\left(\frac{N_0}{C_0}, S_0(0)\right).$$

4.3 Healthy tissue: Limited growth (a priori bound from above)

We also need conditions enforcing tissue homeostasis, meaning that the total cell population density is limited in its growth: for this purpose we assume that for some $\lambda_{\lim} < 0$, there exist a real number $N_{\lim} > 0$ and nonnegative functions $(\varphi_{\lim}, \psi_{\lim})$ satisfying:

(H3) For $\tilde{G} = G(N_{\lim}) = \dfrac{\alpha_1\theta^n}{\theta^n + N_{\lim}^n}$, the first eigenvalue, denoted here as $\lambda_{\lim}$

of system (12) and its adjoint(13), is negative ($\lambda_{\lim} < 0$).
(H4) For the corresponding solutions to (12) and (13) obtained for $\tilde{G} = G(N_{\lim})$, $(p_{\lim}, q_{\lim})$ and $(\varphi_{\lim}, \psi_{\lim})$, there exists a constant $C_{\lim}$, such that $\varphi^* \geq C_{\lim}\varphi_{\lim}$ and $\psi^* \geq C_{\lim}\psi_{\lim}$.

These assumptions express that a large excess of cells is regulated negatively and thus the population remains bounded.

Lemma 2 *Under hypotheses (H3) and (H4) there is a number $m_{\lim}$ such that:*

$$\int_0^{+\infty}\int_0^{+\infty}\Big(\varphi_{\lim}(a,x)p(t,a,x) + \psi_{\lim}(a,x)q(t,a,x)\Big)\,dadx \leq m_{\lim}, \qquad \forall t \geq 0.$$

Proof of Lemma 2 Indeed as for Lemma 1, we define

$$S_{\lim}(t) = \int_0^{+\infty}\int_0^{+\infty}\Big(\varphi_{\lim}(a,x)p(t,a,x) + \psi_{\lim}(a,x)q(t,a,x)\Big)\,dadx.$$

Then,

$$\begin{aligned}\frac{dS_{\lim}}{dt}(t) &= \lambda_{\lim}S_{\lim}(t) - (G(N_{\lim}) - G(N(t)))\,\frac{\lambda_{\lim}+d_2}{G(N_{\lim})}\int_0^{+\infty}\int_0^{+\infty}\psi_{\lim}(a,x)q(t,a,x)dadx \\ &\leq \lambda_{\lim}S_{\lim}(t) - (G(N_{\lim}) - G(C_{\lim}S_{\lim}(t)))\,\frac{\lambda_{\lim}+d_2}{G(N_{\lim})}\int_0^{+\infty}\int_0^{+\infty}\psi_{\lim}(a,x)q(t,a,x)dadx,\end{aligned}$$

because, thanks to assumption (H4):

$$N(t) \geq C_{\lim}S_{\lim}(t).$$

Therefore, following the arguments above,

$$S_{\lim}(t) \leq \max\left(S_{\lim}(0), \frac{N_{\lim}}{C_{\lim}}\right) := m_{\lim}.$$

4.4 Tumoral tissue: Unlimited growth

Following section 3.2, in the tumoral case, the recruitment function from quiescence to proliferation is given by the function (10):

$$G\,(N) = \frac{\alpha_1\theta^n + \alpha_2 N^n}{\theta^n + N^n}.$$

Here, we expect that the population will show unlimited growth, and a condition leading to this property is:

(H5) For $\tilde{G} = G(\infty) = \alpha_2$, the first eigenvalue, denoted here as λ_1, of system (12) and its adjoint (13), is strictly positive ($\lambda_1 > 0$).
(H6) For the corresponding solutions to (12) and (13) obtained for $\tilde{G} = G(\infty)$, (p_1, q_1), (φ_1, ψ_1), there exists a constant C_1, such that $\varphi^* \geq C_1\varphi_1$ and $\psi^* \geq C_1\psi_1$.

Lemma 3 *Under hypotheses (H5) and (H6), we have*

$$N(t) \underset{t\to+\infty}{\longrightarrow} +\infty,$$

and

$$\int_0^{+\infty}\int_0^{+\infty}\Big(\varphi_1(a,x)p(t,a,x) + \psi_1(a,x)q(t,a,x)\Big)\,dadx \underset{t\to+\infty}{\longrightarrow} +\infty.$$

Proof of Lemma 3 Indeed, we define:

$$S_1(t) = \int_0^{+\infty}\int_0^{+\infty}\Big(\varphi_1(a,x)p(t,a,x) + \psi_1(a,x)q(t,a,x)\Big)\,dadx.$$

We have, since G is decreasing,

$$\begin{aligned}\frac{dS_1}{dt}(t) &= \lambda_1 S_1(t) - (G(\infty) - G(N(t)))\,\frac{\lambda_1 + d_2}{G(\infty)}\int_0^{+\infty}\int_0^{+\infty}\psi_1(a,x)q(t,a,x)dadx \\ &\geq \lambda_1 S_1(t).\end{aligned}$$

This implies that $S_1(t)$ has exponential growth. Finally, thanks to (H6) we have $N(t) \geq C_1 S_1(t)$. We conclude that $N(t)$ tends to infinity and Lemma 3 is proved.

Note that we can also consider the case $\lambda_1 = 0$ in (H5). In this case, $S_1(t)$ would have unlimited, but not exponential growth, and we would be closer to actual observations of tumour growth [7, 12]. Such polynomial-like growth behaviour could be obtained in the model by incorporating specific exchange functions L and G between G_0 and G_1 actually yielding $\lambda_1 = 0$.

4.5 Steady state for healthy tissue

Numerical experiments show that in the case of healthy tissues, the cell population goes to a steady state that represents tissue homeostasis. This can be

analysed in the present model, since a steady state (p^*, q^*) for (5) satisfies the following system of equations:

$$\begin{cases} \dfrac{\partial\left(\Gamma_0 p^*\right)}{\partial a} + \dfrac{\partial\left(\Gamma_1\left(a,x\right)p^*\right)}{\partial x} = -\left(L\left(a,x\right) + F(a,x) + d_1\right)p^*\left(a,x\right) + G\left(N^*\right)q^*\left(a,x\right), \\ L\left(a,x\right)p^*\left(a,x\right) - \left(G\left(N^*\right) + d_2\right)q^*\left(a,x\right) = 0, \\ p^*\left(0,x\right) = \dfrac{2}{\Gamma_0}\displaystyle\int_0^{+\infty}\int_0^{+\infty} f(a,x,y)p^*\left(a,y\right)dady, \end{cases}$$

with

$$N^* = \int_0^{+\infty}\int_0^{+\infty}\Big(\varphi^*(a,x)p^*(a,x) + \psi^*(a,x)q^*(a,x)\Big)\,dadx. \tag{15}$$

Substituting q^*, we obtain the equation:

$$\begin{cases} \dfrac{\partial\left(\Gamma_0 p^*\right)}{\partial a} + \dfrac{\partial\left(\Gamma_1\left(a,x\right)p^*\right)}{\partial x} = -r(a,x,N^*)p^*\left(a,x\right), \\ p^*\left(0,x\right) = \dfrac{2}{\Gamma_0}\displaystyle\int_0^{+\infty}\int_0^{+\infty} f(a,x,y)p^*\left(a,y\right)dady, \end{cases} \tag{16}$$

with

$$r(a,x,N^*) = \frac{d_2}{G\left(N^*\right) + d_2}L\left(a,x\right) + F(a,x) + d_1.$$

Proposition 4.1 *With the assumptions (H1), (H2), (H3) and (H4), the system (15), (16) has a unique positive solution* (p^*, q^*).

Proof of Proposition 4.1: Equation (16) is an eigenproblem as is equation (12); therefore, given a steady state population number N^*, we can find $\lambda(N^*)$ solution of (12). We know by (H1), (H2) that $\lambda(0) > 0$ and by (H3) and (H4) that $\lambda(N_{\lim}) < 0$. Because $\lambda(N^*)$ is continuous, and decreasing since r is increasing with N^*, there is a unique value of N^* such that $\lambda(N^*) = 0$. It remains to normalise the eigenvectors properly to obtain (15).

Remark 1 *From (H5) and (H6) we deduce that, for tumour growth, (5) has no steady state.*

5 Numerical simulations

Some of the model parameters are known for specific cells in other settings for functions used in a similar context. For stem cells, the parameters are well documented in the literature on the subject (see e.g. [20]), and we chose parameter values according to these sources, knowing that actually identifying these values on other cell lines would be necessary for experimental validation of the model. Parameter values come from [32] for c_1, c_2, c_4, and from [20] for $d_1, d_2, \alpha_1, n, \theta$. The factors determining transition from proliferation to quiescence have been proved to be directly related to cyclin D [5, 17, 19, 35], but the exact rates are not known. In the same way, parameters A_1, A_2, k_1, k_2, γ_1, γ_2, w_0, Γ_0, α_2, A^*, $\overline{A}$ are not known, but the choices made have been determined either by fixing arbitrary values -as likely as possible, e.g. $A^* = 24\,hours$, $\overline{A} = 15\,hours$- or by giving a range of values within which our numerical simulations exhibit a behaviour illustrating the theoretical properties of the model demonstrated under assumptions $(H1) - (H6)$.

Parameters	Values	Parameters	Values
c_1	0.04	γ_1	$5 - 10$
c_2	0.03	A^*	24 *hours*
c_3	0.3	A_1	$0.8 - 1$
c_4	0.01	A_2	25
w_0	1	γ_2	$5 - 10$
Γ_0	0.5	$\overline{A}$	15 *hours*
d_1	0.07 day^{-1}	α_1	0.8 day^{-1}
d_2	0.07 day^{-1}	θ	0.095×10^6
k_1	1	n	1
k_2	20	α_2	0.7 day^{-1}

Table 1. Parameters and values used in simulations.

In our numerical simulations, we have used $\varphi^* = \psi^* \equiv 1$, which means that all cells are eligible for recruitment control (by cell density inhibition, growth or antigrowth factors) in phase G_1.

For healthy tissues, Figure 1 shows the trend towards a steady state as stated in Proposition 4.1 and Figure 2 shows the distribution of cells according to their age and *cyclin D/(CDK4 or 6)* concentrations in the proliferating phase.

We have verified that assumptions (H1) and (H3) hold true. The so-called power algorithm [13] allowed us to obtain numerically the first eigenvalue for system (12). For $\tilde{G} = \alpha_1 = 0.8$, we have obtained $\lambda_0 = 0.026$, which is compatible with (H1); we have also numerically determined $N_{\text{lim}} = 5.6 \times 10^6$, and

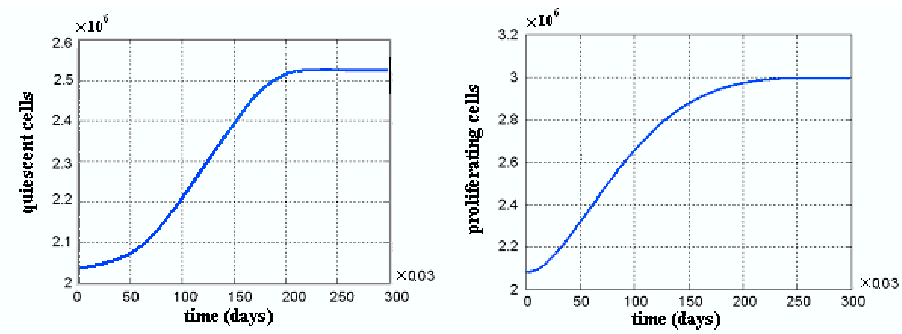

Figure 1: Time evolution of total population for a healthy tissue. Left: total quiescent cells $\int_0^{+\infty}\int_0^{+\infty} q(t,a,x)dadx$; right: total proliferating cells $\int_0^{+\infty}\int_0^{+\infty} p(t,a,x)dadx$.

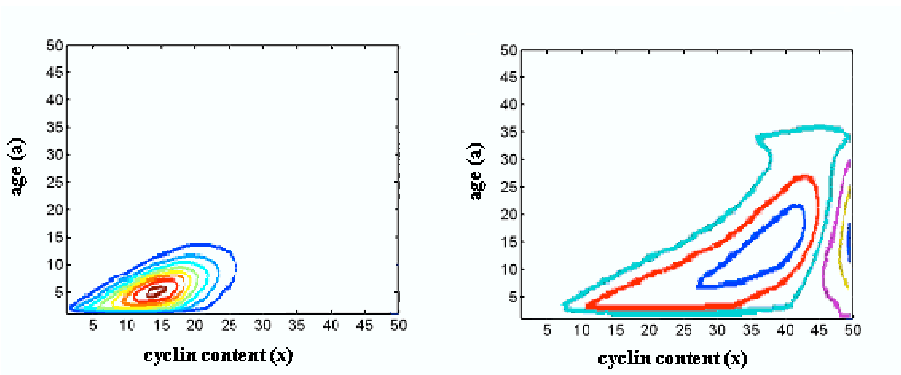

Figure 2: Isovalues of the total cell population for a healthy tissue at steady state (p^*, q^*); variable x (cyclin content) is in abscissae, variable a (age in the proliferating phase) in ordinates, and level lines indicate constant p^* or q^* values. Left: quiescent cells $q^*(a,x)$; right: proliferating cells $p^*(a,x)$.

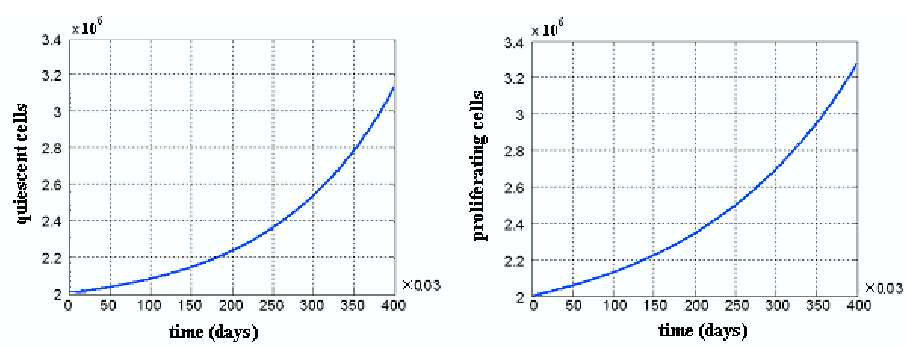

Figure 3: Time evolution of total population for a tumoral tissue. Left: total quiescent cells $\int_0^{+\infty}\int_0^{+\infty} q(t,a,x)dadx$; right: total proliferating cells $\int_0^{+\infty}\int_0^{+\infty} p(t,a,x)dadx$.

obtained $\lambda_{\lim} = -0.12$ for $\tilde{G} = G(N_{\lim}) = \dfrac{\alpha_1\theta^n}{\theta^n + N_{\lim}^n}$, which is compatible with (H3) since the cell population has limited growth.

For a tumoral tissue, Figure 3 shows that the population has unlimited exponential growth.

6 Discussion and conclusion

We have considered a nonlinear model to describe a cell population structured by its age and its amount of cyclin with two compartments: proliferating and quiescent cells. We have structured our cell population model by the amount of *cyclin D/(CDK4 or 6)* since it is the (cyclin/CDK) complex which is the most determinant for the progression in the cell cycle until the restriction point, and it is also important for the transition between proliferation to quiescence, since there is only one proliferating phase in the model, other cyclins, e.g. E, A, B, have not been considered. We have also assumed that the transition from quiescence to proliferation depends on the total ("qualified") cell population. Our cell population model can be applied to both cancer and normal tissue growth.

The analysis we have carried out, assuming reasonable hypotheses on the parameters, exhibits a steady state for a healthy tissue and, on the contrary, unlimited growth for tumoral tissue. In addition, the numerical simulations confirm these results, as illustrated by Figures 1, 2 and 3.

Throughout our analysis, we have particularly studied the role of transitions between quiescence and proliferation, focusing upon the intracellular amount of cyclin D, to connect the physiological behaviour of individual cells with the asymptotic behaviour of the corresponding cell populations with respect to their growth dynamics, for both healthy and tumoral tissues.

In this paper, we did not take space into account, a choice which was unlikely to yield for the solutions of the equations the Fisher-KPP-like long-term behaviour which has been observed by various authors for the growth of solid spheroid tumours [7, 12], i.e., $R(t) \simeq kt$ for the tumour radius as a function of time. But note that these observations deal with tumours that have in common to be described at a late stage, when space limitations are essential to tumour growth kinetic mechanisms. In this respect, the present model, in the tumoral case, may be suitable only for the phenomenological representation of the initial exponential step of solid tumour growth, or of tumours of the hematopoietic system. Other models ([27]) take both space and cell cycle control into account, and adding space as a structuring variable (i.e., designing in the future a model structured in age, cyclin content and space) is an open option.

We can hope that a better understanding of the cell cycle and its control can be used practically in cancer therapy. Drugs used in cancer chemotherapies affect only proliferating cells, often in a specific phase of the cell cycle and are often specific to particular proteins of the cell cycle. In the future, we will add

to this model the representation of the effects on the cell cycle of drugs such as antagonists of *EGFRs* (epidermal growth factor receptors). These receptors, on stimulation by growth factors, act on the G_1 phase inducing quiescent cells to enter into the proliferating phase and these drugs, which are more and more widely used in clinics, inhibit this recruitment. We will also separate the proliferating phase (=the complete cell division cycle) into specific phases (G_1/S-G_2/M) onto which specific drugs act, e.g. 5Fluorouracil on S phase.

Such modelling principles will allow us to represent separately the cytotoxic effects of alkylating agents, such as e.g. platinum compounds, non phase-specific, of antimetabolites, S phase-specific, as well as the cytostatic effects of anti *EGFR* drugs on transitions between quiescent and proliferative states. Taking into account the effects of such different drugs is indeed a necessity in order to actually help clinicians, since modern treatments in oncology use combinations of drugs in standard therapeutic protocols.

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