DISCRETE AND CONTINUOUS COMPARTMENTAL MODELS OF CELLULAR POPULATIONS

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We consider a biological system where several families of cells, differentiated by their activity state and reaction to external factors acting on the system, are present. The dynamics of cell populations is modelled by a compartmental approach, starting from the case of finite number of classes and passing to the continuum range of the variables. In a frame of special attention devoted to the mass balance, the evolution of the system is described by the variation of mass of each species. The well-posedness of the mathematical models is proved.

1. Introduction

Modelling the dynamics of cellular proliferation is a crucial step in studying tumour growth and the possibility of controlling its speed. In the macroscopic description of the formation of solid tumours, even at their early avascular state, it appears that the model should (i) incorporate a correct mass balance including all the molecules that take part in the synthesis of the different cellular components during the cycle leading to mitosis, as well as in the metabolic processes, (ii) take into account density variations occurring during the processes, thus inducing dilatation or shrinkage, (iii) postulate suitable easily verifiable laws relating mechanical quantities.

The three tasks sketched above are far from being trivial and many efforts have been made in recent years.[1−4] Although symmetry assumptions simplify discussion to a large extent, the complexity introduced in order to take into account (ii) and (iii) can result in paying less attention to point (i) and to assume — more or less implicitly — that the substances used by the cells to duplicate themselves are

always "abundant" and do not enter the mass balance significantly. Instead, our point of view is to depict the formation of a new cell as the passage of a given mass of molecules to a higher degree of organization.

In order to isolate difficulties, we decided to focus our attention to point (i) and to disregard, throughout the paper, space variation of the relevant quantities. The resulting model (rather, the resulting models) will be a starting point for future research in which more complex aspects will be encompassed.

It can be noted that the models we will discuss here can be seen as a generalization of models for the dynamics of homogeneous age-structured populations[5,6] and that the continuous model presented at the end of Sec. 3 is in the spirit of the Boltzmann-like approach adopted e.g. in Refs. 7 and 8.

The scheme of the paper is the following: in Sec. 2 we introduce a basic compartmental model in which the cells are divided in N different groups according to their biological activity. Different possible assumptions are presented to describe the dynamics of variations of the distribution among the N groups. In Sec. 3 cellular activity is considered to be a continuous variable. Models are presented and discussed in strict analogy with Sec. 2. Sections 4 and 5 are finally devoted to the proofs of well-posedness of the models.

2. Compartmental Models

According to the arguments above, the mass entering the general mass balance can be classified in three main types:

(i) material organized and forming cells: its mass will be denoted by $m(t)$,
(ii) molecules that are available to the living cells either to feed their metabolism or to provide with the necessary elements for mitosis: their total mass will be denoted by $p(t)$,
(iii) molecules that cannot be used to form new cells nor to be "burned" in the metabolic processes. They are simply waste. Their total mass will be denoted by $q(t)$.

Within each of the three types above, suitable subclasses could be identified. From the point of view of the resulting mathematical model, introducing N_p subclasses in the second group and/or N_q subclasses in the third group is irrelevant and introduces only formal complications that we will avoid in order to stress the main features of the problem. On the other hand, it is often biologically relevant to classify living cells according to their "biologic activity", which is essentially reflected in their proliferating capacity, death rate, metabolic balance: therefore fully proliferating cells will be distinguished from quiescent, pre-necrotic, etc. We will assume that N groups of cells can be identified and the total mass of the cells in each group will be denoted by $m_1(t), m_2(t), \ldots, m_N(t)$, so that

$$m(t) = \sum_{i=1}^{N} m_i(t) \tag{2.1}$$

and hence, if $f_i(t) = m_i(t)/m(t)$ is the fraction of mass in the ith class, it is

$$\sum_{i=1}^{N} f_i(t) = 1 \,. \tag{2.2}$$

Let us write the mass balance in the three types assuming that the duration of the cellular cycle is negligible w.r.t. the time scale of the phenomenon

$$\frac{dm}{dt} = \sum_{i=1}^{N} m_i(F_i - \mu_i) \,, \tag{2.3}$$

$$\frac{dp}{dt} = \sum_{i=1}^{N} m_i(\alpha\mu_i - F_i - G_i) + Q \,, \tag{2.4}$$

$$\frac{dq}{dt} = \sum_{i=1}^{N} m_i((1 - \alpha)\mu_i + G_i) \,, \tag{2.5}$$

where F_i and μ_i represent respectively the proliferation and death rate in the ith cellular state, $\alpha, 0 \leq \alpha \leq 1$, is the fraction[a] of the mass of dead cells which can be used in metabolism and replication (catabolism is considered to be immediate), G_i is the rate at which molecules of the class p are burned by the cells of the ith state and transformed in waste, and Q is external supply rate (oxygen, nutrients, etc.). Quantities μ_i, F_i, G_i will certainly depend on p and possibly on q ("catabolitic poisoning").

We can also assume that they depend on another quantity $\gamma(t)$ representing external inputs such as the presence of drugs or other substances that do not enter the mass balance. From a conceptual point of view there is no difficulty in considering $\gamma(t)$ as an array of quantities $\gamma_1(t), \ldots, \gamma_s(t)$.

Remark 1. Obviously, if $Q \equiv 0$, the material system is closed and summing up (2.3)–(2.5) we find that $M = m(t) + p(t) + q(t)$ is constant. On the other hand, since the model is spatially homogeneous, it is reasonable to assume that whenever interactions with the outer environment exist, they can be described by a distributed source term $Q(t)$ so that $\frac{dM}{dt} = Q(t)$. This is in the same spirit of the mechanism smoothing the spatial dishomogeneity we have introduced.

Remark 2. We note that the structure of the dynamical system does not change if $\gamma = (\gamma_1, \ldots, \gamma_s)$ is not assigned as a function of time but it is a given function of m_i, p, q, t or even if its time derivative is a prescribed function of the same arguments so that γ becomes itself one of the state variables.

We also remark that the equations of the model should incorporate time delays whenever the dynamics is such that cellular cycle and/or metabolic and catabolic processes have durations that are not negligible with respect to the time scale of

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[a]In principle to each ith state we could associate an α_i; complication is just formal.

the experiment. This remark applies to the models discussed in this section as well as to the continuous model of Sec. 3.

Next step is to describe the evolution within the ith compartment of the system. We will consider two different points of view: on one hand the mass fractions $f_i, i = 1, \ldots, N$ can be assumed to be prescribed or related to some equilibrium configuration (Sec. 2.1); on the other hand the balance in each compartment can be formulated by taking into account the biological and chemical processes occurring in each class and of the mass transition from a class to another (Sec. 2.2).

2.1. *Prescribed equilibrium distribution*

A simple assumption consists in prescribing the mass fractions $\{f_1, f_2, \ldots, f_N\}$ as given functions of (time and of) $\gamma(t)$

$$f_i(t) = \bar{f}_i(\gamma(t), t), \quad i = 1, 2, \ldots, N. \tag{2.6}$$

Hence we write in (2.3)–(2.5)

$$m_i(t) = m(t)\bar{f}_i(\gamma(t), t), \tag{2.7}$$

and we solve system (2.3)–(2.5) in the three unknown functions $m(t), p(t), q(t)$.

A relatively more sophisticated approach, within the same general philosophy, would consist of assigning an equilibrium distribution $\{\bar{f}_1, \bar{f}_2, \ldots, \bar{f}_N\}$ for any given γ and assuming that each mass fraction f_i relaxes to equilibrium with a given time τ_i constant

$$\frac{df_i}{dt} = \frac{1}{\tau_i}(f_i(t) - \bar{f}_i(\gamma)), \quad i = 1, \ldots, N. \tag{2.8}$$

Thus, the phenomenon is described by (2.3)–(2.5) and (2.8), once γ is prescribed together with the kinetic functions and data.

Equation (2.8) can be generalized to the following situation:

$$\frac{df_i}{dt} = \mathcal{F}_i(f_i(t), \gamma(t), t), \tag{2.9}$$

where $\mathcal{F}_i$ are functions (or even functionals) of their arguments.

2.2. *Prescribed transition dynamics*

A different approach consists of studying the transitions of cells from one compartment to another as it is usual in compartmental systems. Thus, one writes for $i = 1, 2, \ldots, N$

$$\frac{dm_i}{dt} = \nu_i \sum_{k=1}^{N} F_k m_k - \mu_i m_i + \sum_{k=1}^{N} (P_{k \to i} - P_{i \to k}), \tag{2.10}$$

where $(\nu_1, \nu_2, \ldots, \nu_N)$ is the distribution of the newborn cells in the compartments and $P_{j \to l}$ is the rate of cellular mass transfer from compartment j to compartment l. Obviously, it must be

$$\sum_{i=1}^{N} \nu_i = 1 \,. \tag{2.11}$$

We remark that summing up Eqs. (2.9) with respect to i leads to the global balance (2.3), as we expect.

Concerning $P_{j \to l}$, it is clear that it has to go to zero with m_j and hence its simplest form will be

$$P_{j \to l} = \lambda_{j \to l} m_j \,. \tag{2.12}$$

Moreover, it is usual to assume that transfer is possible only from and to adjacent compartments, i.e. $\lambda_{j \to l} = 0$ if $|j - l| \neq 1$ and we use the following notation

$$\lambda_{k \to k+1} = v_k \,, \quad k = 1, \ldots, N - 1 \,, \tag{2.13}$$

$$\lambda_{k \to k-1} = g_k \,, \quad k = 1, \ldots N \,. \tag{2.14}$$

If we define

$$v_N = 0 \,, \quad g_1 = 0 \,, \tag{2.15}$$

then (2.13) can be written for any $k = 1, \ldots, N$ and (2.10) becomes

$$\frac{dm_i}{dt} = \nu_i \sum_{k+1}^{N} F_k m_k - \mu_i m_i + v_{i-1} m_{i-1} - v_i m_i + g_{i+1} m_{i+1} - g_i m_i \,, \tag{2.16}$$

hold for any $i = 1, \ldots, N$, if we set

$$v_0 = 0 \,, \quad g_{N+1} = 0 \,. \tag{2.17}$$

We conclude this section by noting that transfer coefficients v_j and g_j (as well as mortality fraction ν_j) can be assigned as functions of $\gamma(t)$.

Of course, (2.3) is a consequence of the differential Eqs. (2.10).

3. Models with Continuous Distribution of Cellular Activity

As is usually done when the number of levels of cellular activity that has to be taken into account is large enough, we will introduce an index of cellular activity a, ranging from 0 to 1 and we will denote by $\varphi(a, t)$ the partition function of cellular mass, such that

$$\int_0^1 \varphi(a, t) da = 1 \,, \quad \forall\, t \geq 0 \,. \tag{3.1}$$

The mass of cells with activity state between a_1 and a_2, $0 \leq a_1 < a_2 \leq 1$, is $m(t) \int_{a_1}^{a_2} \varphi(\eta, t) d\eta$.

It is easily found that system (2.3)–(2.5) is replaced by

$$\frac{dm}{dt} = m(t) \int_0^1 \varphi(a,t)(F(a,\ldots) - \mu(a,\ldots))da\,, \tag{3.2}$$

$$\frac{dp}{dt} = m(t) \int_0^1 \varphi(a,t)(\alpha\mu(a,\ldots) - F(a,\ldots) - G(a,\ldots))da + Q(t)\,, \tag{3.3}$$

$$\frac{dq}{dt} = m(t) \int_0^1 \varphi(a,t)((1-\alpha)\mu(a,\ldots) + G(a,\ldots))da\,, \tag{3.4}$$

where the dots in the arguments denote the possible dependence of the kinetic parameters on the state variable p, q, m and on t and $\gamma(t)$ (as pointed out in Remark 2.1 γ — or $\gamma_1, \gamma_2, \ldots, \gamma_s$ — becomes a state variable if it is not a given function but its evolution in terms of the other variables is prescribed).

The closure of the system (3.2)–(3.4) requires some additional information on $\varphi(a,t)$. As in the previous section the simplest situation occurs when it is possible to assume that an equilibrium partition between the activity states exists for any given external situation $\gamma(t)$ and that this partition is reached either instantaneously or through a relaxation kinetics. The two assumptions above correspond to

$$\varphi(a,t) = \bar{\varphi}(a, \gamma(t), t) \tag{3.5}$$

or

$$\frac{\partial \varphi}{\partial t} = \frac{1}{\tau}(\varphi(a,t) - \bar{\varphi}(a, \gamma(t), t))\,, \tag{3.6}$$

or, more generally, $\frac{\partial \varphi}{\partial t} = \mathcal{F}(\varphi, \gamma, t)$

On the other hand, it may be more appropriate to adopt the point of view of Sec. 2.2, i.e. to prescribe the internal transition between different states. In this case, the evolution equation for φ is written in analogy with Eq. (2.9) (with assumption (2.10)):

$$\frac{\partial}{\partial t}(m(t)\varphi(a,t))$$

$$= \nu(a,\ldots)m(t)\int_0^1 F(\eta,\ldots)\varphi(\eta,t)d\eta - m(t)\varphi(a,t)\mu(a,\ldots) + m(t)$$

$$\times \left(\int_0^1 \varphi(\eta,t)\tau(\eta,a,\ldots)d\eta - \int_0^1 \varphi(a,t)\tau(a,\eta,\ldots)d\eta \right)\,, \tag{3.7}$$

where we denoted the transfer function (which replaces $P_{l \to j}$) by $\tau(a, \eta, \ldots)$. The newborn cells distribution function ν must verify (compare with (2.11))

$$\int_0^1 \nu(a,\ldots)da = 1\,. \tag{3.8}$$

On the other hand, if one admits transfers only by contiguous states, then instead of the "scattering" term (last term in (3.7)) one has a "streaming" term of the form (see (2.12) for comparison)

$$m(t) \left(\frac{\partial}{\partial a}\varphi(a,t)g(a,\dots) - \frac{\partial}{\partial a}\varphi(a,t)v(a,\dots) \right), \tag{3.9}$$

where we denoted the transfer functions by g and v to stress the analogy with the discrete case of Sec. 2.2. Of course we can rewrite the term (3.9) as

$$m(t)\frac{\partial}{\partial a}\varphi(a,t)\Gamma(a,\dots), \tag{3.10}$$

with the obvious constraints (corresponding to (2.15) and (2.17) in the discrete case)

$$\Gamma(0,\dots) = \Gamma(1,\dots) = 0. \tag{3.11}$$

We conclude this section by remarking that integrating (3.7) with respect to a in (0,1) (either with the scattering term or with the streaming term (3.10)) and taking into account (3.1), (3.8) and (3.11), we find again the mass balance (3.2).

Sections 4 and 5 will be devoted to proving the well-posedness of models presented and discussed in Sec. 2 and 3 respectively.

4. Compartmental Models: Qualitative Analysis of the Initial Value Problem

A simple case we can imagine for system (2.3)–(2.5), corresponds to assuming that $N = 1$ (hence $f_1 \equiv 1$ and the cells are not distiguished from their activity state):

$$\frac{dm}{dt} = m(F(p,q,\gamma(t),t) - \mu(p,q,\gamma(t),t)), \tag{4.1}$$

$$\frac{dp}{dt} = m(\alpha\mu(p,q,\gamma(t),t) - F(p,q,\gamma(t),t) - G(p,q,\gamma(t),t)) + Q(t), \tag{4.2}$$

$$\frac{dq}{dt} = m((1-\alpha)\mu(p,q,\gamma(t),t) + G(p,q,\gamma(t),t)). \tag{4.3}$$

In this case, the mathematical problem consists of solving the system of O.D.E.s (4.1)–(4.3) where the unknown functions are $m(t)$, $p(t)$ and $q(t)$, with the initial conditions

$$m(0) = m_0, \quad p(0) = p_0, \quad q(0) = q_0. \tag{4.4}$$

It is reasonable to assume that the given functions on the R.H.S. of (4.1)–(4.3) are smooth. If, for instance, Q, γ are continuous and F, G, μ are Lipschitz continuous w.r.t. p, q (uniformly for $t \in [0, +\infty)$) and they are continuous functions w.r.t. t (explicitly and through $\gamma(t)$), existence and uniqueness of a global solution to the system is guaranteed.

The solution m, p, q must verify, owing to the physical meaning of the quantities

$$m(t) \geq 0, \quad p(t) \geq 0, \quad q(t) \geq 0. \tag{4.5}$$

The behaviour of the solution (m, p, q) of (4.1)–(4.4) depends obviously on the properties of the given functions $F \geq 0$, $G \geq 0$, $\mu \geq 0$, $Q \geq 0$ and γ. As a general feature, we easily deduce that the mass $m + p$ is limited by

$$m(t) + p(t) \leq m_0 + p_0 + \int_0^t Q(\tau) d\tau. \tag{4.6}$$

We also remark that $m \equiv 0, p \equiv p_0, q \equiv q_0$ corresponds to a stationary solution of the problem, provided that $Q \equiv 0$. Moreover, if we require, as it is natural,

$$\begin{cases} F(0, q, \gamma(t), t) = 0 & \text{for } q \geq 0, \ t \geq 0, \\ G(0, q, \gamma(t), t) = 0 & \text{for } q \geq 0, \ t \geq 0, \end{cases} \tag{4.7}$$

then we see that the solution verifies (4.5).

In order to describe an even simpler situation, let us consider the autonomous case, with the aim of making explicit some properties of the solution. Equations (4.1) and (4.2) reduce to (dropping also the dependence on q of the given functions and taking Q as a non-negative constant):

$$\frac{dm}{dt} = m(F(p) - \mu(p)), \tag{4.8}$$

$$\frac{dp}{dt} = m(\alpha\mu(p) - F(p) - G(p)) + Q. \tag{4.9}$$

The waste function q can be calculated *a posteriori* by $q(t) = m_0 + p_0 + q_0 - m(t) - p(t) + Qt$.

According to a natural situation, we may think of F and G as increasing functions w.r.t. p, while μ as decreasing function of p. In this case, there is no difficulty in displaying the solution on a (m, p)-phase plane. Set $\mathcal{T}$ the triangle on the phase plane defined by $m \geq 0$, $p \geq 0$, $m + p \leq M_0$. One easily realizes that

1. if $Q = 0$, then $\lim_{t \to +\infty} m(t) = 0$ and p tends to a value p_∞, $0 < p_\infty < M_0 = m_0 + p_0 + q_0$. No further stationary states are possible. The shapes of the orbits depend on the properties of F, G and μ. Essentially, three situations may occur:

   (a) $F(p) < \mu(p)$ and $H(p) \equiv \alpha\mu(p) - F(p) - G(p) > 0$ for $0 \leq p \leq M_0$: in this case, $\mathcal{T}$ is invariant, each point $(0, p)$, $0 \leq 0 \leq M_0$ is a stationary orbit and along any other orbit m decreases (tending to zero) and p increases;

   (b) $F(p) < \mu(p)$ and it exists p_1, $0 < p_1 < M_0$ such that $H(p_1) = 0$: the same situation, apart from the fact that $p = p_1$ is an orbit and p decreases along the orbits for $p_1 < p < M_0$;

   (c) p_2 exists, $0 < p_2 < M_0$ such that $F(p_2) = \mu(p_2)$: in this case there also exists a positive value $p_1 < p_2$ with the property stated in (b); the situation is sketched in Fig. 1, where F, G and μ have linear profiles, $M_1 = 1$, $p_1 = 0.38$ and $p_2 = 0.46$;
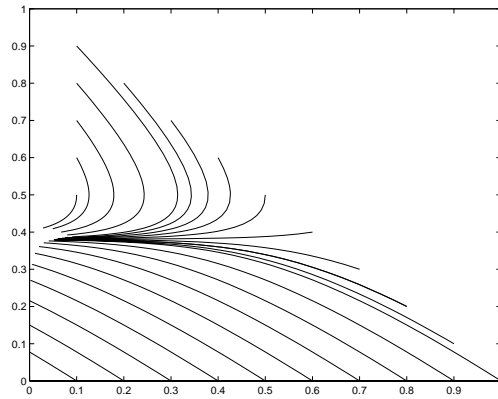
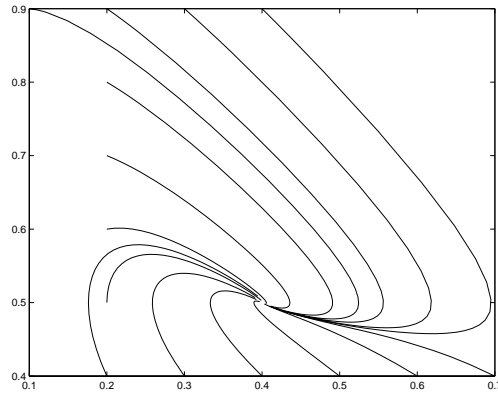Fig. 1.   Orbits on the (m, p) phase plane, case 1(c).

Fig. 2.   Orbits on the (m, p) phase plane, case 2.

2. if $Q \not\equiv 0$, then stationary solutions do not correspond necessarily to $m = 0$; moreover, $\mathcal{T}$ is no longer invariant. The qualitative behaviour of the solution goes along again the cases 1(a)–1(c). In Fig. 2 we sketched the case (c) where the singular point $m = -Q/H(p_2), p = p_2$ is asymptotically stable.

We pass now to discuss the case $N > 1$. As we already noticed, if assumption (2.6) (or (2.8)) is assumed to hold, then the mathematical problem is essentially the same as in the case $N = 1$, since we have to solve (2.3)–(2.5) with m_i given by (2.7), in case of assumption (2.6), or by $m(t)f_i(t)$ with $f_i(t)$ given by

$$f_i(t) = f_i(0)e^{t/\tau_i} - \frac{1}{\tau_i} \int_0^t e^{(t-\theta)/\tau_i} \bar{f}_i(\gamma(\theta))d\theta \tag{4.10}$$

in the case of assumption (2.8).

On the other hand, if system (2.3)–(2.5) is coupled with Eq. (2.9), the mathematical problem consists of solving $N + 2$ O.D.E.s (namely (2.4), (2.5) and (2.9))

together with the initial conditions (4.4) and $m_i(0) = m_{i,0}$, $i = 1, \dots, N$ (as we already observed, (2.3) is nothing but the sum of Eqs. (2.10)).

Again, the well-posedness is guaranteed under standard assumptions on the R.H.S. of the equations of the dynamical system.

5. Continuous Distribution of Cellular Activity: The Mathematical Problem

We are going now to consider the problem (3.2)–(3.4) which describes the continuous distribution of the index $a \in [0, 1]$, introduced in Sec. 3.

If we adopt the point of view (3.5) or (3.6), the distribution function $\varphi(a, t)$ can be calculated once the external factors γ are known, as we already observed in Sec. 2. In case of assumption (3.6), the solution (4.10) is replaced by

$$\varphi(t) = \varphi(0)e^{t/\tau} - \frac{1}{\tau} \int_0^t e^{(t-\theta)/\tau} \bar{\varphi}(\gamma(\theta))d\theta \,. \tag{5.1}$$

Note that (3.1) holds for any $t \geq 0$. Once $\varphi(a, t)$ is known, we can solve ths system of O.D.E.s (3.2)–(3.4) in order to find m, p and q.

On the contrary, if we prescribe the internal transitions by means of (3.7) (possibly with the streaming term (3.10) replacing scattering), we must consider (3.2)–(3.4) and (3.7) simultaneously and the problem consists in integral-differential equations. We will discuss such a system, which we write again in the following form:

$$\frac{dm}{dt} = m(t) \int_0^1 \varphi(a, t)(F(a, p, t) - \mu(a, p, t))da \,, \tag{5.2}$$

$$\frac{dp}{dt} = m(t) \int_0^1 \varphi(a, t)(\alpha\mu(a, p, t) - F(a, p, t)$$
$$- G(a, p, t))da + Q(t) \,, \tag{5.3}$$

$$\frac{\partial}{\partial t}\varphi(a, t) = \int_0^1 (\nu(a, p, t)F(\eta, p, t) + \tau(\eta, a, p, t))\varphi(\eta, t)d\eta$$
$$- \left(\mu(a, t) + \int_0^1 \tau(a, \eta, p, t)d\eta\right)\varphi(a, t)$$
$$+ \varphi(a, t) \int_0^1 (\mu(\eta, p, t) - F(\eta, p, t))\varphi(\eta, t)d\eta \,. \tag{5.4}$$

For the sake of simplicity (but without altering the essence of the mathematical problem) we neglected the dependence of the given functions F, G, μ and ν on q. Moreover, assuming that the external factors $\gamma(t)$ are assigned, we indicated that the same functions depend on t (possibly, through $\gamma(t)$).

Equation (5.4) comes from (3.7), taking also into account (3.1) and replacing $\dot{m}$ by (3.2).

The initial conditions and the constraints that the solution (m, p, φ) must verify are:

$$m(0) = m_0 \geq 0 \,, \quad p(0) = p_0 \geq 0 \,, \tag{5.5}$$

$$\varphi(a, 0) = \varphi_0(a) \,, \quad 0 \leq a \leq 1 \,, \tag{5.6}$$

$$m(t) \geq 0 \,, \quad p(t) \geq 0 \,, \quad t \geq 0 \,, \tag{5.7}$$

$$\varphi(a, t) \geq 0 \,, \quad \int_0^1 \varphi(a, t) da = 1 \,. \tag{5.8}$$

Let T be a fixed positive time. We assume that the given functions have the following properties:

1. The functions $F \geq 0$, $G \geq 0$, $\mu \geq 0$, $\nu \geq 0$, $\tau \geq 0$ are continuous for $a, \eta \in [0, 1]$, $p \geq 0$, $t \in [0, T]$ and Lipschitz continuous w.r.t. p, uniformly in $t \in [0, T]$; moreover, ν verifies (3.8); $Q(t)$ is a continuous function for $t \in [0, T]$;
2. (compare with (4.7))

$$F(a, 0, t) = 0 \,, \quad G(a, 0, t) = 0 \quad \text{for } a \in [0, 1], t \in [0, T] \,. \tag{5.9}$$

3. Function $\varphi_0(a)$ in (5.6) is such that

$$\varphi_0(a) \geq 0 \quad \text{for } 0 \leq a \leq 1 \,, \quad \int_0^1 \varphi_0(a) da = 1 \,. \tag{5.10}$$

We start by remarking that, if a non-negative solution (m, p) is known to exist, then, arguing as in (4.6)

$$0 \leq m(t), p(t) \leq M_1 + \int_0^t Q(\tau) d\tau \,, \tag{5.11}$$

where M_1 is the given initial mass $m_0 + p_0$.

Once a pair (m, p) has been fixed, the structure of (5.4) is the following:

$$\frac{\partial}{\partial t} \varphi(a, t) = \int_0^1 K_1(a, \eta, t) \varphi(\eta, t) d\eta - K_2(a, t) \varphi(a, t)$$

$$+ \varphi(a, t) \int_0^1 K_3(\eta, t) \varphi(\eta, t) d\eta \tag{5.12}$$

with

$$K_1(a, \eta, t) = \nu(a, p(t)) F(\eta, p(t), t) + \tau(\eta, a, p(t), t) \geq 0 \,, \tag{5.13}$$

$$K_2(a, t) = \int_0^1 \tau(a, \eta, p(t), t) d\eta + \mu(a, p(t), t) \geq 0 \,, \tag{5.14}$$

$$K_3(\eta, t) = \mu(\eta, p(t), t) - F(\eta, p(t), t) \,. \tag{5.15}$$

Existence and uniqueness of the solution $\varphi(a, t)$ of (5.16) with the initial datum (5.5) can be proved by semigroups theory arguments as follows.

Consider first the evolution equation $\varphi_t = A(t)\varphi$ in the Banach space of integrable functions (w.r.t. a) $L_1(0, 1)$, where the operator $A(t)$ is defined as $A(t)\varphi = -K_2\varphi$, $t \in [0, T]$. Owing to the assumptions stated in point 1 above, each operator $A(t)$, $t \in [0, T]$ is the infinitesimal generator of a dissipative semigroup, by virtue of the Lumer–Phillips theorem (see e.g. Ref. 9). Hence, $\{A(t)\}_{t \in [0,T]}$ is a stable family of infinitesimal generators of continuous semigroups $S_t(s)$, $s \geq 0$, satisfying $\|S_t\| \leq 1$. We consider now the equation $\varphi_t = A(t)\varphi + B(t)\varphi$, where $B(t)$ is the Fredholm operator $B(t)\varphi = \int_0^1 K_1(a, \eta, t)\varphi d\eta$, which is bounded by

$$\|B(t)\| \leq \bar{K}_1 = \sup_{0 \leq a, \eta \leq 1, 0 \leq t \leq T} K_1(a, \eta, t) < \infty, \quad \text{for all } t \in [0, T].$$

Making use of the linear perturbation Theorem 2.3 of Ref. 10, we conclude that $\{A(t) + B(t)\}_{t \in [0,T]}$ is a stable family of infinitesimal generators with stability constants 1 and $\bar{K}_1$.

We discuss at this point the complete Eq. (5.4) which we write in the form

$$\varphi_t = A(t)\varphi + B(t)\varphi + f(t, \varphi), \quad \varphi(0) = \varphi_0, \tag{5.16}$$

where the nonlinear term f is given by $\varphi \int_0^1 K_3 \varphi d\eta$.

We are in a position to apply Theorem 1.7 of Ref. 10, which provides us with a classical solution of the initial value problem (5.16). Actually, for any $\varphi \in L_1$ f is continuous w.r.t. t and uniformly Lipschitz continuous in φ with respect to the graph norm $\|\varphi\| + \|(A + B)\varphi\|$; hence we get a unique solution $\varphi \in L_1(0, 1)$ w.r.t. a and $C^1(0, T)$ for $t \in (0, T)$ of problem (5.16) for any $\varphi_0 \in L_1(0, 1)$.

We check now that the solution $\varphi(a, t)$ verifies properties (5.8). Indeed, by integrating (5.4) w.r.t. $a \in (0, 1)$ one finds (recall (3.8))

$$\frac{d}{dt}\beta(t) = \beta(t) \int_0^1 K_3(\eta, t)\varphi(\eta, t)d\eta, \tag{5.17}$$

where $\beta(t) = \int_0^1 (1 - \varphi(a, t))da$. Since $\beta(0) = 0$ (from (5.10)), we conclude that $\beta(t) \equiv 0$, hence $\int_0^1 \varphi(a, t)da = 1$, for all $t \in [0, T]$.

We prove now that $\varphi(a, t) \geq 0$. Consider the solution ψ of the evolution problem

$$\psi_t = \int_0^1 K_1(a, \eta, t)\psi(\eta, t)d\eta - K_2(a, t)\psi(a, t), \quad \psi(a, 0) = \varphi_0(a). \tag{5.18}$$

It is immediate that $\psi(a, t) \geq 0$, $t \geq 0$ whenever $\psi(a, 0) \geq 0$, (the existence of the solution is guaranteed by the same theorems we used above). On the other hand, by comparing (5.18) with (5.4), we see that $\varphi \geq \psi$, since $K_1 \geq 0$.

We saw that for any assigned pair (m, p) a unique distribution function φ can be found. On the other hand, for any given φ a pair (m, p) can be calculated by means of (5.2), (5.3).

Such as iterative scheme defines a contractive map on (m, p) in the sense we are going to show. We call $\bar{Q} = \sup_{t \in [0,T]} Q(t) \geq 0$ and define the Banach space of continuous functions

$$\mathcal{B} = \{(m, p) \,|\, m, p \in C^0[0, T], \; 0 \leq m(t), \; p(t) \leq M_1 + \bar{Q}\}, \tag{5.19}$$

endowed with the norm $\|(m, p)\| = \sup_{0 \leq t \leq T} (m(t) + p(t))$, and the operator $\mathcal{F}$

$$\mathcal{F}(m, p) = (\tilde{m}, \tilde{p}), \tag{5.20}$$

where $(\tilde{m}, \tilde{p})$ is the solution of the integral system (see (5.2) and (5.3))

$$\tilde{m} = m_0 H_1(\tilde{p}, p, \tau) d\tau + \int_0^t Q(\tau) d\tau, \tag{5.21}$$

$$\tilde{p} = p_0 + \int_0^t m(\tau) H_2(\tilde{p}, p, \tau) d\tau + \int_0^t Q(\tau) d\tau, \tag{5.22}$$

with

$$H_1(\tilde{p}, p, t) = \int_0^1 (F(a, \tilde{p}, t) - \mu(a, \tilde{p}, t)) \varphi(a, t) da,$$

$$H_2(\tilde{p}, p, t) = \int_0^1 (\alpha \mu(a, \tilde{p}, t) - F(a, \tilde{p}, t) - G(a, \tilde{p}, t)) \varphi(a, t) da$$

(the dependence of H_1 and H_2 on p is through the function φ calculated for a given (m, p) as above).

Existence and uniqueness of the solution $(\tilde{m}, \tilde{p})$ for $t \in [0, T]$ is guaranteed by the assumptions made on the given functions. Moreover, it is immediate that $\tilde{m}(t) \geq 0$ and, by virtue of assumption (5.9), we have that $\tilde{p} \geq 0$. By summing up Eqs. (5.2) and (5.3) we see that

$$\tilde{m}(t) + \tilde{p}(t) \leq M_1 + \int_0^t Q(\tau) d\tau,$$

and, since $\tilde{m}(t)$, $\tilde{p}(t)$ are non-negative functions, we have that they fulfill property (5.11). Hence $\mathcal{F}(\mathcal{B}) \subseteq \mathcal{B}$.

Let us now consider two points (m_1, p_1), $(m_2, p_2) \in \mathcal{B}$. By Eq. (5.4), we find the two solutions $\varphi_1(a, t)$ and $\varphi_2(a, t)$. If one writes the equation for the difference $\varphi_1 - \varphi_2$ and uses the Gronwall's lemma, one can easily find for any $t \in [0, T]$:

$$\int_0^1 |\varphi_1(a, \tau) - \varphi_2(a, \tau)| da \leq \bar{L} \int_0^t |p_1(s) - p_2(s)| ds, \quad 0 \leq \tau \leq t, \tag{5.23}$$

where $\bar{L}$ is a positive constant depending only on the Lipschitz constants of the given functions. By virtue of (5.23), we have from (5.21) and (5.22), by applying Gronwall's lemma once again:

$$|\tilde{m}_1(t) - \tilde{m}_2(t)| + |\tilde{p}_1(t) - \tilde{p}_2(t)|$$

$$\leq \bar{\bar{L}} \int_0^T (|m_1(\tau) - m_2(\tau)| + |p_1(\tau) - p_2(\tau)|) d\tau, \tag{5.24}$$

where $\bar{\bar{L}} > 0$ depends on $\bar{L}$, M_1 (see (5.11)) and Q_0 (see (5.19)). From (5.24) we deduce that $\mathcal{F}$ is a contractive map in $\mathcal{B}$ for some time T_1, possibly $T_1 < T$. Hence, we get a unique solution for $t \in [0, T_1]$. With standard arguments, we can see that the fixed point of the map (solving (5.21) and (5.22) with $(\tilde{m}, \tilde{p}) = (m, p)$) is also solution of (5.2), (5.3). In case of $T_1 < T$, by duplicating the same procedure starting from $t = T_1$ we can obtain existence and uniqueness of the solution up to $T_2 > T_1$. The same scheme can be iterated in order to find the solution (m, p, φ), $t \in [0, T]$.

We will not deal with the case of streaming (3.9), since the proof of well-posedness of the mathematical model is essentially the same: it suffices only to replace the linear integral operator corresponding to τ in (3.7) with the linear differential operator (3.8). Notice that $a = 0$ and $a = 1$ are two characteristic curves of the equation, since (3.9) must hold. Hence, the initial datum (5.6) is sufficient to solve the problem.

6. Summary and Conclusions

We considered a proliferating system of cells and wrote the correct mass balance, taking into account the three different classes m, p and q as defined in Sec. 2.

Having in mind the application to modelling the growth of tumours, $m(t)$ is the total mass of the living cells in the region under consideration and their death originates waste material as well as material which can be used for replication.

Since variation of the relevant quantities w.r.t. position is neglected in this first approach, external supply of nutrients, withdrawal of catabolic products etc. and in general any exchange of mass with the surroundings is assumed to occur simultaneously throughout the region.

On the other hand, a peculiar aspect in tumoral growth is the strong differentiation of cells forming the mass m. Thus, we introduced biological activity as a discrete variable (compartmental models) or as a continuous parameter (Boltzmann-like approach). The influence of treatment is also taken into account (functions γ).

For all classes of models described well-posedness of the corresponding mathematical problems is proved under mild assumptions on the data and parameters.

Next step in the research will be to take into account spatial dependence of the quantities: the "natural" extension of the equations discussed in this paper is the right starting point for the model. However, in this case velocity fields will have to be introduced for the different classes and the phenomenology of the process is indeed much more complicated.

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