MODELS OF CELLULAR POPULATIONS WITH DIFFERENT STATES OF ACTIVITY

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The study of a biological system made of several populations of cells and different constituents is performed. Especially, we refer to the growth of a tumoural mass in the avascular state. A general scheme of the corresponding mathematical problem is obtained and some of the most representative models in literature are discussed. We propose a new approach to the problem, based either on nonlocal interactions among the constituents or on the existence of a chemical potential driving motion of intercellular fluid.

1 Introduction

The process of tumour growth is the result of the interaction of several phenomena of chemical, biological and mechanical type, strictly coupled to each other. An appropriate approach to the problem requires with no doubt a double attention both to the microscopic scale (cellular level) and to the macroscopic one.
The medical and scientific literature pointed out a sequence of stages of tumour growth, which can be essentially summarized as follows:

- a single genetically mutated cell (cancerous cell) proliferates giving rise to a small avascular node (primary tumour);
- the nodule increases its mass by consumption of nutrient *in loco* or transferred by diffusion (avascular phase);
- in a more advanced state the tumour is able to deliver chemical agents which stimulate the formation of a capillary network (angiogenesis) transporting nutrients and inducing a new growth of the tumour mass (vascular phase);
- cancer cells are transported by the blood circulation system (intravasation);
- a new colony of cancer cells (metastasis) initiates to grow in a distant site from the original tumour and a second neoplasia initiates to develop according to the listed sequential steps.

An important feature of biological systems in which tumours evolve is the different state of activity of the cells: necrotic, quiescent and proliferating cells can usually be observed in a formed tumoural spheroid. The dynamics of transfer from one class to the other is governed by a certain number of chemical factors, or by a natural decay of part of the components.
The phenomenon of growth of tumoral systems is at the present time studied not only by researchers in medical, biological and biophysical sciences, but also by mathematicians and computer scientists.

A full mathematical description of the whole process is indeed a difficult task: models in literature concentrate the attention on a specific phase in the tumoural evolution (immune system-mutated cells competition, avascular growth, angiogenesis, metastasis,...).
Our specific interest consists in modelling the dynamics of cellular proliferation, which is a crucial step in studying tumour growth and the possibility of controlling its speed. The present paper intends to continue the study undertaken in [11], where we confined our discussion to a spatially homogeneous medium.
Even referring to the simplest situation, the mathematical model has to take into account that cells can have different states of activity with respect to replication. Moreover, a total mass balance should include, besides of cellular mass, the material which can be used to construct new cells and the material that is "useless" under this aspect.
The theoretical approach by mathematicians produced a series of models, appeared in the literature, which are based on specific assumptions adopted in order to face the problem. A conceptual idea that is often used consists in assuming that the medium is a continuum system where a number of different components coexist: by such an optics, the medium is considered as a multiphase system where processes of modification and migration of the components take place.
Generally speaking, the starting point consists in writing the mass balance for each constituent involved in the process (Section 2). The specification of the dynamical processes of transfer, production or destruction of the various components and their motions in the mixture establishes a particular model of the process: this is discussed in Sections 3 and 4.
Finally, in Section 5 we propose a different approach to the problem, trying to overcome some drastic assumptions existing in literature.

2 Mass conservation

The starting point consists in selecting the quantities involved in the biological process and writing the mass balance for each of them. We study the evolution of a population of cells and in the spirit of continuum mechanics we assume that a function $m(x,t)$ exists such that the cellular mass M_V contained in any domain V at time t is given by

$$M_V = \int_V m(\mathbf{x},t)dx.$$

We will use sometimes the term "cellular concentration" to denote funcion m.
There is no doubt that the coexistence of more than one state of the cells (highly proliferation, dormancy, prenecrosis,...) plays an important role in the tumoural growth. This can be taken into account by introducing N subclasses of cells and defining a concentration m_i, $i = 1, \ldots, N$, for each of them so that

$$m = m_1 + \ldots + m_N. \tag{1}$$

Remark 2.1 *If the number N is large enough, we can introduce, instead of the "compartments" $m_1, \ldots, m_N$ a partition index a ranging from 0 to 1 and a partition*

function of cellular activity $\varphi(a, x, t)$ *with the property*

$$\int_0^1 \varphi(a, \mathbf{x}, t)da = 1, \quad \forall t \geq 0, \tag{2}$$

and such that in any region V *the quantity*

$$\int_V \int_{a_1}^{a_2} m(\mathbf{x}, t)\varphi(a, \mathbf{x}, t)da \, \mathbf{dx}$$

corresponds to the mass of cells having index $a \in (a_1, a_2)$ *and contained in the volume* V *at time* t. *In order to make the discussion of the model more clear, we confine to the discrete compartmental model. Following the arguments we used in* [11]*, the extension to the continuous distribution is straightforward.*
The intercellular space is occupied by:

- molecules which provide cells with nourishment necessary to metabolism and with material to be synthetized for mitosis,

- "waste" material, where we include all the intercellular substances not taking part the cellular synthesis.

Let us denote by p the density of molecules of the first group and by q the density of waste products.
We also define functions $\gamma_j(\mathbf{x}, t)$, $j = 1, \ldots, K$, representing any quantity that can influence the process (e. g. temperature, radioactivity index etc.) but does not take part in the mass balance. Of course, we can also include in this family density of chemical substances that do not affect relevantly the mass balance but play a role in regulating cellular activity. In many cases, partial pressure of oxygen can be one of the γ_j's.
The conservation equations for each component (see, e. g. , [2]) can be written as follows:

$$\frac{\partial m_i}{\partial t} + \nabla \cdot \mathbf{J}_{m_i} = I_{m_i}, \quad i = 1, \ldots, N, \tag{3}$$

$$\frac{\partial p}{\partial t} + \nabla \cdot \mathbf{J}_p = I_p, \tag{4}$$

$$\frac{\partial q}{\partial t} + \nabla \cdot \mathbf{J}_q = I_q. \tag{5}$$

Equations (3)–(5) hold for $x \in \Omega$, which is the region where the process takes place, and $t \geq 0$ [a] and $\mathbf{J}$ is the flux of each constituent ($\mathbf{J} \cdot \mathbf{n}$ corresponds to the amount of mass passing through a unit surface with normal $\mathbf{n}$ in a unit time) and I is the rate of production or loss (increase or decrease of the mass of the constituent per

[a] In principle, we might introduce within the component p a number of subclasses p_i, with different rate of production and different way of acting on the metabolism of the system. However, it is likely to think that internal exchanges of mass among the p_i's are absent, so that the introduction of them in the scheme is nothing but a formal complication.

unit volume and per unit time). In particular, the terms I_{m_i} must incorporate the dynamics of transfers from one class to another.
In our point of view, the constituents m_i, $i = 1, \ldots, N$, p and q are those (and only those) which take part in the general mass balance: the increase or reduction of a single component occurs only at the expenses of the other ones (for a different approach that singles out some components of the mixture considered as an open system, see [9]). Hence, the total mass must be conserved:

$$\int_\Omega \sum_{i=1}^{N} (I_{m_i} + I_p + I_q)\, d\mathbf{x} = 0. \tag{6}$$

Assuming that (6) holds for any volume contained in Ω, i. e. assuming that all processes are localized, we write:

$$\sum_{i=1}^{N} I_{m_i} + I_p + I_q = 0. \tag{7}$$

Therefore the overall mass balance equation for the multi-component continuum formed by cells, by "useful" material and by "waste" is written as

$$\frac{\partial}{\partial t}\left(\sum_{i=1}^{N} m_i + p + q\right) + \nabla \cdot \left(\sum_{i=1}^{N} \mathbf{J}_{m_i} + \mathbf{J}_p + \mathbf{J}_q\right) = 0. \tag{8}$$

If the system occupies the entire available space (saturation), we can write:

$$\eta = \sum_{i=1}^{N} \eta_{m_i} + \eta_p + \eta_q = 1 \tag{9}$$

with

$$\eta_\alpha = \frac{\alpha}{\varrho_\alpha},\ \alpha = m_1, \ldots, m_N, p, q \tag{10}$$

specific volume of each component (volume fraction) and ϱ_α specific density (mass of the constituent in a unit volume occupied by the same constituent), which is assumed to be constant for any α.
In terms of specific volumes, the overall balance is

$$\frac{\partial \eta}{\partial t} + \nabla \cdot \left(\sum_{i=1}^{N} \frac{\mathbf{J}_{m_i}}{\varrho_{m_i}} + \frac{\mathbf{J}_p}{\varrho_p} + \frac{\mathbf{J}_q}{\varrho_q}\right) = \sum_{i=1}^{N} \frac{I_{m_i}}{\varrho_{m_i}} + \frac{I_p}{\varrho_p} + \frac{I_q}{\varrho_q} \tag{11}$$

where the first term in the left-hand side (time derivative) is zero whenever (9) holds.
In the special case of equal specific densities

$$\varrho_\alpha = \varrho, \quad \alpha = m_1, \ldots, m_N, p, q \tag{12}$$

we have that (11) coincides with (8). Moreover, if (9) holds, η is constant and (11) reduces to

$$\nabla \cdot \left(\sum_{i=1}^{N} \mathbf{J}_{m_i} + \mathbf{J}_p + \mathbf{J}_q\right) = 0 \tag{13}$$

corresponding to volume conservation.
Of course, the mass balance equations can also be written by considering the number of elements (cells, molecules, ...) in a REV as the reference variables. Assume that each element of the constituent α occupies a volume V_α and let n_α be the number of elements per unit volume. Then the following relations hold (see (10)):

$$\alpha = n_\alpha \varrho_\alpha V_\alpha = \varrho_\alpha \eta_\alpha \tag{14}$$

Thus, if both ϱ_α and V_α are constant, any of eqq. (3)–(5) writes, in terms of number of elements:

$$\frac{\partial n_\alpha}{\partial t} + \nabla \cdot \tilde{\mathbf{J}}_\alpha = \tilde{I}_\alpha \tag{15}$$

where $\tilde{\mathbf{J}}_\alpha = \mathbf{J}_\alpha / \varrho_\alpha V_\alpha$ is the number of elements passing through a unit surface per unit time, $\tilde{I}_\alpha = I_\alpha / \varrho_\alpha V_\alpha$ is the number of the elements producted (or lost) in a unit volume per unit time.
Obviously, the sum of the right-hand sides of (15) (written for each component) generally is not zero, but, according to (7)

$$\sum_\alpha \varrho_\alpha V_\alpha \tilde{I}_\alpha = 0 \tag{16}$$

3 Modelling the problem

To avoid irrelevant formal complications we assume (12), so that the saturation assumption (9) takes the form

$$\sum_{i=1}^{N} m_i + p + q = 1. \tag{17}$$

The set of $N + 2$ equations (3)–(5) with the constraints (7) and (17) contain the $N + K + 2$ unknown quantities m_i, p, q, γ_j for $i = 1, \ldots, N$, $j = 1, \ldots, K$. We also assume to know the K equations governing the evolution of the quantities γ_j. At this moment, to complete the model we have to give the constitutive assumptions in order to specify:

1. the production and destruction terms I_{m_i}, I_p, I_q,
2. the mass fluxes $\mathbf{J}_{m_i}$, $\mathbf{J}_p$, $\mathbf{J}_q$.

We are going to examine the two aspects separately.

3.1 Production and destruction

As to point 1, the quantities I_{m_i}, $i = 1 \ldots, N$, I_p and I_q have to take account at least of the following main biological processes:

(i) proliferation of cells by mitosis: this requires necessary elements which are supplied by p,

(*ii*) death of cells, which can either be recycled as available material (component p) or become waste material q,

(*iii*) metabolism of the living cells, at expenses of molecules p; the "burned" material appears as waste material q.

(*iv*) transitions from one class m_i to another.

Each of these processes can be stimulated or inhibited by the factors γ_j.
Generally speaking, we expect that I_{m_i} is a function of $m_1, \ldots, m_N$ of p and q (for istance in case of catabolism), of the factors γ_j, $j = 1, \ldots, K$, which may affect the rate of reproduction or decay of cells, of the position $\mathbf{x}$ and of time t. In a more general context, we may assume that the state of the system in a position x is affected by a neighbourhood of the point: nonlocal effects will be discussed in Section 5.
To be more specific, assuming that the transition from one class m_i, $i = 1, \ldots, N$, to another is istantaneous, we write:

$$I_{m_i} = \sum_{l=1}^{N} \nu_{i,l} F_l - \mu_i + \sum_{l=1}^{N} (\tau_{l \to i} - \tau_{i \to l}) \tag{18}$$

where

– each F_l denotes the proliferation of class l (new cellular originating from proliferation of cells of the l-th class per unit time and unit volume, at time t and position x): part of the newborn cells belongs to class i according to a distribution function $\nu_{i,l}$. Obviously, it is

$$\sum_{l=1}^{N} \nu_{i,l} = 1 \tag{19}$$

for each $l = 1, \ldots, N$; in a situation where each class produces only cells of the same class, we have simply $\nu_{i,l} = \delta_{i,l}$, with $\delta_{i,l}$ Kronecker's symbols.

Moreover, following a philosophy of "mass action" law, we may set (as it is often the case in literature)

$$F_l = f_l(p, q, \gamma_1, \ldots, \gamma_K, x, t) m_l. \tag{20}$$

– The quantity μ_i refers to cell death in the i class (loss of mass per unit time and volume in (x, t)), due either to necrosis or apoptosis, or to the action of some factor γ_j; in analogy with (20), one could set

$$\mu_i = \bar{\mu}_i(p, q, \gamma_1, \ldots, \gamma_K, x, t) m_i. \tag{21}$$

– $\tau_{l \to i}$ is the rate of cellular mass transfer from class l to class i; such terms describe the internal dynamics within the population m; it is clear that $\tau_{l \to i}$ must vanish for m_l going to zero: its simplest form (with respect to m_l) will be

$$\tau_{l \to i} = \lambda_{i,l}(p, q, \gamma_1, \ldots, \gamma_K, x, t) m_l \tag{22}$$

Finally, recalling points (i)–(iii), the production and loss terms I_p and I_q can be written

$$I_p = -\sum_{i,l=1}^{N} \nu_{i,l} F_l + \sum_{i=1}^{N} \omega_i \mu_i - \sum_{i=1}^{N} G_i \tag{23}$$

$$I_q = \sum_{i=1}^{N} (1-\omega_i)\mu_i + \sum_{i=1}^{N} G_i \tag{24}$$

where the first sum in (23) corresponds to the molecules necessary to mitosis of cells, the second sum takes into account the fraction ω_i ($0 \leq \omega_i \leq 1$, $i = 1 \ldots, N$) of the mass of dead cells which can be recycled, while G_i is the rate at which molecules p are burned (in metabolic processes) by the cells of the i-th class. The meaning of the terms in (24) is evident.

3.2 Mass fluxes

Point 2 introduced at the beginning of this Section represents indeed a difficult step in modelling the process. Actually, to formulate constitutive laws modelling the fluxes of m_i, $i = 1, \ldots, N$, p and q in terms of the concentrations and possibly of their derivatives appears a complex task.
Let us denote by α any of the "populations" m_i, $i = 1, \ldots, N$, p, q), so that (3), ..., (5) writes

$$\frac{\partial \alpha}{\partial t} + \nabla \cdot \mathbf{J}_\alpha = I_\alpha. \tag{25}$$

In analogy with the approach commonly used in the theory of mixtures (see [2]), one could write:

$$\mathbf{J}_\alpha = \alpha \mathbf{v}_\alpha - \sum_{\bar{\alpha}} D_{\alpha,\bar{\alpha}} \nabla \bar{\alpha} \tag{26}$$

where $\mathbf{v}_\alpha$ would represent a drift (or convective) velocity while the second term denotes diffusion. Thus, the balance equation (3), ..., (5) writes

$$\frac{\partial \alpha}{\partial t} + \nabla \cdot (\alpha \mathbf{v}_\alpha) - \nabla \cdot \left(\sum_{\bar{\alpha}} D_{\alpha,\bar{\alpha}} \nabla \bar{\alpha} \right) = I_\alpha \tag{27}$$

Using (26) extensively in the model of cellular dynamics seems not completely appropriate. For instance, one could postulate the presence of an inert intercellular liquid in which the populations p and q diffuse (more disputable would be assuming a relevant role of diffusion in the motion of the cells); but in such case the concentrations whose gradients drive the diffusion would be the concentrations of p and q relative to the intercellular liquid.
In any case, whenever (26) is assumed, condition (11) (possibly, in its particular form (13)) gives a condition that has to be fulfilled.

4 Closing the problem

At this point, the strategy that can be pursued can follow one of the lines:

(a) completing the set of equations with the momentum balance,

(b) introducing some specific assumptions, that allow to describe movements of the components of the system.

4.1 Momentum balance

Point (a) requires a complete description of the dynamics of the system. We have to write for a generic component α:

$$\frac{\partial(\alpha \mathbf{v}_\alpha)}{\partial t} + \nabla \cdot \left(\bar{\mathbf{J}}_\alpha\right) = \bar{\mathbf{I}}_\alpha \tag{28}$$

where the second-rank tensor $\bar{\mathbf{J}}_\alpha$ is the flux of momentum of the component α and $\bar{\mathbf{I}}_\alpha$ is the rate of production of the momentum density $\alpha \mathbf{v}_\alpha$.
One usually writes (see, for istance, [9]):

$$\bar{\mathbf{J}}_\alpha = \alpha \mathbf{v}_\alpha \otimes \mathbf{v}_\alpha - \mathbf{T}_\alpha \tag{29}$$

$$\bar{\mathbf{I}}_\alpha = \alpha \mathbf{b} + \mathbf{Q}_\alpha + I_\alpha \mathbf{v}_\alpha \tag{30}$$

where in (29) $\otimes$ is the diadic product of the two vectors, $\mathbf{T}_\alpha$ is the Cauchy partial stress tensor, due to the co-presence of the other constituents, in (30) $\mathbf{b}$ refers to the body forces and $\mathbf{Q}_\alpha$ is the momentum supply referring to the mutual interactions of the constituents. The last term in (30) is the momentum supply which corresponds to the production of mass from one component to the other. Furthermore, it is required that

$$\sum_\alpha \left(\mathbf{Q}_\alpha + I_\alpha \mathbf{v}_\alpha\right) = 0 \tag{31}$$

Note that, owing to (25), Eq. (28) (with assumptions (29) and (30)) can be written also in the following way:

$$\alpha \left(\frac{\partial \mathbf{v}_\alpha}{\partial t} + \nabla \cdot (\mathbf{v}_\alpha \otimes \mathbf{v}_\alpha) \right) = \alpha \mathbf{b} + \mathbf{Q}_\alpha. \tag{32}$$

The problem consists at this point in linking the quantities appearing in (32) with the external forces and the stress tensor. For istance, in the "growing porous media" model of [1] (where $N = 1$ and $q \equiv 0$) material p is assumed to behave like a liquid moving in a porous material formed by the cells. Chemical factors γ_j are assumed to diffuse with respect to the moving liquid medium [b]. The mathematical problem consists in Eqs. (25) for m and p, diffusion equations (27) for γ_j and the two momentum equations (32) for m and p, where inertial and external terms are neglected to express $\mathbf{J}_\alpha = \alpha \mathbf{v}_\alpha$. Moreover, constitutive equations for the $\mathbf{T}_\alpha$ and $\mathbf{Q}_\alpha$ are to be assumed. In [1] the system is considered as an elastic viscous fluid, with the constraint (13), written only for the two constituents m and p and assuming (9).

[b] Or, rather, they diffuse with respect to the system liquid + cells since γ_j represent the concentrations with respect to the total volume and not to the volume of the liquid

4.2 Specific assumptions

A. Consider the special case $N = 1$ and assume that m occupies a constant volume fraction (i. e. η_m constant, see(10), or $m \equiv m_0$, constant). This corresponds to claim that at any point x wherever cells are present there is a fixed number of cells per unit volume. Equation (3) becomes $\nabla \cdot \mathbf{J}_m = I_m$. If the population does not diffuse, we have

$$\nabla \cdot \mathbf{v}_m = I_m. \tag{33}$$

Equation (33) says that the volumetric increase of any region in which m has the given concentration m_0 is determined by the proliferation rate. Assume I_m is given (possibly as a function of position and/or concentration of nutrients or inhibitors, see, for instance, [3]). Then, if spherical (or cylindrical, or planar) symmetry is postulated, (33) gives the growth rate of the spheroid occupied by proliferating cells. Note that in this approach no role is played by material p that is assumed to be always present in the quantity needed to fulfill mass balance.

B. Still referring to a symmetry assumption, eq. (25) reduces to:

$$\frac{\partial \alpha}{\partial t} + \frac{1}{r^{n-1}} \frac{\partial}{\partial r} \left(r^{n-1} J_\alpha \right) = I_\alpha \tag{34}$$

($n = 1, 2, 3$ for planar, cylindrical and spherical symmetry respectively) where $J_\alpha = \mathbf{J}_\alpha \cdot \mathbf{e_r}$, with $\mathbf{e_r}$ unit vector along the relevant direction.
In model [5] where the evolution of tumoural cords is studied, three population m_1 (viable cells), m_2 (dead cells) and p (intercellular material) are assumed to saturate the medium. The internal dynamics is defined by the death rate of cells m_1 thus passing to population m_2 (owing to spontaneous death, to chemical agents and to treatment by radiation), by cell proliferation (p towards m_1) and decay of dead cells (m_2 towards p). The concentration of a subsance γ (oxygen) with negligible mass determines the behaviour of the tumoural cells: threshold values of γ establish the boundaries of regions of fully proliferating, quiescent and dead cells, or a mixture of them. Such a point of view is assumed also in several models where the analytical problem (typically, reaction-diffusion equations for γ in free domains) is studied (see, among others, [6], [7]).
The constitutive assumptions are $\mathbf{v}_{m_1} = \mathbf{v}_{m_2}$ and η_p constant (hence η_m constant, by virtue of (9)). By means of (12), one finds:

$$\nabla \cdot (\eta_m \mathbf{v}_m + \eta_p \mathbf{v}_p) = 0 \tag{35}$$

where $\eta_m = \eta_{m_1} + \eta_{m_2}$ and $\mathbf{v}_m = \mathbf{v}_{m_1} = \mathbf{v}_{m_2}$.
The spherical symmetry of the problem allows to determine the velocities by using (35) and (34), which reduces to

$$\frac{\eta_m}{r^2} \frac{\partial}{\partial r}(r^2 v_m) = \frac{1}{\varrho_m}(I_{m_1} + I_{m_2}) \qquad \frac{\eta_p}{r^2} \frac{\partial}{\partial r} \left(r^2 v_p \right) = \frac{I_p}{\varrho_p}.$$

with $\varrho_m = \varrho_{m_1} = \varrho_{m_2}$. Nevertheless, the problem presents in general cases relevant difficulties since I_{m_1} and I_{m_2} exhibit, in practical cases, nontrivial dependence om m_1 and m_2 and the concentration of oxygen.

C. In the model [12] $N = 1$ and $q \equiv 0$. The evolution of a nutrient γ (with negligible mass) affects the dynamics of the process. The living cells m and the recycled material p are assumed to saturate all the available space ((9) holds with η_m and η_p). Eqs. (15) are considered and the terms $\tilde{I}_m$, $\tilde{I}_p$ are modeled by assuming specific relations between the volume of one cell of m and one molecule of p. The drift velocities in (26) are assumed to be equal:

$$\mathbf{v}_m = \mathbf{v}_p = \mathbf{v}.$$

Moreover, a diffusion for p and γ according to Fick's law is postulated.
The drift velocity $\mathbf{v}$ can be determined by means of (see (11) and (15))

$$\nabla \cdot \mathbf{v} = \nabla \cdot (D_p \nabla p) + V_m \tilde{I}_m + V_p \tilde{I}_p$$

where D_p is the diffusivity of material p and V_m, V_p are the volume of a living cell and of a molecule of basic material. It is assumed that a total volume of λV_p of cellular material is required for mitosis. Assuming spherical symmetry of the model provides the closure of the problem. The tumoural spheroid is assumed to expand at the velocity $\mathbf{v}$ and a Robin-type boundary condition (according to which the flux of material p at the boundary is proportional to the jump of concentration) is assumed to hold.

5 A different approach

In the schemes we just described two facts are evident:

(i) the expansion of the tumoural mass is ascribed to the velocity of cells m_i, $i = 1, \ldots, N$,

(ii) threshold values for quantities not entering mass balance define moving/free boundaries which determine the regions of specific type of cells (in full activity, quiescent, ...). The models link the velocities of such boundaries to the velocity fields of the components (for istance, decide whether a boundary is a material surface or not).

Following a different idea and allowing m_i, p and q to depend on x and t, we may think of models incorporating in the balance equations a mechanism of expansion. We will pursue this goal by proposing two alternative ways:

(i) introduce nonlocal (spatially) effects of the cells m,

(ii) relate the movement of intercellular material to the gradient of a "chemical potential".

For the sake of simplicity, let us consider only one class of cells m ($N = 1$) for tumoural cells, one type of a diffusing chemical factor γ ($K = 1$) and assume that the system is saturated, satisfies (12) and a presents planar simmetry. As we anticipated, these assumptions make the presentation more transparent but could be easily relaxed. We write again the balance equations (see (34), $n = 1$):

$$\frac{\partial \alpha}{\partial t} + \frac{\partial J_\alpha}{\partial x} = I_\alpha, \qquad \alpha = m, p, q \tag{36}$$

with the constraint $m+p+q = 1$, or, equivalently (see (13)), $J_q = -(J_m+J_p)+h(t)$, where h is determined by means of the boundary conditions.
Let us examine points (i) and (ii) in detail.

5.1 Nonlocal interactions

During the process of mitosis, the duplicated cell has to seetle itself in some space adjacent to the generating cell. The "search of space" of a living cell m corresponds to the consumption of material p in some neighbourhood of the cell. The birth of a new cell in position x depends on the availability of material p in x and on the presence of cells m in the vicinity. Thus, we model the proliferating term I_m in the following way:

$$I_m = p \int_{-\infty}^{+\infty} K(x, \xi, t)\mathcal{F}(m, q)d\xi - \mu(x, t, m, p, q) \tag{37}$$

where K is a positive with compact support function (say $K(x, \xi) \equiv 0$ for $|x-\xi| \geq \delta$ for some $\delta > 0$), $\mathcal{F}$ going to zero with m. This approach is similar to the one proposed for spread of infections in spatially heterogeneous regions ([10]).
Let us take $J_m = 0$ and $J_p = 0$: we thus assume that cells movement does not play any role in the mechanism of expansion, which is on the contrary incorporated in the proliferating term for m.
Following such an idea, we write the mathematical problem (3)–(5) in the following form:

$$\begin{aligned}
&\frac{\partial m}{\partial t} = p \int_{-\infty}^{+\infty} K(x, \xi, t)\mathcal{F}(m, q)d\xi - \mu(x, t, m, p, q) \qquad (38)\\
&\frac{\partial p}{\partial t} = -p \int_{-\infty}^{+\infty} K(x, \xi, t)\mathcal{F}(m, q)d\xi + \omega\mu(x, t, m, p, q) - G(x, t, m, p, q)\\
&q = 1 - (m + p)
\end{aligned}$$

In order to treat system (38) mathematically, one may start by following the same approach as in [4], [8], by writing the Taylor's series of the functional $\mathcal{F}$ (w. r. t. x) and reduce system (38) to its diffusive approximation (nonlinear parabolic equations).

5.2 Chemical potential

An alternative approach that allows to by-pass the momentum equations (without introducing a free boundary separating a region in which there are no cells from another in which the number of cells per unit volume is constant) consists in postulating that the intercellular material p and q can be assimilated to a fluid that moves under the effect of a chemical potential Φ.

It seems to be natural to think that a more intense reproduction activity of cells m attracts a larger number of molecules p, which are needed for reproduction and survival. Actually, cells "drain" from their environment the molecules they need to synthesize proteins and other macromolecules. Thus, it seems reasonable to assume that Φ is proportional to the proliferation rate defined as the first term in (18). Moreover, we postulate that the gradient of Φ acts on p and q without distinction:

$$\mathbf{J}_p + \mathbf{J}_q = K\nabla\Phi. \tag{39}$$

Equation (39) is a sort of Darcy's law and actually K plays a role of a permeability function. It is reasonable to assume that it drops to zero if m exceeds a threshold value $\bar{m}$:

$$K(m) > 0 \quad for\ 0 \le m < \hat{m}, \tag{40}$$

$$K(m) = 0 \quad for\ \hat{m} < m \le 1, \tag{41}$$

Assumption (40) corresponds to postulate that crowding of the cells m inhibits the supply of p.
If $\mathbf{v}$ is the local speed of the intercellular fluid, we have

$$\mathbf{J}_p = p\mathbf{v}, \qquad \mathbf{J}_q = q\mathbf{v} \tag{42}$$

and we have that Eq. (39) (together with (9) and (12)) allows to close the system with no need of postulating any symmetry, since, from (13), one gets (assume $N = 1$):

$$\nabla \cdot \mathbf{J}_m = -\nabla \cdot (K\nabla\Phi). \tag{43}$$

Indeed, for $N = 1$ we find the following system for m and p:

$$\frac{\partial m}{\partial t} - \nabla \cdot (K\nabla\Phi) = F - \mu$$
$$\frac{\partial p}{\partial t} + \nabla \cdot \left(\frac{p}{1-m} K\nabla\Phi\right) = -F + \omega\mu$$

where the functions K, Φ, F and μ depend on m, p and $q = 1 - (m + p)$.
If more than one class of cells m is present ($N > 1$), one may postulate that Φ is proportional to the sum of the proliferation rates F_i, $i = 1, \ldots, N$ (see (18)). On the other hand, it can be assumed (similarly to (42))

$$\mathbf{J}_{m_i} = m_i\mathbf{u}, \quad i = 1, \ldots, N \tag{44}$$

so that only two drift velocities $\mathbf{u}$ (for the cells) and $\mathbf{v}$ (for the intercellular material) are introduced in the model. Assumption (44) allows to close the problem also in this case, since the balance equation for the populations m_i, $i = 1, \ldots, N$ writes:

$$\frac{\partial m_i}{\partial t} - \nabla \cdot \left(\frac{m_i}{m} K\nabla\Phi\right) = I_{m_i} \tag{45}$$

where $m = \sum_{i=1}^{N} m_i$. Of course, this is not enough to claim that the problem has one and only one solution, but the analysis of the full model is beyond the scope of this

presentation and will be discussed in a future paper. Nevertheless, we can see how the solution looks like in very special simple cases.
We assume planar symmetry (in order to keep the equation formally simpler), we take $N = 1$ and $q \equiv 0$. Therefore we have $m = 1 - p$ and (see (43)):

$$J_m = -K\frac{\partial}{\partial x}\Phi(m,p) = -\Psi(m)\frac{\partial m}{\partial x}$$

with

$$\Psi(m) = K(m)\left(\frac{\partial \Phi}{\partial m}(m,1-m) - \frac{\partial \Phi}{\partial p}(m,1-m)\right) \tag{46}$$

and the equation for $m(x,t)$ has the form

$$\frac{\partial m}{\partial t} - \frac{\partial}{\partial x}\left(\Psi(m)\frac{\partial m}{\partial x}\right) = F(m,1-m) - \mu(m,1-m). \tag{47}$$

Eq. (47) is a nonlinear parabolic equation degenerating for $m \geq \hat{m}$ (see (40)) and possibly for $m = 0$, according to the specific form of the function Φ. This fact may allow for a finite speed of the line $m = 0$ in the (x,t)–plane and at $m = \hat{m}$ where the "crowding" effect inhibits the percolation of intercellular liquid.
Thus the problem is reduced to solving a degenerate parabolic equation with suitable initial and boundary data.
It is easy to see that assumption $q \equiv 0$ is not crucial and can be released. The presence of diffusing substances γ_j can also be taken into account without affecting the structure of the mathematical problem.
Difficulties increase if $N > 1$, i. e. when cells can be encountered in different states, because in this case Φ is determined by the sum of the proliferating rate of each "population" and the degeneration of the i-th equation may depend not on i but on $\sum_i m_i$. Leaving this question aside we present a numerical simulation of (47) in order to emphasize what we sketched above.

5.3 A numerical simulation

The undertaking study of the nonlinear process started by a simple numerical simulation for Eq. (47) which generates the graphs of Figure 1 for the cells m. The input data are:

$$\Phi(m,p) = F(m,p) = mp, \quad \mu(m,p) = 0, \tag{48}$$

$$K(m) = (m - \frac{1}{4})^4\mathcal{H}(1-4m) \quad for\ 0 \leq m \leq 1, \tag{49}$$

$$m(x,0) = (\frac{1}{8} - x^2)\mathcal{H}(\frac{\sqrt{2}}{2} - x), \quad 0 \leq x \leq 1, \tag{50}$$

$$\frac{\partial m}{\partial x}(0,t) = \frac{\partial m}{\partial x}(1,t) = 0 \quad for\ t \geq 0. \tag{51}$$

In (49) and (50) $\mathcal{H}$ is the Heaviside step function. The threshold $\hat{m}$ (see (40)) is $\frac{1}{4}$, while (see (46))

$$\Psi = (m - \frac{1}{4})^4(1-2m) \quad for\ 0 \leq m \leq \hat{m}, \quad \Psi = 0 \quad for\ \hat{m} < m \leq 1.$$

The initial profile (50) is under the threshold $\hat{m}$ for any $x \in [0,1]$. The boundary conditions (51) correspond to the absence of flux at $x = 0$ and $x = 1$.

Figure 1. A simulation for Eq. (47) with the specified data. The lower function corresponds to $m(x,0)$. The increasing profiles of $m(x,t)$ are plotted for 10 sequential times.

The sequence of profiles of $m(x,t)$ is shown in Fig. 1, for different values of t, suggests a finite speed of the front $m = 0$. When m exceeds the threshold $\hat{m}$, the flux of cells stops (due to crowding) but their concentration still increases, tending to the saturation $m = 1$.
Note that in this case equation (47) does not degenerate for $m = 0$, because of the choice (48).

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