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Growth of tumours with stem cells: The effect of crowding and ageing of cells

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ABSTRACT

Mathematical models for the growth of tumours in the presence of stem cells (CSCs) and differentiated tumour cells (CCs) are presented and discussed. The CSCs are assumed to be immortal and multipotent, i.e. capable of generating several possible lineages of CCs that may undergo ageing and apoptosis. Each CC is characterised by two indexes, related to the differentiation lineage and the class of age, respectively. Furthermore, the effect of crowding is taken into account, assuming that mitosis can be hindered by the presence of cells in the vicinity of the would-be mother cell. Two families of models are proposed. First, models based on cellular automata are considered, whose evolution is governed by stochastic rules. Then, by averaging over the cells with the same pair of indexes, we obtain a deterministic model that consists of a system of Ordinary Differential Equations (ODEs) whose unknown functions are the fractions of the cells in each lineage and the class of age. The system presents a basic novelty with respect to the other compartmental models proposed in the literature as it cannot be solved hierarchically because of the presence of the crowding effect. Numerical simulations based on the two families of models give the same qualitative results and, in particular, they evidentiate the occurrence of the tumour paradox: an increased mortality of the CCs may induce a faster growth of the tumour. A final section of the paper is devoted to the case in which the age distribution of the CCs is continuous and not discrete. In this case, an interesting mathematical problem is obtained that consists of one ODE for the fraction of CSCs and m first-order Partial Differential Equations (PDEs); one for each lineage of CCs.

1. Introduction

The heterogeneity of cancer cells is currently considered to be a key factor in determining the evolution of many tumours. The basic idea in explaining the genesis of the inhomogeneities consists, in its simplest version, of assuming that the entire tumour is generated by a small number of cancer stem cells (CSCs) that are immortal and multipotent, in the sense that they are able to proliferate indefinitely and to produce either new-born CSCs or differentiated cancer cells (CCs). The differentiation can occur following distinct lineages of the CCs with their usual cycle of ageing, mitosis,

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and apoptosis [1,2]. CSCs (originally called tumorigenic cells) were first isolated and described in the haematopoietic system [3], and the importance of their role in tumour growth has been described [4,5]. In the early 2000's, the existence of CSCs was shown for solid tumours, such as breast and brain cancers [6]. Since then, the number of papers that present theoretical and experimental results in this area has been steadily increasing, and we will limit ourselves to quoting some review papers that contain extensive reference lists [7–10] and, more recently, [11–14]. Furthermore, we refer the reader to the webpage [15] containing a weekly updated list of published papers on CSCs.

In the past decade, many papers have also been devoted to mathematical modelling of the growth of tumours in the presence of CSCs, applying the methods of population dynamics. We can quote, e.g. [16–24], as well as [25] that has an extensive bibliography in this area, updated to 2017.

Several papers use compartmental models: the unknown functions represent abundances of each type of cells $(v_0, v_1, \ldots, v_N)$ where v_0 is the fraction of CSCs and $v_1 \ldots v_N$ is the fraction of the N classes of successively differentiated cells. In the simplest case (differentiation in cascade), these functions obey $N+1$ ordinary differential equations of the type

$$\begin{cases} \dfrac{dv_0}{dt} &= r_0 v_0 - a_0 v_0 - m_0 v_0\,, \\ &\vdots \\ \dfrac{dv_i}{dt} &= a_{i-1} v_{i-1} - a_i v_i - m_i v_i + r_i v_i\,, \qquad i = 1, 2, \ldots, N-1\,, \\ &\vdots \\ \dfrac{dv_N}{dt} &= a_{N-1} v_{N-1} - m_N v_N + r_N v_N\,, \end{cases} \tag{1}$$

supplemented with initial conditions. Here a_i $(i = 0, 1, \ldots, N-1)$ represents the differentiation rate of the ith class of cells, and m_i and r_i $(i = 0, 1, \ldots, N-1)$ are the mortality and the reproduction rate without differentiation. Models of this class are called hierarchical models since the equations can be solved recursively, starting from the first one.

In other cases, agent-based computer models are used to find mechanisms that drive tumour development and progression; see, e.g. [26,27], as well the more recent works [28–33].

The stem cell assumption is also crucial for describing the tumour growth paradox that consists of an accelerated tumour growth that can be found with an increased cell death that, for example, can result from the immune response or from cytotoxic treatments [27,34,35].

Of course, this fact could have a crucial relevance in connection with the strategy of treatment, to avoid the fact that the latter produces a faster progression of the tumour [34–36].

The occurrence of the paradox has been associated with a crowding effect [28,37–40], assuming that mitosis can be inhibited when the density of the cells in the vicinity of the would-be mother cells exceeds a threshold value.[1] Indeed, numerical simulations based on different models incorporating the crowding effect evidentiate this paradoxical behaviour.

The papers quoted in this context introduce two basic approximations: (i) they neglect the age-dependence of the replication potential and of the mortality of the non-stem cells, and (ii) they group all the non-stem cancer cells in a single population.

The present paper releases these assumptions and considers the simultaneous effects of crowding, multiple differentiation, and ageing.

Throughout this paper, we will assume that CSCs have zero mortality and a constant replicative potential, and that they are capable of generating new CSCs or ordinary non-stem cancer cells (CCs). In the first case, we speak of symmetrical mitosis, while the second case is denoted as asymmetrical mitosis.[2] The fraction of asymmetrical mitosis will be denoted by d (usually larger than 90%).

We will consider two families of models. In the first family we present agent-based models consisting of the application of cellular automata whose evolution is governed by stochastic rules, in the sense that given probabilities of replication and apoptosis are prescribed for each class of age and for each differentiation lineage.[3] The models in the second family are deterministic, since the behaviour of the cells is averaged (in each class of age and in each differentiation lineage) as in typical mean field approximations. The mathematical structure of these models, presented in Section. 3, consists of a mean field approximation and results in a system of Ordinary Differential Equations (ODEs) in which the unknown functions are fractions of the age classes in each lineage of CCs, irrespective of their position in the region under consideration. Thus, the population of CCs is composed of m sub-populations of differentiated cells with n classes of age (from new-born to

[1] In [41] general mechanisms of negative feedback are assumed in computational simulations.

[2] As far as the mathematical models are concerned, it is immaterial whether different classes of differentiated CCs are generated in cascade or in parallel.

[3] In the example that will be displayed in Section 2 all the probabilities are supposed to be space-independent and constant-in-time. Moreover, the ageing process is assumed to be deterministic. However, generalisations in these directions could be incorporated with some additional computational work.

old). All of them can only generate new CCs and may undergo apoptosis. The replicative potential and the mortality rate of class kth ($k = 1, 2, \ldots, m$) and age i ($i = 1, 2, \ldots, n$) will be denoted by ρ_{ki} and μ_{ki}, respectively. We are still in the class of compartmental models but, because of the presence of the crowding term depending on the total number of CCs, the system is much more complex and qualitatively different from the hierarchical models quoted above.

In Sections 2 and 3 , we display some numerical simulations that show that both families of models give the same qualitative results and that both evidentiate the occurrence of the tumour paradox, i.e. an accelerated tumour growth when the mortality of the CCs is increased. It should be noted that the numerical values of the parameters used in the simulations are only speculative, but the role of this kind of conceptual model consists of giving the correct qualitative information regarding the complex mechanisms involved in the phenomenon.

Finally, in Section 4, we consider a generalisation of the family of deterministic models, assuming that a continuous age distribution, instead of a structure in age classes, is given. The mathematical aspects of the problem are substantially different. Here, we have a system of one ODE for the evolution of the fraction of CSCs and m first-order Partial Differential Equations (PDEs), one for each lineage of CCs.

2. Cellular automata

For the sake of simplicity, we will confine ourselves to the case of a single lineage of CCs (i.e. we take $m = 1$) and three classes of age ($n = 3$): new-born cells ($i = 1$), adult cells ($i = 2$), and old cells ($i = 3$). More general cases give essentially similar results. We imagine the cells to be living in a square lattice[4] of 50×50 sites, and we prescribe probabilistic rules for their replication or death. At each time step, each site in the lattice can be in one of the following states:

- vacant sites (white);
- sites occupied by a CSC (black);
- sites occupied by a young CC (red);
- sites occupied by an adult CC (orange);
- sites occupied by an old CC (yellow).

Starting from a given situation at time t_k, each CC (red, orange, or yellow) has a probability μ_1, μ_2, μ_3 of undergoing apoptosis (becoming white) in the time interval corresponding to the time step of the Cellular Automata (CA). Then, the surviving cells have probabilities ρ_1, ρ_2, ρ_3 of being potentially replicant. However, in this case, mitosis is only possible if there are vacant (white) sites in the chosen neighbourhood; if this situation occurs a daughter CC appears and one of these white sites (randomly chosen) becomes red, as well as the site of the mother cell. The situation with CSCs is similar but with two differences: (i) $\mu = 0$, and (ii) if mitosis occurs a daughter CSC appears with probability $1 - d$, while the asymmetrical proliferation (i.e. the appearance of a new-born CC) has probability d. The replication probability is ρ_0.

Remark. Of course, the phenomenon might be much more complex with respect to this simplified scheme. For instance, possible dormancy of some CSCs should be considered, so that the replicative probability is not the same for all cells but a (possibly variable) stochastic distribution should be introduced. Similarly, distribution for ageing and mortality of the CCs could be taken into consideration. We remark that the model is sufficiently flexible to deal with these generalisations. We choose to keep the number of parameters as small as possible to illustrate some fundamental aspects of this complex phenomenon.

It is natural to assume that $\rho_0 > \rho_1 > \rho_2 > \rho_3$ and that $\mu_1 < \mu_2 < \mu_3$.

In what follows we assume that dying cells leave the site they occupied immediately blank, but we can also simulate cases in which apoptosis gives rise to necrotic material that occupies the site for some time (grey sites), and, possibly, this material influences the surrounding cells (intoxicating effect).

According to the crowding effect, we have assumed that cells can proliferate only if in their neighbourhood.[5] Some lattice sites are vacant; more specifically, the replicative potential is scaled in the function of the sites that are vacant in the neighbourhood.

On the other hand, it is possible that the mother cell pushes the adjacent cells if all of the close neighbourhood is occupied. To take this effect into account, we consider a hierarchy of neighbourhoods: the 1st order is formed by the 8 sites of the Moore's neighbourhood, the second order is formed by the 24 cells of the 5×5 neighbourhood and so on. If the first-order neighbourhood is occupied, the algorithm counts the vacant sites in the 2nd order neighbourhood, and so on. However, we postulate that some energy is spent in the case of displacement, thus decreasing the replicative potential accordingly.

Finally, we remark that in our simulations, cells will be supposed to be immobile, but it is evident that random motion (e.g. diffusion) or drift can be incorporated into the model as well. In the sequel, we display results in the basic case (no intoxication nor pushing).

[4] A tri-dimensional lattice could easily be considered with a little computational work (see [42]).

[5] Different definitions of neighbourhood are possible: for the $2 - D$ lattice, a Von Neumann or Moore neighbourhood can be used (4 orthogonal neighbours – north, south, east, west – or 8 neighbours – adding northwest, northeast, southwest, southeast – respectively). We use Moore neighbourhoods unless otherwise specified.

As the initial condition for the simulations displayed below, we took a single CSC situated in the centre of the grid. The setup of the parameters is

$$d = 0.9, \quad \rho_0 = 1, \quad \rho_i = \rho_1(1 - i\varphi), \quad \mu_i = \mu_1(1 + i\theta), \quad i = 2, 3. \tag{2}$$

Parameters θ and φ were fixed to be 0.1, while ρ_1 and μ_1 were chosen in each experiment.

The choice of the value of the parameters is only speculative because the model is aimed at reproducing the characteristics of the evolution of tumour growth and not at giving an exact prediction of the dimension of the tumour. In fact, the role of conceptual modelling is to mimic the relevant features of the phenomenon. Nevertheless, even in this oversimplified model, it is, in principle, possible to experimentally determine realistic values for the parameters. We remark that

(i) choosing $\rho_0 = 1$ is nothing other than choosing the time unit equal to the average length of the reproduction cycle of CSCs under consideration;
(ii) the average fraction d of the asymmetric reproduction can be determined by in vitro experiments;
(iii) in the simulations we have assumed that the permanence of the CCs in each age class is, on average, the same as the lifecycle of the CSCs, i.e. we chose the amplitude of the age classes accordingly, and this can be easily changed to correspond with the experimental conditions;
(iv) plausible values for θ and φ could easily be found, once the amplitude of the age classes has been chosen.

We assume that at each time step the CCs that do not replicate or die change their state (from new-born to adult, to old). Thus, to take $\rho_0 = 1$ corresponds to assuming that the interval between the two replications of a CSC is of the same order as the time of permanence of a CC in an age class.

In Fig. 1 we show some screenshots (at different times) of a simulation corresponding to $\rho_1 = 0.5$ and $\mu_1 = 0.25$.

It is a common characteristic of agent-based models that the individual behaviour of each cell contributes to the evolution of the system and that the latter can be visualised as a collective behaviour, possibly averaging over several simulations in the same conditions to evidentiate the response of the model to different setups of parameters and conditions. This is what is shown in Fig. 2, where the averages are taken over 20 simulations. The curves show the evolution of the total number of cancer cells (CSCs and the three classes of CCs) as a function of time. Next, we compare the behaviour for two different values of the mortality rate. In Fig. 3, the blue curve corresponds to $\mu_1 = 0.25$, while the magenta curve corresponds to $\mu_1 = 0.35$. The tumour paradox is clearly evident: a higher mortality of the CCs produces a faster progression of the tumour.

The same algorithm can be used to simulate the effect of a treatment that, for some prescribed time, destroys a fraction g of the CCs. For instance, it assumes that in the time interval $t \in [200, 350]$ μ_1 is switched from 0.25 to 1. As can be seen in Fig. 4, the reduction of the dimensions of the tumour is only temporary. Comparing the situation with this aggressive treatment with the one with constant $\mu_1 = 0.25$ for all time, the paradox is evident.

3. Compartmental models

A general compartmental model for a system of CSCs and m lineages of differentiated cells and n classes of age can generally be written in the following form

$$\begin{cases} \dfrac{du}{dt} &= \rho\,(1-d)\,u\,, \\ \dfrac{dv_{1i}}{dt} &= \rho\, d_i\, u + 2\displaystyle\sum_{j=1}^{n}\sum_{k=1}^{m}{}_{jk\neq 1i}\ \rho_{jk\to i} v_{jk} - \sum_{k=1}^{m}\rho_{1i\to k} v_{1i} \\ &- (\mu_{1i} + \psi_i)\, v_{1i} + \rho_{1i\to i} v_i\,, \\ &\vdots \\ \dfrac{dv_{ki}}{dt} &= \psi_i v_{k-1,i} - \psi_i v_{ki} - \mu_{ki} v_{ki} - \displaystyle\sum_{j=1}^{n}\rho_{ki\to j} v_{ki}\,, \\ &\vdots \\ \dfrac{dv_{ni}}{dt} &= \psi_i v_{n-1,i} - \mu_{ni} v_{ni} - \displaystyle\sum_{j=1}^{n}\rho_{ni\to j} v_{ni}\,. \end{cases} \tag{3}$$

Here v_{ki} is the fraction of cells of lineage i and the class age k, ρ is the replication potential of the CSCs; $d = \sum_{i=1}^{m} d_i$ is the ratio of asymmetrical mitosis,[6] μ_{ki} is the mortality of the cells in the compartment (ki), $\rho_{ki\to j}$ is the replication potential of the cells in compartment (ki) to produce cells in the lineage j, and ψ_i represents the ageing for lineage i.

[6] To save notation we have assumed that a mitosis with differentiation produces two cells (in the age class 1) of the same lineage.

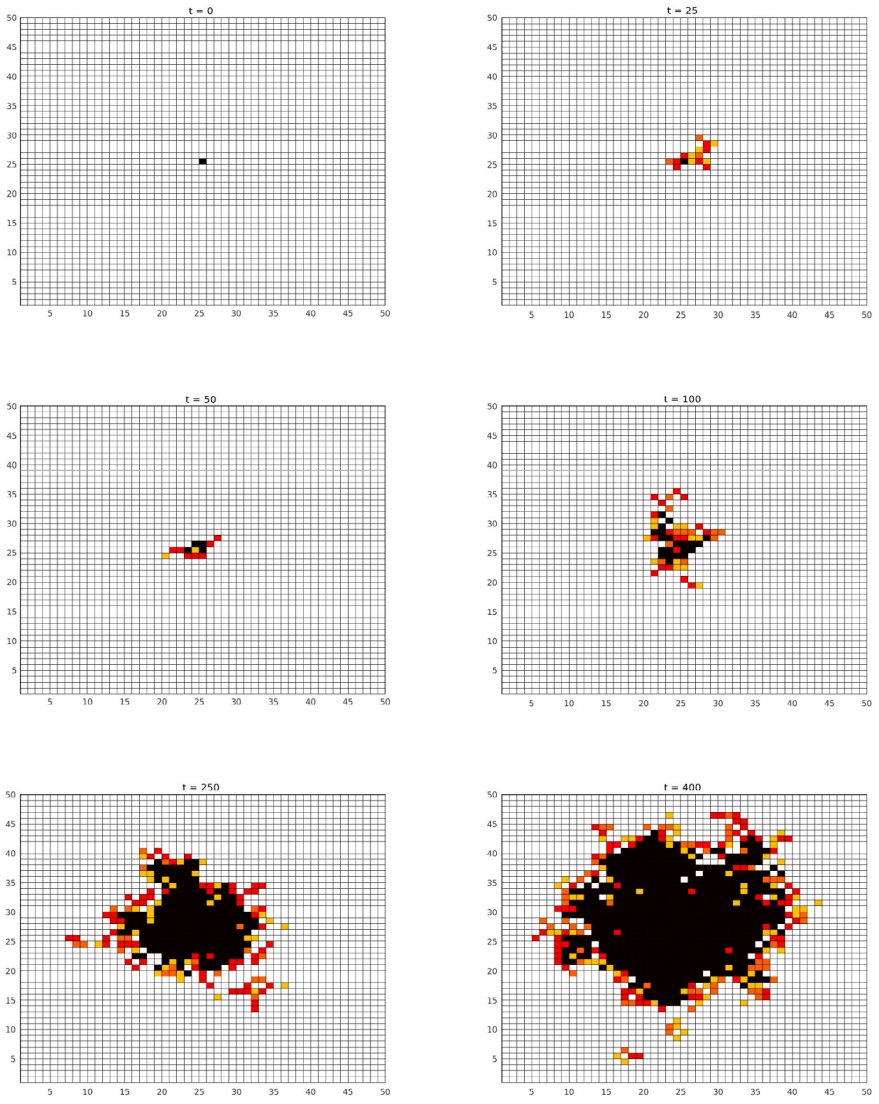

Fig. 1. Screenshots of the simulation of the evolution of the tumour growth according to the setup (2) and $\rho_1 = 0.5$ and $\mu_1 = 0.25$. In white, we display the vacant sites; in black we show the sites occupied by a CSC, while red, orange, and yellow show the sites occupied by a young, adult, and old CC, respectively.

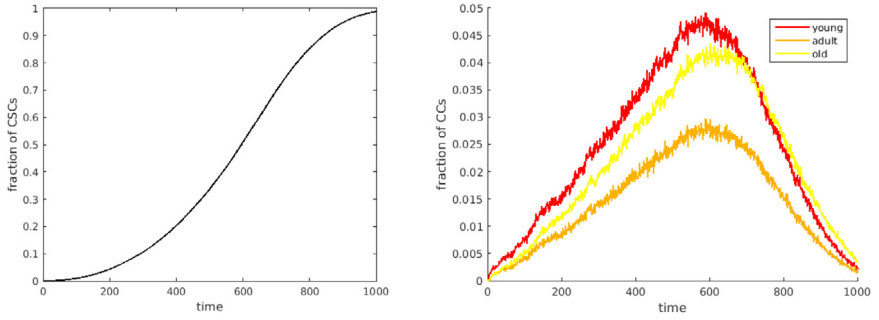

Fig. 2. Evolution of the fraction of cancer cells (CSCs on the top and the three classes of CCs on the bottom) as a function of time.

The system (3) is composed of $n \times m + 1$ first-order ordinary differential equations that have to be solved starting from an equal number of initial conditions. It is clear that the system represents a *mean field approximation* of the tumour,

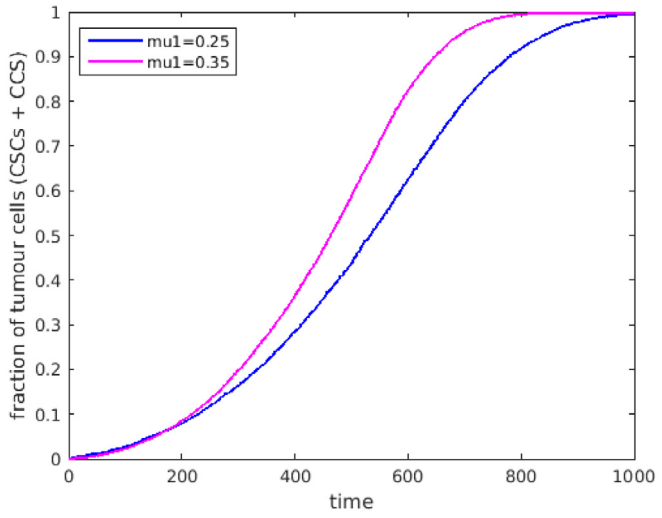

Fig. 3. Evolution of the fraction of all cancer cells (CSCs and CCs) applying $\mu_1 = 0.25$ (blue curve) and $\mu_1 = 0.35$ (magenta curve).

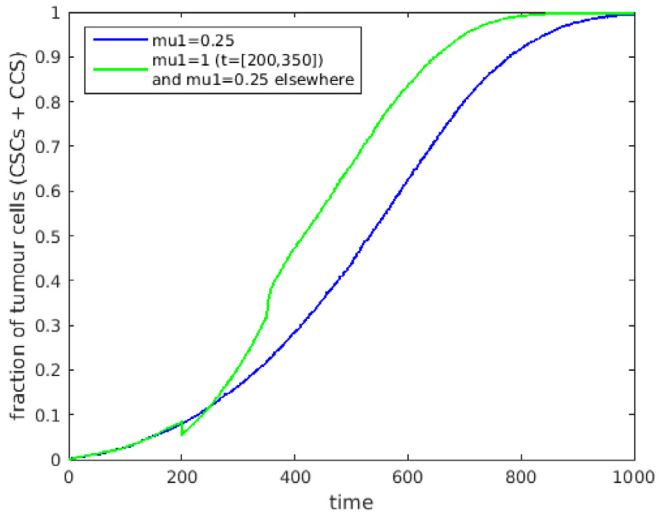

Fig. 4. Evolution of the fraction of all cancer cells (CSCs and CCs) applying $\mu_1 = 0.25$ (blue curve) and $\mu_1 = 1$ when $t \in [200, 350]$ and $\mu_1 = 0.25$ elsewhere (green curve).

because the dependence of the cell fractions on the position is not taken into account. Of course, some of the parameters appearing in (3) may vanish. For instance, if each lineage of CC can only be generated by a CSC and evolves with age, independently of the others, then the only replication terms appearing in the equations are $\rho_{ki\to i}$.

So far, no crowding effect has been taken into account. In the spirit of the mean field approximation, we can introduce this effect by multiplying each replicative potential in (3) by a function $F(p)$ of the total fraction p of all the cells present in the domain. Quantity p is given by

$$p = u + \sum_{j=1}^{n} \sum_{k=1}^{m} v_{jk}\,, \tag{4}$$

and the function $F(p)$ will be a decreasing function of p such that $F(0) = 1$ and $F(1) = 0$.

It is clear at this point that the system is no longer hierarchical. Even in the simplest cases, the term $F(p)$ introduces in each equation the full set of the unknown functions. This means that is it not possible to solve the system recursively, and, of course, this fact introduces a relevant difference and complexity with respect to the other compartmental models quoted in Section 1.

To be specific, to avoid dealing with cumbersome notation and increasing the number of parameters to be chosen, from now on, we will consider the case $m = 1$ (one lineage of non-stem cells) and three classes of age (new-born, adult

and old cells) as we did in the simulations with cellular automata. Simultaneously, we will include the crowding factor $F(p)$ in the differential equations. We point out that all the simulations we will show can be duplicated in more complex cases with some additional computational work.

Thus we will study in detail the following system of ODE

$$\begin{cases} \dfrac{du}{dt} &= \rho_0\,(1-d)\,F(p(t))\,u(t), \\ \dfrac{dv_1}{dt} &= \rho_0\,d\,F(p(t))\,u(t) + \rho_1 v_1 F(p) + 2\rho_2 v_2 F(p) + 2\rho_3 v_3 F(p) - \mu_1 v_1 - \psi v_1, \\ \dfrac{dv_2}{dt} &= \psi\ v_1 - \rho_2 v_2 F(p(t)) - \mu_2 v_2 - \psi v_2, \\ \dfrac{dv_3}{dt} &= \psi\ v_2 - \rho_3 v_3 F(p(t)) - \mu_3 v_3, \end{cases} \tag{5}$$

$$u(0) = u_0 \geq 0,\ v_1(0) = v_{10} \geq 0,\ v_2(0) = v_{20} \geq 0,\ v_3(0) = v_{30} \geq 0\,, \tag{6}$$

where

$$p(t) = u(t) + v_1(t) + v_2(t) + v_3(t)\,, \tag{7}$$

and it is assumed that

$$p(0) = u_0 + v_{10} + v_{20} + v_{30} \leq 1. \tag{8}$$

The case $u_0 = 0$ would correspond to a model without CSCs and is (simpler but) outside our interest.

We will assume that $F(p)$ is a Lipschitz continuous decreasing function such that $F(0) = 1$ and $F(1) = 0$. For technical reasons, we will extend $F(p)$ so that

$$F(p) = 1 \text{ for } p \leq 0, \quad F(p) = 0 \text{ for } p \geq 1. \tag{9}$$

The ageing ψ represents the inverse of the time of permanence of the cells in each age class. Of course, the conclusions we will reach in this section also apply to cases in which there is a different value of ψ for each class.

By standard techniques, it can be easily proved that the set $u \in (0, 1)$, $v_i \in (0, 1)$ and $p \in (0, 1)$ is invariant for system (5).

As a consequence, $u = 1$, $v_i = 0$, $i = 1, 2, 3$ is the unique equilibrium point for (5)–(8). It is globally attractive and the solution of

$$\frac{du}{dt} = \rho_0(1-d)\,F(u)\,u \tag{10}$$

is a super-solution for (5). For the case of $F(p) = 1 - p$, the solution of (10) is a logistic.

In the following simulations, we assume, as in Section 2

$$d = 0.9, \quad \rho_0 = 1, \quad \rho_1 = 0.5, \quad \rho_i = \rho_1(1 - i\varphi), \quad \mu_i = \mu_1(1 + i\theta), \quad i = 2, 3. \tag{11}$$

We take $\theta = \varphi = 0.1$ and $F(p) = 1p$, and the initial conditions are chosen in accordance with the simulations that we carried out with CA

$$u(0) = 1/2500, \quad v_1(0) = v_2(0) = v_3(0) = 0. \tag{12}$$

Since time has been normalised by choosing $\rho_0 = 1$, we set ψ accordingly as the ratio of the average time between two replications (for CSCs without space constraints) and the average time spent in each age class. In what follows, we set $\psi = 1$ according to the CA simulations.

We can numerically solve the system (5) with initial conditions (6) with standard solvers for ordinary differential equations as the Matlab function `ode45` that implements a Runge–Kutta method with a variable time step for efficient computation.

In Fig. 5, we show the quantity $p(t)$ (representing the normalised volume of the tumour) and we compare the cases of $\mu_1 = 0.25$ and $\mu_1 = 0.35$. The curves exhibit the occurrence of the tumour paradox, although this fact is less evident than in the curves of Fig. 3 that correspond to the CA approach. This fact can be easily explained in terms of the different choice of the crowding term: in the case of simulations with CA, crowding was introduced as a local effect, counting the empty sites in the vicinity of the mother cell. In the mean field approximation of this section we chose to mimic crowding by a term $F(p)$ and, thus, depending on the fraction of the total space available. This is also the reason why the speed of growth is larger in this case.

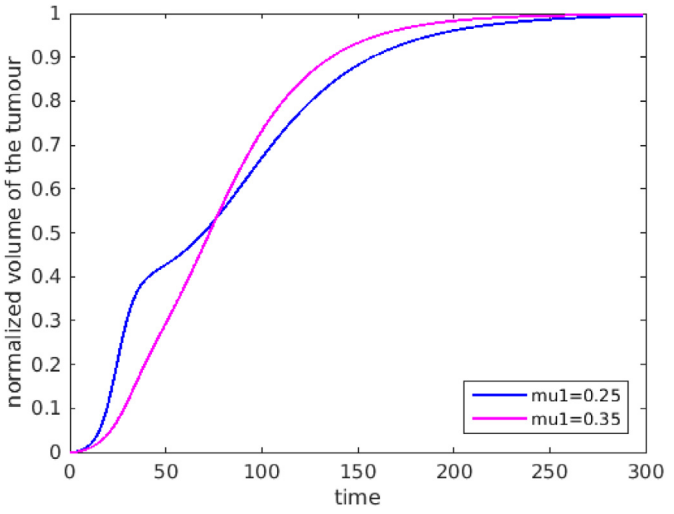

Fig. 5. Evolution of the normalised volume $p(t)$ of the tumour cells (CSCs and CCs) applying $\mu_1 = 0.25$ (blue curve) and $\mu_1 = 0.35$ (magenta curve).

4. Continuous age-structure for the non-stem cells

In this section, we will model the evolution of the tumour assuming that there is a single lineage of CCs but considering the case of a continuous age structure.

As in the usual models of population dynamics, the age structure of the population of non-stem cells can be represented by introducing a function $v(a, t)$ such that, for any non-negative t, a_1 and a_2 ($a_1 < a_2$), the integral

$$\int_{a_1}^{a_2} v(a, t)\, da \tag{13}$$

represents the fraction of CCs that, at time t, have an age between a_1 and a_2.

Assuming that the biological age coincides with the chronological age,[7] the equation regulating the evolution of the age distribution in the population of the CCs will be:

$$\frac{\partial v(a,t)}{\partial a} + \frac{\partial v(a,t)}{\partial t} = -\bar{\mu}(a)\, v(a,t) - \bar{\rho}(a)\, v(a,t)\, F(p), \quad t > 0, \quad a > 0\,, \tag{14}$$

while the fraction $u(t)$ will still obey

$$\frac{du}{dt} = \rho_0\,(1-d)\,u(t)\,F(p), \quad t > 0\,, \tag{15}$$

where

$$p(t) = u(t) + \int_0^{+\infty} v(a,t)\, dt, \quad t > 0\,, \tag{16}$$

In (14), we denoted the mortality and replication potential of the CCs as functions of their age by $\bar{\mu}(a)$ and $\bar{\rho}(a)$.

The system has to be supplemented by initial conditions

$$u(0) = u_0, \quad v(a,t) = v_0(a), \quad a > 0, \tag{17}$$

and by a boundary condition expressing the number of new-born CCs ($a = 0$) generated by the replication of the whole population, i.e.

$$v(0,t) = v_0(0) + \rho_0\, d \int_0^t F(p(\tau))\, u(\tau)\, d\tau \; + \; 2 \int_0^t F(p(\tau)) \int_0^{+\infty} \bar{\rho}(a)\, v(a,\tau)\, da\, d\tau\,. \tag{18}$$

We assume

H1 $u_0 > 0, \quad \rho > 0, \quad d \in (0,1)$,
H2 $0 < \underline{b} \le v_0(a) \le \bar{b} < 1$ is continuous in $[0, \alpha]$ and vanishes for $a > \alpha$,
H3 $0 < \underline{C} \le \int_0^{\alpha} v_0(a)\, da + u_0 \le \bar{C} < 1$.

[7] Otherwise a constant factor would appear in the first term of Eq. (14).

We have the following immediate result

Proposition 4.1. *For any solution (14)–(18) with data satisfying (H1)–(H3) and for any $T > 0$, there exists $A > 0$ such that:*

$$v(a,t) = 0, \quad \text{for } a > A, \quad t \in (0,T). \tag{19}$$

Proof. The characteristic lines for (14) are the straight lines $t = a + c$. Therefore (19) is satisfied for any $A \geq \alpha + T$. □

We define S to be the support of v, and we will look for a pair (u, v), $u \in C^1[0,T]$, $v \in C(\bar{S}) \cap C^1(S \cap (0,T))$, $v \equiv 0$ in $(0,A) \times (0,T) \setminus S$ satisfying (17) and such that (14) holds in $(0,A) \times (0,T)$, (15) holds in $(0,T)$, and (18) is satisfied where the upper limit in the integrals is A instead of $+\infty$.

We will assume:

H4 $\bar{\rho}(a)$ and $\bar{\mu}(a)$ are positive and continuous in $[0,A]$,
H5 $F(p)$ is a non-increasing Lipschitz-continuous function in $(-\infty, +\infty)$, with $F(p) = 1$, $p \leq 0$ and $F(p) = 0$, $p \geq 1$.

Let us consider the following auxiliary problem:

$$\begin{cases} \dfrac{\partial w}{\partial a} + \dfrac{\partial w}{\partial t} &= g(a,t), & 0 < a \leq A, \quad 0 < t < T, \\ w(a,0) &= w_0(a), & 0 \leq a \leq \alpha, \quad w_0(a) = 0, \quad a \in [\alpha, A], \\ w(0,t) &= \Gamma(t; w(a,t)), & 0 < t < T, \end{cases} \tag{20}$$

where

$$g(a,t) \leq 0, \quad -b_1 \leq w_0(a) \leq -b_2 < 0, \tag{21}$$

and $\Gamma(t; w)$ is a functional such that for any bounded w and suitably small T it is:

$$-B_1 \leq \Gamma(t; w) \leq -B_2 < 0, \tag{22}$$

$$|\, \Gamma(t; w_1) - \Gamma(t; w_2) \,| \leq c(t) \| w_1 - w_2 \|\,, \tag{23}$$

where $c(t) = O(T)$ and $\| \ \|$ is the uniform norm.

We choose $\hat{w}(a,t) \in C([0,A] \times [0,T])$, and define $G(t) = \Gamma(t; \hat{w}(a,t))$. Then we solve (20) where the third condition is replaced by $w(0,t) = G(t)$.

We have immediately

$$w(a,t) = \begin{cases} w_0(a-t) + \displaystyle\int_0^t g(z + a - t, z)\, dz, & t < a < A, \, 0 < t < T, \\ G(t-a) + \displaystyle\int_0^a g(z, z + t - a)\, dz, & 0 < a < t, \, 0 < t < T. \end{cases} \tag{24}$$

We denote the set of continuous functions $[0,A] \times [0,T]$ by Σ such that $-C_1 \leq w \leq -C_2 < 0$ where $C_1 > \max(B_1, b_1)$ and $C_2 = \min(B_2, b_2)$. The procedure just described defines a mapping of Σ into itself for suitable small T because of (21), (22), (24).

Moreover, (23) guarantees that the mapping is contractive (reducing T if necessary). Using Banach's fixed point theorem we conclude the proof of

Proposition 4.2. *If (21)–(23) are satisfied, problem (20) has one unique solution in a suitable time interval* $(0,T)$.

We are now in a position to prove the following

Theorem 4.3. *Under the assumptions (H1)–(H5), the problem (14)–(18) has one unique solution for a suitable T.*

Proof. We again use a fixed point argument. We prescribe a continuous function $\tilde{p}(t)$ such that

$$0 < \underline{K} \leq \tilde{p}(t) \leq \bar{K} < 1\,, \tag{25}$$

when $\bar{K} > C$ and $\underline{K} < \underline{C}$ of assumption (H3). Let $\tilde{F}(t) = F(\tilde{p}(t))$ and consider the problem

$$\begin{cases} \dfrac{du}{dt} &= \rho\,(1-d)\,\tilde{F}(t)\,u, & t \in (0,T), \\ \dfrac{\partial v}{\partial a} + \dfrac{\partial v}{\partial t} &= -(\bar{\mu}(a) + \bar{\rho}(a)\tilde{F}(t))\,v, & a \in (0,A), \ t \in (0,T), \end{cases} \tag{26}$$

with conditions

$$u(0) = u_0, \qquad v(a,0) = v_0(a), \tag{27}$$

$$v(0,t) = v_0(0) + \rho\, d \int_0^t \tilde{F}(\tau)\, u(\tau)\, d\tau \;+\; 2 \int_0^t \tilde{F}(\tau) \int_0^{+\infty} \bar{\rho}(a)\, v(a,\tau)\, da\, d\tau. \tag{28}$$

Hence

$$u(t) = u_0 \,\exp[\rho\,(1-d) \int_0^t \tilde{F}(\tau)\, d\tau], \tag{29}$$

and the function

$$w(a,t) = \ln\, v(a,t) \tag{30}$$

solves a problem of type (20) where

$$g(a,t) = -\bar{\mu}(a) - \bar{\rho}(a)\tilde{F}(t), \tag{31}$$

$$w_0(a) = \ln v_0(a)\,, \tag{32}$$

$$\Gamma(t; w(a,t)) = \ln[v_0 + \rho\, d \int_0^t \tilde{F}(\tau) u(\tau)\, d\tau + 2 \int_0^t \tilde{F}(\tau) \int_0^A \bar{\rho}(a) \exp[w(a,t)]\, da\, d\tau]. \tag{33}$$

Of course (29) and (30) guarantee that (21) is fulfilled since (H2), (H4), and (H5) are supposed to hold. Moreover (H1) and (27) ensure that, for any bounded w, the functional Γ defined by (33) is the logarithm of v_0 plus a positive function of $O(t)$ so that, since v_0 satisfies (H2), there exist two constants B_1 and B_2 such that (22) holds for a suitable $T > 0$.

By reducing, if necessary, T we have that (23) holds as well. Therefore, problem (26)–(28) is uniquely solvable by Proposition 4.2.

This means that, for any $\tilde{p}(t) \in C[0,T]$, $0 < \underline{C} \le \tilde{p} \le \bar{C} < 1$ we have found two functions $u(t)$ given by (29) and

$$v(a,t) = \exp(w(a,t)),$$

with

$$v(a,t) = \begin{cases} v_0(a-t) + O(t), & t < a < A, \\ v_0(t-a) + O(t) & 0 < a < t. \end{cases}$$

Therefore

$$\int_0^A v(a,t)\, da = \int_0^A v_0(a)\, da + O(t).$$

But it is also

$$u(t) = u_0 + O(t),$$

so that

$$p(t) = u(t) + \int_0^A v(a,t)\, da + O(t),$$

and reducing T if necessary we conclude

$$\underline{K} \le p(t) \le \bar{K}. \tag{34}$$

This means that we have defined a mapping

$$p(t) = \mathcal{T}\,\tilde{p}(t)$$

that maps the set of continuous functions satisfying (34) into itself.

To prove that T can be chosen so that $\mathcal{T}$ is a contraction is immediate: take $\tilde{p}_1$ and $\tilde{p}_2$ and define $\Delta\tilde{p} = \|\hat{p}_1 - \hat{p}_2\|$ and $\Delta\tilde{F} = \|F(\tilde{p}_1) - F(\tilde{p}_2)\|$. Assume (H5) yields $\Delta\tilde{F} \le D\,\Delta\tilde{p}$.

Now let $u_i(t)$, $v_i(a,t)$ be the solutions of (26)–(28) with $\tilde{F}$ replaced by $F(p_i(t))$, $i = 1, 2$. We have

$$\Delta u = |\, u_1 - u_2 \,| = O(t)\,\Delta\tilde{p}, \tag{35}$$

$$\Delta v = |\, v_1 - v_2 \,| = O(t)\,\Delta\tilde{p}. \tag{36}$$

Consequently

$$\Delta p = \Delta u + \int_0^A \Delta v\, da = O(t)\,\Delta\tilde{p},$$

and T can be chosen so that $O(t) < 1$, thus proving the contractivity of the mapping.

The application of Banach's fixed point theorem concludes the proof. □

We conclude this section by remarking that the proof of existence and uniqueness can be extended as long as, for $t = T$, assumptions (H2) and (H3) are fulfilled for some constants $\underline{b}$, $\bar{b}$, $\underline{C}$ and $\bar{C}$.

5. Conclusions

We have presented two families of models for the growth of tumours in the presence CSCs and of CC's. We have considered the simultaneous effect of crowding, differentiation, and ageing. First, we have considered agent-based models based on the application of cellular automata. Then, a non-hierarchical compartmental model has been presented in which the crowding effect is not included as a local effect but is averaged over the whole domain. Numerical results of simulations for the two families of models have been displayed, showing the same qualitative behaviour. In particular, we have shown in both cases the occurrence of the tumour paradox: tumours in which the death rate of the CCs is higher may have faster growth. This fact is, of course, relevant in connection with the treatment strategies and, indeed, an example has been displayed in which the killing of tumour cells may not induce, in the long run, the slowing down of the growth of the cancer.

While in the models just described, the ageing has been modelled dividing the differentiated cells in age classes, in a final section, we have considered the more general case in which there is a continuous distribution in the age of the population of the differentiated cells. The resulting mathematical model is non-standard but its being well posed has been proved.

CRediT authorship contribution statement

Luca Meacci: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Writing - review & editing. **Mario Primicerio:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Gustavo Carlos Buscaglia:** Validation, Supervision, Investigation, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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