Modelling and Mathematical Problems Related to Tumor Evolution and Its Interaction with the Immune System

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Abstract—This paper provides a survey of mathematical models and methods dealing with the analysis and simulation of tumor dynamics in competition with the immune system. The characteristic scales of the phenomena are identified and the mathematical literature on models and problems developed on each scale is reviewed and critically analysed. The aim is to provide a general framework towards the development of immuno-mathematical theories and to develop research perspectives in this promising new field of applied mathematics. © 2000 Elsevier Science Ltd. All rights reserved.

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1. INTRODUCTION

Cancer is one of the greatest killers in the world, particularly in western countries, although medical activity has been successful, despite great difficulties, at least for some pathologies. A great effort of human and economical resources is devoted, with successful outputs (but also with failures), to cancer research with particular attention to experimental and theoretical immunology.

The following question can be naturally posed: can research activity in immunology possibly take advantage of a certain, however limited, interaction with mathematics? Moreover, can the models described in this paper contribute to the above interaction?

An additional question from the viewpoint of applied mathematicians is the following: does the application of mathematical models in immunology generate interesting and challenging mathematical problems?

The reply to the first two questions is positive. In the authors' opinion, research in immunology may hopefully take advantage of a certain interaction with mathematics, even though mathematics cannot directly solve problems in immunology. However, models and simulations of particular aspects and behaviors of the immune system might reduce the amount of experiments which are necessary for therapy developments. In principle, mathematical models can even be developed toward the elaboration of immuno-mathematical theories, suitable to support the progress of theoretical immunology. However, this is not a simple task and a great amount of work has still to be done to the above objective. As an additional task, mathematical models can be used to support the application of control actions in the framework of mathematical control theories.

The reply to the third question is certainly positive. Mathematical problems generated in the framework dealt with in this paper often represent a challenging task for applied mathematicians, both on the analytic and the computational ground. Some of these problems have not been solved yet and are the object of research activity.

The above outlined discussion, which defines the background motivating this paper, is certainly worth being further developed. However, it is useful to postpone it to the last section of this paper after having reported the state-of-the-art related to the existing literature. Indeed, several interesting papers proposed models and mathematical problems which already constitute a broad framework of challenging and stimulating hints for applied mathematicians.

A vast literature is already reported in a few review papers devoted to modelling, analysis, and control of tumor immune system interactions. In particular, we focus the reader's attention to the surveys collected in [1,2] which provide a rather complete description of the state of the art. Additional bibliography can be recovered in the review papers [3], devoted to the various macroscopic stages of evolution of the tumor; [4], mainly concerned with the assessment of the framework for the development of immuno-mathematical theories; and [5], dealing with the analysis of mathematical control models and theory. Additional detailed citations will be given in the sections that follow with direct reference to specific aspects of the whole topic.

The aim of this paper is not, however, limited to a description of the state-of-the-art, but it aims to develop new ideas towards analytic and computational problems in this promising new area of applied mathematics. The contents are proposed in nine sections.

- Section 1 is this introduction which formulates the aims of the paper and its contents.
- Section 2 provides a description of the phenomenology of the system from the viewpoint of applied mathematicians. In particular, the different scales characterizing the system, from the subcellular scale to the macroscopic behavior, are identified, thus assessing the general framework for mathematical modelling.
- Section 3 deals with a review of mathematical models developed at a cellular scale, which found the so-called cellular kinetic theory as it is developed by methods similar to nonlinear kinetic theory. The model describes statistically the behavior of the system with particular attention to the competition between tumor and immune cells. It also retains certain aspects of phenomena developed at the subcellular scale. This means modelling cell activity and signaling in relation with loss of differentiation and interactions between tumor cells and the immune system.
- Section 4 deals with modelling macroscopic phenomena by nonlinear partial differential equations and free boundary problems, thus describing the interactions of solid tumors with the outer environment. As above, macroscopic models retain certain aspects of phenomena developed at the cellular scale.
- Section 5 discusses the links among models developed at different scales with special attention to the transition from the cellular to the macroscopic description.
- Section 6 provides the description of some mathematical problems related to the application of the model and a survey of simulation results which have to be compared with known qualitative results. This section also brings to the attention of applied mathematicians some analytic and computational problems which may be of interest for their research activity in this field.
- Section 7 deals with the analysis of mathematical problems related to control actions, which can be developed at both scales: the microscopic and the macroscopic one.
- Section 8 deals with a critical analysis of the contents of this survey and indicates research perspectives towards further development of the immuno-mathematical theory as much as towards the mathematical problems generated by the models reviewed in this paper.
- Finally, Section 9 comes back to some of the questions posed above and namely refers to the possibility of success of the cooperation between immunology and mathematics. This aspect is examined in the light of the various results reviewed in this paper.

We need to mention that this review paper does not deal with a survey of models stated in terms of ordinary differential equations developed in a framework similar to population dynamic models. This class of models was generated by the pioneer work by Gompertz [6], and was developed by several authors, e.g., Gyllemberg and Webbs [7], Michelson and Leith [8–10], Lo Schiavo [11], Kirschner and Panetta [12], etc. These models are often used, as we shall see in Section 7, to deal with mathematical control problems. We do not critically discuss the utility of the above models, but simply mention that we have chosen to deal with models which retain the main phenomenological behavior of the real system.

2. PHENOMENOLOGY AND SCALING

The evolution of a cell, as described by various authors, e.g., Heberman [13] and Forni *et al.* [14], is regulated by the genes contained in its nucleus. These genes can either be activated or suppressed, when signals stimulate receptors on the cell surface and are then transmitted to the nucleus of the cell. The reception of particular signals can modify the usual behavior of a cell. In extreme situations, particular signals can induce a cell to reproduce itself in the form of identical descendants, that is the so-called clonal expansion or mitosis, or to die, that is the so-called apoptosis or programmed death.

Tumor cells compete with the immune system and, if not recognized and depleted, start to condense into a solid form. The solid tumor interacts with other cells through signals which diffuse in the outer environment. The sequential steps of the evolution of the system may be summarized, from the view point of a mathematician, as follows:

1. genetic changes, distortion in the cell cycle, and loss of apoptosis;
2. interaction and competition at the cellular level with immune and environmental cells (this stage includes activation and inhibition of the immune system; this action is also developed through cytokine signal emission and reception which regulate cell activities);
3. condensation of tumor cells into solid forms, macroscopic diffusion, and angiogenesis;
4. detachment of metastases and invasion.

The first two steps are mainly related to cellular phenomena, the last two need macroscopic descriptions, although cellular phenomena cannot be neglected as they are always the entities generating the macroscopic behavior. Mathematical models related to cellular phenomena are generally stated in terms of ordinary differential equations and deal with the behavior of a single cell, while integro-differential kinetic equations are used for collective phenomena. On the other hand, macroscopic behaviors are generally described by nonlinear partial differential equations which should bring to problems stated as moving boundary problems. The development of control activities can be organized along each of the steps above.

In principle, an immuno-mathematical theory should make it possible to describe all relevant features of the system in evolution with direct reference to the pertinent scales. Specifically, a theory requires the identification of the natural scales characterizing the phenomenon. It is possible to distinguish three main scales: the subcellular, the cellular, and the macroscopic scale. Indeed, the system shows interesting phenomena on each single scale. A theory should retain all relevant features from the lower to the higher scale.

To begin with, we limit the description to some and hopefully most relevant phenomena occurring at each scale, artificially separating them on the basis of the scale involved.

The **subcellular scale** refers to the main activities within the cells or at the cell membrane. Among an enormous number of phenomena, one can focus on

(i) genetic changes, distortion in the cell cycle and loss of apoptosis;
(ii) expression and transduction of signals between cells;
(iii) response of the cellular activity to the signals received;
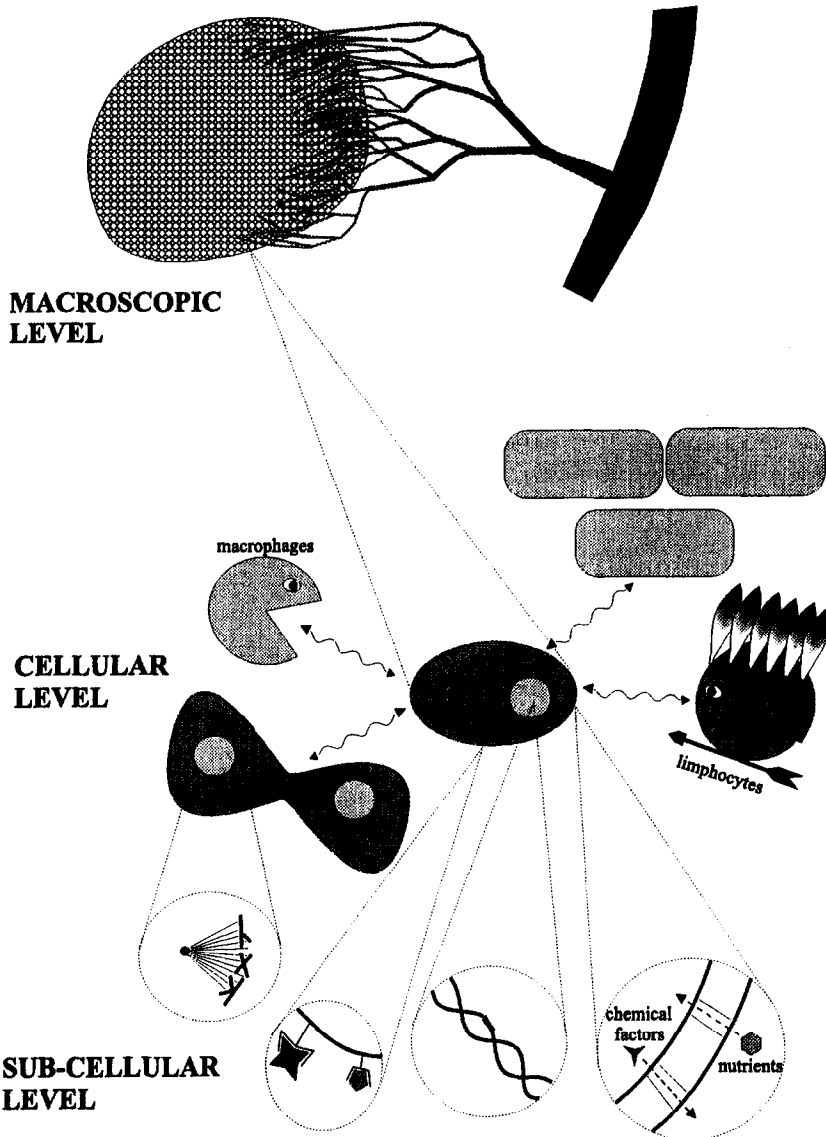(iv) absorption of vital nutrients.

Figure 1. Subcellular, cellular, and macroscopic scale.

The **cellular scale** refers to the main (interactive) activities of the cells: activation and proliferation of tumor cells and competition with immune cells. More specifically, referring to Figure 2, one has the following.

(i) Fast proliferation of tumor cells, which are often degenerated endothelial cells, happens when an environmental cell looses its death program and/or starts undergoing mitosis without control.

(ii) Competition with the immune system starts when tumor cells are recognized by immune cells, resulting either in the destruction of tumor cells or in the inhibition and depression of the immune system.

(iii) After differentiation, tumor cells undergo a process of maturation, which make them more and more proliferative and aggressive toward the environment and the immune system. Tumor cells can be additionally activated towards proliferation by nutrient supply from environmental cells.

(iv) Activation and inhibition of the immune cells in their competition with tumor cells is regulated by cytokine signals. These interactions, developed at the cellular level, are ruled by processes which are performed at the subcellular scale.
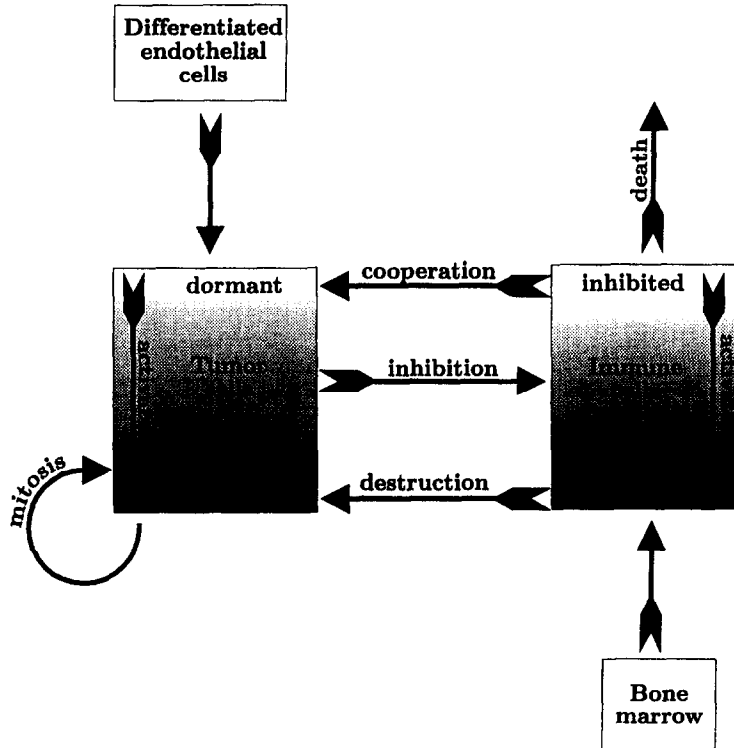
Figure 2. Cellular interactions.

(v) Activation and inhibition of cells belonging to the tumor and to the immune system can also be induced by a properly addressed medical treatment.

The **macroscopic scale** refers to phenomena which are typical of continuum systems: cell migration, convection, diffusion (of chemical factors, nutrients), phase transition (from free to bound cells, and vice versa detachment of cells and formation of metastases), and so on. After a suitable maturation time, tumor cells start to condense and aggregate into a quasi-spherical nucleus and interact with the outer environment.

In this stage, three overlapping phases of growth are usually identified: the avascular phase, the angiogenic phase, and the vascular phase. The avascular phase can be observed and studied in the lab by culturing *in vitro* cancer cells. These cells which take the form of multicell spheroids are usually characterized by an inner zone of necrotic cells dead for lack of nutrients, an outer zone of active tumor cells, and possibly an intermediate layer of quiescent cells (see Figure 3a). The angiogenic phase is characterized by the ability of the tumor to stimulate the proliferation of endothelial cells and by the formation of capillary sprouts that bring more nutrients to the tumor (see Figure 3b). The vascular phase is characterized by the ability of the tumor to invade the surrounding tissue and to metastasize to different parts of the body.

In particular, the **avascular stage of growth** is characterized by

(i) formation of a necrotic core of dead tumor cells where a process of destroying cellular debris may take place;

(ii) formation of an outer region of proliferating tumor cells and of an intermediate region of quiescent cells;

(iii) production of chemical factors, among which several growth inhibitory factors, generally called GIF, and growth promoting factors, called GPF, by the tumor mass, thus controlling the mitosis;

(iv) dependence of the tumor cells mitotic rate on the GIF and GPF concentration;

(v) nonuniformities in the proliferation of cells and in the consumption of nutrients, which filtrate through the surface of the spheroid and diffuse in the intracellular space.
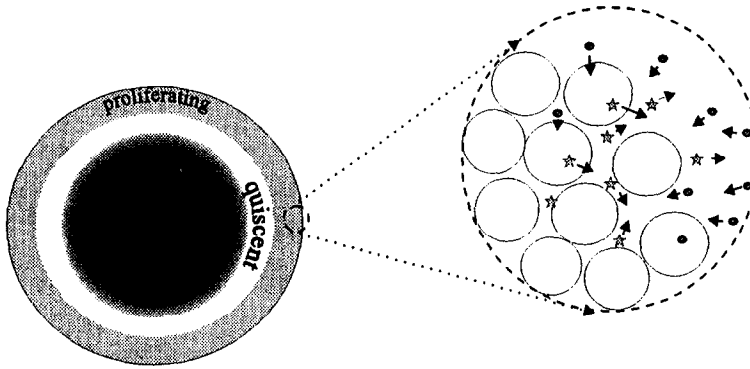
(a) Diffusion of vital nutrients in the tumor (circles) and of chemical factors produced by the tumor (stars).
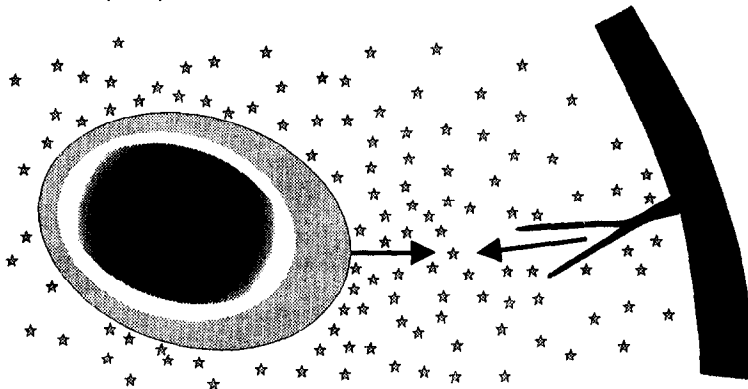
(b) Beginning of the angiogenic phase which will produce a configuration like the one shown at the top of Figure 1.

Figure 3. Macroscopic evolution.

On the other hand, the **tumor angiogenic phase** is characterized by

(i) secretion of tumor angiogenesis factors, generally called TAF, by the solid tumor and diffusion through the surrounding tissue;

(ii) release of enzymes by the environmental cells reached and stimulated by TAF, which degrade their basement membrane. Endothelial cells then proliferate and migrate towards the source of the angiogenic stimulus;

(iii) formation of capillary sprouts by accumulation of endothelial cells;

(iv) increase of tumor growth rate with the formation of the capillary network.

A macroscopic description of the system should focus on these features and aim at giving their evolution in time. Models based on reaction diffusion equations can, for instance, be found in [3,15–32]. Obviously, the macroscopic behavior depends on phenomena occurring at the cellular level, e.g., proliferation, death, activation, and inhibition of single cells, interaction between pairs of cells.

The above naive description retains some aspects of the way of thinking of an applied mathematician, who has in mind transferring the phenomenologic observation into equations. No problem in admitting that an immunologist can be highly disappointed by this attitude. He will deeply look at a certain phenomenon without an immediate aim to transfer this observation into mathematical equations. When the phenomenologic description becomes very detailed, transferring it into mathematical equations may become a very difficult task. On the other hand, once the said program is ended, the mathematical description can hopefully put in evidence behaviors which are not, or even cannot, be observed.

Additional details concerning the mathematical structure of models developed in the framework of the above scales can now be given with reference to mathematical modelling theory [33].

Conventionally, we state that a model developed at the microscopic scale defines the time evolution of the physical state of a single cell. Often these models are stated in terms of ordinary differential equations.

On the other hand, if we aim to describe the evolution of a system constituted of a large number of cells, one may replace the system of ordinary differential equations (one for each cell) by a kinetic equation on the statistical distribution of the state of all cells. This approach, which generates the so-called kinetic cellular theory, has the advantage of simplifying the complexity of the model. Indeed, one can obtain macroscopic observables by suitable moments derived by the statistical distribution.

The evolution of macroscopic observables can be described by models developed in the framework of continuum phenomenologic theories, e.g., those of continuum mechanics. These models are generally stated in terms of partial differential equations.

The link between the microscopic and the macroscopic description is one of the main open problems, as we shall see in Section 5, for scientists involved in the research field with which we are dealing.

3. MATHEMATICAL ASPECTS OF THE KINETIC CELLULAR THEORY

During the first stages of evolution, tumor cells have not yet condensed into a solid form. They have just differentiated from the other endothelial cells and, if recognized by the immune system, they are attacked. This interaction and competition with the immune system may end up either with the control of tumor growth or with the inhibition of the immune system, and hence, with the growth and condensation of the tumor into a solid form. In this scheme, each cell can be characterized by one or more activation states. These activation states are supposed to represent the relevant activities of the cells in the collective phenomena.

The evolution related to the above collective behavior can be described by the so-called kinetic cellular theory which is based on methods typical of the kinetic theory and provides a statistical description of the evolution of large populations of cells undergoing kinetic type interactions. The results of these interactions depend on the activation state of the cells. They can both modify the activation state of the interacting cells and generate proliferation/destruction phenomena.

The cellular theory was proposed and developed in a sequel of papers [34–39]. General aspects are reported in the surveys [4,36]. Computational schemes and applications are developed in [39]. The theory provides a system of evolution equations for the distribution function over the activation state of the cells of each cell population. The action of cytokine signals and external actions are also taken into account. They may be cast into the mathematical description either as an additional population or in the form of coupling parameters between the various cell populations. The sequential steps of this approach may be listed as follows.

STEP 1. Selection of the cell populations which play a role (in the model) in the quantitative and qualitative evolution of the system and identification of the peculiar activity of the cells belonging to a certain population, and of the cytokine signals regulating such an activity.

STEP 2. Modelling the dynamics of cell-cell interactions based on phenomena occurring at the subcellular scale.

STEP 3. Derivation of the equation suitable to describe the evolution of the size and state of each cell population.

STEP 4. Development of simulation tools to visualize the role of cell interactions during the evolution of the system with particular attention to the possibility of depleting the presence of tumor cells by suitable control actions.

The technical development of the above steps needs detailed analysis and assumptions on the interactions between cells in the environment. We are interested, at this stage, in a critical analysis

of the theory proposed in the literature so that suitable indication for its improvement can be taken into account. Before getting into technical aspects, we remark that the interaction with the lower subcellular scale is dealt with by modelling the emission and reception of signals between cells. In addition, in statistical mechanics, observability is not claimed. Cell-cell interactions may even be observed for pair interactions, while one cannot do that for the whole ensemble of interacting cells.

The above program is here described in two steps. The first one refers to a general framework, which defines the mathematical structure of the evolution model without entering into technical details. The second one deals with the description of a particular model, which has to be regarded as a particular application within the general framework mentioned above. Therefore, such a model can, and should, be improved (as also discussed in the last section) on the basis of a relatively deeper analysis of cellular phenomena.

3.1. Mathematical Structure of Cellular Kinetic Models

As mentioned above, we aim at describing a general framework for the derivation of evolution kinetic models. We follow the line reviewed in [4], which is based on the following assumptions.

ASSUMPTION 3.1. *The functional state of each cell, also called activation, is described by the real number u which conventionally can take values in the interval $[-1, 1]$. The variable u denotes the ability of the cell to express its main activity, which differs from cell type to cell type. Positive values of u denote an aggressive activity of a tumor cell, while negative values correspond to dormant states; positive values of u denote an inhibitory and destructive activity of the immune cells while negative values of u denote cooperation with the tumor system, e.g., feeding; the activity of the environment cells consists in feeding the tumor.*

ASSUMPTION 3.2. *After differentiation tumor cells gradually mature, becoming more and more proliferative and aggressive toward the environment and, in particular, toward the immune system. Depending on the level of differentiation one can, for instance, identify dormant and active cells, so that this property spans from the value $u = -1$ corresponding to highly latent state, to $u = 1$ corresponding to highly aggressive state.*

ASSUMPTION 3.3. *Referring to Figure 4, the state u or the number of cells can change because of*

(i) **intrinsic evolution,** *e.g., the spontaneous maturation of the tumor cells toward activation recalled in Assumption 3.2, the pharmacological activation of cells of the immune system, or the weakening of tumor aggressivity again as a result of properly addressed medical treatments;*

(ii) **mass conservative interactions** *between pairs of cells, i.e., interactions which are not responsible of proliferation or destruction of cells but only of a change in the activation state of one or both interacting cells;*

(iii) **proliferation** *of cells as a result of interactions between cell pairs;*

(iv) **death** *of cells as a result of destructive encounters with other cells;*

(v) **external sources or sinks** *of cells (or input/output), e.g., production of immune cells by the bone marrow, possibly pharmacologically stimulated, destruction of tumor cells by medical treatment, biological control of the number of immune cells, injection of cells.*

The problem now is to derive an evolution equation, based on the assumptions above and on the more specific assumptions below, for the distribution densities $N_i = N_i(t, u)$ for each population. The densities are such that $dn_i = N_i(t, u)\, du$ denotes the number of cells per unit volume whose state is, at time t, in the interval $[u, u + du]$. In particular,

$$n_i = \int_{-1}^{1} N_i(t, u)\, du \tag{3.1}$$

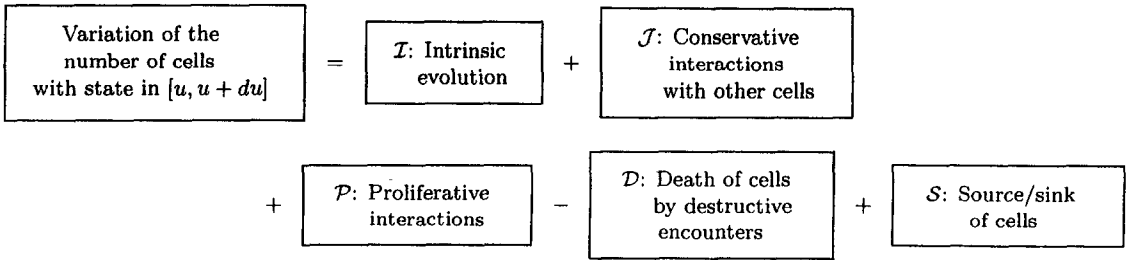is the number of cells of the ith population at the time t in a reference unit volume.

Figure 4. Representation of the operators involved in the evolution of $f_i(t, u)$.

If n_{e0} is the number per unit volume of environmental cells at $t = 0$, the following normalization of N_i with respect to n_{e0} can be applied:

$$\mathbf{f} = \{f_i\}_{i=1}^n, \qquad f_i(t, u) = \frac{1}{n_{e0}} N_i(t, u). \tag{3.2}$$

The evolution equations for f_i can be derived on the basis of suitable balance equations which equate the derivative of f_i to the operators mentioned in Assumption 3.3, that is,

$$\frac{\partial f_i}{\partial t}(t, u) = \mathcal{I}_i [f_i] (t, u) + \mathcal{J}_i[\mathbf{f}](t, u) + \mathcal{P}_i[\mathbf{f}](t, u) - \mathcal{D}_i[\mathbf{f}](t, u) + \mathcal{S}_i[\mathbf{f}](t, u), \tag{3.3}$$

where $\mathcal{I}_i$ is called intrinsic evolution operator, $\mathcal{J}_i$ conservative collision operator, $\mathcal{P}_i$ proliferative collision operator, $\mathcal{D}_i$ destructive collision operator, and $\mathcal{S}_i$ source/sink operator.

REMARK 3.1. As the operators $\mathcal{J}_i$, $\mathcal{D}_i$, and $\mathcal{P}_i$ describe the result of binary interactions between cells of the ith populations with all the others, they are quadratic operators involving f_i. For instance, encounters involving the ith- and j^{th}-population will contain both f_i and f_j. On the other hand, the operator $\mathcal{I}_i$ only involve f_i. In fact, the intrinsic evolution operator $\mathcal{I}_i$ deals with the inner development of cells of the ith-population, independently of their contacts with other cells. Finally, the source/sink operator $\mathcal{S}_i$ may depend on all cells as, for instance, the input/output of cells of a population from outside can depend on the state of the other populations.

The specific form of the operators in (3.3) can be determined looking more in detail at the phenomena already mentioned in Assumption 3.3. The model will be developed here under the following specific assumptions.

ASSUMPTION 3.4. Cell interactions in the case of mass conservative encounters will be defined by means of two physical quantities: the encounter rate η_{ij} and the transition probability density ψ_{ij}. More in detail, conservative encounters between the cell of the ith-population with state v and the cell of the jth-population with state w are quantitatively described by the transition rate

$$T_{ij}(v, w; u) = \eta_{ij}(v, w)\psi_{ij}(v, w; u), \tag{3.4}$$

where $\eta_{ij}(v, w)$ 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 ith-cell to the state u, given its initial state v and the state w of the encountering cells belonging to the jth-population. Hence, $T_{ij}(v, w; u)$ 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, with transition of the ith-cells into the state u.

ASSUMPTION 3.5. Proliferative encounters will be described by two quantities: the proliferation rate p_{ij} and the proliferation probability density φ_{ij}. These encounters occur between cell pairs of the same or of different populations, and generate new cells in one or both populations. These interactions are quantitatively described by the proliferation transition rate

$$P_{ij}(v, w; u) = p_{ij}(v, w)\varphi_{ij}(v, w; u), \tag{3.5}$$

where $p_{ij}(v, w)$ denotes the number of cells produced per unit volume and unit time due to the encounters of cell pairs of the $(i, j)^{th}$-populations with states v and w, respectively, and $\varphi_{ij}(v, w; u)$ is the probability density of proliferation of the ith-cell in the state u by encounters of cells belonging to the ith- and j^{th}-populations with state v and w, respectively. Hence, $P_{ij}(v, w; u)$ denotes the number of ith-cells in the state u per unit volume and unit time which proliferate because of the encounters between cell pairs of the $(i, j)^{th}$-populations with states v and w, respectively.

ASSUMPTION 3.6. *Destructive encounters occur between cell pairs of different populations, and generate a destruction in one or both populations. These interactions are quantitatively described by the* **destruction rate** $d_{ij}(v, w)$, *which is the number of* i^{th}-cells with state v destroyed as the result of the interaction with j^{th}-cells with state w.

ASSUMPTION 3.7. *For each population, it is possible to identify a function* $c_i(t, u)$, *such that in the interval* $[t, t + dt]$, *the cells of the* i^{th}-population change their state because of spontaneous maturation or induced actions from u to $u + du = u + c_i(t, u) dt$.

Focusing first on the cellular interaction operator, one can observe that, as in the Boltzmann equation, in $\mathcal{J}_i$ it is possible to distinguish a **gain** term $\mathcal{G}_i$ referring to those cells that after the interaction with other cells end up with a state u and a **loss** term $\mathcal{L}_i$ related to loss of cells having state u because of their transition into another state after their interactions with another cell, that is,

$$\mathcal{J}_i = \mathcal{G}_i - \mathcal{L}_i. \tag{3.6}$$

One can then summarize the results of cellular interactions as in Figure 5 and write for $i = 1, \ldots, n$,

$$\mathcal{G}_i = \sum_{j=1}^{n} \int_{-1}^{1} \int_{-1}^{1} T_{ij}(v, w; u) f_i(t, v) f_j(t, w) \, dv \, dw, \tag{3.7}$$

$$\mathcal{L}_i = f_i(t, u) \sum_{j=1}^{n} \int_{-1}^{1} \eta_{ij}(u, w) f_j(t, w) \, dw, \tag{3.8}$$

$$\mathcal{P}_i = \sum_{j=1}^{n} \int_{-1}^{1} \int_{-1}^{1} P_{ij}(v, w; u) f_i(t, v) f_j(t, w) \, dv \, dw, \tag{3.9}$$

$$\mathcal{D}_i = f_i(t, u) \sum_{j=1}^{n} \int_{-1}^{1} d_{ij}(u, w) f_j(t, w) \, dw, \tag{3.10}$$

where n is the number of populations.

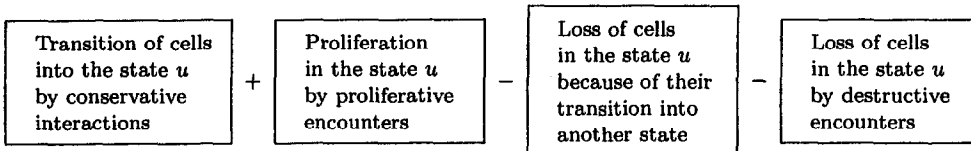| Transition of cells into the state u by conservative interactions | + | Proliferation in the state u by proliferative encounters | − | Loss of cells in the state u because of their transition into another state | − | Loss of cells in the state u by destructive encounters |

Figure 5. Representation of the interaction operator.

REMARK 3.2. The mass preserving action of the operator $\mathcal{J}_i$ reflects in the property

$$\int_{-1}^{1} \psi_{ij}(v, w; u) \, du = 1, \tag{3.11}$$

which implies that

$$\int_{-1}^{1} \mathcal{J}_i[\mathbf{f}](t, u) \, du = 0, \qquad \forall t, \quad i = 1, \ldots, n. \tag{3.12}$$

Focusing now on the intrinsic evolution operator, recalling Assumption 3.7 and Figure 6, one has that the i-cells with state in the interval $[\hat{u}, \tilde{u}]$ after a time element dt will have as a result of spontaneous maturation or induced action a new state in $[\hat{u} + d\hat{u}, \tilde{u} + d\tilde{u}] = [\hat{u} + c_i(t, \hat{u})\, dt, \tilde{u} + c_i(t, \tilde{u})\, dt]$. In particular, those which at time t were in $[u_1 - c_i(t, u_1)\, dt, u_1]$ at time $t + dt$ are in $[u_1, u_1 + c_i(t, u_1)\, dt]$, and therefore, they were outside $[u_1, u_2]$ and entered the interval. On the contrary, those with state in $[u_2 - c_i(t, u_2)\, dt, u_2]$ no longer belong to the interval $[u_1, u_2]$.
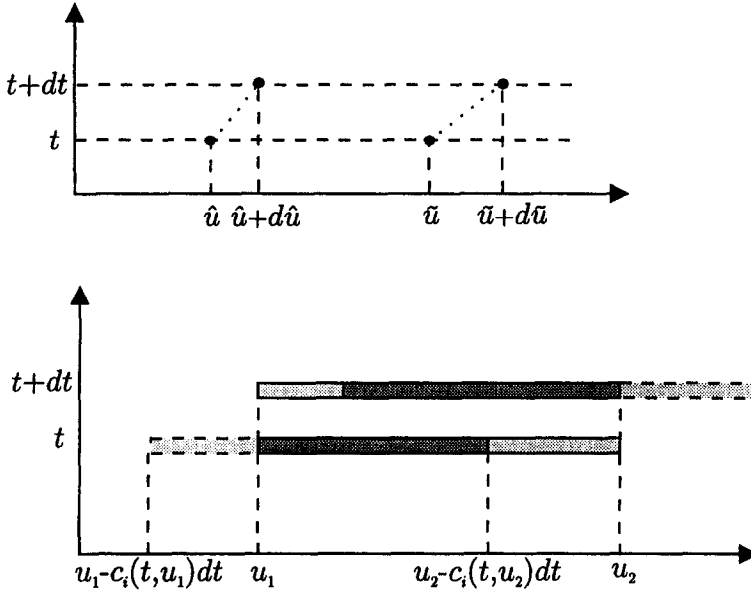

Figure 6. Graphical representation relative to the intrinsic operator.

Referring to [37] for more details, one can then write

$$\mathcal{I}_i\,[f_i]\,(t, u) = -\frac{\partial}{\partial u}\,[c_i(t, u) f_i(t, u)], \tag{3.13}$$

where c_i is the **activation velocity**, which may depend on time and, above all, on the state of the cell. Examples of physical meaning of such a term are the following:

$c_i > 0$ for tumor cells means natural transition from dormant into aggressive states,

$c_i < 0$ for tumor cells means weakening of aggressiveness due to medical actions,

$c_i > 0$ for immune cells means transition to immuno-active states,

$c_i < 0$ for immune cells means transition to immuno-depressive states.

REMARK 3.3. It can be observed that as spontaneous maturation or induced activation/deactivation is a mass preserving action

$$\int_{-1}^{1} \mathcal{I}_i\,[f_i]\,(t, u)\, du = 0, \qquad \forall t, \quad i = 1, \dots, n, \tag{3.14}$$

which is satisfied if

$$c_i(t, u = -1) f_i(t, u = -1) = c_i(t, u = 1) f_i(t, u = 1) = 0. \tag{3.15}$$

This represents a restriction on the form of the velocities of intrinsic evolution c_i and on the boundary condition to impose on f_i.

Summarizing, the general model can then be written as

$$\frac{\partial f_i}{\partial t}(t, u) + \frac{\partial}{\partial u}\left[c_i(t, u)f_i(t, u)\right] = s_i(t, u, \mathbf{f})$$

$$+ \sum_{j=1}^{n} \int_{-1}^{1}\int_{-1}^{1}\left[T_{ij}(v, w; u) + P_{ij}(v, w; u)\right]f_i(t, v)f_j(t, w)\, dv\, dw \qquad (3.16)$$

$$- f_i(t, u)\sum_{j=1}^{n}\int_{-1}^{1}\left[\eta_{ij}(u, w) + d_{ij}(u, w)\right]f_j(t, w)\, dw,$$

where the terms s_i refer to the introduction or destruction of i-cells from the outer ambient (see item (iv) of Assumption 3.3), which may generally depend on time, on the state of the cells, and on all f_j.

The evolution equation (3.16) represents a general framework which may include specific models to be developed after having specialized the populations and their interactions. This modelling should also take into account the role of cytokine signals.

It can be observed that if the right-hand side of equation (3.16) vanishes, i.e., in absence of cellular interactions and source/sinks terms, the equation writes as a conservation equation. Moreover, thanks to Remarks 3.2 and 3.3, the integration of (3.16) over u yields

$$\frac{\partial}{\partial t}\int_{-1}^{1}f_i(t, u)\, du = \int_{-1}^{1}s_i(t, u; \mathbf{f})\, du + \sum_{j=1}^{n}\int_{-1}^{1}\int_{-1}^{1}\tilde{P}_{ij}(v, w)f_i(t, v)f_j(t, w)\, dv\, dw, \qquad (3.17)$$

where

$$\tilde{P}_{ij}(v, w) = \int_{-1}^{1}P_{ij}(v, w; u)\, du - d_{ij}(v, w)$$

represents the net proliferation of cells due to encounters with other cells and recalling (3.1)

$$\int_{-1}^{1}f_i(t, u)\, du = \frac{n_i}{n_{e0}}.$$

3.2. The BFGP Kinetic Model

A specific model, originally proposed in [35] and further developed in [37], is reported in what follows. It concerns a simple two-population system, tumor and immune cells, where the number of environmental cells is constant in time, with activation localized on the value $u = 1$, and it is assumed that the rate of cytokine signals is known in time.

Moreover, the model is such that the large number of populations of the immune system are collected into one population only. This means that only an overall cooperative effect is considered which consists in the competition with tumor cells. Similarly, the same assumption is applied to environmental cells although not all of them have the same activation.

The activity of cytokine signals is assumed to regulate the interactions between tumor cells and the immune system. As a particular case, the signals may produce an activation of the immune system. In general, it is necessary to specialize and classify each signal, in order to properly model its activity.

Such a model is an example, certainly to be improved, of how the general theory of Section 3.1 can be particularized. Bearing this in mind, consider a physical system consisting of three interacting cell populations, each one denoted by the subscript i, with $i = 1, 2, 3$:

$i = 1$ refers to the tumor cells;

$i = 2$ corresponds to the cells of the immune system;

$i = 3$ corresponds to the cells of the host environment which in this case are assumed to be of constant population size.

Referring to **conservative encounters**, which are ruled by cytokine signals, the transition probability densities ψ are modelled with two parameters: variance σ and most probable output value m_{ij}. Interactions are described in the following models.

MODEL 3.1. Conservative encounters are only significant between tumor and immune cells. The **encounter rate** η, which refers to the rate of conservative encounters, is assumed to be constant and independent of the states of the interacting cells

$$\eta_{i3} = \eta_{11} = \eta_{22} = 0, \qquad \eta_{12} = \eta_{21}.$$

(Under this assumption, the time can be rescaled with respect to $\eta_{12} = \eta_{21}$.)

MODEL 3.2. Transitions of tumor cells after interactions between a tumor cell with state v and an immune cell with state w are characterized by the following expression for the most probable output value m_{12}:

$$v > 0 \begin{cases} w > 0 & \Rightarrow m_{12}(v,w) = v - \beta_{12}^+ wv, \\ w = 0 & \Rightarrow m_{12}(v,w) = v, \\ w < 0 & \Rightarrow m_{12}(v,w) = v - \beta_{12}^- w(1-v), \end{cases} \tag{3.18}$$

and

$$v \leq 0 \begin{cases} w > 0 & \Rightarrow m_{12}(v,w) = v, \\ w = 0 & \Rightarrow m_{12}(v,w) = v, \\ w < 0 & \Rightarrow m_{12}(v,w) = v - \beta_{12}^- w(1-v), \end{cases} \tag{3.19}$$

where $\beta_{12}^+, \beta_{12}^- \in [0,1]$. This model corresponds to the following.

- If the interacting immune cell is active ($w > 0$), the state of the active tumor cell decreases, being always above the limit dormant state $v = 0 : 0 \leq m_{12}(v,w) \leq v$.
- If the immune cell is inactive ($w = 0$), then the state of the tumor cell does not change.
- If the immune cell is degenerated ($w < 0$), then the state of the active tumor cell increases, being always below the limit activation state $v = 1 : v \leq m_{12}(v,w) \leq 1$. If the tumor cell has already reached its maximum activity $v = 1$, it cannot increases further: $m_{12}(v = 1, w < 0) = 1$.
- If the tumor cell is dormant, its state does not change, whether the immune cell is active or not.
- If the tumor cell is dormant and the immune cell is degenerated, then the state of the tumor cell increases (and eventually become aggressive).

MODEL 3.3. Transitions of immune cells after interactions between an immune cell with state v and a tumor cell with state w are characterized by the following expression for the most probable output value $m_{21}(v, w)$:

$$\begin{aligned} w > 0 &\Rightarrow m_{21}(v,w) = v - \beta_{21} w(1+v), \\ w \leq 0 &\Rightarrow m_{21}(v,w) = v, \end{aligned} \tag{3.20}$$

where $\beta_{21} \in [0,1]$. The model corresponds to the following.

- If the interacting tumor cell is active, i.e., $w > 0$, then the state of the immune cell decreases, being always above the maximum degeneration state $v = -1: -1 \leq m_{21}(v,w) \leq v$. If the immune cell has already reached its maximum degeneration state $v = -1$, it cannot decrease further, $m_{21}(v = -1, w > 0) = -1$. The higher the activity w of the tumor cell, the stronger is the disactivation of the immune cell.
- If the tumor cell is dormant ($w \leq 0$), the state of the immune cell does not change.

MODEL 3.4. Cytokine signals are assumed to operate on conservative encounters only. This means that the signals operate only on the parameters β in (3.18)–(3.20). The activity of cytokine signals depends both on the type and on the amount of signal itself. We define

$$\beta_{ij} = \beta_{ij}^c \, c_{ij}(t), \tag{3.21}$$

where β_{ij}^c characterizes the type of signal and c_{ij} the normalized amount of signal itself, which is assumed to be a known function of time.

Referring now to **proliferative and destructive encounters**, we start specializing the form of the probability density assuming the following.

MODEL 3.5. When a cell, stimulated by the interaction with other cells, undergoes mitosis, the newborn cell inherit the same aggressive state as the mother cell. This means saying that

$$P_{ij}(v, w; u) = p_{ij}(v, w)\delta(v - u),$$

where δ is the Dirac delta function.

The proliferation term (3.9) then simplifies to

$$\mathcal{P}_i = f_i(t, u) \sum_{j=1}^{n} \int_1^1 p_{ij}(u, w) f_j(t, w) \, dw. \tag{3.22}$$

Therefore, the net generation of cells is given by

$$\mathcal{P}_i - \mathcal{D}_i = f_i(t, u) \sum_{j=1}^{n} \int_1^1 \mu_{ij}(u, w) f_j(t, w) \, dw, \tag{3.23}$$

where

$$\mu_{ij}(u, w) = p_{ij}(u, w) - d_{ij}(u, w). \tag{3.24}$$

The total change μ resulting from proliferation and destruction can be positive (net proliferation) or negative (net destruction) depending on the prevailing action. Interactions are modelled as follows.

MODEL 3.6. The destructive and proliferative actions are a consequence of the activation state of each cell. Interactions between a tumor cell with state v and environmental or immune cells with state w are modelled by the following proliferation and destruction terms:

$$\mu_{11}(v, w) = 0, \tag{3.25}$$

$$v > 0 \begin{cases} w \geq 0 & \Rightarrow \mu_{12}(v, w) = -\delta_{12}w, \\ w < 0 & \Rightarrow \mu_{12}(v, w) = -\gamma_{12}vw, \end{cases} \tag{3.26}$$

and

$$\begin{aligned} v \leq 0 &\Rightarrow \mu_{12}(v, w) = 0, \\ v \leq 0 &\Rightarrow \mu_{13}(v, w) = 0, \\ v > 0 &\Rightarrow \mu_{13}(v, w) = \gamma_{13}vw. \end{aligned} \tag{3.27}$$

Interactions between an immune cell with state v and environmental or tumor cells with state w are modelled by the following proliferation and destruction terms:

$$\begin{aligned} w \geq 0 &\Rightarrow \mu_{21}(v, w) = \gamma_{21}, \\ w < 0 &\Rightarrow \mu_{21}(v, w) = 0, \end{aligned} \tag{3.28}$$

$$\begin{aligned} \mu_{22}(v, w) &= 0, \\ \mu_{23}(v, w) &= -\delta_{23}w, \end{aligned} \tag{3.29}$$

where the terms γ and δ refer, respectively, to proliferation and destruction. The above models correspond to the following.

  – Proliferation of tumor cells is significant only for interactions with the degenerated immune cells and for interactions with the environmental cells. Proliferation only occurs for

aggressive states $v > 0$, and is directly proportional to the aggressivity of the tumor v and to the negative activation of the degenerated immune cells $-w$ and to the activation of the environmental cells.

- Proliferation of immune cells occurs in the interaction with active tumor cells and is independent on the activation state of the pair.
- Destruction of aggressive tumor cells only occurs in the interaction with active immune cells and is directly proportional to the activation state of the immune cells.

The intrinsic evolution of cells is modelled as follows.

MODEL 3.7. Cells belonging to the tumor and to the immune system can both increase their peculiar activity even in absence of interaction with other cells. The tumor cells are assumed to have a spontaneous tendency to pass from a dormant $(u < 0)$ to an aggressive state $(u \geq 0)$. The immune system can be, instead, pharmacologically stimulated. In both cases, activation cannot overcome the maximum value $u = 1$ and can be modelled as

$$c_i^+(u) = \alpha_i^+(1 - u), \qquad \alpha_i^+ \geq 0, \quad i = 1, 2. \tag{3.30}$$

In addition, tumor cells can be medically deactivated and induced in a dormant state. This action cannot overcome the limit dormant state $u = -1$ and can be modelled as

$$c_1^-(u) = -\alpha_1^-(1 + u), \qquad \alpha_1^- \geq 0. \tag{3.31}$$

It is useful to remark explicitly that the dependence of c_i on u is not related to the medical action, which, of course, cannot be state dependent, but on the fact that a drug acts differently on cells having different states. For instance, a "good drug" aimed at activating the immune system will have a stronger impact on those cells which are inactive $(u = 0)$ or even degenerate $(u < 0)$ than on those cells which are already active $(u > 0)$. In particular, it will have no effect at all on those cells which are already fully active $(u = 1)$.

In addition, both the medical action and its effects are naturally time dependent. Therefore, a better description would have to include, for instance, the time dependence of α_2^+ and α_1^-.

Finally, among several possible actions, source/sink terms are modelled as follows.

MODEL 3.8. Source/sink terms are related to the introduction of newborn cells and of the destruction of existing cells. Some of these phenomena occur naturally, others have a medical origin. For instance, one can have

(i) destruction of tumor cells by medical treatment

$$g_1(t, u) = -\delta_1 f_1(t, u); \tag{3.32}$$

(ii) production of cells from the bone marrow, which can possibly be pharmacologically stimulated

$$g_2(u) = \gamma_2 u H(u), \tag{3.33}$$

where $H(u)$ is the Heaviside function;

(iii) destruction of cells of the immune system as a by-product of the medical therapy in (i)

$$g_2^-(t, u) = -\delta_2 f_2(t, u). \tag{3.34}$$

Also in this case, as medical therapies are time dependent, the coefficients should depend on time.

The evolution equation obtained using the above assumption consists in the following system of two coupled integro-differential equations:

$$\frac{\partial f_1}{\partial t}(t, u) + \frac{\partial}{\partial u}\left[c_1(u) f_1(t, u)\right] = \int_{-1}^{1} \int_{-1}^{1} \psi_{12}\left(u, m_{12}(v, w); \beta_{12}^c c_{12}(t), \sigma\right) f_1(t, v) f_2(t, w)\, dv\, dw$$

$$+ f_1(t, u) H(u) \left[\gamma_{13} u - \gamma_{12} u \int_{-1}^{0} w f_2(t, w)\, dw - \delta_{12} \int_{0}^{1} w f_2(t, w)\, dw\right]$$

$$- f_1(t, u) \left[\delta_1 + \int_{-1}^{1} f_2(t, w)\, dw\right], \tag{3.35}$$

$$\frac{\partial f_2}{\partial t}(t, u) + \frac{\partial}{\partial u}\left[c_2^+(u) f_2(t, u)\right] = \int_{-1}^{1} \int_{-1}^{1} \psi_{21}\left(u, m_{21}(v, w); \beta_{21}^c c_{21}(t), \sigma\right) f_2(t, v) f_1(t, w)\, dv\, dw$$

$$+ f_2(t, u) \left[- \int_{-1}^{1} f_1(t, w)\, dw + \gamma_{21} \int_{0}^{1} f_1(t, w)\, dw - \delta_{23} - \delta_2\right] + \gamma_2 u H(u),$$

where

$$c_1(u) = \alpha_1^+(1 - u) - \alpha_1^-(1 + u) \tag{3.36}$$

and the detailed expression of the ψ terms and the meaning of the various parameters have been defined above.

4. MATHEMATICAL ASPECTS OF MACROSCOPIC MODELLING

Macroscopic models are needed when tumor cells are not suppressed after their formation by the immune system, and aggregate into a multicell spheroid. The tumor then interacts with the outer environment mainly by the use of chemical signals which diffuse through the tumor and outside it. In addition, cells located on the surface can interact with other cells of the environment and capillary sprouts can penetrate into the spheroid. The phenomenological behavior of the system was briefly described in Section 2. Mathematical models should be able to simulate such a behavior both for the avascular and the vascular phase. Microscopic cellular description can be used to support continuum theories as an alternative to a totally phenomenological approach developed without a proper link between the cellular and the macroscopic scale.

In general, the following sequential steps towards modelling can be indicated.

STEP 1. Definition of the macroscopic geometry of the material system, and hence, of the independent variables.

STEP 2. Selection of the dependent variables to describe the evolution of the biological system.

STEP 3. Modelling of the diffusion and transport phenomena related to the evolution of the dependent variables in time and space.

STEP 4. Modelling generation and death phenomena related to several cellular activities as those described in Section 3.

Several interesting contributions are available in the literature, which develop continuum models where the relevant phenomena are described by simple diffusion equations.

Reference prior to 1995 can be recovered in [1,3,40,41]. Regarding the most recent papers, one can classify the papers according to the phase of growth they focus on.

Most of the papers consider the avascular phase, focusing on different aspects: the effect of time delays [19], the death mechanisms [20], the role of growth factors [21,22], and the inclusion of the intercellular fluid or of other cell populations [30–32]. In particular, the interaction between the tumor and macrophages is studied in [28,29].

Regarding angionesis, [15,16] study the interactions between the capillary sprout tip density, the vessel density within a sprout, and the concentration of TAF. On the other hand, [24,25,27] focus on the evolution of endothelial cells in presence of TAF and fibronectin.

Regarding the study of the vascular phase and the formation of metastasis, the paper by Orme and Chaplain [26] and the special issue edited by Michelson [42] represent good starting points. In addition, the effect of cell adhesion in tumor invasion and in the development of carcinomas is studied in [43,44]. Comparisons between predictions of the model and experimental results are also developed in [45–47].

In principle, modelling should be able to take into account the whole variety of the evolution through the sequential phases: avascular, angiogenic, and vascular. Bearing this in mind, we refer mainly to [48] where the analysis was specifically developed to provide a model suitable to provide the overall description. Nevertheless, several contributions available in the literature will not be ignored.

Following the same line of the preceding section, we first provide a description of the general mathematical framework which can be used to generate the models, then specific examples of models describing the material behavior of the system are given. In this case, both a continuum mechanics and a random walk framework can be used, which also allows us to put in evidence the relation between microscopic phenomena and macroscopic parameters. Linking the material models to the general evolution equation yields the specific evolution model. Again, such a model can, and should, be improved (as discussed in the last section) on the basis of a relatively deeper analysis of cellular phenomena.

4.1. Mathematical Structure of Continuum Models

In order to describe the mathematical structure of continuum models, some geometrical notations have to be introduced. Referring to Figure 7, $\mathcal{T}(t)$ is the region occupied by the tumor mass. This is a time dependent domain included in a much larger fixed domain $\mathcal{D}$ which will be called environment. The region $\mathcal{D} - \mathcal{T}$ will be called outer environment. According to the observations above, it is expected that the evolution of the tumor leads to the formation of a necrotic region inside $\mathcal{T}$ (the darker region in Figure 7). Capillaries initially exist only outside $\mathcal{T}$, i.e., in the outer environment, but because of angiogenesis, they can penetrate into the tumor, and therefore, it is expected that the evolution leads to the formation of capillary sprouts within $\mathcal{T}$. Growth inhibitory factors and tumor angiogenesis factors are produced inside $\mathcal{T}$ but can diffuse in the outer environment. The former have no effect outside the tumor as there are no tumor cells to act upon, the latter have outside their main functional activity as initially the endothelial cells to be stimulated are in $\mathcal{D} - \mathcal{T}$.
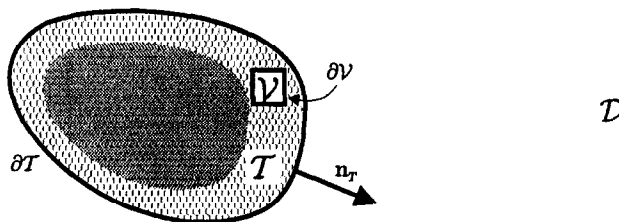

Figure 7. Geometry of solid tumors.

The macroscopic mathematical model consists in an evolution equation for the variable $\mathbf{u} = \mathbf{u}(t, \mathbf{x})$ deemed to describe, in time (t) and space $(\mathbf{x})$, the physical state of the system. The variable $\mathbf{u}$ includes both cell populations and chemical substances (or factors) produced in the environment by interacting cells.

Between these two classes there is, however, a deep difference as cells are much larger than chemical factors and macromolecules. In addition, cells occupy part of the available space and cannot penetrate each other, so that one can take as state variables their volume ratio, i.e., the volume occupied by the ith-species over the total volume. If each cell is modelled as a deformable membrane containing a definite amount of an incompressible liquid, this choice is equivalent to choosing as state variables the number densities or the mass densities.

Chemical factors and nutrients are molecules which diffuse in the intercellular space, attach to the cell membrane, or pass through it, so that it can be assumed that they do not occupy space. One can then take as state variables their concentrations.

The derivation of the model here described is developed, following [48], on the basis of mass balance equations, also supported by a random walk scheme. The former viewpoint corresponds to write integral balances on the basis of the following scheme:

Rate of change of the number of cells in a control volume	=	Generation of cells in the control volume	−	Death of cells in the control volume

−	Advective outflow through the boundary of the control volume	−	Random outflow through the boundary of the control volume

(4.1)
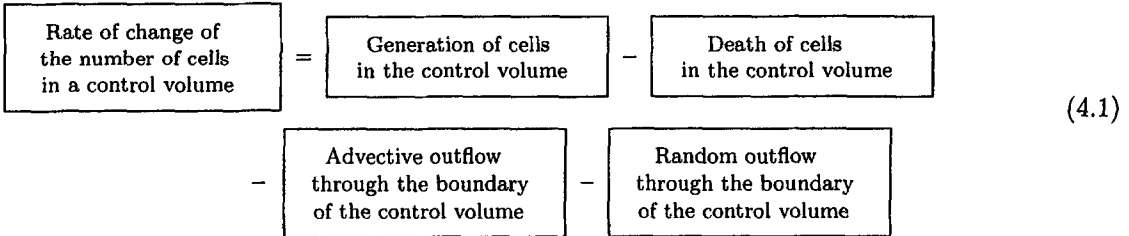
Under suitable regularity assumptions, one can then write the following general balance law in local form:

$$\frac{\partial u}{\partial t} = -\nabla \cdot (\mathbf{W}u) - \nabla \cdot (Q\nabla u) + \Gamma - Lu, \qquad (4.2)$$

where $\mathbf{W}$ is the convective velocity, Q is the diffusion coefficient, Γ is the proliferation term per unit volume, and L is the death coefficient.

The general idea of the random walk approach consists in defining a framework model for the advection-diffusion phenomena for a system on a cubic lattice.

All cells and chemical factors contained in the elementary volume $\mathcal{V}_{ijk}$ centered in the point (x_i, y_j, z_k) of the lattice are considered concentrated in the lattice point (x_i, y_j, z_k). One aims at studying the evolution of the number of a particular cell (or chemical factor) $N_{ijk}(t)$ found in the node (x_i, y_j, z_k) at time t, which is related to its density through

$$N_{ijk}(t) = \int_{\mathcal{V}_{ijk}} u(t, \mathbf{x}) \, d\mathbf{x}. \qquad (4.3)$$

The evolution is governed by the probabilities of motion along the lattice, of proliferation, and of death.

A comparison between the two approaches is particularly interesting not only to draw a line between observations done at a microscopic level and macroscopic parameters, but also as a simulation tool, for instance, as done in [25,30,49].

4.2. The DP Mathematical Model

A specific model generated within the above general framework is here described with reference to [48] for more details. The model aims at describing the evolution of the following variables:

  - the density u_T of living tumor cells;
  - the density u_D of dead tumor cells;
  - the density u_I of growth inhibitory factor, usually shortened as GIF;
  - the density u_A of tumor angiogenesis factor, usually shortened as TAF;
  - the density u_C of the endothelial cells;
  - the density u_N of nutrient.

The specific form of the drift, diffusion, gain, and loss terms is based on the following assumptions.

MODEL 4.1. TUMOR EVOLUTION.

  - Mitosis occurs only if tumor cells receive a quantity of nutrient $\tilde{u}_N$, which can be strictly larger than the amount $\bar{u}_N$ necessary for its survival.

- Proliferation is affected by a chemical factor called growth inhibitory factor (GIF), which inhibits mitosis and by the amount of nutrient which promotes it.
- Tumor cells die only if the nutrient is not sufficient to feed all cells.
- There exists a threshold density $\overline{u}$ characterized by the fact that if the total density of all cells in a point is above it, then tumor cells feel pressed by their neighbours and tend to migrate towards a region characterized by a lower total density.
- Dead tumor cells do not move.
- Dead tumor cells naturally disintegrate into waste products, mainly water.
- Dead tumor cells outside the tumor are eaten by macrophages.

MODEL 4.2. CHEMICAL FACTOR EVOLUTION.

- Living tumor cells constantly produce the chemical factors (GIF and TAF).
- The chemical factors diffuse both in the region $\mathcal{T}(t)$ occupied by the tumor and in the tumor-free region.
- The diffusion mechanism of the chemical factors is the same and may depend on the effective overall density, as cells occupy part of the space where the factors diffuse. In particular, it may be drastically different inside and outside the tumor.
- Chemical factors naturally degrade.

MODEL 4.3. ANGIOGENESIS.

- When stimulated by TAF, endothelial cells proliferate at a rate proportional to the concentration of TAF. In addition, proliferation decreases with the density of new capillaries. In particular, it stops if the density of endothelial cells is higher than a threshold value.
- Newborn endothelial cells both move randomly and migrate toward the source of angiogenic stimulus giving rise to the formation of capillary sprouts by accumulation of endothelial cells.
- Newborn endothelial cells undergo natural death, while old capillaries are constantly replaced so that their distribution is constant in time.
- Proteins like angiostatins are modelled as having the ability of stopping the proliferation of endothelial cells, e.g., by drastically reducing their sensitivity to the presence of TAF.

MODEL 4.4. NUTRIENT DIFFUSION.

- Nutrients are mainly carried by the capillary network, though some nutrients diffuse through the environment outside the capillary network. In particular, in absence of capillaries the region outside the tumor is kept at a constant amount of nutrient. With the formation of capillaries, the nutrient reaching the tumor surface increases proportionally to the capillary density.
- Nutrient diffusion in the tumor is promoted by the presence of capillaries.
- Nutrient is absorbed by living tumor cells.

According to these hypotheses, one can formalize the description above specializing the different terms in (4.2) as detailed in Table 1, where $\chi_T(t, \mathbf{x})$ is the characteristic function of $\mathcal{T}(t)$, $\widehat{u}_C = \widehat{u}_C(\mathbf{x})$ is the density of the pre-existing capillary density, and $u = u_T + u_D + u_C + \widehat{u}_C$ is the overall density of all cells.

Summing up the model writes

$$
\text{in } \mathcal{D}: \quad
\begin{cases}
\dfrac{\partial u_I}{\partial t} = k_F \nabla^2 u_I + \gamma_I \chi_T u_T - \delta_I u_I, \\[2mm]
\dfrac{\partial u_A}{\partial t} = k_F \nabla^2 u_A + \gamma_A \chi_T u_T - \delta_A u_A, \\[2mm]
\dfrac{\partial u_C}{\partial t} + w_C \nabla \cdot (u_C \nabla u_A) = k_C \nabla^2 u_C + \gamma_C u_A \left(\overline{u}_C - u_C\right)_+ \left(u_C + \widehat{u}_C\right) - \delta_C u_C,
\end{cases}
\tag{4.4a}
$$

Table 1.

	W	Q	Γ	L
u_I	0	k_F	$\gamma_I \chi_T(t,\mathbf{x}) u_T$	δ_I
u_A	0	k_F	$\gamma_A \chi_T(t,\mathbf{x}) u_T$	δ_A
u_C	$w_C \nabla u_A$	k_C	$\gamma_C u_A \left(\bar{u}_C - u_C\right)_+ \left(u_C + \hat{u}_C\right)$	δ_C
u_T	$-w_T \nabla u$	0	$\dfrac{\gamma_T u_N u_T H\left(u_N - \tilde{u}_N u_T\right)}{\varepsilon + \alpha u_I}$	$\delta_T H\left(\bar{u}_N u_T - u_N\right)$
u_D	0	0	$\delta_T H\left(\bar{u}_N u_T - u_N\right) u_T$	δ_D
u_N	0	$k_E + k_N\left(u_C + \hat{u}_C\right)$	0	$\delta_N u_T$

$$
\text{in } \mathcal{T}(t): \quad \begin{cases} \dfrac{\partial u_T}{\partial t} = w_T \nabla \cdot (u_T \nabla u) + \dfrac{\gamma_T u_N u_T}{\varepsilon + \alpha u_I} H\left(u_N - \tilde{u}_N u_T\right) - \delta_T H\left(\bar{u}_N u_T - u_N\right) u_T, \\[2mm] \dfrac{\partial u_D}{\partial t} = \delta_T H\left(\bar{u}_N u_T - u_N\right) u_T - \delta_D u_D, \\[2mm] \dfrac{\partial u_N}{\partial t} = \nabla \cdot \left[\left(k_E + k_N\left(u_C + \hat{u}_C\right)\right) \nabla u_N\right] - \delta_N u_T u_N. \end{cases} \quad (4.4b)
$$

Some of the state variables in (4.4), more precisely u_I, u_A, and u_C, are defined in the whole environment $\mathcal{D}$, while others, namely u_T, u_D, and u_N, are defined in the tumor only $\mathcal{T}(t)$. As this region depends on time (e.g., the tumor grows), one has to give an evolution equation which is in charge of determining the position $\mathbf{x} = \mathbf{x}_T(t)$ of the border $\partial \mathcal{T}(t)$ of the tumor. Referring to Figure 7, it can be realized that this interface is a material boundary for the tumor, and therefore, moves solidly with the tumor cells at the free surface, i.e., referring more specifically to Table 1 and to (4.4)

$$
\mathbf{n}_T \cdot \frac{d\mathbf{x}_T}{dt} = \mathbf{n}_T \cdot \mathbf{W}_T\left(\mathbf{x}_T\right) = -w_T \mathbf{n}_T \cdot \nabla u\left(\mathbf{x}_T\right). \quad (4.5)
$$

The mathematical problem describing the evolution of the tumor in presence of angiogenesis then writes as a free-boundary value problem. The mathematical structure of the model is rather complex. It consists of three parabolic equations valid in the whole domain $\mathcal{D}$. Those referring to the chemical factors are diffusion equations, while that referring to the formation of capillary sprouts is an advection-diffusion equation which can be advection dominated, i.e., dominated by chemotaxis. Within the time dependent domain referring to the tumor, one has parabolic equations for the nutrient and for the living tumor cells and a hyperbolic equation for the dead cells.

This last equation needs a boundary condition to be imposed on the border of the tumor when the tumor is growing, corresponding to the case of characteristics related to the hyperbolic equation entering the expanding domain $\mathcal{T}(t)$.

As the motion is due to the generation and motion of living tumor cells, one can impose that there are no dead cells at the surface

$$
u_D\left(\mathbf{x}_T(t), t\right) = 0. \quad (4.6)
$$

Furthermore, as the tumor surface is stress-free, the cells are not compressed there and the overall density u is equal to the close packing one $\bar{u}$, so that one can write

$$
u_T\left(\mathbf{x}_T(t), t\right) = \bar{u} - u_C\left(\mathbf{x}_T(t), t\right) - \hat{u}_C\left(\mathbf{x}_T(t)\right). \quad (4.7)
$$

In summary, (4.4) is supplemented by the boundary conditions

$$
\text{on } \partial \mathcal{D}: \quad u_I = 0, \quad u_A = 0, \quad u_C = 0, \quad (4.8)
$$

and

$$\text{on } \partial\mathcal{T}(t): \quad \begin{cases} u_T = \overline{u} - u_D - u_C - \widehat{u}_C, \\ u_N = \varepsilon + \beta\,(u_C + \widehat{u}_C), \\ u_D = 0, \quad \text{if } \mathbf{W}_T \cdot \mathbf{n}_T > 0. \end{cases} \tag{4.9}$$

The free boundary value problem can be formulated in a dimensionless form by normalizing, for instance, space by $\sqrt{k_E/\delta_N\overline{u}}$, time by γ_T, cell densities (i.e., u_T, u_D, u_C, $\widehat{u}_C$, and u) by $\overline{u}$, nutrient density by ε, and chemical factor densities by $\gamma_i\overline{u}/\gamma_T$, $(i = A, I)$. Denoting by a star the dimensionless quantities the free boundary problem writes

$$\text{in } \mathcal{D}: \quad \begin{cases} \dfrac{\partial u_I^*}{\partial t^*} = k_F^* \nabla^2 u_I^* + \chi_T u_T^* - \delta_I^* u_I^*, \\[2mm] \dfrac{\partial u_A^*}{\partial t^*} = k_F^* \nabla^2 u_A^* + \chi_T u_T^* - \delta_A^* u_A^*, \\[2mm] \dfrac{\partial u_C^*}{\partial t^*} + w_C^* \nabla \cdot (u_C^* \nabla u_A^*) = k_C^* \nabla^2 u_C^* + \gamma_C^* u_A^* \,(\overline{u}_c^* - u_C^*)_+ \,(u_C^* + \widehat{u}_C^*) - \delta_C^* u_C^*, \end{cases} \tag{4.10}$$

$$\text{in } \mathcal{T}(t^*): \quad \begin{cases} \dfrac{\partial u_T^*}{\partial t^*} = w_T^* \nabla \cdot (u_T^* \nabla u^*) + \dfrac{u_T^* u_N^*}{1 + \alpha^* u_I^*} H\,(u_N^* - \widetilde{u}_N^* u_T^*) - \delta_T^* H\,(\overline{u}_N^* u_T^* - u_N^*)\,u_T^*, \\[2mm] \dfrac{\partial u_D^*}{\partial t^*} = \delta_T^* H\,(\overline{u}_N^* u_T^* - u_N^*)\,u_T^* - \delta_D^* u_D^*, \\[2mm] \dfrac{\partial u_N^*}{\partial t^*} = \delta_N^* \{\nabla \cdot [(1 + k_N^*\,(u_C^* + \widehat{u}_C^*))\,\nabla u_N^*] - u_T^* u_N^*\}, \end{cases} \tag{4.11}$$

with boundary conditions

$$\text{on } \partial\mathcal{T}(t^*): \quad \begin{cases} u_T^* = 1 - u_D^* - u_C^* - \widehat{u}_C^*, \\ u_N^* = 1 + \beta^*\,(u_C^* + \widehat{u}_C^*), \\ u_D^* = 0, \quad \text{if } \mathbf{W}_T^* \cdot \mathbf{n}_T > 0, \end{cases} \tag{4.12}$$

$$\text{on } \partial\mathcal{D}: \qquad u_I^* = u_A^* = u_C^* = 0, \tag{4.13}$$

and initial conditions

$$\text{in } \mathcal{D}: \qquad u_I^* = u_A^* = u_C^* = 0, \tag{4.14}$$

$$\text{in } \mathcal{T}(t^* = 0): \quad u_T^* = u_N^* = 1, \qquad u_D^* = 0, \tag{4.15}$$

$$\mathbf{x}_T^*(0) = \mathbf{x}_0^*, \tag{4.16}$$

where

$$\delta_N^* = \frac{\delta_N\overline{u}}{\gamma_T}, \qquad \delta_i^* = \frac{\delta_i}{\gamma_T}, \qquad i = A, C, D, I, T,$$

$$k_F^* = \frac{k_F\delta_N\overline{u}}{k_E\gamma_T}, \qquad k_N^* = \frac{k_N\overline{u}}{k_E}, \qquad k_C^* = \frac{k_C\delta_N\overline{u}}{k_E\gamma_T},$$

$$\alpha^* = \frac{\alpha\gamma_I\overline{u}}{\gamma_T\varepsilon}, \qquad \beta^* = \frac{\beta\overline{u}}{\varepsilon}, \qquad \gamma_C^* = \frac{\gamma_C\gamma_A\overline{u}^2}{\gamma_T^2}, \tag{4.17}$$

$$w_C^* = \frac{w_C\delta_N\gamma_A\overline{u}^2}{k_E\gamma_T^2}, \qquad w_T^* = \frac{w_T\delta_N\overline{u}^2}{k_E\gamma_T},$$

$$\widetilde{u}_N^* = \frac{\overline{u}\widetilde{u}_N}{\varepsilon}, \qquad \overline{u}_N^* = \frac{\overline{u}\,u_N}{\varepsilon}.$$

Useful dimensionless numbers can also be

$$\kappa_C^* = \frac{k_C}{k_E} = \frac{k_C^*}{\delta_C^*}, \qquad \kappa_F^* = \frac{k_F}{k_E} = \frac{k_F^*}{\delta_C^*}, \tag{4.18}$$

which are the ratio of the diffusion coefficients, and

$$\omega_C^* = \frac{w_C^*}{k_C^*} = \frac{w_C \gamma_A \overline{u}}{k_C \gamma_T}, \qquad \omega_T^* = \frac{w_T^*}{w_C^*} = \frac{w_T \gamma_T}{w_C \gamma_A}, \qquad (4.19)$$

which, respectively, give an indication of the relative importance of the **diffusion term** versus the **chemotactic one** in the equation for the capillaries and of the ratio of **tumor growth acceleration** over **chemotactic acceleration** in the equation for the living tumor cells.

5. ON THE LINKS AMONG SUBCELLULAR, CELLULAR, AND MACROSCOPIC SCALES

The relevant phenomena describing the immune competition are developed, as shown in Section 3, at the cellular scale. Cellular phenomena are also crucial when tumor cells aggregate into a solid form, or when a solid structure releases metastases. Research papers show a constant effort to link cellular models to macroscopic ones. Analyzing this aspect is a challenging, however difficult, topic which will definitively attract future research activity of applied mathematicians. At present, we have to recognize that despite great efforts and some encouraging results, a satisfactory analysis still has to be developed. This means that our review will be limited to describe some open problems, and to give some hints toward their analysis.

Following the presentation of the preceding sections, we deal separately with cellular and macroscopic models.

5.1. Kinetic Cellular Models

Kinetic cellular models are developed within a general framework which ends up into a system of evolution equations providing the statistical behavior of the system. These models have to be particularized by using microscopic models suitable to describe cellular interactions. Specifically, microscopic models should be able to describe activation and inhibition of immune cells and destructive proliferative processes.

Cellular models available in the literature, e.g., [34–39], can certainly be improved on the basis of theories available in cellular biology. The task consists in interpreting the relevant subcellular actions and modelling their effect on cellular interactions. An aspect which is not taken into account in the models reviewed in Section 3 is the onset of neoplastic cells. This phenomenon may be studied by suitable analysis and modelling of the cell properties. Specifically, one has to analyze the problem of loss of differentiation of cells which degenerate, due to DNA modifications, into neoplastic cells, see, for instance, [50].

Referring to models available in the literature and reviewed in Section 3, we observe that three classes of parameters characterize the model:

- β-type parameters characterize conservative interactions which generate modification of the state, but not of the number of cells;
- γ-type parameters characterize proliferative interactions which generate an increase in the number of cells;
- δ-type parameters characterize destructive interactions which generate a decrease in the number of cells.

As suggested in [4], their identification can be based either on modelling subcellular properties, or on experiments addressed to estimate the parameters by observed data on the growth of tumors. For instance, γ-type parameters can be estimated observing the growth in absence of the competition of the immune system, that is, when it is suppressed.

A preliminary analysis was developed in [34], where experimental results have put in evidence the large quantitative difference between the growth in an environment with active or suppressed immune system. Then, once the proliferation parameters have been identified, one can proceed in a similar way to the identification of the δ-type parameters.

On the other hand, no useful suggestion is given, until now, for the assessment of β-type parameters. What we know is that computational simulations have put in evidence, as it will be discussed in Section 7, that the role of the above parameters is relevant in determining the asymptotic behaviour of the solution. Indeed, one can identify a bifurcation parameter separating a behaviour with suppression of tumor cells, to that characterized by their continuous growth. The bifurcation parameter may be put in relation to the action of cytokine signals.

Moreover, one should investigate whether the mathematical structure given in Section 3 needs further developments in order to include relatively sophisticated models. For instance, an interesting model, however different from that given above, was proposed in [51]. The papers suggest to introduce for each cell a state, called **progression**, which characterizes the progression of the cell toward degenerate states. Low values correspond to normal cells, high values progressively to loss of differentiation, dormant state, proliferative, metastatic, etc. The system is regarded as a population of cells with statistical distribution over their state. Indeed, it is a framework similar to the one described in Section 3. However, the difference is not simply technical and deserves the development of a suitable mathematical framework. Possibly, a new framework will require different modelling of cell interactions, and hence, of subcellular models.

5.2. Macroscopic Models

Macroscopic models were derived using diffusion equations related to mass balance and including mass production and destruction. The link between the macroscopic and microscopic and cellular scales has to be referred to the parameters characterizing the model. These parameters can be grouped as follows: production coefficients are denoted by the letter γ, death coefficients by the letter δ, diffusion coefficients by the letter k, transport coefficients by the letter w, and reference densities by $(\overline{u}_i, \widehat{u}_i)$. More in detail follows.

GROWTH COEFFICIENTS.

   α refers to the inhibited proliferative effect due to the presence of GIF.

   γ_I is the production coefficient of GIF from living tumor cells.

   γ_A is the production coefficient of TAF from living tumor cells.

   γ_C is the proliferative coefficient of endothelial cells.

   γ_T is the proliferative coefficient of tumor cells.

DESTRUCTION COEFFICIENTS.

   δ_I is the degradation coefficient of GIF.

   δ_A is the degradation coefficient of TAF.

   δ_C is the natural death coefficient of endothelial cells.

   δ_T is the death coefficient of tumor cells when the nutrient is not sufficient to feed all cells.

   δ_D is the disintegration coefficient into waste products of dead tumor cells.

   δ_N is the absorption coefficient of nutrient from active tumor cells.

REFERENCE AND THRESHOLD DENSITIES.

   $\overline{u}_N$ is the amount of nutrient needed to feed a tumor cell.

   $\widetilde{u}_N$ is the amount of nutrient needed per tumor cell to start proliferating.

   $\overline{u}$ is the threshold density, here called close packing density, above which living tumor cells are pushed toward regions with smaller effective overall density.

   $\overline{u}_C$ is the threshold overall density above which endothelial cells are not generated.

   $\widehat{u}_C$ is the density of pre-existing capillaries from which new capillaries start being generated. This is a space dependent function.

DIFFUSION COEFFICIENTS.

   k_F is the diffusion coefficient of chemical factors.

   k_C is the diffusion coefficient of endothelial cells.

k_E is the diffusion coefficient of nutrient outside the capillary network inside the tumor.

k_N is the diffusion coefficient of nutrient through the capillary network inside the tumor.

DRIFT VELOCITIES.

w_C is the migration coefficient of capillary sprouts towards the source of angiogenic stimulus.

w_T is the migration coefficient of active tumor cells toward less compressed regions.

Each parameter refers to a well-defined phenomenon and has a particular effect on a specific cell population. Some of the parameters should be identified by models developed at the cellular scale. On the other hand, when this is not possible, *ad hoc* experiments can lead to their evaluation.

To be more specific, growth and destruction coefficients, and reference and threshold densities can be evaluated looking at the system at the cellular scale. More in detail, growth coefficients can be evaluated by looking at the mitotic rate of cells, and death coefficient by looking at the rate at which cells die in absence of mitosis. Degradation coefficients relative to chemical factors and the absorption coefficient of the nutrient by the tumor cells can be evaluated measuring their evolution when they are no longer produced by the cells or by the environment, respectively. The amount of nutrient which promotes proliferation or that causes death can be evaluated by looking at the behavior of the cells for decreasing amounts of nutrient. The close packing reference density can be evaluated by counting the number of cells in a stationary configuration.

The development of direct measurements of diffusion and drift coefficients is more difficult because they might involve observations at a subcellular scale and might be affected by strong random fluctuations.

However, as for cellular models, the simulation should be able to indicate the sensitivity of the solution to the parameters. Some of them do not effectively modify the qualitative behavior of the solutions. Some effectively do. This means that experimental activity has to refer specifically to these parameters.

In particular, we can observe some agreements and inconsistencies with respect to cellular theories. Specifically, proliferation and feeding terms are similar. (Later we will discuss the role of feeding related to the action of angiostatines.) On the other hand, at present, kinetic models are developed in a space-independent framework. Hence, in order to link cellular models to macroscopic ones, i.e., integro-differential models to advection-diffusion models, an effort has to be done in the direction of the introduction of the space variable and of the dynamics generating the motions of the cell populations. However, when this is done, cellular models still would represent a relatively more detailed dynamics, as in them the evolution depends on the state of the cells, e.g., the probability of proliferation of a cell depends on the state of the mother-cell and on that of the other interacting cell. This piece of information is lost in macroscopic models as can be realized comparing (3.17) and (4.2) in the spatially homogeneous case or for nonmoving cells.

6. MATHEMATICAL PROBLEMS AND A SURVEY OF SIMULATIONS

The class of models described in the preceding sections may simulate the behavior of the real physical system. As usual, the simulation is obtained solving mathematical problems related to the application of the model by suitable computational schemes. A qualitative analysis should be developed before solving the computational problems, and may provide useful information both toward the qualitative behavior of the solution, and toward the application of computational algorithms.

The above program is certainly an interesting field of speculation for applied mathematicians. Only a small part of it is dealt with in the literature. The hope is that future activity will be addressed toward the solution of the above problems. Indeed, the development of mathematics towards the above paths is pushed by strong motivations. As usual, a mathematical model may

hopefully contribute to research activity in the field of immunology, both reducing the amount of the experiments and addressing them towards directions identified with the aid of the model. As a matter of fact, developing a simulator of the immune system in the competition with pathological carriers is one of the great challenges for cooperation between applied mathematicians and immunologists. This matter is well emphasized in the article by Taubes [52], which favours scientific activity towards the simulation of the various phenomena, such as interaction and competition of cells *in vivo*. The following aspects are of particular interest:

(i) qualitative and quantitative prediction of the evolution of the system after suitable identification (based on experimental data) of the parameters of the model;

(ii) parameter sensitivity analysis with special attention to identify the modifications to the qualitative behavior of the system induced by small variation of the parameters;

(iii) identification of physical behaviors which may be described by the model without particular evidence given by experiments.

Here, the statement of mathematical problems is reported and a small survey of mathematical results and simulations existing in the literature is reported. In particular, we refer to the initial value problem for kinetic models, the initial-boundary value problem for kinetic models with internal structure, and finally the moving boundary problem for solid tumor models.

6.1. The Initial and Initial-Boundary Value Problems for Kinetic Models

The statement of the evolution problems for kinetic models was given in Section 3. The qualitative analysis of these problems is developed in [53] where results on existence, regularity, and asymptotic behavior of the solutions are given for a class of kinetic models related to those specifically described in this review. The same analysis can be technically generalized in the framework of the general class of models described in Section 3. The mathematical methods are those developed in [54].

The qualitative analysis is not yet able to predict asymptotic behaviors with direct reference to specific values of the parameters. However, a computational analysis gives interesting results. Preliminarily, it can be observed that the various parameters characterizing the model can be divided into the following groups:

(i) β-type parameters characterize the transitions in conservative encounters;

(ii) γ-type parameters characterize proliferation activity;

(iii) δ-type parameters characterize destruction activity.

Particularly interesting is the analysis related to β-type parameters corresponding to conservative encounters. The output of the above encounters can be modified by cytokine signals [14] artificially produced. Hence, the analysis may point out the sensitivity of the qualitative evolution to the above parameters and, in particular, to the existence of bifurcation parameters separating the following different qualitative behaviors: blow up of tumor cells and inhibition of the immune system; or alternatively, blow up and activation of immune cells and destruction of the tumor cells.

The substantial difference with respect to bifurcation phenomena for ordinary differential equations is that the evolution (and hence, the bifurcation) refers not only to the densities $n_i(t)$, but to the distributions $f_i(t, u)$. Hence, the bifurcation phenomenon must be referred to the change, in time, of the distribution over the variable u, which models the state of the interacting cells. The biological interpretation is an evolution toward states of activation and aggression opposed to inhibition and dormancy.

Quantitative results have been obtained by classical discretization schemes, e.g., [33, Chapter 4]. For instance, the behavior observed for a large variety of fixed values of the parameters δ and γ is the following.

- β_{21} behaves as a bifurcation parameter: there exists a critical value β_c of β_{21} such that if $\beta_{21} < \beta_c$, the activation of the immune system is able to control the growth of tumor cells, while if $\beta_{21} > \beta_c$, tumor cells succeed inhibiting immune cells and grows without opposition.

In order to visualize the above behavior, a simulation corresponding to the following values of the parameters:

$$\beta_{12}^- = \beta_{12}^+ = 0.1, \qquad \gamma_{12} = \gamma_{21} = 0.5, \qquad \gamma_{13} = 1, \qquad \gamma_2 = 0.2, \qquad \delta_{12} = 0.5, \qquad \delta_{23} = 0.2,$$

is shown, while the parameter β_{21} is made variable.

The simulation is shown in Figures 8 and 9, which, respectively, refer to $\beta_{21} = 0.11$ and $\beta_{21} = 0.12$. In the first case, it can be seen how the growth of tumor cells induces a reaction of the immune system which depletes in part the tumor weakening its aggressivity. In fact, the distribution slightly shifts towards low values of u. However, part of the tumor survives and represents several times, though in weaker form. This is a lucky case in which eventually the immune cells are able to control the growth of tumor cells. In the second case, obtained for a slightly larger value of β_{21}, an opposite evolution of the competition is described. Indeed, as shown in Figure 9, when tumor cells increase for the first time, the immune system is only in part able to control it. In fact, there is a local maximum of tumor cell density after which the number of tumor cells decreases. However, in the fight tumor cells have succeeded in inhibiting the immune cells. In fact, their distribution shifts towards low values of u with a maximum that goes from 0.4 to 0. Hence, when tumor re-exhibits, the immune cells are no longer able to compete and control the growth of tumor cells, in spite of the fact that the number of cells grows fast. The calculations developed in [38] identify the bifurcation value up to the fifth digit.

The analysis of models with internal structure confirms the above behavior. Detailed analysis is reported in [37], where it is also shown how the external action can contribute to reach a control of the asymptotic behavior.

6.2. The Free Boundary Value Problems for Macroscopic Models

We have already seen in Section 4 that the mathematical problem describing the macroscopic evolution of the tumor interacting with the outer environment, e.g., in presence of angiogenesis, writes as a free-boundary value problem and has a rather complex mathematical structure.

In order to understand something more on the effects produced by the different terms characterizing the model, the qualitative behavior of the solution for the one-dimensional problem will be first examined in the avascular case with $w_T = 0$, so that the tumor cells and the tumor free surface do not move. In this case, the equation for u_T^* becomes hyperbolic and does not need boundary conditions.

First of all, as the nutrient evolution is governed by a diffusion equation with a sink term, the amount of nutrient available u_N^* will attain its maximum at the tumor surface and will decrease with increasing distance from the surface.

Referring to Figure 10, we first consider the case $\widetilde{u}_N^* < 1$, i.e., the amount of nutrient arriving at the tumor surface is larger than that needed by all cells living there to proliferate. In this case, there is a rim near the tumor surface of proliferating cells (darker grey strip in Figure 10). Mitosis stops when $u_T^* = u_N^*/\widetilde{u}_N^*$ (see Figure 11a) as at this point the nutrient does not furnish to the cells that surplus necessary to promote proliferation.

There can then be two points x_Q^* and x_N^* such that u_N^* is equal to $\widetilde{u}_N^* u_T^*(x_Q^*)$ and $\overline{u}_N^* u_T^*(x_N^*)$, respectively.

In the layer between x_N^* and x_Q^* (or, in absence of x_N^*, below x_Q^*) neither the gain, nor the loss term are present in the evolution equation for the living tumor cells. This is then a quiescent region represented in Figure 10 by a lighter grey strip.
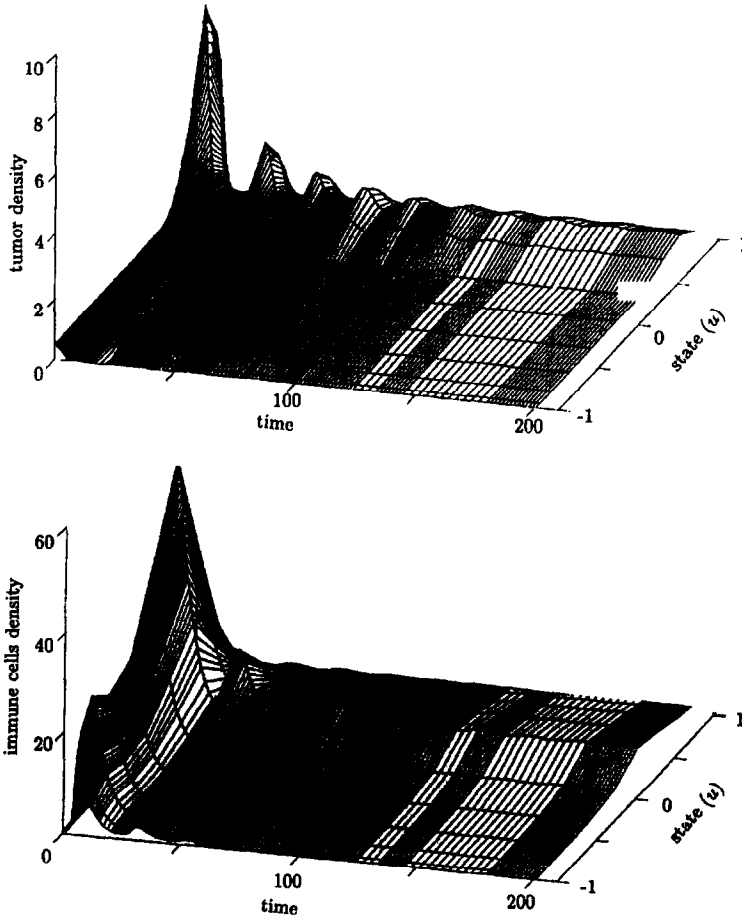
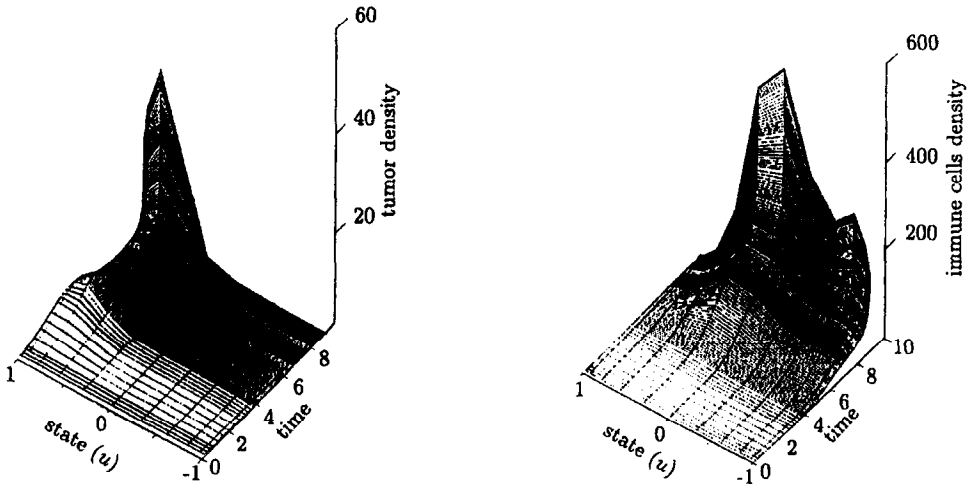Figure 8. Evolution of tumor cells (top) and immune cells densities (bottom) for $\beta_{21} = 0.11$.

Figure 9. Evolution of tumor cells (left) and immune cells densities (right) for $\beta_{21} = 0.12$.

Finally, below x_N^* only the loss term is present in the evolution equation for the living tumor cells. In this region (represented in white in Figure 10), tumor cells do not have enough nutrient to survive all and start dying. They will continue doing so, until the amount of nutrient reaching that point is sufficient to feed the remaining cells. This occurs when $u_T^*(t^*, x^*)$ has decreased to $u_N^*(t^*, x^*)/\overline{u}_N^*$ (see Figure 11).
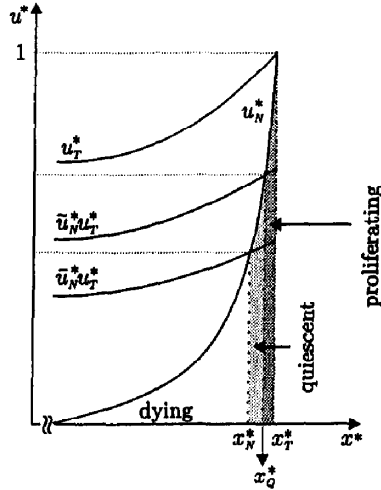
Figure 10. Identification of the interfaces delimiting the proliferating (darker grey), the quiescent (lighter grey), and the region with dead cells (white).
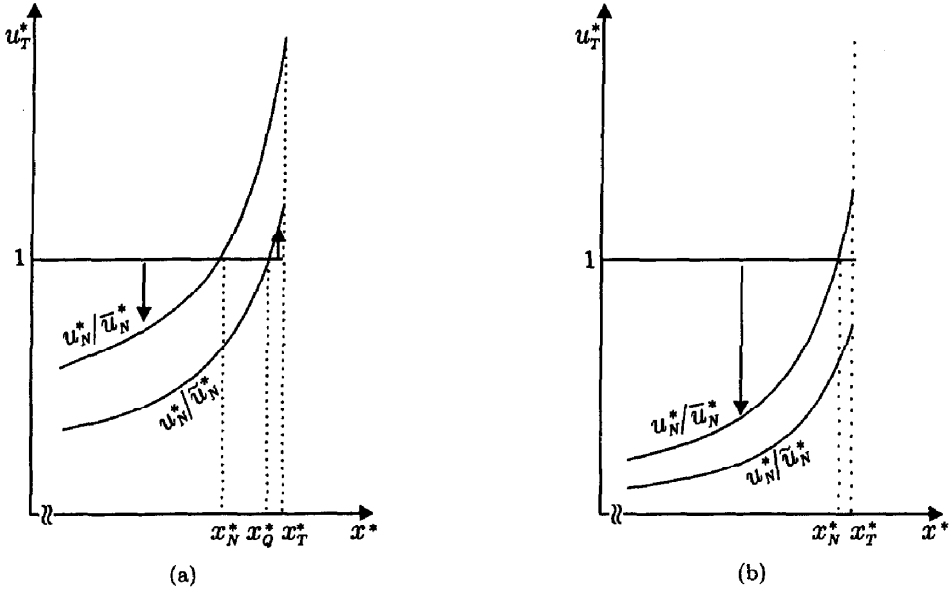

(a)   (b)

Figure 11. Proliferation and death of cells for (a) $\overline{u}_N^* < \widetilde{u}_N^* < 1$ and (b) $\overline{u}_N^* < 1 < \widetilde{u}_N^*$.

There is then, in agreement with the description given in [55], a thin transition layer with copresence of living and dead tumor cells near x_N^*, which represents the transition to the necrotic region.

To be more specific, assume that u_T^* be constantly equal to one. In this particular case, the nutrient would decrease exponentially in time with a dimensionless characteristic time $t^* \approx 1/\delta_N^*$ to the stationary distribution

$$u_N^* = \frac{\cosh x^*}{\cosh x_T^*}. \tag{6.1}$$

Hence, in this case one has that the nutrient distribution within the tumor drops exponentially in a (dimensional) depth of order $\sqrt{k_E/\delta_N \overline{u}}$.

If

$$1 > \widetilde{u}_N^* > \overline{u}_N^* > \frac{1}{\cosh x_T^*} \tag{6.2}$$

(where the last term of the inequality is the amount of nutrient reaching the center of the tumor),

the two points x_Q^* such that $u_N^*(x_Q^*) = \widetilde{u}_N^*$ and x_N^* such that $u_N^*(x_N^*) = \overline{u}_N^*$ are given by

$$x_Q^* = \cosh^{-1}\left(\widetilde{u}_N^* \cosh x_T^*\right), \qquad x_N^* = \cosh^{-1}\left(\overline{u}_N^* \cosh x_T^*\right). \tag{6.3}$$

Figure 12 is a contour plot. Each line refers to a nutrient level and states at what depth from the tumor surface that amount of nutrient is found as a function of the dimensionless tumor size. It shows that these levels rapidly become independent of the tumor size, e.g., the depth of the proliferating layer is nearly given, say, for $x_T^* > \log 10/\widetilde{u}_N^*)$ by $-\log \widetilde{u}_N^*$. In fact, the given level of nutrient is achieved at a distance from the tumor surface which rapidly tends to a constant. A similar thing occurs for the quiescent layer with $x_Q^* - x_N^* \approx \log \widetilde{u}_N^*/\overline{u}_N^*$. This means that (if $u_T^* = 1$) while evolving, the depths of the proliferating and of the quiescent layers remain constant, as experimentally confirmed by the observations reported in [56]. In Figure 12, this is put in evidence considering $\widetilde{u}_N^* = 0.8$ and $\overline{u}_N^* = 0.5$. The darker grey region represents then the thickness of the proliferating rim, and the lighter one the thickness of the quiescent region. As x_T^* grows, both layers tend to a constant. Consequently, the necrotic region grows (white region).
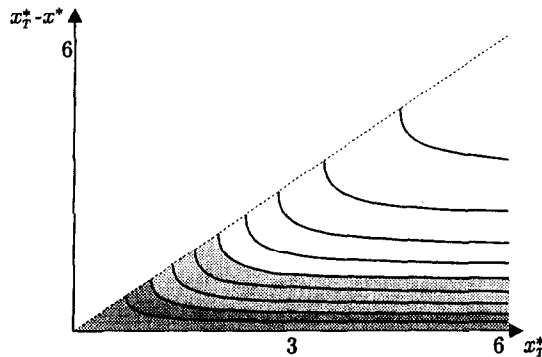

Figure 12. Location of given nutrient levels from the tumor surface as a function of the dimension of the tumor. From below, the curves refer to $u_N^* = 0.9, 0.8, 0.7, 0.6, 0.5,$ $0.4, 0.3, 0.2, 0.1$. The darker region represents the thickness of the proliferating layer if $\widetilde{u}_N^* = 0.8$ and the lighter region that of the quiescent layer if $\overline{u}_N^* = 0.5$.

As already mentioned, in the necrotic region cells will stop dying when $u_T^* = u_N^*/\overline{u}_N^*$. This state is reached in a time of order $t^* \approx 1/\delta_T^*$. In this situation, the solution near x_N^* can be approximated (if $x_N^* \gg 1$) by

$$u_N^* \approx \frac{\overline{u}_N^*}{\left[1 + (x_N^* - x^*)/\sqrt{6}\right]^2}, \qquad u_T^* \approx \frac{1}{\left[1 + (x_N^* - x^*)/\sqrt{6}\right]^2} \tag{6.4}$$

showing the presence of a layer of copresence of living and dead cells of dimensional width $\Delta = \sqrt{6k_E/\delta_N \overline{u}}$. One can then say that the necrotic region becomes evident for depths of order $x_T - x_N + \sqrt{6k_E/\delta_N \overline{u}}$.

It need be mentioned that, if the assumption $w_T^* = 0$ is dropped, the increase in cell density in the proliferating rim tends generating an expansion. On the other hand, the disintegration of dead cells in waste products in the necrotic region with the consequent decrease in cell density tends generating a contraction. The balance between the two terms

$$P = \int_{x_Q^*}^{x_T^*} \frac{u_T^* u_N^*}{1 + \alpha^* u_I^*}\, dx^* \qquad \text{and} \qquad D = \delta_T^* \int_0^{x_N^*} u_D^*\, dx^* \tag{6.5}$$

will determine whether the tumor expands or contracts. In particular, the steady state is achieved when the two terms are equal.

For instance, if $\overline{u}_N^* < 1 < \widetilde{u}_N^*$, then at the tumor surface there are no proliferating cells and $P = 0$. If nothing new happens, e.g., angiogenesis, the tumor will then start shrinking up until
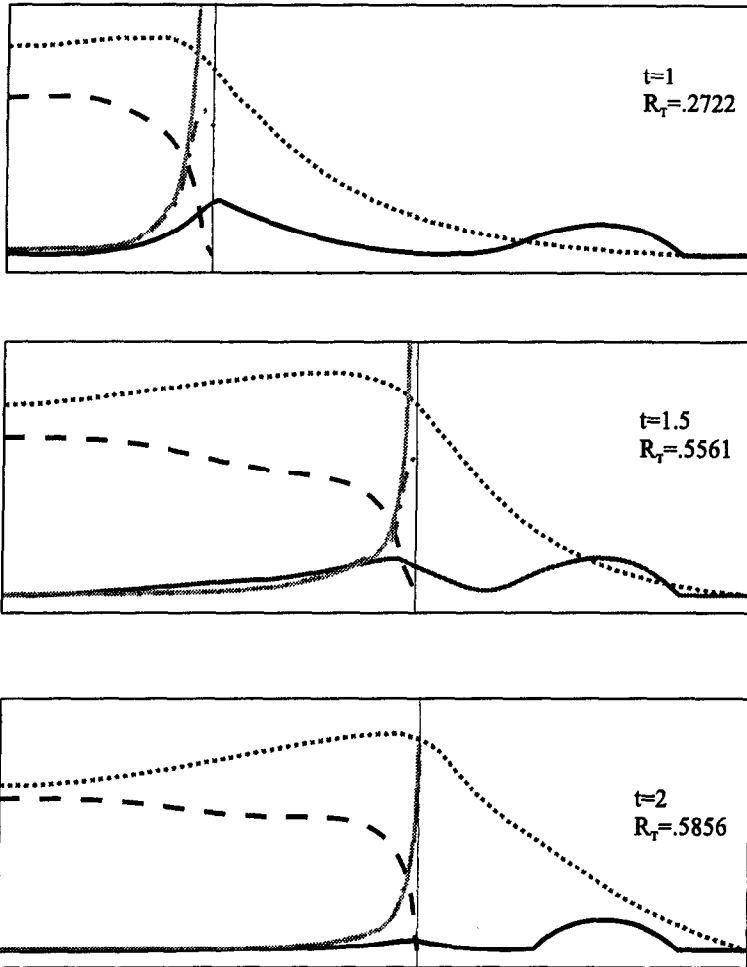
Figure 13. Regression of capillary network as an effect of angiostatins. The vertical line is the border of the tumor. The grey line represents the nutrient distribution. The dot-dashed line represents the distribution of living tumor cells. The dashed line represents the distribution of dead tumor cells. The dotted line represents the distribution of tumor angiogenic factor. Dark full line represents the capillary density. R_T is the dimensionless radius of the tumor.

all dead cells are disintegrated. In this situation, the tumor reduces to a very small spheroid with only quiescent cells, ready, however, to become active again when the new capillary sprouts bring them more nutrient.

More in general, the formation of capillary sprouts increases the amount of nutrient reaching the tumor to $u_N^*(x_T^*) = 1 + \beta^*(u_C^* + \widetilde{u}_C^*)(x_T^*) \equiv \varepsilon^*$. Besides increasing the mitotic rate of the already active cells, this moves down the interface between active and quiescent cells waking up some tumor cells which will start proliferating and contributing to the growth of the tumor. For instance, equations (6.1) and (6.3) rewrite as

$$u_N^* = \varepsilon^* \frac{\cosh x^*}{\cosh x_T^*}, \qquad x_Q^* = \cosh^{-1}\left(\frac{\widetilde{u}_N^*}{\varepsilon^*} \cosh x_T^* \right). \tag{6.6}$$

Setting γ_C^* to zero (i.e., with the injection of angiostatins) will generate a regression of the new capillary network in a time of order $t^* \approx 1/\delta_C^*$. This will decrease the amount of available nutrient, generating a regression of the tumor size. In particular, if $\overline{u}_N^* < 1 < \widetilde{u}_N^*$, it will induce a regression of the tumor to the quiescent state as mentioned above.

The qualitative behavior just described is put in evidence in Figures 13 and 14. The vertical line in the figures represents the border of the tumor. Focusing on what happens inside the
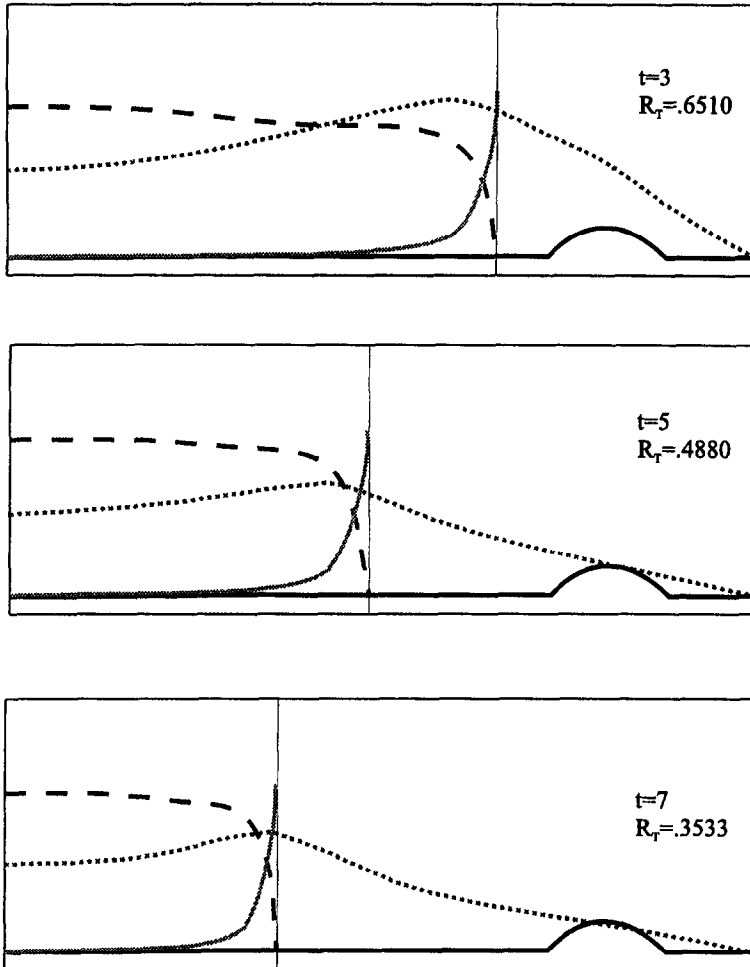
Figure 14. Subsequent regression of tumor size due to lack of nutrient. The vertical
line is the border of the tumor. The grey line represents the nutrient distribution.
The dot-dashed line represents the distribution of living tumor cells. The dashed
line represents the distribution of dead tumor cells. The dotted line represents the
distribution of tumor angiogenic factor. Dark full line represents the capillary density.
R_T is the dimensionless radius of the tumor.

tumor, it can be seen that the nutrient (grey line) rapidly decreases with increasing distance
from the tumor surface. As a consequence, living tumor cells (dot-dashed line) are only found
very near the tumor surface with formation of a larger and larger necrotic core (the dashed line
represents the density of dead cells). However, proliferation in the small rim is strong enough to
induce tumor growth. It is important to notice how the width of the proliferating rim is nearly
constant as tumor evolves as predicted analytically.

The dotted line represents how the tumor angiogenic factor produced by the cells from the
beginning diffuses in the environment. In the first plot, some TAF has already reached the pre-
existing capillary network (the bump in the figure outside the tumor). This induced the formation
of new capillary sprouts which start from the pre-existing network and rapidly tend toward the
tumor surface (the black line). At a dimensionless time $t^* = 1$, they have already reached the
tumor surface and penetrated into the tumor. From this point, the simulation is developed having
in mind possible medical actions like those suggested in [57,58]. The aim is then to focus on what
happens when angiostatins are injected so that the endothelial cells are no longer sensitive to the
presence of TAF and do not feel stimulated in duplicating. Injection is simulated at $t = 1.4$ by
putting $\gamma_C^* = 0$. This brings up a progressive death of capillaries because the endothelial cells
dying of natural death are no longer replaced as they no longer feel stimulated. This well-known

process is similar to what happens in wound healing. New capillaries form because there is a stimulus of doing so, but as the wound is cured, the stimulus ceases and the new capillaries are destroyed leaving unchanged the pre-existing network they originated from.

When the capillary network is destroyed, the tumor does not have enough nutrient. The outer rim is not so proliferative anymore, and more and more cells start dying. The size of the tumor starts decreasing. Actually, Figure 14 shows how a regression of tumor size is induced by the mass lost as a result of disintegration of dead cells not balanced by proliferation.

The final plot represents the steady situation with the original configuration of capillaries (the bump on the right) and a nonexpanding tumor with balance between new cells proliferating in the outer rim and dead cells disintegrating in the necrotic core.

The above qualitative analysis is the preliminary step of the role of the parameters of the model upon the asymptotic behavior of the solutions. Other qualitative results for a relatively simpler model are given in some papers by Cui and Friedman [59,62] and Friedman and Reitich [61].

7. CONTROL PROBLEMS

Mathematical control problems related to models of tumor immune system competition can be developed on the basis of qualitative and computational analysis of the effect of external actions over the dynamical response of the system. Also this topic can potentially become a useful cooperation ground between mathematics and immunology. This statement is true if, at least, the following conditions are verified.

(i) The mathematical model describes realistically the evolution of the biophysical system.
(ii) The parameters which are peculiar to the system can be effectively related to biophysical quantities.
(iii) Medical therapeutic actions can be developed in order to modify the above parameters.

Certainly research activity can avoid cooperation with mathematics. We are simply looking at conceivable potential links between these two disciplines which are, at present, still very far away. Mathematics cannot deal with the technical devices to obtain a certain medical action. It can simply support such an action with the aim of addressing it more precisely or of reducing quantitatively the time needed by experiments.

Within the above framework, we can now assess the sequential steps to develop a mathematical theory concerning the control of the system. In detail, the following line is proposed:

1. assessment of the mathematical model which is the object of the control analysis (this also means identifying the regime characterizing the physical system: cellular or continuum);
2. identification of the parameters of the model which may be modified by suitable medical action (chemotherapy, cytokine signals activation, use of angiostatins, etc.);
3. analysis of the potential ability of the above action to modify the asymptotic behavior of the competition.

The general ideas stated above do not substantially differ from the ones posed in the review paper by Swan [5], which still is one of the main reference papers dealing with control problems in cancer therapy. The content of the above paper refers to models stated in terms of ordinary differential equations. Indeed, until now, control problems seem organized for simple models described by ordinary differential equations. In practice, models are obtained as suitable modifications of population dynamics which describe the competition between tumors and immune system. This feature is not only documented in [5], but also by more recent approaches such as [12,62]. These models are certainly based on crude simplifications of physical reality, although the above papers have the great merit of analysing the complex (and for certain aspects ambiguous) relationship between medical actions and physical system.

The role of medical actions and their control is indeed the object of interesting and effectively useful studies. We refer, among others, to the activity by Agur [63] and Shochat et al. [64].

The effective contribution of this type of analysis appears highly useful. On the other hand, we forward the idea that applied mathematicians should also study actions that are related to models which are not oversimplified in order to reduce mathematical complexity. Indeed, we are convinced that recent progress in tumor modelling which leads to more sophisticated models deserves a deep analysis of the control problems. The mathematical problem is hard. As stated in [4], the physical system we are dealing with is characterized by a great inner complexity, so that one cannot really hope, and should not look for, simplification of the mathematical problem. Maybe this is a great challenge for applied mathematicians and this paper aims to focus on it.

Bearing this in mind, a description of some (among several ones) control problems is given in what follows. Then we discuss how some of the simulations, already reviewed in the preceding section, may contribute to the analysis of the above problem.

All problems described in what follows have to be regarded as research perspectives brought to the attention of applied mathematicians. In fact, suitable literature on the above topic is not yet developed.

7.1. Medical Actions on the Parameter of Kinetic Models

We refer to kinetic (cellular) models which have been described in Section 5, and, in particular, to model (3.36) in the case $c_1 = c_2 = 0$. Moreover, we assume that the time variable is rescaled with respect to η_{12}, while the parameters β, γ, and δ are, under suitable external actions, given function of time.

The evolution problem can be formally written as follows:

$$
\begin{aligned}
\frac{\partial f_1}{\partial t} &= J_1\left(f_1, f_2; \beta(t), \gamma(t), \delta(t)\right), \\
\frac{\partial f_2}{\partial t} &= J_2\left(f_1, f_2; \beta(t), \gamma(t), \delta(t)\right).
\end{aligned}
\tag{7.1}
$$

The external action is supposed to be able to increase or decrease the initial value of each parameter

$$
\beta(t) = \beta_0 + \Delta_\beta U\left(t, t_a\right), \qquad \gamma(t) = \gamma_0 + \Delta_\gamma U\left(t, t_a\right), \qquad \delta(t) = \delta_0 + \Delta_\delta U\left(t, t_a\right), \tag{7.2}
$$

where

$$
U = \begin{cases} 1, & \text{if } t \in [0, t_\alpha], \\ 0, & \text{otherwise.} \end{cases}
\tag{7.3}
$$

The above problem was posed and dealt with by a computational analysis in [38], where it was shown that a parameter sensitive to define the output of the competition is β_{12}, which refers to conservative encounters between tumor and immune cells. In fact, β_{12} is a bifurcation parameter separating the asymptotic opposite behaviors: inhibition of the immune system and tumor growth, or activation of the immune system and tumor depletion. This feature is confirmed in a few systematic calculations developed in [64].

The above analysis suggests to operate on β_{12} by suitable cytokine signals which may modify it, at least for a certain time interval, thus reducing the inhibition action of tumor cells. Still several problems are left open. The following ones are indicated among several:

(i) modification of the proliferative activity of tumor cells (increasing the parameter δ_1) by medical actions such as chemotherapy or use of proteins able to generate apoptosis (without increasing δ_2);

(ii) modification of the defense activity of immune cells (increasing the parameter γ_{21}) in order to have a faster response;

(iii) modification of the degenerative trend of immune cells (reducing the parameter β_{21}) in order to have still an active immune system when the tumor re-exhibits;

(iv) modification of the resistance of immune cells to mortal attacks (reducing the parameter δ_{21}) in order to avoid immuno-depressive states;

(v) modification of the production of immune cells from the bone marrow (increasing the parameter γ_2) in order to have a stronger immune system;

(vi) modification of the aggressivity of immune cells against the tumor (increasing the parameter δ_{12}) in order to have a more efficient response.

A preliminary analysis of the behavior with respect to the actions in (i) and (v) has been performed in [37]. Analyzing separately the role of the variation of each class of parameters allows a direct insight over their role. However, also joint actions can be analyzed, which may be studied also in connection to those described in the next section. What one hopes to observe is that after a certain action time the external action is effectively able to modify the output of the competition, although this ability may not be observed. The opposite trend may also be studied. For instance, one can analyze if a temporary weakening of the immune defense may negatively modify the desired trend.

The above-posed problems have not yet been dealt with systematically in the literature, and are here indicated as research perspectives. The only effects which are studied in some detail are the bifurcation phenomena already discussed in Section 6.

7.2. Medical Actions Operating on the Intrinsic Activity of Tumor and Immune Cells

This type of analysis does not formally differ from the one described in the preceding section. Again, we refer to kinetic (cellular) models which have been described in Section 5, and, in particular, to model (3.35) in the case $c_1 \neq 0$ and/or $c_2 \neq 0$, while the parameters β, γ, and δ are assumed to be constant in time.

The evolution problem can be formally written as follows:

$$\frac{\partial f_1}{\partial t} + \frac{\partial}{\partial u} [c_1(u,t) f_1] = J_1 (f_1, f_2; \beta_0, \gamma_0, \delta_0),$$
$$\frac{\partial f_2}{\partial t} + \frac{\partial}{\partial u} [c_2(u,t) f_2] = J_2 (f_1, f_2; \beta_0, \gamma_0, \delta_0),$$

(7.4)

where, for instance,

$$c_1(u,t) = \alpha_1^+ (1 - u) - \alpha_1^- U(t, t_\alpha)(1 + u) \tag{7.5}$$

is related to externally induced reduction (or increase) of the activation (**rate of growth**) of tumor cells, and

$$c_2(u,t) = \alpha_2^+ U(t, t_\beta)(1 - u) \tag{7.6}$$

is related to externally induced increase (or reduction) of the immune defense.

As before, analyzing separately the role of the variation of the two terms above allows a direct insight over their role. However, also joint actions can be analyzed. What one hopes to observe is that after a certain action time, the external action is effectively able to modify the output of the competition, although this ability may not be observed. The opposite trend may also be studied.

The above-posed problems have been posed in [37] where a preliminary analysis was also developed as already discussed in Section 6. The above analysis can be developed in connection with the one described in Section 7.1.

7.3. Control Problems for Continuous Models

The analysis of mathematical control problems for continuous models described in Section 4 can be developed again to analyze the effect of external medically induced actions over the evolution of the system.

In particular, the qualitative and quantitative analysis of Section 6 has put in evidence that for several values of the parameters, there exists a stationary configuration with equilibrium of disintegration of dead cells and proliferation of new cells. The fact that, for a given amount of nutrient, the width of the proliferating rim is nearly independent of the tumor size has also been stressed. The equilibrium size of the tumor depends on the amount of nutrient. In particular, it increases with the amount of available nutrient reaching the tumor surface. If the tumor is reached by the capillary network, the amount of nutrient available becomes incredibly high. Therefore, a possibility of controlling the tumor size depends on the ability of controlling the angiogenic process and of inducing capillary regression.

One of the crucial issues in medical research consists, then, in conceiving drugs which, for instance, make the endothelial cells less sensible to the presence of tumor angiogenic factors either by decreasing their proliferation (related to the parameter γ_C) or their chemotactic motility (related to the parameter w_C). This can be done by the use of proteins like angiostatins and endostatins; see, for instance, [57].

In the simulation of Figures 13 and 14, the response predicted by the mathematical model to a drastic decrease of the growth coefficient of the capillaries γ_C was studied.

One of the points in which mathematical modelling can be of help consists in understanding

- to which degree one needs to decrease γ_C (or w_C) in order to have an efficient action on the tumor;
- for how long that parameter has to be kept low;
- when the therapy can be stopped;
- when the therapy needs to be repeated.

This is particularly important when one considers also the fact that the use of a drug is usually toxic and cannot be given to the patient forever and in indefinite amounts. Therefore, the minimization problem involved in defining the control action is not as trivial as one can think. Actually, it is very hard to be defined. In fact, to be more specific, it is not just a matter of killing a tumor in the shortest time possible, but reducing its size in a suitable time with a therapy the patient can stand.

It need be mentioned that in the framework of medical actions which can be modelled from a macroscopic viewpoint the control of angiogenesis by angiostatins and endostatins is one possibility. One can also use control parameters which describe a medical action aimed at increasing the effects of growth inhibitory factors, or at introducing in the tumor genetically engineered macrophages which carry drugs which kill tumor cells, and so on.

8. CRITICAL ANALYSIS AND RESEARCH PERSPECTIVES

A critical analysis concerning the state-of-the-art may start from some of the questions posed in Section 1. In particular, we will first consider the effective possibility of mathematics to cooperate with immunology. Then, also on the basis of the critical analysis, some research perspectives may be indicated.

8.1. Kinetic Cellular Models

The first remark concerning the kinetic cellular approach is that models reviewed in this paper can be technically improved in order to provide a relatively more accurate description of the biophysical system with which we are dealing. It is not difficult to indicate some perspective ideas, although it is certainly not easy developing them at a technical level. In detail, we find the following.

(i) The number of cell populations can be increased in order to include, at least in part, the large variety of interacting populations. For instance, populations of immune cells can be further specialized in order to take into account different activities and specializations of the immune system which reacts to tumor cells and acts over it.

(ii) Enlarging the number of cell populations may necessarily lead to increase the dimension of the state variable u to a vector one in order to include the relevant different activities of the cells.

(iii) Development of models with transition of cells from one population to another. This type of modelling can even take into account the onset of neoplastic cells, and may be related to various complex phenomena, e.g., DNA modifications [50], corruption of the mechanical structure of cells [65].

(iv) Looking for new mathematical structures such as the one related to the phenomenologic description proposed in [51] concerning the statistical evolution of the progression factor.

A technical difficulty is that the increasing number of parameters may lead (despite some valuable efforts, e.g., [66]) to unsolvable identification problems. The challenging problem refers to the possibility that the phenomenologic description of cell interactions given in Section 4 may be replaced by microscopic models related to cellular properties and, in particular, of cell signalling [67].

8.2. Continuous Models

A critical analysis and the indication of perspectives concerning macroscopic diffusion models can be developed in a way similar to that related to microscopic models. Specifically, technical improvements can be developed by increasing the number of cells and substances and by describing more carefully their activities.

The main problem is still the analysis of the links between microscopic and macroscopic behaviors. In particular, it should be analyzed how cellular behaviors are properly related to the various diffusion processes described in the the macroscopic model. Maybe a deeper analysis of the above problem may lead to a modelling somehow different from the one reported in Section 5.

The model recalled in Section 4 is already able to predict several interesting phenomena:

- diffusion of nutrient through the surface of the tumor and the capillary network and its difficulty in reaching the central region of the tumor;
- formation of necrotic regions as a result of lack of nutrient, even starting from a situation of all living cells in an environment full of nutrient;
- existence of an outer proliferating layer in condition of sufficient nutrient, which for large tumor size has nearly a constant depth;
- existence of a layer of quiescent cells which can activate when the amount of nutrient present in the environment increases, e.g., after the formation of the induced capillary network;
- existence of a limit tumor radius in the avascular phase depending on the amount of nutrient present in the environment;
- tumor expansion due to the birth of new cells;
- control of tumor mitosis by the presence of inhibitory factors;
- angiogenic process with proliferation of capillaries just outside the tumor surface and penetration of capillary sprouts inside the tumor and increase of tumor growth rate with the formation of capillary sprouts;
- regression of the new capillary network induced by the tumor as an effect of proteins inhibiting angiogenesis as angiostatins;
- shrinking of tumor radius when the induced capillary network is destroyed.

On the other hand, the model should be further improved going in deeper detail in describing some phenomena, or including several other phenomena. Specifically, we point out the following perspectives:

(i) cell-to-cell interaction, e.g., adhesion, response to compression, and formation and diffusion of metastasis;

(ii) competition with the immune system similar to that one considered in cellular models;

(iii) inclusion of the extracellular liquid as the phase in which tumor cells live;

(iv) inclusion of other chemical factors, e.g., growth promoting factors, growth inhibitory factors, for endothelial cells;

 (v) modelling cell aggregation phenomena which play an important role in the formation of solid tumors. In order to model them, one has to look at the dynamics in a space of cells. Interactions generate a sticking phenomena similar to those of cluster formation;

(vi) mechanical interactions between tumor and external tissues;

(vii) degradation of external tissues by the production of chemical factors.

8.3. Control Problems

The main remarks concerning the development of a mathematical control theory have been already posed in Section 7. This topic related to the rather sophisticated models reported in this paper is totally open to research activity. Indeed, as reported in the review paper by Swan [5], the mathematical literature on optimal control on cancer therapy is limited to simple models with a structure similar to those of population dynamics.

Now the main question concerns again the ability of the model to retain the main features of the real system. Moreover, the modelling of the external actions should be effectively related to the possibility of producing actions in the real system. However, the feeling on the possibility of describing the real behavior of the biophysical system, and hence, of developing a real control action is pessimistic. This may be a personal, however questionable, opinion. On the other hand, simple mathematical models can possibly simulate the evolution of gross quantities, but very little of the inner behavior of the system itself. Dealing with the description of the real system may even bring to design sophisticated computer simulators as indicated in the promising paper [68].

More specifically, the parameters of the model are based on phenomenologic interpretation, so that it seems difficult both assessing them and referring the external actions to them. Moreover, these models neglect all relevant geometrical features, which are peculiar to continuous models and, indeed, play an important role in the evolution of real systems. They are, in fact, related to relevant phenomena such as angiogenesis, effects of angiostatins, and detachment of metastasis, which cannot be described without assumptions on the geometry. This information is totally lost by simple models.

9. ON THE INTERACTIONS BETWEEN MATHEMATICS AND IMMUNOLOGY

As already announced in the Introduction, we conclude this review paper with a critical discussion concerning the interaction between mathematics and immunology. The question already posed was: how far is this interaction useful to research activity in immunology, and which are the correct directions to be developed within such a collaboration?

This paper attempted to show that it can be useful. Indeed, a great amount of work was already developed, as documented in the vast literature cited. One cannot hope that mathematics can directly solve problems in immunology. However, it can contribute to a research program by means of modelling and simulation referred to particular aspects and behaviors of the immune system: for instance, developing a simulator of the immune system in competition with pathology carriers. This target keeps its relevance even if it is restricted to some very special physical situations. In fact, if one considers that in this research field it is necessary to perform expensive and lengthy experiments *in vivo*, then one has to make any effort to reduce the amount of experiments and, indeed, the simulation of the behavior of the system can serve to this scope.

This last consideration is the one which induced to deal mainly with models closely related to the real phenomenologic behavior of the system. Relatively simple models, such as those generated by the Gompertz model, can even provide realistic overall descriptions. On the other

hand, if one operates with models which have to be related to experiments, then the descriptions need to become relatively more sophisticated and able to retain all relevant cellular phenomena.

This appears to be a correct direction to develop mathematical research activity. Mathematicians should develop models and related simulations as close as possible to the real behavior of the system. Possibly, the simulation should specifically refer to experiments either substituting or properly addressing them.

On the other hand, sophisticated descriptions should be made understood to immunologists. In frameworks where the dialogue is consistent, several useful results can be achieved starting from the reduction and qualification of the experimental activity.

This difficulty may be tackled with a gradual approach. The first step refers to the statement of the physical assumptions concerning the derivation of the model. These assumptions should be carefully and critically examined by immunologists. Then the derivation of the evolution equations and the related simulations should be again handled by applied mathematicians. The dialogue with immunologists will continue with a joint analysis of the simulations. This analysis may contribute to the efficiency of the experimental activity and possibly improve the model. A first step of the type of collaboration is documented in the WEB page http://calvino.polito.it/~preziosi/bioweb.html.

In some cases, the joint cooperation between immunology and mathematics can hopefully provide an immuno-mathematical theory suitable to intrinsically contain information on the evolution of the system based on a direct measurement of biological parameters. It can be hoped that mathematical models anticipate aspects of such a theory. This aim may be ambitious and even unrealistic. However, it is worth trying.

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