Some mathematical aspects of tumor growth and therapy

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Abstract

Mathematical models of tumor growth, written as partial differential equations or free boundary problems, are now in the toolbox for predicting the evolution of some cancers, using model based image analysis for example. These models serve not only to predict the evolution of cancers in medical treatments but also to understand the biological and mechanical effects that are involved in the tissue growth, the optimal therapy and, in some cases, in their implication in therapeutic failures.

The models under consideration contain several levels of complexity, both in terms of the biological and mechanical effects, and therefore in their mathematical description. The number of scales, from the molecules, to the cell, to the organ and the entire body, explains partly the complexity of the problem.

This paper focusses on two aspects of the problem which can be described with mathematical models keeping some simplicity. They have been chosen so as to cover mathematical questions which stem from both mechanical laws and biological considerations. I shall first present an asymptotic problem describing some mechanical properties of tumor growth and secondly, models of resistance to therapy and cell adaptation again using asymptotic analysis.

Key words: Tumor growth; Hele-Shaw equation; Free boundary problems; Structured population dynamics; Resistance to therapy

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1 Introduction

Since the paper of H. P. Greenspan [36] in 1972, an increasing mathematical activity has been developing, that creates new models, new numerical methods, new analysis of partial differential equations

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representing various aspects of tumor growth and therapy. This activity follows the National Cancer Act, usually called 'war on cancer', signed in 1971 and the awareness that the disease becomes a major health problem in many countries. Despite several decisive progresses (more than 1500 americans are declared recovered from cancer every day), the many faces of the problem, and their complexity in terms of scales, agents and scientific background, explain that cancer remains a challenge for XXIst century medicine.

Interestingly enough, many aspects have lead to mathematical modeling and I would like to mention some of them. The molecular basis of tumors are mutations of cells, which are modeled by random processes [32], and which opens the route of molecular targets for drug design. The number of scales, from the molecule, to the cell , to the tumor itself and to the organ, also explains the complexity of the phenomena. Considering an assembly of cells, bridging gene activity to cell behavior, are possible with agent based methods, and related discrete methods, giving a detailed account of tissue growth and organization [3, 15, 38, 52]. However, in these notes, I will consider continuous models, used for large populations of cells, and only solid tumors even if liquid tumors (blood or lymphatic cancers) have also led to a core of mathematical literature, see [23, 2] and the references therein.

Ordinary differential equations are however the first modeling tool. They are efficient because parameter identification is simpler than in the more elaborate partial differential equations. They can can also provide direct qualitative behaviours in complex situations when several effects combine. This is the case for several examples when modeling angiogenesis (see below also) and supply both of nutrients and therapy to the tumor by neovasculature which can be of low quality [37, 9], tumor-immune system interaction [29, 7, 43], metastases development [10], drug optimization during therapy [44], interactions between cell cycle and circadian cycle, [21, 20]. Note that, in these works, the model description based on ODEs can be complemented with physiological variables, thus leading to integro-differential equations, the so-called 'structured population' models.

Continuous models allow for numerical simulations at the scale of the organ and are used for predicting tumor progression in combination with medical imaging [63, 48, 26, 25]. These models can incorporate several features as nutrients availability, angiogenesis (the process by which necrotic cells in the core of the tumor emit molecular signals attracting new vasculature), adhesion to the extracellular matrix and its degradation, interaction with the healthy cells, proliferative or quiescent or necrotic states of the cells; these features and many others are described in the many papers and in several surveys available in the literature [14, 62, 4, 6, 7, 35, 36, 48, 60].

In order to present both the impact of physical laws and biological aspects, these notes address two different aspects of tumor growth. Considering fluid mechanical aspects, section 2 describes one of the simplest models in the area and is followed, in section 3 by the derivation of a free boundary problem in the 'stiff law-of-state' limit. Then, we turn to an approach, based on asymptotic analysis, to a question related to therapy and resistance to drugs; this is section 4.

2 Mechanical aspects of tissue growth

Solid tumors grow under the effect of cell proliferation limited by several factors. Space availability, and the pressure induced by higher cell population, appears to be the first cause of growth limitation

by contact inhibition [15, 59]. This can be included in the simplest models for a cell population density $n(x,t)$ where pressure generates both movement and growth limitation, leading to write

$$\left\{\begin{array}{l} \frac{\partial}{\partial t} n + \mathrm{div}\big(nv\big) = nG(p), \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ n(x, t=0) = n^0(x) \geq 0, \\ v(x,t) = -\nabla p(x,t), \qquad p(x,t) \equiv \Pi_\gamma\big(n(x,t)\big) := n(x,t)^\gamma, \quad \gamma > 1. \end{array}\right. \tag{1}$$

The rule $v(x,t) = -\nabla p(x,t)$ is a simplified version of Darcy's law expressing isotropic and homogeneous friction with the surrounding environment. This expression for the velocity field means that cells are only pushed by mechanical forces (variants are mentioned later). The particular choice for the law-of-state $\Pi_\gamma(n) := n^\gamma$ is made for simplicity, see considerations on this issue in [19]. Finally the growth term, the right hand side in (1), is of Lotka-Volterra type, and takes into birth and death of cells. Because pressure generates contact inhibition, we assume that the C^1 function $G(\cdot)$ satisfies

$$G(0) = G_M > 0, \qquad G'(\cdot) < 0, \qquad G(P_h) = 0, \quad \text{for some } \ G_M > 0,\ P_h > 0. \tag{2}$$

The name 'homeostatic pressure' has been proposed for P_h ([59]). At this stage it might also be useful to mention that dimensions $d = 2$ is relevant for *in vitro* experiments on a dish and $d = 3$ is relevant both *in vitro* and *in vivo*. As well known for the porous medium equation, one property of such partial differential equations is to describe solutions with compact support than expand [65]. For our purpose here, this is enough and we do not bother with a bounded domain and associated boundary conditions. This feature is however relevant both for realistic models and numerics.

As far as existence is concerned, this equation is standard and is a semi-linear version of the 'porous medium equation', [65]. Therefore, several bounds are known under some assumptions on the initial data.

Now, we follow closely [55]. Because we are interested in the dependence on the parameter γ (and large values of it), we consider a family of initial data n^0_γ such that for some constant K^0,

$$\int_{\mathbb{R}^d} n^0_\gamma dx \leq K^0, \qquad p^0_\gamma := \Pi_\gamma(n^0_\gamma) \leq P_h, \qquad \int_{\mathbb{R}^d} |\nabla n^0_\gamma| dx \leq K^0. \tag{3}$$

Proposition 2.1 *With assumptions* (2)–(3)*, the solution of equation* (1) *satisfies the followinf a priori estimates*

$$n(x,t) \geq 0, \qquad p(x,t) \leq P_h,$$

$$\int_{\mathbb{R}^d} n(x,t)dx \leq K^0 e^{G_M t}, \quad \int_{\mathbb{R}^d} |\nabla n(x,t)|dx \leq K^0 e^{G_M t}, \quad \int_0^T \int_{\mathbb{R}^d} |\nabla p(x,t)|dxdt \leq C(T, P_h, K^0),$$

$$\int_{\mathbb{R}^d} p(x,t)dx \leq P_h^{(\gamma-1)/\gamma} K^0, \qquad \int_0^T \int_{\mathbb{R}^d} |\nabla p(x,t)|^2 dxdt \leq \frac{1+\gamma G_M T}{\gamma - 1} P_h^{(\gamma-1)/\gamma} K^0.$$

Proof. The estimates for n are straightforward. For the TV bound, we just notice that, the equation for n can also be written

$$\frac{\partial}{\partial t} n - \Delta \Phi(n) = nG\big(p(x,t)\big), \qquad \text{with } \ \Phi'(n) = n\Pi'_\gamma(n).$$

Therefore, the equation for $w_i = \frac{\partial n(x,t)}{\partial x_i}$ is

$$\frac{\partial}{\partial t} w_i - \mathrm{div}[\Phi'(n)\nabla w_i] = w_i G\big(p(x,t)\big) + nG'\big(p(x,t)\big)\frac{\partial p(x,t)}{\partial x_i},$$

and finally

$$\frac{\partial}{\partial t}|w_i| - \mathrm{div}[\Phi'(n)\nabla|w_i|] = |w_i| G\big(p(x,t)\big) - n\big|G'\big(p(x,t)\big)\big|\,\big|\frac{\partial p(x,t)}{\partial x_i}\big| \le |w_i| G_M.$$

After integration and use of the Gronwall lemma, this gives the L^1 estimate on the gradient of n and keeping the term with $\big|\frac{\partial p}{\partial x_i}\big|$ gives the bound on the gradient of p (see [55] for details).

The second line of bounds in Proposition 2.1 follows from the equation on the pressure. Namely, we compute

$$\frac{\partial}{\partial t} p - n\Pi'(n)\Delta p - |\nabla p|^2 = n\Pi'(n) G\big(p(x,t)\big). \tag{4}$$

This equation is in the strong form, the maximum principle applies and gives the bound $p \le P_h$. It gives the L^1 control on p because

$$p = n^\gamma = n n^{\gamma-1} = n p^{(\gamma-1)/\gamma} \le n P_h^{(\gamma-1)/\gamma},$$

and it remains to apply the L^1 control on n.

The L^2 estimate on the gradient is better seen when identifying the pressure, as $p = n^\gamma$ in (4), to find

$$\frac{\partial}{\partial t} p - \gamma p \Delta p - |\nabla p|^2 = \gamma p G(p). \tag{5}$$

Integrating by parts, we obtain, for $T > 0$,

$$\int_{\mathbb{R}^d} [p(x,T) - p^0(x)]dx + (\gamma - 1)\int_0^T \int_{\mathbb{R}^d} |\nabla p|^2 dxdt \le \gamma G_M \int_0^T \int_{\mathbb{R}^d} p(x,t) dxdt.$$

which, combined with the L^1 estimate for p gives the last inequality. □

The bounds in Proposition 2.1 are fine to ensure compactness in space. It remains to prove estimates implying time compactness. An easy way is to notice that under the assumption that n^0 is a subsolution, that is

$$-\mathrm{div}\big(n^0 \nabla \Pi(n^0)\big) \le n^0 G\big(p^0(x)\big),$$

we have $\frac{\partial}{\partial t} n^0 \ge 0$. We may apply the same argument as for space derivatives and $w = \frac{\partial}{\partial t} n$ satisfies

$$\frac{\partial}{\partial t} w - \mathrm{div}[\Phi'(n)\nabla w] = wG\big(p(x,t)\big) + nG'\big(p(x,t)\big)\gamma n^{\gamma-1} w,$$

an equation which gives us the property

$$\frac{\partial}{\partial t} n^0 \ge 0 \implies \frac{\partial}{\partial t} n \ge 0. \tag{6}$$

This property is very strong and shows one limitation of the model at hand. It is incompatible with the observations that the cell population decreases in the center of the tumor, the necrotic core. This

effect, which typically occurs at the size of $1mm^3$, can be obtained when the effects of nutrients are included in the equation, see (8) below.

In this situation, which we call 'well prepared initial data', we conclude

$$\frac{d}{dt}\int_{\mathbb{R}^d}|w(x,t)|dx \le G_M\int_{\mathbb{R}^d}|w(x,t)|dx,$$

and thus

$$\int_{\mathbb{R}^d}\left|\frac{\partial}{\partial t}n(x,t)\right|dx \le \int_{\mathbb{R}^d}\left|\mathrm{div}\big(n^0\nabla\Pi(n^0)\big)+n^0G\big(p^0(x)\big)\right|dx. \tag{7}$$

It is possible to improve these estimates and avoid the restrictive assumption that the initial data is a subsolution. We recall from [55] the

Proposition 2.2 *For a constant r_G depending only on $G(\cdot)$, the estimates hold, for all $t>0$,*

$$\frac{\partial}{\partial t}p(x,t) \ge -\gamma\, r_G\, p(x,t)\,\frac{e^{-\gamma r_G t}}{1-e^{-\gamma r_G t}}, \qquad \frac{\partial}{\partial t}n(x,t) \ge -r_G\, n(x,t)\,\frac{e^{-\gamma r_G t}}{1-e^{-\gamma r_G t}}.$$

These inequalities express a regularizing effect with a fast transition at $t=0$ (the right hand side is singular then). They extend a family of similar inequalities initiated in [27]. They are stronger than those in (6) because they do not assume any further assumption on the initial data than those in Proposition 2.1 (no nedd that n^0 is a subsolution of the stationary equation). A remarkable feature here, is that the semi-linear source term improves the usual inequalities for the porous medium equations, which are recovered for $r_G\to 0$.

To conclude this section, we present some additional effects which are used in more realistic models of tumor growth. A possible additional ingredient is to take into account nutrients. Then, we arrive to the model, also treated in details in [55]

$$\begin{cases}\partial_t n-\mathrm{div}(n\nabla p)=n\,\Phi(p,c),\\ \partial_t c-\Delta c=-n\,\Psi(p,c),\\ c(x,t)=c_B>0 \qquad \text{as } |x|\to\infty,\end{cases} \tag{8}$$

where c denotes the density of nutrients, and c_B the far field supply of nutrients (from blood vessels). The coupling functions Φ, Ψ are assumed to be smooth and to satisfy the intuitive hypotheses

$$\begin{cases}\partial_p\Phi<0, \qquad \partial_c\Phi\ge 0, \qquad \Phi(P_h,c_B)=0,\\ \partial_p\Psi\le 0, \qquad \partial_c\Psi\ge 0, \qquad \Psi(p,0)=0.\end{cases} \tag{9}$$

Variants are possible; for instance, we could assume that nutrients are released continuously from a vasculature or an other source [19], several nutrients (oxygen, glucose) can be considered. Traveling wave profiles are special one-diemensional solutions under the form $n(x,t)=\widetilde{n}(x-\sigma t)$, $c(x,t)=\widetilde{c}(x-\sigma t)$, which connect the healthy to the cancer states for $y=\pm\infty$ and $y=x-\sigma t$; they give an insight of the local shape of solutions when a permanent regime is established. The determinatination of such profiles is usual in this field [62, 57].

Another ingredient is to take into account active movement of cells and not only their passive movement under pressure forces. This leads to write the model, which is analyzed in [56],

$$\partial_t n - \operatorname{div}\big(n\nabla p\big) - \nu\Delta n = nG\big(p\big). \tag{10}$$

The effect of the diffusion term $-\nu\Delta n$ is drastic and progression is much faster with smoother profile (but [56] show that a free boundary problem can still be defined as we do it in the next section).

Finally, Darcy's law relating velocity and pressure can also extended to a visco-elastic fluid and gives

$$\begin{cases} \partial_t n - \operatorname{div}\big(n\nabla W\big) - \nu\Delta n = nG\big(p\big), \\ -\nu\Delta W + W = p, \end{cases}$$

see [13].

More generally, the formalism of multiphase fluids can be used in the present context [16, 58] in order to represent the complexity of cell surrounding. One can also add many additional biological features, which have led to mathematical models, and which we do not mention here.

3 The Hele-Shaw asymptotic and free boundary formulation

As long as cells are well separated, the pressure forces are negligible. When the population density increases, there is a maximum possible compaction which cannot be exceeded. To represent this effect with a fast transition, the simplest formalism is to consider the limit as $\gamma \to \infty$ in the equation of state, see (1), and which we call the *stiff pressure asymptotic*. This type of modeling is mostly used in practical use of cancer models and software development [35, 48, 60, 24, 25, 28].

3.1 Free boundary problem

This limit results in a model that generalizes the Hele-Shaw equation of fluid mechanics and which is usually seen as a free boundary problem. The tumor occupies a domain $\Omega(t)$, healthy cells fill the space outside $\Omega(t)$. The boundary $\partial\Omega(t)$ of the domain $\Omega(t)$ is moving with the velocity

$$v_\infty(x,t) = -\nabla p_\infty(x,t) \tag{11}$$

where the pressure field is computed thanks to the equation

$$\begin{cases} -\Delta p_\infty = G(p_\infty) \qquad x \in \Omega(t), \\ p_\infty = 0 \qquad \text{on } \partial\Omega(t). \end{cases} \tag{12}$$

In order to define this dynamic, some smoothness of the free boundary is necessary. Such a property has been widely studied, see [35, 33] and the references therein. An alternative is to set this problem in the general framework of viscosity solutions with a correct viscosity condition on the interface, see [40, 41]. Surface tension may also be included [33, 35, 1], then the Dirichlet boundary condition has to be changed to $p_\infty = a\kappa(x,t)$ with a a parameter and κ the mean curvature.

As we mentioned earlier, the biophysical modeling gives growth terms G that depend on p, and not on n as in [8] for instance. Remarkably, this property allows us to extend nicely the usual Hele-Shaw theory and recover the semi-linear elliptic equation (12). A recent interest for the Hele-Shaw equation also arises in other fields of mathematics with the stochastic Loewner evolutions, Laplacian growth, diffusion limited aggregation, etc

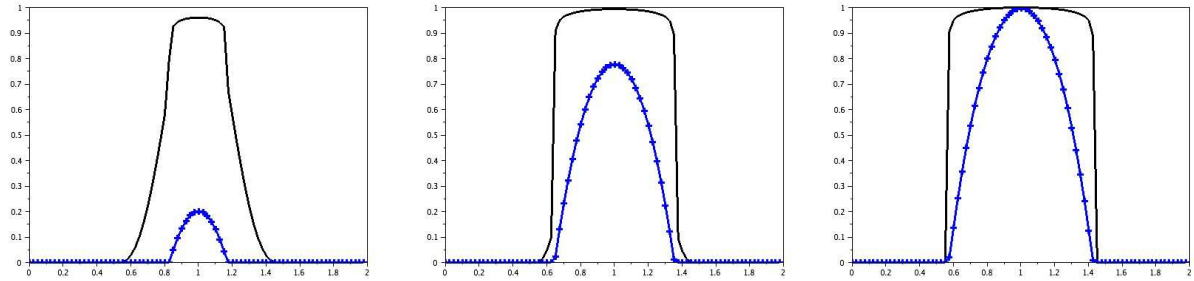

Figure 1: Numerical simulations at three different times of the system (1) with $\gamma = 40$ and $G(p) = 5(2-p)$. The density n is plotted in solid line whereas the pressure p is represented with $-+-$ (smoother curve).

3.2 Weak formulation

Besides the free boundary formulation, there is also a weak formulation of the limit $\gamma \to \infty$ in the equation (1). This limit gives a more general setting allowing a 'pretumor zone' where healthy and tumor cells are present in a mixed state. This weak formulation was derived in [55] and leads to the equation

$$\begin{cases} \frac{\partial}{\partial t} n_\infty - \operatorname{div}\big(n_\infty \nabla p_\infty\big) = n_\infty G\big(p_\infty(x,t)\big), \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ n_\infty(x, t=0) = n_\infty^0(x) \geq 0, \\ p_\infty(1 - n_\infty) = 0, \qquad 0 \leq n_\infty \leq 1. \end{cases} \tag{13}$$

In other words, when $n_\infty < 1$ then $p_\infty = 0$. Consequently, n_∞ and p_∞ are so weakly related that their dynamics can be somewhat independent. Nevertheless, a remarkable property is that the weak solution of (13) is unique (see [55]).

To present the result, we now insert the index γ to the notations n and p for the solutions of (1). The following result holds

Theorem 3.1 (Hele-Shaw limit, [55]) *With the assumptions of Proposition 2.1, as $\gamma \to \infty$, we have*

$$\begin{gathered} n_\gamma \to n_\infty \leq 1, \qquad p \to p_\infty \leq P_h \qquad a.e.\ in\ \ \mathbb{R}^d \times (0,\infty), \\ \nabla p_\gamma \rightharpoonup \nabla p_\infty \qquad in\ \ L^2\big(\mathbb{R}^d \times (0,T)\big) - weak, \quad \forall T > 0, \\ \frac{\partial}{\partial t} n_\infty \geq 0, \qquad \frac{\partial}{\partial t} p_\infty \geq 0. \end{gathered}$$

The limit of equation (1) *is equation* (13).

Notice that, from the BV (bounded variation) properties of n_γ and p_γ in Proposition 2.1, we derive strong compactness. We also conclude that

$$n_\infty \in L^\infty\big((0,T); L^1 \cap L^\infty(\mathbb{R}^d)\big), \quad p_\infty \in L^\infty\big((0,T) \times \mathbb{R}^d\big) \cap L^1\big((0,T) \times \mathbb{R}^d\big)$$

and that, as measures although we use the notation of L^1 functions, $|\nabla n_\infty(x,t)|$ and $|\nabla p_\infty(x,t)|$ are bounded with

$$\int_{\mathbb{R}^d} |\nabla n_\infty(x,t)| dx \leq K^0 e^{G_M t}, \quad \int_0^T \int_{\mathbb{R}^d} |\nabla p_\infty(x,t)| dx dt \leq C(T, P_h, K^0).$$

The other results follow immediately. For example, because

$$n_\gamma p_\gamma = n^{\gamma+1} = p_\gamma^{\frac{\gamma+1}{\gamma}},$$

and passing to the strong limits, we find in the limit the relation $p_\infty(1-n_\infty)=0$. Another property follows immediately from the same argument; because $n_\gamma \nabla p_\gamma = \nabla p_\gamma^{\frac{\gamma+1}{\gamma}}$, we find the relation

$$n_\infty \nabla p_\infty = \nabla p_\infty, /quada.e..$$

In other words, the equation on n_∞, in (13), can also be written

$$\frac{\partial}{\partial t} n_\infty - \Delta p_\infty = n_\infty G\big(p_\infty(x,t)\big).$$

This is the form used in [55] to prove uniqueness of weak solutions.

A more difficult result is the derivation of the 'complementary relation', (14) below, which is equivalent to the strong convergence of ∇p_γ.

Theorem 3.2 (Complementary relation) *Additionally to Theorem 3.1, one also has*

$$\nabla p_\gamma \to \nabla p_\infty \qquad in \;\; L^2_{\rm loc}\big(\mathbb{R}^d \times (0,\infty)\big) - strong,$$

The 'complementary relation' also holds

$$p_\infty \left(\Delta p_\infty + G(p_\infty)\right) = 0 \qquad in \;\; \mathcal{D}\big(\mathbb{R}^d \times (0,\infty)\big). \tag{14}$$

The *complementary relation* (14) is not an obstacle problem (a sign is incompatible) and the solution is not unique. It is a weak version of the equation (12) with

$$\Omega(t) = \big\{\; p_\infty(x,t) > 0 \;\big\}, \tag{15}$$

as set which evolution cannot be deduced from (14), but from the weak formulation (13).

the meaning, in distributions, of (14) is that for all smooth test functions φ with compact support, it holds

$$\int_{\mathbb{R}^d\times(0,\infty)} \varphi(x,t)\;\left[-|\nabla p_\infty|^2 + p_\infty G(p_\infty)\right] - \int_{\mathbb{R}^d\times(0,\infty)} p_\infty \nabla\varphi.\nabla p_\infty = 0$$

which makes sense with the available regularity for p_∞ in Proposition 2.1.

The proof of Theorem 3.2 relies on a functional analysis argument which uses the L^∞ control from below for $\frac{\partial}{\partial t} n_\gamma \geq 0$ as given in Proposition 2.2.

3.3 From the weak formulation to the free boundary statement

To begin withn notice that $\mathbb{1}_{\{\Omega(t)\}} = \mathbb{1}_{\{n_\infty(x,t)=1\}}$. Indeed, on the one hand, $\mathbb{1}_{\{\Omega(t)\}} \subset \mathbb{1}_{\{n_\infty(x,t)=1\}}$. On the other hand, when $p_\infty = 0$, then from (13), we conclude that $\frac{\partial}{\partial t} n_\infty = n_\infty G_M$, which means that we cannot have $n_\infty(x,t)=1$ otherwise n_∞ would continue to grow thus contradicting the bound $n_\infty(x,t) \leq 1$.

Therefore, when $n_\infty(x,t)$ takes the values 0 or 1 only, then we have

$$n_\infty(x,t) = \mathbb{1}_{\{\Omega(t)\}}. \tag{16}$$

In this situation and assuming some smoothness for $\Omega(t)$, it is easy to derive the Hele-Shaw free boundary formulation mentioned in Section 3.1. This is written in details (and in more generality in the sense below) when $\Omega(t)$ is a ball in [55], then one can establish precisely the speed of the free boundary given by (11).

However, the weak formulation contains more than the free boundary statements (11), (12) which only holds true when initially $n^0 = \mathbb{1}_{\{\Omega(t=0)\}}$ so as to ensure (16). One can formally see this, because in the interior of $\Omega(t)$, we can write $\frac{\partial}{\partial t} n_\infty = 0$ and thus the weak formulation (13) gives immediately the elliptic equation (12). But, if there is a zone where $n^0 < 1$, then we still have $n_\infty(x,t) < 1$ for some time. In this space-time zone, we have $p_\infty = 0$ and (13) is reduced to the simple differential equation

$$\frac{\partial}{\partial t} n_\infty = n_\infty G_M.$$

A numerical simulation, illustrating this interpretation is displayed in Figure 1.

A similar, but less complete, theory can be carried out for the case with active motion (10), see [56], and for the system with nutrient (8) and furthermore, the permanent shape, given by a traveling wave can be written exactly [57].

4 Adaptation and resistance to drugs

Besides mechanical aspects which we have presented so far, mathematical models of tumor growth also deal with questions which are more connected to biology than mechanics, and resistance to treatment is a typical example. The subject of resistance is considered presently as one of the challenges is medical treatment (see [42, 64, 46, 45] and the references therein).

A possible modeling of this phenomena is related to Darwinian evolution and to selection of the fittest traits. A subject that bridges probability [18] for finite populations, game theory as introduced by J. Maynard Smith and PDEs, the formalism we use below.

4.1 Population adaptive dynamic

In the view of [46, 45], cells are assumed to carry a resistance phenotype $y \in [0,1]$. In the simplest description, one considers the population density $n(y,t)$, this is usually called a *structured population*, [53]. One can postulate an equation for the dynamic of $n(y,t)$, expressing birth and death of cells. A general, yet simple, formalism is, following [54, 47, 49], to write a type of Lotka-Volterra equation

$$\frac{\partial}{\partial t} n(y,t) = n(y,t) R(y,\rho(t)) + \mu \Delta n(y,t), \qquad \rho(t) = \int_0^1 n(y,t)dy,$$

with Neuman boundary conditions (these are somewhat artificial but simplify the presentation). The diffusion term stands for mutations; several other forms are possible as integral operators [5] and, as well as diffusion, can de derived from stochastic individual models [18]. Again the choice of diffusion is made for simplicity. The term $R(y,\rho)$ represents the growth rate (death and birth), an example being

$$R(y,\rho) = b(y) - \rho\, k(y) - d(y)\, c_{\rm th}, \tag{17}$$

with $b(\cdot)$ the intrinsic division rate, $d(\cdot)$ the death rate induced by the therapeutic drug given with the concentration $c_{\rm th}$. Finally, $k(\cdot)$ represents the death rate due to competition, for space and nutrients, with all the cells whatever is their resistance level. Therefore, in the general setting, we assume that, for some constant $\alpha > 0$,

$$\frac{\partial}{\partial\rho}R(y,\rho) \leq -\alpha < 0.$$

Then, according to the interpretation of y as a resistance gene expression, we can assume some kind of resource allocation. When a cell uses energy to generate resistance, there is less energy for the cell division cycle, therefore we have

$$b'(\cdot) < 0, \qquad d'(\cdot) < 0, \qquad k'(y) < 0,$$

the last assumption means that resistant cells are also better competitors (an assumption that could be released by introducing another phenotypic trait).

The main qualitative property of solutions is better stated with a renormalization of time according to the scale $\mu = \varepsilon^2\mu_0$, $t_{\rm new} = \varepsilon t_{\rm old}$, with $t_{\rm old}$ the generation time, $t_{\rm new}$ the evolution time. This renormalization leads to re-write the equation on $n(y,t)$ as

$$\varepsilon\frac{\partial}{\partial t}n_\varepsilon(y,t) = n_\varepsilon(y,t)R(y,\rho_\varepsilon(t)) + \varepsilon^2\mu_0\Delta n_\varepsilon(y,t), \qquad \rho_\varepsilon(t) = \int_0^1 n_\varepsilon(y,t)dy. \tag{18}$$

This rescaling is standard in parabolic equation, in particular because it is the basis for deriving various front motions, see [34, 61] for instance.

The analysis carried out in [31, 53, 54, 47, 49] leads to use two main tools. The first one is a uniform Total Variation bound (TV in short) on $\rho_\varepsilon(t)$

$$0 < c \leq \rho_\varepsilon(t) \leq C, \qquad \int_0^T \big|\dot\rho_\varepsilon(t)\big|dt \leq C. \tag{19}$$

The lower bound expresses non-extinction and can be recovered a posteriori, it is however convenient to have it proved directly when this is possible. The BV bound is needed for nonlinear dependence on ρ in $R(x,\rho)$; it is not fundamental for the case (17) for instance.

The second tool is the WKB change of unknown

$$u_\varepsilon(y,t) = \varepsilon\ln\big(n_\varepsilon(y,t)\big)$$

and according to the observation of natural selection, as is standard in adaptive dynamics [30], the population should be highly concentrated around the fittest trait (think of a Gaussian). Then, initially one assumes that for some $\overline{y}^0 \in (0,1)$,

$$\begin{cases} n^0_\varepsilon(y) \underset{\varepsilon\to0}{\longrightarrow} \delta(y-\overline{y}^0) \text{ (weakly)}, \qquad u^0_\varepsilon \text{ is bounded in } \mathrm{Lip}(0,1), \\ u^0_\varepsilon \underset{\varepsilon\to0}{\longrightarrow} u^0, \qquad \max\limits_{0<y<1} u^0(y) = u^0(\overline{y}^0) \text{ (strict maximum)}. \end{cases} \tag{20}$$

This initial concentration effect remains true for all times under structural assumptions on (e.g. assuming that R is monotonic in y as in [54], or that R is concave in y as in [47]). Then, it is established that

$$\begin{cases} \rho_\varepsilon(t) \underset{\varepsilon\to0}{\longrightarrow} \overline{\rho}(t) \in L^\infty \cap TV(0,+\infty), \quad a.e. \\ n_\varepsilon(y,t) \underset{\varepsilon\to0}{\longrightarrow} \overline{\rho}(t)\delta\big(y-\overline{y}(t)\big). \end{cases} \tag{21}$$

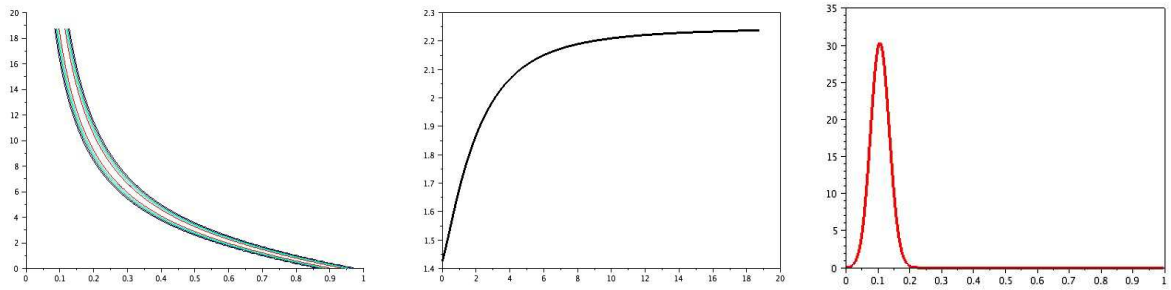

Figure 2: **No therapy.** Solution of system (18) with $\mu_0 = 0$ for $R(y,\rho) = \frac{3}{2} - y + \frac{\rho}{1.5+y}$, and departing from a distribution concentrated near $y = .95$ as a Gaussian with parameter $\varepsilon = 0.02$. Left: the isovalues of $n(y,t)$, abscissae are y and ordinates are t. Center: the function $t \mapsto \rho(t)$. Right: the distribution $n(y, t_{\text{final}})$ at $t_{\text{final}} = 20$, which concentrates at the point $y = \overline{y}_\infty = 0$.

The next question is to characterize the dynamic of the two unknowns $\overline{\rho}(t)$ and $\overline{y}(t)$. The answer is expressed through the limiting behavior of $u_\varepsilon(t)$. Still under technical assumptions depending on the case at hand (monotonic or concave function R), one has

$$u_\varepsilon(y,t) \underset{\varepsilon\to 0}{\longrightarrow} u(y,t) \quad \text{uniformly, locally in time,}$$

and the functions $u(y,t)$ and $\overline{\rho}(t)$ satisfy the *constrained Hamilton-Jacobi equation*

$$\begin{cases} \frac{\partial}{\partial t} u(y,t) = R\big(y, \overline{\rho}(t)\big) + \mu_0 |\nabla u|^2, \qquad 0 < x < 1,\ t \geq 0, \\ \max\limits_{0\leq y\leq 1} u(y,t) = 0 = u\big(\overline{y}(t), t\big), \\ u(y, t=0) = u^0(y), \end{cases} \tag{22}$$

with Neuman boundary conditions (note that only cases in the full line have been studied so far). The interpretation is as follows: $\overline{\rho}(t)$ is a Lagrange multiplier associated with the algebraic constraint that $\max_y u(y,t) = 0$. For this reason, the usual property of contraction in L^∞ of Hamilton-Jacobi equations is lost in the case with a constraint. However Lipschitz bounds for $u(y,t)$ are still available (and motivate the corresponding assumption in (20)) and are enough to prove existence of a viscosity solution. Uniqueness is only known in the particular case when R has a specific form as in (17), see [54].

4.2 Canonical equation and evolutionary stable distribution

One can go further (to the expense of more regularity on u, a condition that can be proved with concavity assumptions on R) and establish the form of canonical equation ([30]) as follows:

$$\begin{cases} R\big(\overline{y}(t), \overline{\rho}(t)\big) = 0, \\ \dot{\overline{y}}(t) = \big(-D^2 u(\overline{y}(t), t)\big)^{-1} \cdot D_y R(\overline{y}(t), \overline{\rho}(t)). \end{cases}$$

Because R is invertible in ρ, the first equation gives $\overline{\rho}(t)$ as a function of $\overline{y}(t)$, and then the ordinary differential equation for $\overline{y}(t)$ is in closed form when u is known.

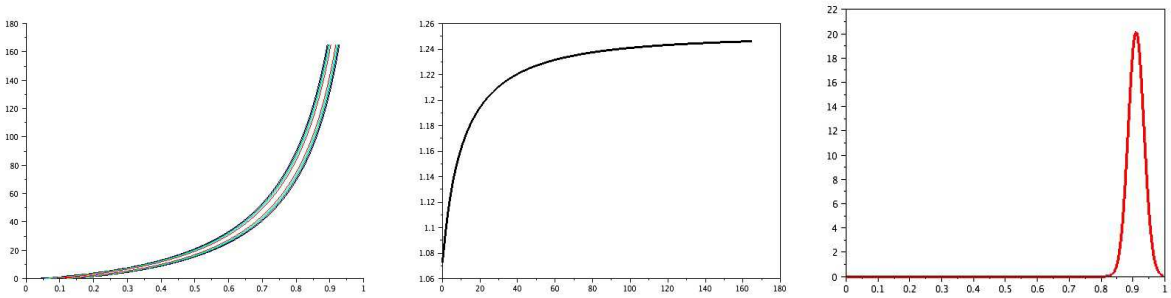

Figure 3: **With therapy.** Solution of system (18) with $\mu_0 = 0$ for $R(y,\rho) = \frac{3}{2} - y + \frac{\rho}{1.5+y} - C_{\rm Tox}(1-x)$, and departing from a distribution concentrated near $y = .05$ as a Gaussian with parameter $\varepsilon = 0.02$. Left: the isovalues of $n(y,t)$, abscissae are y and ordinates are t. Center: the function $t \mapsto \rho(t)$. Right: the distribution $n(y, t_{\rm final})$ at $t_{\rm final} = 180$, which concentrates at the point $y = \overline{y}_\infty = 1$.

This form of a canonical equation is not explicit as long as u is not computed, but can however give some information on the sign of $\dot{\overline{y}}(t)$ and on the long term dynamics of $\overline{y}(t)$. When a steady state is attained, it is called the evolutionary stable distribution [39] (ESD in short), a notion closely related the evolutionary stable strategy in adaptive dynamics [30].

For instance, for the case of (17) with no therapy, $c_{\rm th} = 0$, and weak competition compared to proliferation ($|b'|$ large compared to $|k'|$, then we find

$$\dot{\overline{y}}(t) \le 0 \quad \text{as} \quad b' < 0,$$

because $D^2 u(\overline{y}(t), t) \le 0$ at a maximum point. And we conclude that less resistant cells are selected. The dynamics will stop at an ESD $(\overline{\rho}_\infty, \overline{y}_\infty)$ which achieves both conditions

$$R\big(\overline{y}_\infty, \overline{\rho}_\infty\big) = 0, \qquad D_y R(\overline{y}_\infty, \overline{\rho}_\infty) = 0, \tag{23}$$

and this value $\overline{y}_\infty$ corresponds to a maximum of R in y. Here we should emphasize that because $\mu_0 = 0$, the restriction that $y \in (0,1)$ is only useful for the biological interpretation. Mathematically, the dynamics might lead $y(t)$ to become negative. This ESD is illustrated by Figure 2; with the rate function $R(y,\rho)$ used in this figure, one can readily check that $\overline{y}_\infty = 0$.

For a strong drug concentration, $c_{\rm th}$ large, then one finds on the contrary

$$\dot{\overline{y}}(t) \ge 0 \quad \text{as} \quad -d' > 0$$

and thus resistant cells are selected which escape therapy if $\rho(t)$ does not vanish. Here, it might occur that, for $c_{\rm th}$ large enough, then $\rho(t)$ vanishes and the lower bound in (19) fails; this can be interpreted as recovery. In such a case, the constraint in the constrained Hamilton-Jacobi equation (22) does not hold because the Lagrange multiplier is fixed at $\rho(t) = 0$. The Figure 3 illustrates a case where resistance occurs and the ESD, characterized by (23), is for $\overline{y}_\infty = 1$.

The effect of a multi-therapy to prevent resistance can be included in the model and gives rise to the following extension

$$\frac{\partial}{\partial t} n(y,t) = n(y,t) \left[\frac{b(y)}{1 + c_{\rm Stat}} - \rho(t)\, k(y) - d(y)\, c_{\rm Tox} \right], \qquad \rho(t) = \int_0^1 n(y,t) dy. \tag{24}$$

Here two types of effects are taken into account; $c_{\rm Tox}$ represents the cytotoxic drugs which induce apoptosis (usually by DNA damage during the Synthesis phase of the cell cycle), and $c_{\rm Stat}$ represents cytostatic effects which slow down the cell cycle (for instance using molecules that inhibit cyclines). Then the question is to determine the optimal scheduling $c_{\rm Stat}(t)$, $c_{\rm Tox}(t)$ with constraints on total toxicity. This is studied in [22] with the constraints to keep a high enough population of healthy cells.

4.3 Space structure and heterogeneity

Selection of a monomorphic population (that means a single Dirac mass) as derived before is compatible with the Gause competitive exclusion principle which is used in ecology; with N environmental variables, a bioreactor can sustain N interacting species, [17]. Here $N = 1$ and the environmental variable is just measured by the total population. However, genetic tests show a wide heterogeneity in tumor cells. Several explanations are possible as random mutations which generate a peaked distribution $n(y,t)$ but not exactly a Dirac mass; the parameter ε is small but not zero. Another possible explanation is spacial heterogeneity within tumor environment due to local availability of nutrients. In order to write corresponding equations, one should describe population densities $n(x,y,t)$ where x stands for the position and y for the phenotypical trait. With space and trait, to derive statements similar to those in (21)-(22) is a much more recent topic, see [11, 51, 12], with unexpected outcomes and difficulties. New phenomena as accelerating waves occur and mathematically, a priori bounds are more complicated because they should reflect the L^1 theory in the trait and the L^∞ theory in space.

The model proposed in [46] contains aspects coming both from the spatial model with nutrient (8) and the evolutionary aspects introduced in Section 4.1. To begin with, we present a simpler version, taken from [50], which explains the expected behavior of the solutions. We denote by $n_\varepsilon(y,x,t)$ the population density of cells which are located at the position x, with the trait y. To simplify we choose $y \in (0,1)$ and $x \in \mathbb{R}$ to simplify the statements. The spatial dependence determines local conditions for trait adaptation, according to available nutrient concentration $c(x,t)$. Following the rescaling proposed in (18), we write

$$\varepsilon\partial_t n_\varepsilon(y,x,t) = \left[r(y)c_\varepsilon(t,x) - d(y)(1+\varrho_\varepsilon(x,t))\right] n_\varepsilon(y,x,t), \qquad x\in\mathbb{R},\ 0<y<1,\ t\geq 0, \tag{25}$$

$$\frac{\partial}{\partial t}c_\varepsilon - \Delta_x c_\varepsilon(x,t) + \left[\varrho_\varepsilon(x,t)+\lambda\right] c_\varepsilon(x,t) = \lambda c_B, \qquad x\in\mathbb{R},\ t\geq 0, \tag{26}$$

$$\varrho_\varepsilon(x,t) = \int n_\varepsilon(y,x,t)dx, \qquad x\in\mathbb{R},\ t\geq 0. \tag{27}$$

In other words, we have chosen $k(y) = d(y)$ in (17), neglected mutations and added a parameter x which dependency is ruled by a parabolic PDE. To handle the asymptotic behavior in (25), the main difficulty is to find strong estimates for $\varrho_\varepsilon(x,t)$. Uniform L^∞ bounds are immediate but strong compactness, as derived from (19) in the x-independent case, are not available. With technical assumptions that we skip here, it is proved in [50], that there is $\varrho(y,t)$, $X(y,t)$ such that

$$c_\varepsilon(x,t) \underset{\varepsilon\to 0}{\longrightarrow} c(x,t) \quad \text{locally uniformly,}$$

$$\varrho_\varepsilon(x,t) \underset{\varepsilon\to 0}{\longrightarrow} \varrho(x,t) \quad \text{pointwise,}$$

$$n_\varepsilon(y,x,t) \underset{\varepsilon\to 0}{\longrightarrow} \varrho(x,t)\delta\big(y - Y(x,t)\big) \quad \text{weakly in measures.}$$

A qualitative consequence is heterogeneity which is expressed by the phenotypes $Y(x,t)$, $x\in\mathbb{R}$, which are represented at a time t.

To be closer to the case of tumor treatment, the system used in [46] includes additional matter. The space variable represents the distance to the center, effect of therapeutic drugs are included (following the ideas leading to the equation (24)), and both nutrients and therapy are delivered from a vasculature on the boundary of the tumor.

5 Conclusion

One should keep in mind that mathematical biology is not a recent subject. It has a long record of success as the Lotka-Volterra equations in ecology, statistics and random processes in genetics, the Turing instability for pattern formation and developmental biology, the Hodgkin-Huxley system for electric pulse propagation along nerves, the Keller-Segel system for cell chemotaxis, and many others. Subjects as epidemiology, population genetics, neuroscience use mathematical models for a long time. Biofluids, biomechanics are now well established subjects with applications to medicine and medical industry. Even though more recent, mathematics motivated by questions around tumor growth are now numerous and a search on publications data basis shows a fast growing activity in the field. This fast development, can be observed in many other fields of life sciences under two effects. Biologists have now access to new experimental devices giving enormous quantities of data as images; data analysis is needed to handle them and mathematical modeling is needed to give sense to them. Physicists have entered the field massively and have now access to simplified living systems; it might be simpler for mathematicians to speak with them. However, because of the specificities of the living matter, classical models must be revisited with new variants. But new questions, on new models, also appear which require to develop new mathematical tools. This paper is an attempt to show these two faces.

References

[1] N. D. Alikakos, P. W. Bates and X. Chen. Convergence of the Cahn-Hilliard Equation to the Hele-Shaw Model. Arch. Rational Mech. Anal. 128 (1994) 165-205.

[2] M. Adimy, F. Crauste, and L. Pujo-Menjouet. On the stability of a maturity structured model of cellular proliferation. Discret. Cont. Dyn. Sys. Ser. A 12 (3) (2005) 501–522.

[3] A. Anderson, M. A. J. Chaplain, and K. Rejniak. Single-cell-based models in biology and medicine. Birkhauser, Basel, 2007.

[4] R. Araujo, D. McElwain. A history of the study of solid tumour growth: the contribution of mathematical models. Bull. Math. Biol. 66 (2004), 1039–1091.

[5] G. Barles, S. Mirrahimi and B. Perthame. Concentration in Lotka-Volterra parabolic or integral equations: a general convergence result. Methods Appl. Anal. 16(3) (2009) 321–340.

[6] N. Bellomo, N. K. Li., and P. K. Maini. On the foundations of cancer modelling: selected topics, speculations, and perspectives. Math. Models Methods Appl. Sci. 4 (2008), 593–646.

[7] N. Bellomo and L. Preziosi. Modelling and mathematical problems related to tumor evolution and its interaction with the immune system. Math. Comput. Model. 32 (2000) 413–452.

[8] P. Bénilan and N. Igbida. The mesa problem for Neumann boundary value problem. J. Differential Equations 196 (2004) 301–315.

[9] S. Benzekry, G. Chapuisat, J. Ciccolini, A. Erlinger, and F. Hubert. A new mathematical model for optimizing the combination between antiangiogenic and cytotoxic drugs in oncology. C. R. Acad. Sc. Paris, Series I, Mathematics 350 (2012) 23–28.

[10] S. Benzekry, P. Hahnfeldt. Maximum Tolerated Dose Versus Metronomic Scheduling in the Treatment of Metastatic Cancers. J. Th. Biol. 335 (2013) 235–244.

[11] E. Bouin, V. Calvez, N. Meunier, S. Mirrahimi, B. Perthame, G. Raoul, and R. Voituriez. Invasion fronts with variable motility: phenotype selection, spatial sorting and wave acceleration. C. R. Math. Acad. Sci. Paris, Series I, Mathematics, 350 (2012) 761–766.

[12] E. Bouin and S. Mirrahimi. A Hamilton-Jacobi approach for a model of population structured by space and trait. Preprint HAL (2013).

[13] D. Bresch, T. Colin, E. Grenier, B. Ribba, and O. Saut. A viscoelastic model for avascular tumor growth. DCDS Supplements Vol. 2009, Issue Special, 2009, 101–108.

[14] H. M. Byrne and M. A. J. Chaplain. Free boundary value problems associated with the growth and development of multicellular spheroids. Eur. J. Appl. Math., 8, 639–658 (1997)

[15] H. Byrne and D. Drasdo. Individual-based and continuum models of growing cell populations: a comparison. J. Math. Biol. 58 (2009) 657–687.

[16] H. M. Byrne, J. R. King, D. L. S. McElwain, and L. Preziosi. A two-phase model of solid tumor growth. Appl. Math. Lett. (2003) 16: 567-573.

[17] N. Champagnat and P.-E. Jabin. The evolutionary limit for models of populations interacting competitively with many resources. J. Differential Equations 251 (2011) 176–195.

[18] N. Champagnat , R. Ferrière, and S. Méléard. From Individual Stochastic Processes to Macroscopic Models in Adaptive Evolution. Stochastic Models 24, S1 (2008) 2–44.

[19] P. Ciarletta, L. Foret, and M. Ben Amar. The radial growth phase of malignant melanoma: multi-phase modelling, numerical simulations and linear stability analysis. J. R. Soc. Interface 8 (2011) no 56, 345–368.

[20] J. Clairambault, S. Gaubert, and T. Lepoutre. Circadian rhythm and cell population growth. Mathematical and Computer Modelling, 53(7-8), 1558–1567, 2011.

[21] J. Clairambault, S. Gaubert, and B. Perthame. Comparison of the Perron and Floquet eigenvalues in monotone differential systems and age structured equations. C. R. Acad. Sc. Paris (2007), 345(10), 549–555.

[22] J. Clairambault, A. Lorz, and E. Trélat. Optimal control of cancer chemotherapies to overcome drug resistance. Work in progress.

[23] C. Colijn and M. C. Mackey. Bifurcation and bistability in a model of hematopoietic regulation. SIAM J. App. Dynam. Sys. 6(2) (2007) 378–394.

[24] T. Colin, D. Bresch, E. Grenier, B. Ribba, and O. Saut. Computational modeling of solid tumor growth: the avascular stage. SIAM Journal of Scientific Computing (2010) 32 (4) 2321–2344.

[25] T. Colin, A. Iollo, D. Lombardi and O. Saut. System identification in tumor growth modeling using semi-empirical eigenfunctions. Mathematical Models and Methods in Applied Sciences, Vol. 22, No. 6 (2012) 1250003 (30 pp).

[26] F. Cornelis, O. Saut, P. Cumsille, D. Lombardi, A. Iollo, J. Palussière, and T. Colin. In vivo mathematical modeling of tumor growth from imaging date: Soon to come in the future? Diagnostic and Interventional Imaging 94(6) (2013), 593–600.

[27] M. G. Crandall and M. Pierre. Regularizing effects for $u_t = \Delta\phi(u)$. Trans. Am. Math. Soc. Vol 274, no 1 (1982), 159–168.

[28] V. Cristini, J. Lowengrub, and Q. Nie. Nonlinear simulations of tumor growth. J. Math. Biol. 46 (2003), 191–224.

[29] De Angelis E., and Jabin P.E.,Qualitative Analysis of a mean field model of tumor-immune system competition, Mathematical Models and Methods in Applied Sciences, 13, 187–206 (2003).

[30] O. Diekmann. A beginner's guide to adaptive dynamics. In Rudnicki, R. (Ed.), Mathematical modeling of population dynamics. Banach Center Publications Vol. 63, (2004) 47–86.

[31] O. Diekmann, P.-E. Jabin, S. Mischler, and B. Perthame. The dynamics of adaptation: an illuminating example and a Hamilton-Jacobi approach. Th. Pop. Biol., 67(4):257–271, 2005.

[32] Richard Durrett. *Probability Models for DNA Sequence Evolution*. Springer, 2nd edition 2008.

[33] J. Escher and G. Simonett. Classical solutions for Hele-Shaw models with surface tension. Adv. Differential Equations, 2(4):619642, 1997.

[34] L. C. Evans and P. E. Souganidis. A PDE approach to geometric optics for certain semilinear parabolic equations. Indiana Univ. Math. J., 38(1):141–172, 1989.

[35] A. Friedman. A hierarchy of cancer models and their mathematical challenges. DCDS(B) 4(1) (2004), 147–159.

[36] H. P. Greenspan. Models for the growth of a solid tumor by diffusion. Stud. Appl. Math. 51 (1972), no. 4, 317–340.

[37] P. Hahnfeldt, D. Panigraphy, J. Folkman, and L. Hlatky. Tumor development under angiogenic signaling : a dynamical theory of tumor growth, treatment, response and postvascular dormancy. Cancer Research, 59:4770–4775, 1999.

[38] S. Hoehme and D. Drasdo. A cell-based simulation software for multi-cellular systems. Bioinformatics 26(20) (2010) 2641–2642.

[39] P.-E. Jabin and G. Raoul. On selection dynamics for competitive interactions. J. Math. Biol., 63(3):493–517, 2011.

[40] I. C. Kim. Uniqueness and existence results on viscosity solutions of the Hele-Shaw and the Stefan problems. Arch. Rat. Mech. Anal. 168 (2003), no. 4, 299–328.

[41] I. C Kim and A. Mellet. Homogenization of a Hele-Shaw problem in periodic and random media. Arch. Ration. Mech. Anal. 194 (2009), no. 2, 507–530.

[42] M. Kimmel and A. Świerniak. Control theory approach to cancer chemotherapy: benefiting from phase dependence and overcoming drug resistance. pp. 185–221 in Tutorials in Mathematical Biosciences III, Lect. Notes Math. 1872, A. Friedman ed., Springer, 2006.

[43] D. Kirschner and A. Tsygvintsev. On the global dynamics of a model for tumor immunotherapy, Journal of Mathematical Biosciences and Engineering Volume 6(3), 573–583, 2009

[44] U. Ledzewicz and H. Schaettler. Singular controls and chattering arcs in optimal control problems arising in biomedicine. Control and Cybernetics, 38, (2009), 1501–1523.

[45] A. Lorz, T. Lorenzi, M. E. Hochberg, J. Clairambault, and B. Perthame. Populational adaptive evolution, chemotherapeutic resistance and multiple anti-cancer therapies. ESAIM: Mathematical Modelling and Numerical Analysis Volume 47 (2), 2013, 377–399. DOI 10.1051/m2an/2012031

[46] A. Lorz, T. Lorenzi, J. Clairambault, A. Escargueil, and B. Perthame. Effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors. HAL-00921266 (dec. 2013).

[47] A. Lorz A., S. Mirrahimi, and B. Perthame. Dirac mass dynamics in multidimensional nonlocal parabolic equations. Comm. in P. D. E. Vol. 36(6), 2011, 1071–1098.

[48] J. S. Lowengrub, H. B. Frieboes, F. Jin, Y.-L. Chuang, X. Li, P. Macklin, S. M. Wise, and V. Cristini. Nonlinear modelling of cancer: bridging the gap between cells and tumours. Nonlinearity 23 (2010) R1–R91.

[49] S. Mirrahimi, G. Barles, B. Perthame, and P. E. Souganidis. A singular Hamilton-Jacobi equation modeling the tail problem. SIAM J. Math. Anal. 2012, Vol. 44, No. 6, 4297–4319.

[50] S. Mirrahimi and B. Perthame. Asymptotic analysis of a selection model with space. arXiv : 1407.5870 (2014).

[51] S. Mirrahimi and G. Raoul. Dynamics of sexual populations structured by a space variable and a phenotypical trait. Theoretical Population Biology 84 (2013), 87–103.

[52] J. Moreira and A. Deutsch. Cellular automata models of tumour developmenta critical review. Adv Complex Syst. 5(1) (2002) 247–267.

[53] B. Perthame. *Transport equations in biology*. Series 'Frontiers in Mathematics', Birkhauser (2007).

[54] B. Perthame and G. Barles. Dirac concentrations in Lotka-Volterra parabolic PDEs. Indiana Univ. Math. J. 57(7) 2008, 3275–3301.

[55] B. Perthame, F. Quiròs, and J.-L. Vàzquez. The Hele-Shaw asymptotics for mechanical models of tumor growth. Arch. Ration. Mech. Anal., Vol. 212, No 1 (2014) 93–127. HAL-UPMC.

[56] B. Perthame, F. Quiròs, M. Tang and N. Vauchelet. Derivation of a Hele-Shaw type system from a cell model with active motion. Interfaces and Free Boundaries, in press. HAL-UPMC : hal-00906168

[57] B. Perthame, M. Tang, and N. Vauchelet. Traveling wave solution of the Hele-Shaw model of tumor growth with nutrient. Mathematical Models and Methods in Applied Sciences, in press.

[58] L. Preziosi and A. Tosin. Multiphase modeling of tumor growth and extracellular matrix interaction: mathematical tools and applications, J. Math. Biol. 58 (2009) 625–656.

[59] J. Ranft, M. Basan, J. Elgeti, J.-F. Joanny, J. Prost, and F. Jülicher. Fluidization of tissues by cell division and apaptosis, PNAS 107 No 49 (2010) 20863–20868.

[60] T. Roose, S. Chapman, and P. Maini. Mathematical models of avascular tumour growth: a review, SIAM Rev. 49 2, (2007) 179–208.

[61] P. E. Souganidis. Front propagation: theory and applications, CIME course on 'viscosity solutions'. Lecture Notes in Math., Springer-Verlag, Berlin, 1998.

[62] J. A. Sherratt and M. A. J. Chaplain. A new mathematical model for avascular tumour growth. J. Math. Biol. 43, 291–312 (2001).

[63] K. R. Swanson, R. C. Rockne, J. Claridge, M. A. J. Chaplain, E.C. Alvord Jr, and A.R.A. Anderson. Quantifying the role of angiogenesis in malignant progression of gliomas: in silico modeling integrates imaging and histology. Cancer Res. 71(2011) 7366–7375.

[64] C. Tomasetti and D. Levy. An elementary approach to modeling drug resistance in cancer. Math. Biosci. Eng. 7 No 4 (2010), 905-18. [doi: 10.3934/mbe.2010.7.905.]

[65] J.-L. Vázquez. *The porous medium equation. Mathematical theory*. Oxford Mathematical Monographs. The Clarendon Press, Oxford University Press, Oxford, 2007. ISBN: 978-0-19-856903-9.