
Modelling Tumour Growth and Progression

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1 Modelling Path

To develop the path that goes from the clinical experience to the laboratories and back to the clinic, research in cancer modelling need the establishment of strong interactions among different branches of science and a genuinely multidisciplinary approach. In fact, starting from very practical situations this path passes through progressive abstractions and simplification steps to gain insight into the complex phenomena occurring during tumour evolution and growth and this involves different research areas (see Fig. 1).

So, from the phenomenological observation of a certain phenomenon in real patients, scientists in bio-medicine try to conceive more handy, reproducible, and relatively harmless biological models, which can be *in vivo* (e.g., mouse, chicken embryo) or *in vitro*. They then perform a series of experiments on that model. Either directly from the phenomenological observation or from the biological model, mathematicians and physicists can generate mathematical models aimed at describing the phenomenon of interest. The simulations stemming from them are usually called *in silico* models by the biologists.

The acquisition of this knowledge is then tested back through experimental phases of increasing complexity and hopefully applied in the clinical practice. It is common knowledge that this stepwise process also mean different levels of ethical involvement.

Including mathematical modelling and computer simulations in the path mentioned above can speed up the process, provide insight into the mechanisms that control tumour evolution and growth, and, hence, suggest directions for new therapies. The theoretical predictions generated from the models and their simulations can help optimising the experimental protocol by identifying the most promising candidates for further clinical investigation. In fact, the ease with which physical parameters can be manipulated in a computer simulation and the speed with which large numbers of simulations can be performed can help reducing the number of animal experiments to be carried out

and identifying new experimental programmes and optimal tumour therapy schedules.

However, dealing with living matter is much more complex than dealing with inert matter, not only because biological phenomena are intrinsically multiscale, but also because modelling biological phenomena introduces a peculiar characteristic not encountered in other fields and well expressed by the following sentence by Hartwell, Hopfield, Leibner, and Murray [24] “Although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiates biology from other natural sciences”. These characteristics represent on one hand a big difficulty and on the other a big stimulus for developing new research areas and theories.

The aim of this paper is to give an overview of some mathematical models recently developed at the cellular and tissue level to support cancer research. In the following only references published after 2000 will be cited because the field is in rapid development. In these works it is however possible to recover previous references. In particular, a starting point to look at the historical development of cancer research is the volume [1] and the special issues [11] and [17]. More recent results can be found in the volume [32] and in the special issues [34] and [10].

2 Modelling Scales

As just mentioned tumour evolution and growth is intrinsically a multiscale problem. Even the first step of any modelling process, the phenomenological description, depends on the enlargement used in the real or ideal microscope used by the biologist or by the modeller. A researcher in the field of biomedicine would probably describe the phenomena occurring during the evolution of tumours using three natural viewpoints: the sub-cellular level, the cellular level, and the tissue level. From the modelling viewpoint a connection can be approximately drawn between the description levels above and the microscopic, mesoscopic, and macroscopic scales.

In fact, at the macroscopic scale referring to the tissue level one can focus on

- the growth of multicellular spheroids in the avascular phase (i.e. when they are not yet surrounded by a capillary network) [8], [13], [16], [33];
- the formation of capsules surrounding the spheroid and their degradation [26];
- the mechanical interaction between the tumour and the external tissues [6], [9], [15];
- the process of angiogenesis (i.e. the growth of this capillary network) [29], [25];
- the vascular growth (i.e. when the multicell spheroid is surrounded by a capillary network) [31];

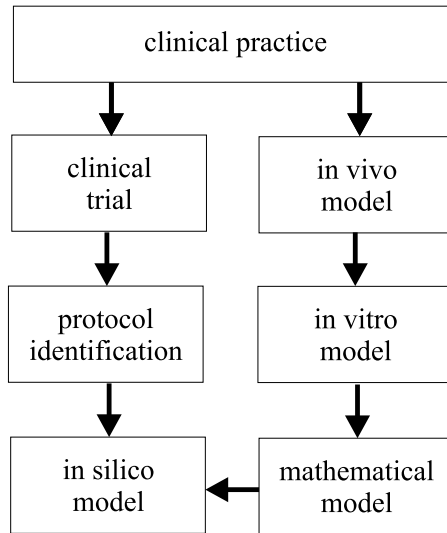


Fig. 1. Modelling levels.

- the detachment of metastases, their diffusion and their settlement in a new site [7].

All this depends on what happens at a smaller scale, the cellular scale. Taking into account that all cells evolve, one then has to introduce a new independent variable defined as state of a cell and determine the evolution in terms of a statistical description over the progression and activation state. Finally one has to define the interactions among tumour cells and the other types of cells present in the body such as endothelial cells, macrophages, lymphocytes. This mesoscopic scale also includes aggregation and disaggregation phenomena [4], [22] and intravasation and extravasation processes.

In turn, these phenomena depend on what happens at an even smaller scale, the microscopic scale which refers to those phenomena that occur at the sub-cellular level and therefore to activities that take place within the cell or at the cell membrane, for instance DNA synthesis and degradation and gene expression, alteration mechanisms of the cell cycle, absorption of vital nutrients, activation or inactivation of receptors, transduction of chemical signals between cells that regulate cellular activities, such as duplication, motion, adhesion, or detachment.

Of course what happens at a certain scale is strongly linked to what happens at the other scales. Therefore it is impossible to completely describe a phenomenon without taking into account others occurring at a smaller or a larger scale. This means that mathematical models and methods characteristic of different scales should be interlaced to achieve a better description of

the phenomena and the use of multiscale methods is often desirable if not necessary.

3 Modelling the Growth of Tumour Masses

Looking at a tumour from the tissue level, i.e. as an ensemble of cells packed in a multicellular spheroid, it is possible to realise that the evolution depends on the distribution of oxygen, glucose and other nutrients and on the production and reception of growth modulating chemical substances, phenomena involving the sub-cellular level. This phase can be described by mass balance equations and reaction-diffusion equations that can be derived not only on the basis of principles of continuum mechanics but also on the basis of cell-based models and random walk models [30], [18]. Actually, in the latter modelling framework it is easier to introduce cellular and sub-cellular mechanisms, while in the former framework it is easier to deal with macroscopic mechanisms, such as the interaction with external tissues.

When dealing with macroscopic models one can distinguish between two types of actors: the cell populations considered important for the process and the chemical factors that influence their motion and proliferation. In the case of one cell population only (the case of more cell populations is discussed in [8]) the structure of the model is the following

$$\frac{\partial \phi}{\partial t} + \nabla \cdot (\phi \mathbf{u}) = \Gamma, \quad (1)$$

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (c_i \mathbf{W}) = \nabla \cdot (Q_i \nabla c_i) + G_i - D_i c_i, \quad i = 1, \dots, m, \quad (2)$$

where ϕ is the density of tumour cells, \mathbf{u} the cell velocity, c_i are the concentrations of chemical factors, \mathbf{W} their convective velocity, Q_i their diffusion coefficient, and D_i their degradation coefficient. Finally, we explicitly remark that the production terms G_i and Γ depend on both ϕ and $\mathbf{c} = (c_1, \dots, c_m)$.

Of course this set of equations need be closed by describing how cells move and how chemical factors are transported. In most papers \mathbf{W} is assumed to be negligible and \mathbf{u} is decomposed into a density related contribution and a chemotactic contribution

$$\mathbf{u} = \nabla f(\phi) + \sum_i w_i(c_i) \nabla c_i. \quad (3)$$

For instance, in [19] it is assumed that in absence of chemical gradients cells tend to move towards the regions where they feel less pressed, therefore $f(\phi) = -K \Sigma(\phi)$ where Σ is a measure of the stresses and K is a measure of the motility of cells being related to the presence of an extra-cellular matrix to crawl upon. In fact, cells move on a network of fibres moving from adhesive site to adhesive site towards the most convenient region like a bunch of cars

moving on the streets toward a region (chemotactic attraction) avoiding traffic jams.

It is clear that the mathematical problems deriving from (1)–(3) are typically free boundary problems with an internal domain $\mathcal{T}(t)$ (where Equation (1) is defined) and an external domain and with the border of the tumour which represents the material interface moving according to

$$\mathbf{n} \cdot \frac{d\mathbf{x}}{dt} = \mathbf{n} \cdot \mathbf{u}. \quad (4)$$

On it one need to specify the value of the density of tumour cells, e.g. the natural density (which is usually also the initial state). On the other hand Equation (2) is defined everywhere and one has to provide initial and boundary values which of course depend on the problem and on the chemical factor, e.g. the diffusion of nutrients from a capillary vessel at the boundary of the domain corresponds to a Robin-type boundary condition in which the flux of nutrients is related to the difference between the concentration of nutrients in the capillary and outside it.

It need be mentioned that the phenomena occurring in the two domains influence each other. The simplest example is the mitosis of tumour cells which is influenced by the perfusion of nutrients through the capillary walls and the diffusion in the environment [12]. Another example is the process called angiogenesis where tumour cells produce chemical factor which diffuse out where they stimulate the existing capillaries to produce new capillaries to bring the tumour more nutrient [25], [19], [29]. For instance, if one focuses on the process called metallo-proteases, one has to describe how the tumour to grow has to destroy the surrounding extracellular matrix by producing enzymes that digest it allowing tumour growth.

In spite it is clear that to study the growth of these multi-cellular spheroid one should use mass balances and write free boundary problems, often models consisting of a set of reaction-diffusion equations are used. This is especially done to deal with problems with many interactive populations or that present strong heterogeneities (for instance [35], [30]).

We end this section by mentioning that recently a new class of models in the framework of mixture theory have been developed writing force balance equations for the cell populations involved (neglecting inertia) [8], [13]. In the case of a bi-component mixture Eq.(2) might be joined to the following equations

$$\frac{\partial \phi}{\partial t} + \nabla \cdot (\phi \mathbf{u}) = \Gamma, \quad (5)$$

$$\nabla \cdot (\phi \mathbf{u} + (1 - \phi) \mathbf{W}) = 0, \quad (6)$$

$$\nabla \cdot \mathbf{T}_m = 0, \quad (7)$$

$$\mathbf{W} - \mathbf{u} = -\kappa(\phi) \nabla P, \quad (8)$$

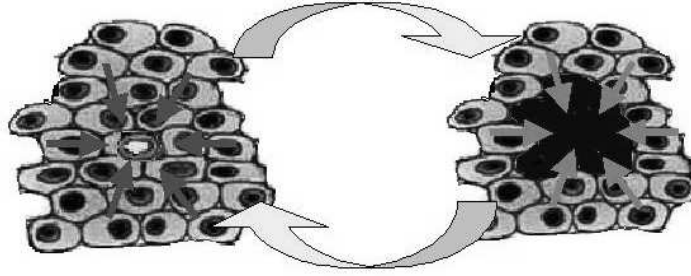


Fig. 2. A growing tumour presses on an immature capillary, which collapses. Tumour cells starve to death and produce in hypoxia vascular endothelial growth factors which stimulate the formation of new blood vessel forming a cycle.

where \mathbf{W} is the velocity of the extracellular liquid, \mathbf{T}_m is the stress tensor for the multicell spheroid, κ is related to its permeability and P is the interstitial pressure.

This framework is particularly important to study phenomena involving stresses, e.g. the forces exerted by the surrounding tissues influence tumour growth and viceversa growing tumours press the surrounding vessels and tissues. Another example is given in Fig. 2. This brings some open issues regarding the correct formulation of a continuous mechanics of growing materials addressed in [6], [21].

4 Fluid-Dynamic and Kinetic Model of Vasculogenesis and Angiogenesis

Zooming in, we describe here more in detail the process of formation of the vascular networks, also because it is an example of phenomenon that can be treated with both a continuous and a kinetic approach. In this process endothelial cells are randomly seeded on the plain surface of a gel substratum. They migrate over distances which are an order of magnitude larger than their radius and stick together when they get in contact with their neighbours forming complex vascular structures [27]. Motion is apparently directed towards zones of higher cell concentration. In fact, tracking of individual trajectories shows marked persistence in the direction of cell motion, with a small random component superimposed [4] (see Fig. 3).

After some hours cells form a continuous multicellular network which can be described as a collection of nodes connected by cords (Fig. 4b). It is experimentally observed that

- i) the mean chord length $\bar{\ell}$ is approximately independent on the initial cell density ($\bar{\ell} \simeq 200 \pm 20 \mu\text{m}$).

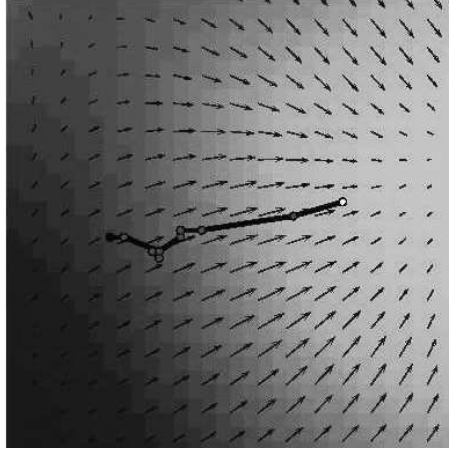


Fig. 3. Trajectory of a cells in the field of chemoattractant generated by the ensemble of endothelial cells.

- ii) connected networks are formed only above a critical density $n_c \sim 100$ cells/mm². At lower densities one observes only the formation of isolated clusters (Fig. 4a). The transition is sharp, characterised by a well defined critical density n_c .
- iii) at higher cell densities the cord thickness grows in order to accommodate a larger number of cells, until around 400 cells/mm², a sort of “Swiss-cheese” structure is observed (Fig. 4c).

The model proposed in [22] is based on the assumption that endothelial cells communicate via the emission and reception of a chemotactic chemical signal. This hypothesis has been confirmed by successive experiments (see Fig. 3 and [4]). Cells are then accelerated by gradients of soluble mediators and slowed down by friction due to the interaction with the fixed substratum. A chemotactic factor is constantly released by the cells, diffuses and degrades. A phenomenological, density dependent pressure $p(n)$, vanishing at low densities and rapidly increasing when cells become closely packed, controls cell overcrowding.

Denoting by n the cell density, \mathbf{u} their velocity and c the concentration of vascular endothelial growth factor (VEGF) the model writes

$$\begin{cases} \frac{\partial n}{\partial t} + \nabla \cdot (n\mathbf{u}) = 0, \\ \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = \mu \nabla c - \beta \mathbf{u} - \nabla p(n), \\ \frac{\partial c}{\partial t} = D \nabla^2 c + an - \frac{c}{\tau}. \end{cases} \quad (9)$$

EXPERIMENTS

SIMULATIONS

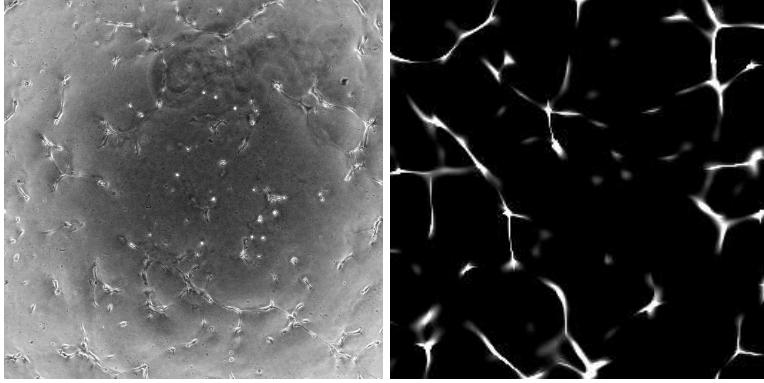
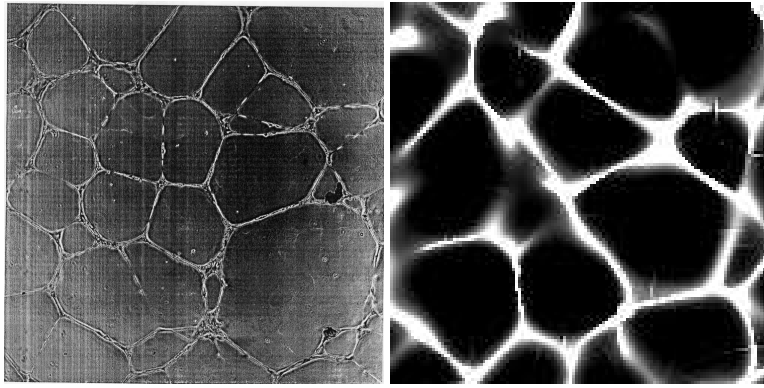
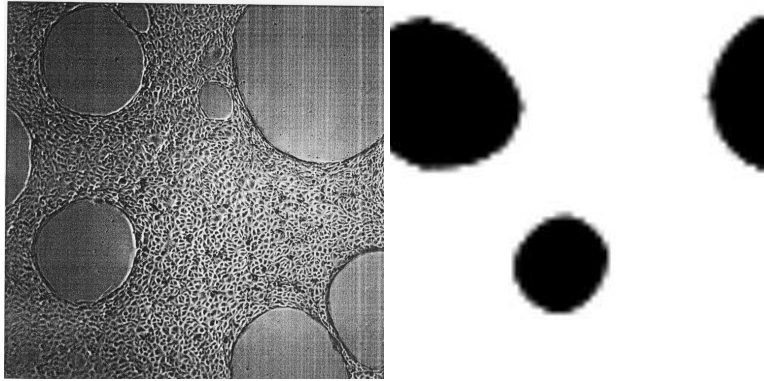
(a) $\bar{n} = 50$ cells/ mm^2 (b) $\bar{n} = 250$ cells/ mm^2 (c) $\bar{n} = 1000$ cells/ mm^2 

Fig. 4. Types of capillary-like networks formed by plating different numbers of cells (cited on the left) on a Matrigel surface. The left column refers to experiments (pictures kindly provided by F. Bussolino and G. Serini, Institute for Cancer Research and Treatment, Candiolo, Italy), while the right column refers to numerical simulations of the model (9), using measured values of the physical parameters and initial conditions mimicking the initial random placement of cells.

where the parameter μ measures the strength of the cell response to the chemo-tactic stimulus, β is a drag coefficient, D is the diffusion coefficient, a is the rate of release of VEGF, and τ is its characteristic degradation time.

Initial conditions are given in the form of a discrete set of Gaussian bumps of width of the order of the average cell diameter ($\sim 30\mu\text{m}$), placed at random position with uniform probability over a square surface.

The coupling of the ‘‘persistence’’ equation $(9)_2$ with the diffusion equation $(9)_3$ for the chemoattractant introduces in the problem a natural length scale $\ell = \sqrt{D\tau}$, corresponding to the effective range of chemical interaction. Numerical simulations show that this natural length scale is responsible for the characteristic scale of formed network structures, which is a physiologically relevant feature of real vascular networks. The process of network formation is then understood in the following way. Initially, non zero velocities are built up by the chemoattractive term due to the presence of random inhomogeneities in the density distribution. Density inhomogeneities are translated in a landscape of concentration of the chemoattractant factor where details of scales ℓ are averaged out. The cellular matter move toward the ridges of the concentration landscape. A dynamics similar to that encountered in Burgers equation sharpens the ridges and empties the valleys in the concentration landscape, eventually producing a network structure characterised by a length scale of order ℓ . This way, the model provides a direct link between the dimensions of the structure and the range of intercellular interaction.

The model is not only able to foresee the exact dynamics starting from realistic initial data which mimic a set of randomly seeded cells initially at rest (see Fig. 4) and the exact size of the structure as a function of physically measurable quantities, but also the transitions. In particular, methods of statistical mechanics were used in [22] to characterise quantitatively the sharp percolative transition in the neighbourhood of $n_c \sim 100$ cells/ mm^2 . Stability methods were used in [28] to study the smoother crossover from the continuous monolayer to the ‘‘Swiss-cheese’’ configuration of Fig. 4c. In addition, the model reproduces the fractal dimension D_H of network structures both at small ($D_H = 1.50 \pm 0.02$) and large scales ($D_H = 1.87 \pm 0.03$) and the set of experimentally observed critical indices [22].

It is important to notice that in principle one can deal with the same phenomena using a kinetic approach writing for the distribution function $f(t, \mathbf{x}, \mathbf{v})$ of the endothelial cell population an evolution equation with a force term with a drag contribution $\mathbf{F}_1 = -\beta\mathbf{v}$ and a chemotactic contribution $\mathbf{F}_2 = \mu\nabla c$. Introducing also a dissipative collision operator J (preserving mass and momentum, but dissipating energy in the collision between cells) one has the following model

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla f + \nabla_{\mathbf{v}} \cdot [(-\beta\mathbf{v} + \mu\nabla c)f] = J, \quad (10)$$

where

$$\nabla_{\mathbf{v}}(\cdot) = \frac{\partial(\cdot)}{\partial v_x}\mathbf{e}_x + \frac{\partial(\cdot)}{\partial v_y}\mathbf{e}_y + \frac{\partial(\cdot)}{\partial v_z}\mathbf{e}_z,$$

is the gradient with respect to velocity. The interscale link between (9) and (10) can be obtained through classical fluid dynamic limit procedures. In fact, integrating (10) over the velocity space, one has the first equation in (9), and integrating (10) after multiplying it by \mathbf{v} gives the momentum equation

$$\frac{\partial}{\partial t}(n\mathbf{u}) + \nabla(n\mathbf{u} \otimes \mathbf{u}) = n\mu\nabla c - n\beta\mathbf{u} - \nabla\Pi, \quad (11)$$

where Π is the pressure tensor. If one can prove that Π is an isotropic function of n one readily has the second equation in (9).

5 Tumour Progression

Looking at the population of tumour cells at the cellular scale it is possible to realise that the behaviour of the cells is not always the same and that also from the morphological viewpoint they present differences, e.g. presence of particular receptors or organelles. To be more specific, the progression of a normal cell into a tumour cell implies several key steps and the switch of several mechanisms. For instance, one of the path from normal to cancer cell is given by the achievement of the following sequential characteristics and abilities

- Insensitivity to anti-growth signals;
- Self-sufficiency in growth signals;
- Ability in evading apoptosis;
- Acquisition of limitless replicative potential;
- Ability in stimulating angiogenesis (angiogenic switch);
- Tissue invasion and metastasis.

As tumour cells, also the cells of the immune system are subject to a maturation and an activation. For these reasons the models aimed at the description of the evolution of such systems need to incorporate a new independent variable which is able to describe the state (or the states) of the cells and how their behaviour depends on such a state. This state might refer to the aggressiveness, the activity, the maturation state, and so on.

This necessity has been addressed by some biologists [23] who produced a picture like Fig. 5. At the same time Bellomo and co-workers were organising exactly that mathematical framework (see the volume [14] the more recent papers [2], [3], [5], [10] and references therein) and the simulation obtained closely recall what Geller, Tobin and Paste [23] describe on the basis of phenomenological information.

The key steps in the modelling process are then the selection of the cell populations of interest for the evolution and the identification of their specific activity/ies, their mechanisms of progression, of proliferation and of interaction (see Fig. 6). Of course, the behaviour of the cells depend on their activation state.

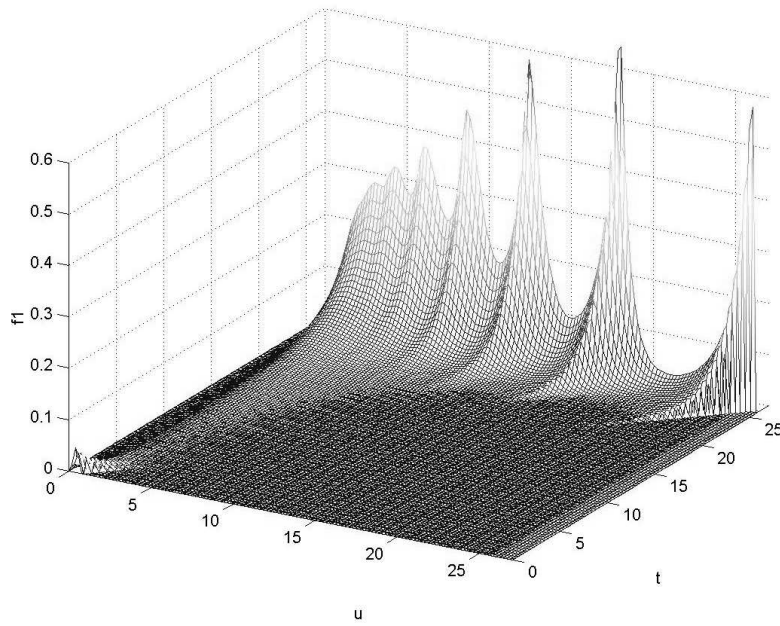
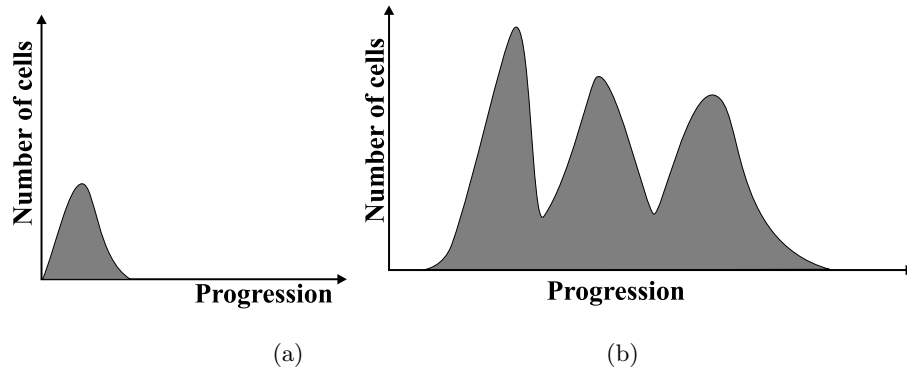


Fig. 5. Number of cells versus progression at earlier (a) and later (b) times as argued by Greller, Tobin and Poste [23] and (c) as obtained using the model deduced in [3].

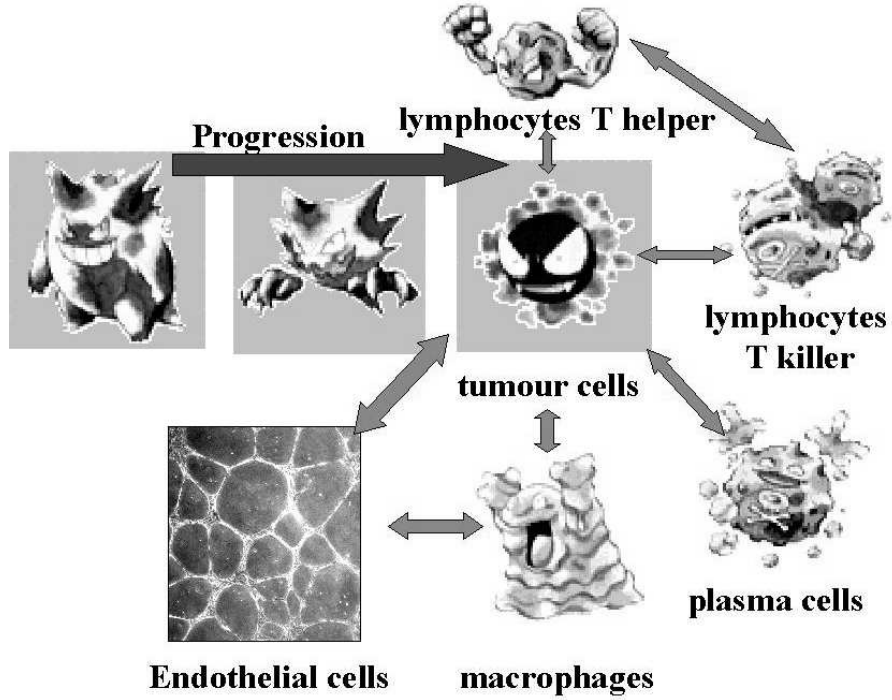


Fig. 6. Progression of tumour cells and interaction between cells.

The structure of the model is then the following

$$\begin{aligned}
 \frac{\partial f_i}{\partial t} + \frac{\partial}{\partial u} [c_i(t, u) f_i(t, u)] &= \mathcal{S}_i + f_i(t, u) \sum_{j=1}^n \int_{-1}^1 p_{ij}(u, w) f_j(t, w) dw \\
 &+ \sum_{j=1}^n \left[\int_{-1}^1 \int_{-1}^1 \eta_{ij}(v, w) \Psi_{ij}(v, w; u) f_i(t, v) f_j(t, w) dv dw \right. \\
 &\left. - f_i(t, u) \int_{-1}^1 \eta_{ij}(u, w) f_j(t, w) dw \right], \tag{12}
 \end{aligned}$$

where the second term on the l.h.s. represents the intrinsic evolution operator which takes into account of the progression of the cells even in absence of interactions and proliferation/death. The second term on the r.h.s. represents the net proliferation operator, i.e. stimulated mitosis minus killing due to interaction with other cells. In it $\eta_{ij}(v, w)$ denotes the number of encounters per unit volume and unit time between cell pairs of the (i, j) -th populations with states v and w , respectively, and $\psi_{ij}(v, w; u)$ denotes the probability of

transition of the i -th cell to the state u , given its initial state v and the state w of the encountering cells belonging to the j -th population. The last two terms are related to interactions which only change state in the interacting cells, while the second one refers to proliferative/destructive interactions. Finally \mathcal{S}_i is the source term which may be external (e.g., input from the bone marrow of immune cells) or internal, like the net proliferation term (mitosis-apoptosis) $\gamma_i(t, u)f_i(t, u)$.

We end up mentioning that very recently a new class of models falling in the category of mean field models have been developed in response to the observation that in most cases the interaction among cells is mediated by chemical factors and cytokines released by the cells and diffusing in the environment [20].

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