A Nash Topology Game for Tumoral Anti-angiogenesis

Abderrahmane Habbal

INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

A Nash Topology Game for Tumoral Anti-angiogenesis

Abderrahmane Habbal

N° 5252

Juillet 2004

Thème NUM

ISSN 0249-6399 ISRN INRIA/RR--5252--FR+ENG

INRIA
SOPHIA ANTIPOLIS

A Nash Topology Game for Tumoral Anti-angiogenesis

Abderrahmane Habbal

Thème NUM — Systèmes numériques
Projet Opale

Rapport de recherche n° 5252 — Juillet 2004 — 21 pages

Abstract: Tumoral angiogenesis and anti-angiogenesis are modeled as a Nash game. We consider the vessel-matrix-tumor system as a porous medium from the tumor viewpoint and as an elastic structural medium from the host tissue viewpoint. We define a competition between two density functions which are intended to represent respectively activators and inhibitors of angiogenesis. The activators want to minimize the pressure drop while the inhibitors intend to minimize the elastic compliance of the matrix or the drainage of the tumoral neovascularization. Numerical results illustrate how -theoretical- tumors develop multiple channels as an optimal response to optimal distribution of inhibitors.

Key-words: angiogenesis, Nash game, topology optimization.

Unité de recherche INRIA Sophia Antipolis
2004, route des Lucioles, BP 93, 06902 Sophia Antipolis Cedex (France)
Téléphone : +33 4 92 38 77 77 — Télécopie : +33 4 92 38 77 65

Jeux de Nash en anti-angiogénèse tumorale

Résumé : L'angiogénèse tumorale et les stratégies d'anti-angiogénèse sont modélisées comme un jeu de Nash. Notre approche consiste à considérer le système "vaisseau pré-existant+matrice extracellulaire + tumeur" comme un milieu poreux du point de vue de la tumeur et comme une structure élastique du point de vue du tissu hôte -matrice-. Nous définissons une compétition entre deux densités qui représentent respectivement les activateurs et les inhibiteurs d'angiogénèse. Les activateurs ont pour objectif de minimiser la perte en charge du milieu poreux, alors que les inhibiteurs ont comme objectif de minimiser la compliance élastique de la matrice, ou encore, dans la version implémentée numériquement, de minimiser le drainage du milieu poreux (jeu à somme nulle). Des résultats numériques illustrent comment la tumeur développe des canaux multiples comme réponse optimale à une distribution optimale d'inhibiteurs.

Mots-clés : angiogénèse, jeux de Nash, optimisation topologique.

1 Introduction

Angiogenesis is the biological process by which networks of blood vessels are initiated and proliferate towards a mature vasculature.
At early development and growth, angiogenesis is necessary to go from the embryonic vasculogenesis into a complete and mature blood circulatory system. Moreover, angiogenesis plays an important role in wound healing and tissue repairing.

But from other part, angiogenesis plays also a pathological role, being a fundamental step in the growth of cancer tumors and in tumoral metastasis. Recently, oncologists have suggested that the use of inhibitors of angiogenesis, an approach that is often referred to as anti-angiogenesis, could prove effective in cancer treatment. Dozains of anti-angiogenic drugs are currently undergoing clinical trials. Complete evidence of clinical efficiency for human beings is still lacking, but specialists share a strong belief that anti-angiogenesis is a promising therapy. Combined with directly curative drugs, anti-angiogenic drugs are intended to efficiently stop the expansion of tumoral mass, forcing the tumor to dormancy or even regression.

Angiogenesis and *a fortiori* anti-angiogenesis are however complex phenomena, with complex set of interactions and external parameters. So there is a crucial need for tools, amongst which mathematical modeling and computational methods, that could help the specialist to acquire a qualitative understanding of *effects* of naturally present or medically introduced (drugs) inhibitors, as well as yield indications on *optimal use* of them.

In the present work, we consider angiogenesis and anti-angiogenesis processes as resulting from a mathematical game between two players : activators of angiogenesis, willing to provide the tumor with an efficient feeding (and waste expelling) network of blood vessels, and inhibitors, with a specific action on the tumor vasculature.

From the tumoral angiogenesis viewpoint, the vessel-matrix-tumor system is seen as a porous medium, defined by its porosity distribution. The latter is defined as a result of an interaction between activators and inhibitors. Activators would like to design the porosity in order to yield the minimal pressure drop.
From the host tissue viewpoint, the vessel-matrix-tumor system is seen as a linear elastic continuum medium, defined by its material elasticity tensor. As for the porosity, the material properties are defined as a result of an interaction between activators and inhibitors. Inhibitors would like to design the material distribution in order to provide the matrix with the minimal mechanical compliance.

Next section, we briefly outline some of basic and simple facts known to pro and anti angiogenesis processes. Then, in section 3 we introduce the mathematical -fluid and structural- models. Follows section 4, devoted to the presentation of a Nash game framework, well suited to our problem. An existence theorem of a Nash equilibrium is proved.

Within section 5, some computational issues are detailed, then we present two numerical experiments related to a zero-sum game version where players want to minimize versus maximize the pressure drop of the vasculature. Finally, section 6 ends the paper with some concluding remarks.

2 Angiogenesis and anti-angiogenesis

At their early stage of growth, solid tumors are avascular. They do not need a blood network, being small enough to get nutrients mainly by tissue diffusion.
However, their needs are proportional to their -growing- volume, while the feeding is proportional to the surface in contact with the host tissue. So, they rapidly reach a critical size for which the supply by diffusion is no more enough to continue developing. Then, avascular tumors sometimes turn into a dormant phase during which the growth stops, as a result of balance between proliferation and apoptosis of cancer cells.
Tumors which do not enter dormancy need ways alternative to diffusion. It is now well known that solid tumors use vascular supply. Tumor-associated neovascularization allows the tumor cells to express their critical growth advantage as reported by Saaristo *et al.*[1]. The process by which solid tumors develop a vascular network is called *angiogenesis*. Angiogenesis is a complex process, a complete description of which is outside the scope of the present paper. Readers interested in fundamental basics, particularly in view of mathematical modeling could refer to the well documented review paper by Mantzaris, Webb and Othmer [18]. Readers could refer to the beginners tutorial of the US National Institute for Cancer [14] for an illustrated introduction.

We sketch hereafter a -very- simplified description of angiogenesis process. Tumor cells produce and release in the surrounding tissue specific growth factors which target endothelial cells. There are two major growth factor families, the vascular endothelial growth factor -VEGF- and angiopoietin -Ang-. These growth factors induce a chemotactic migration, proliferation and division of endothelial cells, from a nearby existing vessel toward the tumor. In order to find a way to the tumoral cluster, the endothelial cells produce enzymes which degrade the extracellular matrix (host tissue surrounding the tumor), called matrix metalloproteinases -MMPs-. The endothelial cells organize into hollow tubes, forming capillary then vascular networks.
Growth factors, endothelial cells and degrading enzymes are the three angiogenic key factors that promote neovascularization, hence invasive growth of the tumors.
Moreover, experimental and clinical evidence suggests that the process of metastasis, which makes cancer disease potentially lethal is angiogenesis-dependent. J. Folkman *et al.* [15] have first proposed that anti-angiogenic therapy could be used as anti-cancer strategy, with the help of natural or artificial *inhibitors* to the cited three angiogenic key factors. Examples of inhibitors are anti-VEGF, anti-MMPs and inducers of apoptosis of endothelial cells.

Due to its complexity, anti-angiogenic therapy is nowaddays still a subject of discussion between pros and cons [17]. Mathematical modeling and computational experiments related to some of its simplified mechanisms could be useful to answer questions rised by the specialists.

3 Mathematical modeling

Most of the contributions to continuum mathematical models of tumor-induced angiogenesis are of nonlinear parabolic reaction-diffusion type, see e.g. [8], [9] [4] and [18] where an exhaustive bibliography is presented.

These models are based on equations which express balance or conservation laws of physical relevant quantities like as blood cells or extracellular matrix densities. An illustrative presentation excerpt from Chaplain [3] is as follows :

$$\begin{aligned} n_t &= \overbrace{\nabla.d_n\nabla n}^{random\ motility} - \overbrace{\chi\nabla.\left(\frac{n}{k+c}\nabla c\right)}^{chemotaxis} - \overbrace{\rho\nabla.n\nabla f}^{haptotaxis} \\ f_t &= \overbrace{\omega n}^{production} - \overbrace{\mu n f}^{degradation} \\ c_t &= -\overbrace{\lambda n c}^{uptake} \end{aligned} \tag{1}$$

where
n : density of the blood vessels
f :density of the matrix tissue
c : concentration of angiogenic factors

Our approach is slightly different from the above modelings.
While still viewing the *tumor+extracellular matrix+existing vessel* as an overall system, in our case a porous media and linear elastic competing models are considered.

Our aim is to define a framework well adapted to the formulation of angiogenesis and anti-angiogenesis as a game in the mathematical sense.
We shall deal with rather classical linear elliptic partial differential equations, within a framework for which existence and uniqueness of solutions is well known, [10]. So, for the sake of clarity of the exposure, we do not detail standard functional spaces, weak formulations and regularity assumptions on the data, unless if necessary.

3.1 A porous media model for the tumor

The extracellular matrix as well as the tumoral vasculature (its blood network) are seen as a porous medium, which occupies a volume $\Omega \subset \mathbb{R}^N$ ($N = 2$ or 3), see figure-1, with a

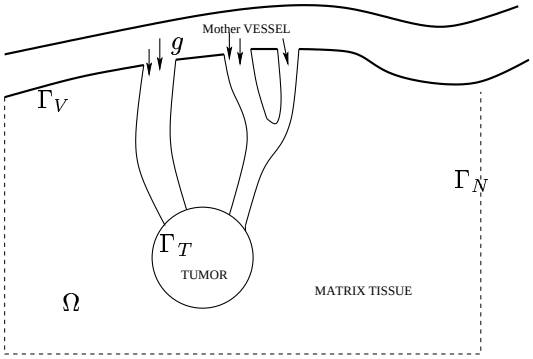

Figure 1: A Fluid viewpoint

variable porosity denoted by ρ , which lies between the matrix porosity ρ_M and blood vessel porosity ρ_V :

$$0 \leq \rho_M \leq \rho \leq \rho_V$$

The simplest *effective* model for porous media is the following, also known as the D'Arcy Law, where the physical unknown variable is pressure p :

$$\begin{cases} -div\,(\rho \nabla p) &= Q & \text{in } \Omega \\ \rho \dfrac{\partial p}{\partial n} &= \rho g & \text{over } \Gamma_V \\ \dfrac{\partial p}{\partial n} &= 0 & \text{over } \Gamma_N \\ p &= 0 & \text{over } \Gamma_T \end{cases} \tag{2}$$

The term Q represents a residual source of nutrients by diffusion through the host tissue, it is assumed to be negligible compared to the inward blood flow g. It should be noticed that we do not take into account what happens inside the tumor itself, considering only its boundary Γ_T as an outlet.

Obviously, the pressure field depends on the porosity distribution.

We postulate that angiogenesis provides the tumor with an optimal drainage mechanism, i.e. with a porosity such that the tumor optimal blood network minimizes the averaged pressure drop.

The pressure drop denoted by $L_1(\rho; p)$ is given by the formula :

$$L_1(\rho; p) = \int_\Omega Qp\,dx + \int_{\Gamma_V} \rho g p\,ds$$

3.2 A structural model for the extracellular matrix

Now, one may also consider the host surrounding tissue as a continuum mechanics medium as in figure-2, let say a linear isotropic, nonhomogeneous, elastic material. This model is of course a coarse approximation of the actual mechanical behavior of the living tissue ; see the book [11] for an introduction to biomechanics. This medium is composed of healthy and degraded tissues. The degradation could be due to established vascularization or to an early enzyme's action, like as the MMPs family.The elasticity tensor $\mathbf{E}$ lies then (in a certain sense) between the degraded material tensor $\mathbf{E_D}$, and the original -sane- extracellular matrix tensor $\mathbf{E_M}$.

Conforming to the linear elasticity classical equilibrium equations, the displacement vector $\mathbf{u} = (u_j)$ solves

$$\left\{ \begin{array}{lcll} -div\,(\mathbf{E}\epsilon(\mathbf{u})) & = & \mathbf{b} & \text{in } \Omega \\ \mathbf{u} & = & \mathbf{0} & \text{over } \Gamma_V \\ \mathbf{E}\epsilon(\mathbf{u}).\mathbf{n} & = & \mathbf{0} & \text{over } \Gamma_N \\ \mathbf{E}\epsilon(\mathbf{u}).\mathbf{n} & = & \mathbf{t} & \text{over } \Gamma_T \end{array} \right. \tag{3}$$

The strain tensor denoted by $\epsilon(u)$ is defined with obvious notations as

$$\epsilon(u)_{ij} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)$$

The mechanical stress tensor is given by $\sigma(u) = \mathbf{E}\epsilon(\mathbf{u})$.

The body forces -such as selfweight- are denoted by $\mathbf{b}$, and the normal tension which models the stress induced by the tumor growthis denoted by $\mathbf{t}$. The tissue is assumed to be clamped to the mother vessel Γ_V. A related model can be found in [2] where the authors study the stress induced during avascular tumor growth.

The displacement vector $\mathbf{u}$ depends on the Elasticity tensor $\mathbf{E}$. The latter itself depends on the interaction between activators and inhibitors of tissue degradation.

A second fundamental assumption is that the host tissue is willing to keep its integrity, by using all available factors it could control (one example is inhibitors of MMPs).
In continuum mechanics, it is usual to consider that such goal is achieved by maximizing the stiffness, or equivalently, minimizing the compliance :

$$L_2(\mathbf{E};\mathbf{u}) \;= \int_\Omega \mathbf{b}.\mathbf{u}\,dx + \int_{\Gamma_T} \mathbf{t}.\mathbf{u}\,ds$$

4 The Nash game

Any medical treatment could be seen as an *interaction between two or more agents*, the illness and the healing agents. These agents are expected to have antagonistic objectives.

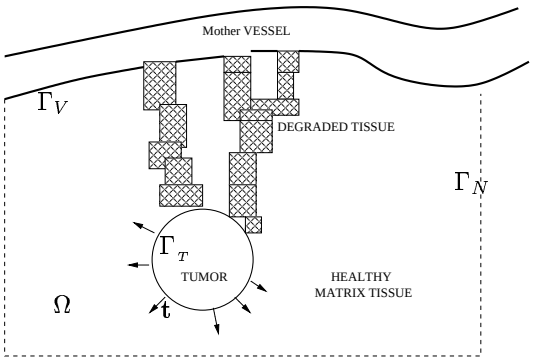

Figure 2: A Structural viewpoint

Angiogenesis and anti-angiogenesis fit into this description, for which a game-theoretical framework is well adapted.
Mathematical games are defined by the number of players and the strategy space as well as a loss (or objective) function, for each of the players. Games differ from classical optimization, each player's objective depends not only on her or his own played strategy, but also on the strategies played by all the other players. Games may be static or dynamic, meaning in the latter sense that there is an ordering in time of the play, and leading often to emergence of a leader and followers behavior. Readers may refer to the book by Gibbons [13].

Static games, referred to sometimes as blind or simultaneous, are designed for situations where there is no preponderance in the order of play. For simplicity, we skip here the important notion of rationality of the players, and the fundamental assumption that this rationality is a common knowledge. Static and dynamic games could also be with complete or incomplete information, meaning that each player has a complete (deterministic) or an incomplete (probabilistic) knowledge of the other's objective, when a couple of strategies is played.

Solutions to game problems are called equilibria. In the present study, *we consider a static with complete* information modeling of the game between angiogenesis and anti-angiogenesis. In this case, notion of equilibrium which is pertinent is the non-cooperative Nash equilibium, see cited reference above.

Let us first briefly describe the antagonistic interaction. The illness agent, mainly composed of the tumor itself and the proliferating endothelial cells, may use mechanisms and proteins, generically denominated by Tumoral Angiogenic Factors or TAF -such as MMPs and VEGF-, which favor the development of blood networks. Hence, without inhibition :

$$\rho = \rho\,(\mathrm{TAF}) \text{ and } \mathbf{E} = \mathbf{E}\,(\mathrm{TAF})$$

On the other hand, the healing agent may use antagonistic mechanisms and proteins, generically termed anti-Angiogenic Factors or aAF, which interfere with TAF, trying to stop or destroy the tumor neovascularisation. Such anti-Angiogenic Factors could be endogeneous like as inhibitors of MMPs produced by the extracellular matrix, or inhibitors produced and released by the endothelial and tumoral cells themselves (Interferon α, Angiostatin, Endostatin,...) [16], or artificially introduced drugs.
Thus, in presence of inhibitors :

$$\rho = \rho\,(\mathrm{TAF}, \mathrm{aAF}) \text{ and } \mathbf{E} = \mathbf{E}\,(\mathrm{TAF}, \mathrm{aAF}).$$

Intuitively, the porosity ρ increases with respect to TAF aggressive presence, and decreases with respect to aAF's, while the elasticity tensor $\mathbf{E}$ is expected to have opposite behavior.

4.1 Mathematical formulation of the game

It turns out that our approach naturally fits into the so called *topology design* framework, amongst a large literature, one could refer to [6] [12] and the references therein.A multidisciplinary topolgy design formulated within a Nash game framework can be found in [19].

As previously noticed, we consider a two-players static game of complete information. The two players are the Tumoral Angiogenic Factors (TAF) which control density functions of the activators, denoted by μ, and anti-Angiogenic Factors (aAF) which control density functions of the inhibitors, denoted by k.

Strategy spaces are defined as follows :

- (TAF) is equipped with a strategy space

$$S_1 = \{\mu \in L^\infty(\Omega) \quad 0 \leq \mu \leq 1 \quad \int_\Omega \mu dx \leq \gamma_1 |\Omega|\}$$

- (aAF) is equipped with a strategy space

$$S_2 = \{k \in L^\infty(\Omega) \quad 0 \leq k \leq 1 \quad \int_\Omega k dx \leq \gamma_2 |\Omega|\}$$

The constraints on two relative volume fractions express the fact that there is only a limited available amount of activators and inhibitors.

A simultaneous (or blind) choice of $(\mu; k)$ prompts an interaction between TAF and aAF, which is modeled as follows :

- Interaction Law : $\theta = \mu(1 - k)$

- Porosity : $\rho = \rho(\mu; k) = \rho_M + (\rho_V - \rho_M)P(\theta)$
- Elasticity tensor : $\mathbf{E} = \mathbf{E}(\mu; k) = \mathbf{E}_M + (\mathbf{E}_D - \mathbf{E}_M)P(\theta)$

where $P(\theta)$ is the identity, an exact homogenization operator, or an interpolated SIMP-like (Solid Isotropic Material Penalization) operator, see [7].

The interaction law is a very simple, arbitrary, choice. It states for example that the inhibitor action is completely and immediately efficient. Realworld situations are of course much more complex.

From other part, even if we content ourselves with linear porous media and elasticity models, there is a need for a more accurate effective fluid and structural equations, taking into account at least microscopic progressive degradation of the medium.

To end with the definition of the game, objective or loss functions are defined respectively as :

$$\text{Pressure Drop} \quad j_1(\mu; k) = L_1(\rho; p) \ \text{ for player (TAF)} \tag{4}$$

$$\text{Mechanical Compliance} \quad j_2(\mu; k) = L_2(\mathbf{E}; \mathbf{u}) \ \text{for player (aAF)} \tag{5}$$

where p is the pressure solution to the D'Arcy equation (2), and $\mathbf{u}$ is the displacement vector solution to the elasticity equation (3).

Let us finally remark that even if the original game considered here is a noncooperative static game, computational requirments lead us to consider *iterative* solving methods. The algorithmic version mimics then a repeated, *partially non-cooperative* game since the two players exchange information about their respective partial optima during the iterative process.

4.2 Existence of a Nash equilibrium

We consider the cases where either $P(\theta) = \theta$ or $P(\theta)$ is a restriction operator, *i.e.* $P(\theta) = g \circ S_R(\theta)$, with g convex and S_R a linear compact filter, cf [7] for details. We have the

Theorem 4.1 *There exists a Nash equilibrium, i.e. a pair of strategies* $(\mu^\star, k^\star) \in S_1 \times S_2$ *such that*

$$\mu^\star \ \textit{solves} \quad \min_{\mu \in S_1} j_1(\mu, k^\star) \tag{6}$$

$$k^\star \ \textit{solves} \quad \min_{k \in S_2} j_2(\mu^\star, k) \tag{7}$$

Proof. Let us first notice that the strategy spaces S_1 and S_2 are convex and compact for the weak-star L^∞ topology.

From one part, in case of $P(\theta) = \theta$ and since the functions j_1 and j_2 are the respective compliances of D'arcy and Elasticity equations, it is well known that these functions can be expressed as supremum envelops of continuous *affine* functions with respect to respectively μ and to k (using a variational formulation of the equations (2) and (3)), so these functions are convex and weak-star lower semicontinuous.

From other part, if $P(\theta)$ is a restriction operator, j_1 and j_2 can still be expressed as supremum envelops of continuous convex (but not necessarily affine) functions with respect to respectively μ and k. Convexity is preserved thanks to the linearity of the filter (and convexity of g) and compactness of the filter implies the weak-star lower semicontinuity of the objectives.

The assumptions are fulfilled in order to apply the Nash existence theorem,which yields the existence of a Nash equilibrium, see Aubin [5].

Notice that the use of a restriction operator in topology design framework is generally a necessary condition to get optimal solutions which are not a gray diffuse densities, but close to black-or-white distributions.

For numerical experiments, we considered the minimax (or duel) problem

$$j_2(\mu; k) = -j_1(\mu; k) = -L_1(\rho; p)$$

which models a game where the first player wants to minimize the pressure drop, while on the contrary the second player wants to maximize it (or, equivalently, wants to minimize the drainage of the network).

Such a game is also known as a zero-sum game.

5 Computational experiments

Solving a game consists mainly in finding its equilibrium or set of equilibria.

For a Nash game, due to the generally strongly nonlinear coupling between the players strategies, one uses iterative methods. For each overall iteration, one must solve as many as the number of players minimization problems. These minimization problems are, in a context implying partial differential equations, of high computational cost, so a particular attention must be paid to efficient, time saving algorithms.

We used a simple decomposition algorithm, which is well suited to coarse grained parallelization of the two partial minimization problems.

Start from an initial guess $s^{(0)} = (\mu^{(0)}, k^{(0)}) \in S_1 \times S_2$

(1) compute $\hat{\mu}$ which solves $\min_{\mu \in S_1} j_1(\mu, k^{(n)})$;

(2) compute (eventually in parallel) $\hat{k}$ which solves $\min_{k \in S_2} j_2(\mu^{(n)}, k)$;

(3) Set $s^{(n)} = (\hat{\mu}, \hat{k})$. Redo **(1)**, until the sequence $(s^{(n)})$ converges.

From the game theory viewpoint, this algorithm represents an *iterative, partially cooperative* game (with partial exchange of information on the partially optimal strategies between the players at the end of each iteration).

5.1 Approximations

The porous media equation is solved using a Triangular $P1$ finite element method. The FEM solver was implemented within the Modulef library environment [20].

Triangular $P0$ (i.e. constant over each triangle) approximation is used for the strategies μ and k ; the function $\theta = \mu(1-k)$ is then of the same nature.

The porosity is given by $\rho(\mu; k) = \rho_M + (\rho_V - \rho_M)P(\theta)$, where $P(\theta) = g \circ S_R(\theta)$ is a restriction of θ, used to obtain more or less black-or-white acceptable solutions, see [7].

Notice that the formula $\theta = \mu(1-k)$ implies that if θ is forced to take only 0 or 1 values, then the strategies μ and k are implicitely forced the same way. Numerical experiments corroborate this observation.

The following choices are inspired from the cited reference :

- $g(\sigma) = \dfrac{\sigma}{1 + (q-1)(1-\sigma)} \quad q \approx 3,$
- $S_R(\theta) = \Phi_R * \theta$, $\Phi_R(x, y) = \max\{0; 1 - \dfrac{|x-y|}{R}\}$

Partial optimizations described in steps **1** and **2** of the algorithm are achieved by means of a descent algorithm. We used the optimizer SCPIP written by Christian Zillober [22]. It is based on sequential convex programming combined with the method of moving asymptotes [21].

The optimizer needs that the user provides the gradient information. We used a classical adjoint state method in order to compute the respective gradients $\dfrac{\partial j_1}{\partial \mu}$ and $\dfrac{\partial j_2}{\partial k}$ [19].

5.2 Two Experiments

The Nash game between Tumoral Angiogenic Factors with a density μ and anti-Angiogenic Factors with a density k is the following :

(TAF) $\min_\mu$ Pressure Drop
(aAF) $\max_k$ Pressure Drop

We used the following physical data :

$Q = 10^{-3}$ $\quad g = +1$
$\rho_V = 10$ $\quad \rho_M = 10^{-3}$

These data do not correspond to particular biological parameters, the data calibration for what may be called *tumoral rheology* is a still challenging problem, which must be taken into account for the relevance of future applications.

We next present two numerical experiments. In both cases, the initial μ and k densities were chosen uniformly distributed, given by $\mu = \gamma_1$ and $k = \gamma_2$ everywhere, in order to fulfill the volume constraints.

5.2.1 Numerical Case I

The domain Ω is a rectangle. The upper side is Γ_V, and the lower is Γ_T.

Maximal allowed volume fractions are 40% for (TAF) and10% for (aAF).
The Nash overall loop converged in three iterations ; each partial optimization took around thirty iterations (and two hundred FEM runs) to converge.
The strategies, converging to a Nash equilibrium, are presented in figures 3-4-5.

In figure-3, the first player (TAF), informed that the second player (aAF) has played a uniform strategy, plays its optimal strategy which consists, as could be expected, in a single channel, preserving the volume constraint, located at the central line of the rectangle (thanks to the symmetry of the problem). At its turn, the second player, informed that the first player has played a uniform strategy, simply puts as much anti-angiogenic as possible around the tumor Γ_T. Quite unexpectedly, (aAF) does not play a uniform horizontal density, but creates a small excavation.

Then, at the second Nash iteration, the first player knows that the second one has cut off the way to the tumor, so it starts to develop alternative channels. At the same time, the second player knows now that the TAF has a strong presence within the excavation, which is then filled, see figure-4.
The final iteration, yielding a numerical Nash equilibrium is shown in figure-5. The resulting porosity distribution in figure-6 does not exhibit any arterial-tree branching struc-

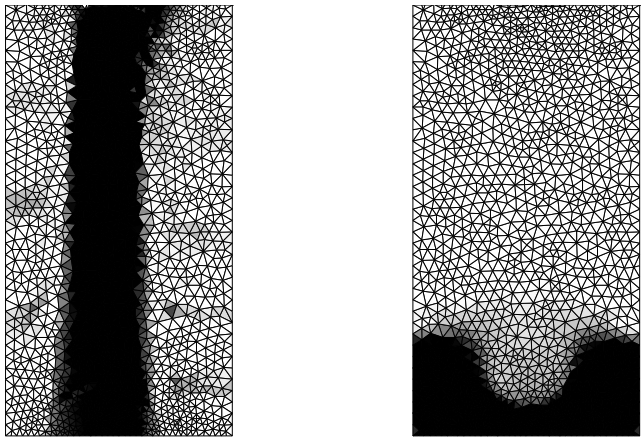

Figure 3: First Nash loop iteration.
Left: density μ of the TAF. **Right:** density k of the aAF.

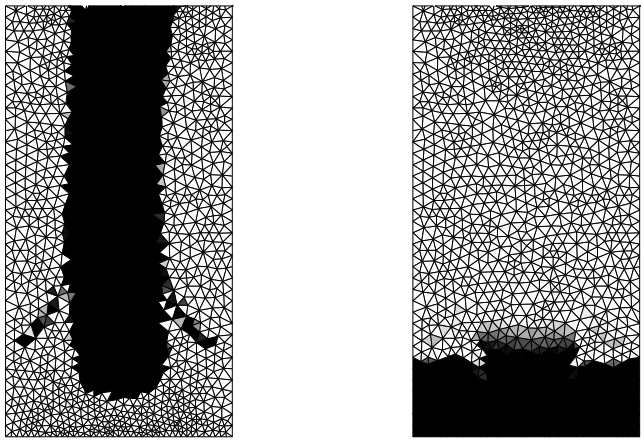

Figure 4: Second Nash loop iteration.
Left: density μ of the TAF. **Right:** density k of the aAF.

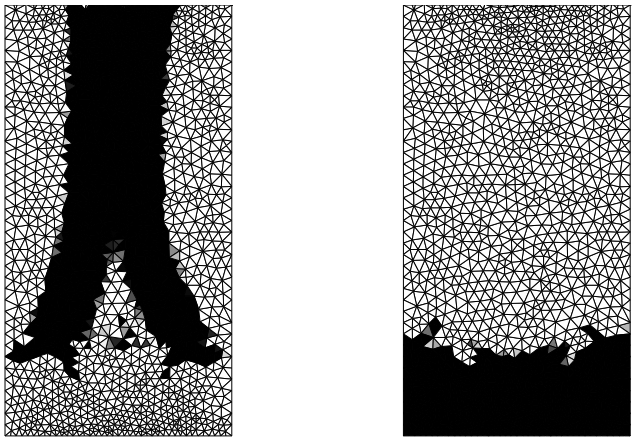

Figure 5: Final (3rd) Nash loop iteration.
Left: density μ of the TAF. **Right:** density k of the aAF.

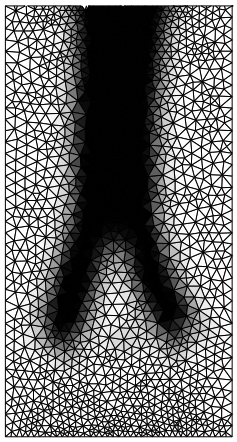

Figure 6: Final (3rd) Nash loop iteration.
Porosity distribution ρ.

ture, but only multiple channels.

Multiple channels seem to be the best response of the activators to optimally distributed inhibitors.

5.2.2 Numerical Case II

The geometry of the domain Ω is a trapezium with a circular hole, the upper side is Γ_V,and the circular hole is Γ_T.

The maximal allowed volume fractions are 30% for (TAF) and 5% for (aAF). Notice that with this volume fraction, (aAF) is not able to completely surround the circle Γ_T.

The Nash overall loop converged in 22 iterations ; strategies converging to a Nash equilibrium are presented in figures 7-8-9.

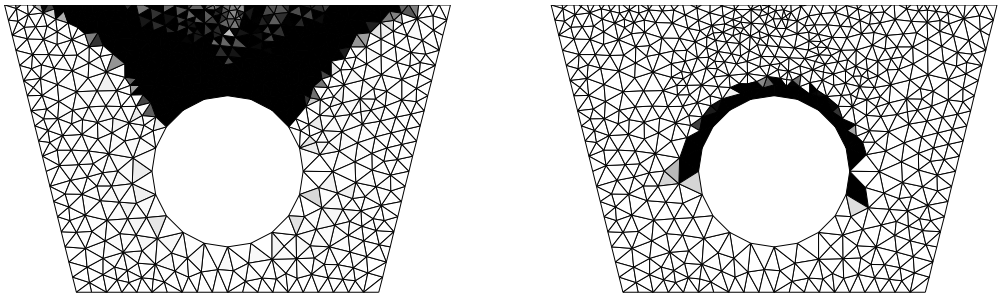

Figure 7: First Nash loop iteration.
Left: density μ of the TAF. **Right:** density k of the aAF.

As observed with the first numerical experiment, during the first iteration, each player has the information that the adverse party has played a uniform strategy, so as one may expect, the tumor opens a wide channel to the vessel, and the anti-angiogenic tries to cut off the way from the vessel to the tumor, by surrounding the latter as much as possible, see figure-7.

Next, figure-8 shows the strategies obtained at the second iteration. The first player now knows that the second one has surrounded the tumor, so it tries to develop alternative ways, and creates channels, while the second player, having the information on the strategy played by the first one (wide open channel) still keeps surrounding the tumor at places where outlet of the wide open channel is located.

Finally, at the 22nd iteration, a numerical Nash equilibrium is reached. As shown in figure-8, multiple channels are developed. Remark also that with a few available volume, the best response of the inhibitors is *not* to surround the tumor.

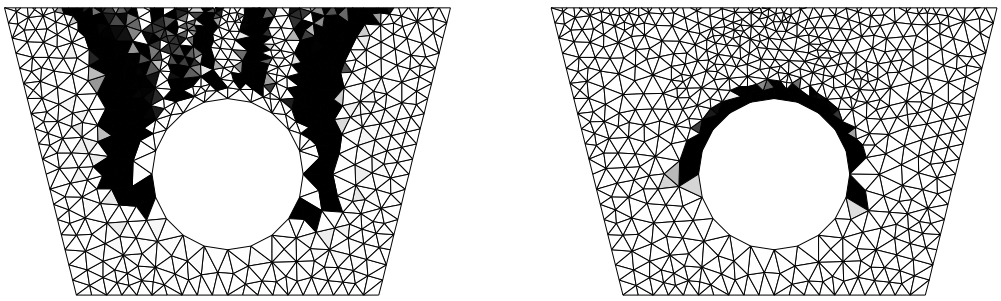

Figure 8: Second Nash loop iteration.
Left: density μ of the TAF. **Right:** density k of the aAF.

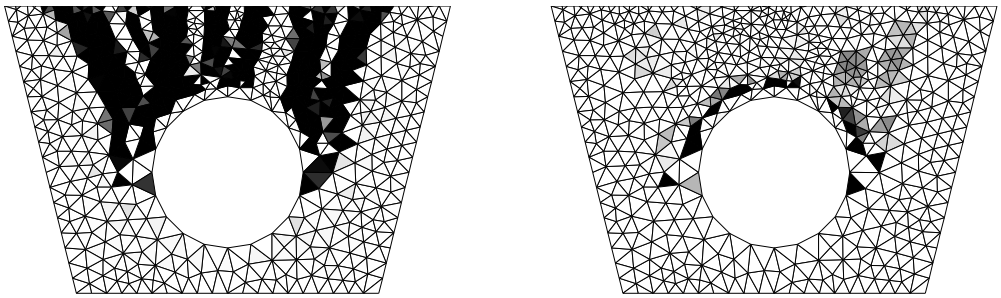

Figure 9: Final (22nd) Nash loop iteration.
Left: density μ of the TAF. **Right:** density k of the aAF.

Again, multiple channels is the best response of the activators to the best distribution of inhibitors.

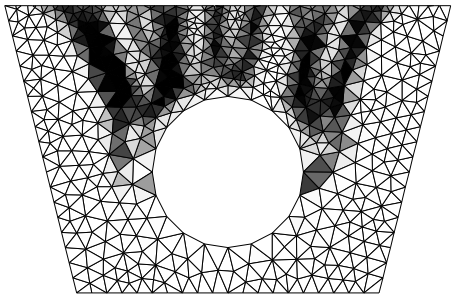

Figure 10: Final (22nd) Nash loop iteration.
Porosity distribution (filtered) ρ.

6 Concluding Remarks

An original approach based on game theory framework was proposed to model anti-angiogenesis. It relies on a competition between two density functions which are intended to represent respectively activators and inhibitors of angiogenesis.

To illustrate our approach, we defined a porous media versus structural linear elasticity theoretic game. The problem was formulated as a topology design static with complete information game, for which existence of a Nash equilibrium is proved. We assumed that activators would act to provide the tumor with an optimal drainage network, while the inhibitors would try to keep the structural compliance of the extracellular matrix as low as possible (or try to minimize the drainage of the blood vessels network in the case of zero-sum version). Computational issues were adressed, and numerical experiments related to a zero-sum game were presented.
The numerical results clearly caracterize the multiplicity of feeding channels as an optimal response of the activators to optimally distributed inhibitors.

This study is however based on simplified modeling and assumptions. Many improvements should be considered.

First, the dynamic growth of the tumor must be taken into account, and more generally a *dynamic* with incomplete information game is likely to be closer to the actual angiogenesis

process.

Then, the fundamental assumptions on the nature of *objectives* targetted by angiogenesis and anti-angiogenesis should be validated, confronting numerical results to biological data. Another important direction of validation is related to the determination of actual rheological data as well as models of interaction between pro and anti agiogenesis factors.

References

[1] T. Karpanen A. Saaristo and K. Alitalo. Mechanisms of angiogenesis and their use in the inhibition of tumor growth and metastasis. *Oncogene*, 19:6122–6129, 2000.

[2] J.S. Gibson A.F. Jones, H.M. Byrne and J.W. Dold. A mathematical model of the stress induced during avascular tumour growth. *J. Math. Biol.*, 40(6):473–499, 2000.

[3] A.R.A. Anderson and M.A.J. Chaplain. Continuous and discrete mathematical models of tumour induced angiogenesis. *Bull. Math. Biol.*, 60:857–899, 1998.

[4] C.Garcia-Reimbert C.A. Vargas A.R.A. Anderson, M.A.J. Chaplain. A gradient-driven mathematical model of antiangiogenesis. *Math. Comput. Modelling*, 32(10):1141–1152, 2000.

[5] J.P. Aubin. *Mathematical methods of game and economic theory.* North-Holland Publishing Co. Amsterdam, New York, 1979.

[6] M.P. Bendsoe. *Optimization of structural topology, shape, and material.* Berlin: Springer-Verlag., 1995.

[7] T. Borrvall and J. Petersson. Topology optimization using regularized intermediate density control. *Comput. Methods Appl. Mech. Eng.*, 190(37-38):4911–4928, 2001.

[8] M.A.J. Chaplain and B.D. Sleeman. A mathematical model for the production and secretion of tumour angiogenesis factor in tumours. *IMA J. Math. Appl. Med. Biol.*, 7(2):93–108, 1990.

[9] M.A.J. Chaplain and B.D. Sleeman. Modelling the growth of solid tumours and incorporating a method for their classification using nonlinear elasticity theory. *J. Math. Biol.*, 31(5):431–473, 1993.

[10] N.S. Trudinger D. Gilbarg D. *Elliptic Partial Differential Equations of Second Order.* Springer-Verlag, Berlin Heidelberg NewYork, 1977.

[11] Y.C. Fung. *Biomechanics. Mechanical properties of living tissues. 2nd ed.* Springer-Verlag New York Berlin Heidelberg., 1993.

[12] G. Francfort F. Jouve G. Allaire, E. Bonnetier. Shape optimization by the homogenization method. *Numer. Math.*, 76(1):27–68, 1997.

[13] R. Gibbons. *A primer in game theory.* New York: Harvester Wheatsheaf, 1992.

[14] National Cancer Institute. Understanding angiogenesis. http://press2.nci.nih.gov/sciencebehind/angiogenesis/angio00.htm.

[15] C. Abernathy J. Folkman, E. Merler and G. Williams. Isolation of a tumor factor responsible for angiogenesis. *J. Exp. Med.*, 133:275–288, 1971.

[16] W. Lasek M. Jacobisiak and J. Golab. Natural mechanisms protecting against cancer. *Immunology Letters*, (90), 2003.

[17] J. Folkman M.W. Kieran and J. Heymach. Angiogenesis inhibitors and hypoxia. *Nature-medecine*, 9(9):1104, september 2003.

[18] H.G. Othmer N.V. Mantzaris, S. Webb. Mathematical modeling of tumor-induced angiogenesis. *J. Math. Biol.*, 2004.

[19] A. Habbal J. Petersson and M. Thellner. Multidisciplinary topology optimization solved as a nash game. *Int. J. Numer. Methods in Eng.*, 2004. To appear.

[20] INRIA Modulef Project. Modulef guides. http://www-rocq.inria.fr/modulef/.

[21] K. Svanberg. The method of moving asymptotes - A new method for structural optimization. *Int. J. Numer. Methods Eng.*, 24:359–373, 1987.

[22] Ch. Zillober. Global convergence of a nonlinear programming method using convex approximations. *Numer. Algorithms*, 27(3):265–289, 2001.

Unité de recherche INRIA Sophia Antipolis
2004, route des Lucioles - BP 93 - 06902 Sophia Antipolis Cedex (France)

Unité de recherche INRIA Futurs : Parc Club Orsay Université - ZAC des Vignes
4, rue Jacques Monod - 91893 ORSAY Cedex (France)
Unité de recherche INRIA Lorraine : LORIA, Technopôle de Nancy-Brabois - Campus scientifique
615, rue du Jardin Botanique - BP 101 - 54602 Villers-lès-Nancy Cedex (France)
Unité de recherche INRIA Rennes : IRISA, Campus universitaire de Beaulieu - 35042 Rennes Cedex (France)
Unité de recherche INRIA Rhône-Alpes : 655, avenue de l'Europe - 38334 Montbonnot Saint-Ismier (France)
Unité de recherche INRIA Rocquencourt : Domaine de Voluceau - Rocquencourt - BP 105 - 78153 Le Chesnay Cedex (France)

Éditeur
INRIA - Domaine de Voluceau - Rocquencourt, BP 105 - 78153 Le Chesnay Cedex (France)
http://www.inria.fr
ISSN 0249-6399