Mathematical Modeling of Tumour Growth in Inhomogeneous Spheroidal Environment

Foteini Kariotou, Panayiotis Vafeas and Polycarpos K. Papadopoulos

***Abstract*—** Developing a mathematical model for cancer tumour growth that can be treated analytically and produce analytical results, is useful in the qualitative study of such complicated phenomenon. Most of such models consider radially symmetric tumours growing in homogeneous conditions, due to the availability of experimental data that concern mainly spherical tumours. Though, in vivo, the inhomogeneity of the host environment affects the geometrical features of the growing tumour mass, as shown in cases like the esophageal cancer. In the present work, we assume that the host tissue imposes the axisymmetric structure of a prolate spheroidal tumour via an appropriate pressure field and we investigate the evolution of such growth in a consistent nutritive microenvironment. To that purpose, the mathematical model that we consider consists of three boundary value problems, which describe the nutrient concentration, the inhibitor concentration and the pressure field in the interior and in the exterior of a layered prolate spheroid that models the tumour. These problems provide the necessary data for solving the evolution equation of the tumour's exterior boundary, which is a highly nonlinear ordinary differential equation. Additionally, our model exhibits a geometrical reduction to special cases and, mainly, to the spherical geometry in order to recover the existing results for the sphere.

***Keywords*—**Mathematical modeling, boundary value problems, avascular tumour growth, prolate spheroidal geometry.

I. Introduction

UNDERSTANDING the growth of a cancer tumour inside a healthy tissue is crucial for developing effective treatment and fighting such life threatening disease. Though, tumour growth is a very complicated phenomenon that involves many interrelated parameters, the investigation of which has drawn great multidiscipline scientific interest over the last century.

A cancer tumour is a cell colony that grows, invading a healthy host tissue. Roughly speaking, it consists of cells that consume nutrients and proliferate uncontrollably before they die out of programmed death, called apoptosis or out of lack of nutrients, called necrosis. As a tumour grows, different interrelated procedures take place, such as nutrient diffusion from the surrounding into the tumour, cell proliferation when the nutrient is enough and growth inhibition when either the nutrient is insufficient or an inhibitory substance is present. Supplementary, we may refer to several other processes such as cell death or disintegration, as well as inner pressure effects. As the tumour develops it enjoys an avascular phase that starts with tumorigenesis and ends with a steady state, where the tumour's volume gain, due to the new cancerous cells birth, balance the volume loss from the cells' death and disintegration. As the tumour's evolution proceeds, new phenomena, as angiogenesis, take place and the vascular phase begins, where the tumour develops a vascular net around it that provides the tumour cells with limitless nutrient supply and also it permits metastasis. At the present work we focus on the avascular phase of tumour evolution, while details on the proceeding phases can be found in the literature [1–3].

Mathematical modeling of avascular tumours has offered a great contribution in understanding the mechanisms involved with tumour growth. Starting back to mid sixties, Burton in [4] first suggested a relation between the size of the tumour and the nutrient concentration available in the tumour's surrounding. Greenspan in [5,6] offered the basic mathematic formulation for most of the subsequent models that were developed and also he introduced the idea of a surface tension that holds the tumour in a compact form. He also sought for an answer where the inhibitor substance comes from. Since then, many mathematicians have developed models that search several aspects of tumour growth, such as the effects of the geometry, the functional form of the consumption rates and so on, for the avascular and also the vascular tumours [1–3]. Though, most analytical works in the literature consider spherical tumour growth. This is not surprising since, during the steady state, the avascular tumour is bounded in a sphere with an approximate diameter of 2mm. This feature justifies the consideration of spherical tumours in most of the related works, since in such small lengths, scale deviations from a spherical symmetry are not considered quantitatively significant. Moreover, tumours grown in vitro form spherical aggregates [5–7]. However, the theoretical and experimental analysis viewed in [8–9], has revealed that non–symmetric tumours may occur in a confined surrounding as a result of the pressure effects on the growing tissue. In such cases, there are qualitative features that need to be addressed, as it is reported in [8–13] for several problems of different geometries.

In the present work, we study the evolution of a fully developed avascular tumour colony consisting of distinct layers occupied by cells at different stage of their cell cycle. The colony is assumed to maintain all its boundary interfaces as confocal prolate spheroids throughout its growth. Our work

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aims to predict the evolution of the tumour's exterior boundary and consequently the evolution of all its boundary interfaces. Within this frame, the exact exterior conditions that can support such a model and secure its compatibility with both the physics and the geometry, is under investigation. In addition to most of the relative works that consider homogeneous exterior conditions in an infinite environment, we investigate the impact, on the tumour's evolution, of a transversally isotropic pressure field imposed from the immediate surrounding tissue on the growing tumour. It turns out that the nutrient field should be inhomogeneous and that only a special type of inhomogeneity is compatible with the particular evolution, under such pressure assumption. Since the evolution of the tumour depends on the balance between the enhancement and the inhibition of the cell proliferation which depends mainly on the available nutrient, on the present inhibitors and on the pressure impact, it is important to have an accurate mathematical model for the determination of those parameters in the interior of the tumour structure.

To this purpose we consider a prolate spheroidal tumour that grows under the basic principles assumed in [6]. The tumour and the surrounding behave as incompressible fluids of different densities. The tumour receives nutrients by diffusion from its surrounding according to Fick's law, while the motility of the tumour cells is governed by a modification of Darcy's law. Our model concerns a fully developed tumour consisted of four regions, formed with respect to the nutrient and the inhibitor concentration levels. The dead cell debris form a necrotic core covered by a layer occupied by quiescent cells that do not have enough nutrient to proliferate. In the next layer the cells are also quiescent, but this is due to high inhibitor levels, even though the nutrient present is adequate to support proliferation. In the exterior tumour layer the nutrient concentration is high enough and the inhibitor concentration is low enough so that the cells there proliferate. All parts of the fully developed tumour are characterized by the same diffusion constant, while a physical interpretation, described in details in [12], allows us to work in quasistatic conditions, since the diffusion time scale is significantly shorter than the growth time scale [14].

When the cancer tumour is avascular, the nutrient concentration, denoted by σ, is the primary parameter. The other two basic parameters of physical growth are the inhibitor concentration β and the pressure field P. To this end, we denote by σ_∞ the nutrient supply provided by the surrounding tissue and by P_∞ the pressure field imposed, in a form that attributes the characteristics of a transversally isotropic medium. Therein, cell life is sustained if $\sigma > \sigma_n^*$, while cell proliferation is possible if both $\sigma > \sigma_p^*$ and $\beta < \beta^*$ hold, where σ_n^*, σ_p^* and β^* are critical concentration values, which are characteristic of the host tissue. Then, the mathematical formulation of the nutrient, the inhibitor and the pressure field consists of boundary value problems joint together in a highly non–linear ordinary differential equation, which describes the tumour evolution. The analytical manipulation of the Poisson's and the Laplace's partial differential equations in combination with the application of appropriate boundary conditions at every compartment's interface, in order to obtain all the aforementioned fields, is mostly based on classical analytical techniques mainly drawn from references [15–17]. Such kind of analysis must be accompanied of an adequate numerical implementation, which is necessary for tumour applications [18]. Therefore, the analytical part of the present paper is followed by the application of the obtained solutions to the computation of the basic fields. In details, those results include plots that depict the development of the nutrient and inhibitor concentrations, as well as of the pressure field, as we move outwards all the tumour's boundaries.

In section II the prolate spheroidal geometry of our model is postulated and the avascular tumour's domains with their boundaries are strictly defined. The corresponding boundary value problems in the prolate spheroidal coordinate system are stated in sections III and IV along with their implementation. In details, the analytical solution to obtain the nutrient and the inhibitor concentration is included in section III, while in section IV we derive the pressure field. In section V the evolution equation of the tumour's exterior boundary is provided and the conditions, which secure self–consistency of the mathematical problem, are obtained. These conditions provide one of the paper's main results on supporting a prolate spheroidal avascular growth. In addition, section VI is devoted to a geometrical reduction of the results drawn in this work into special cases and the spherical model to obtain the known results for the sphere. Numerical implementation of our results is considered in section VII, using the derived formulae. Finally, in section VIII there is an outline of our work, which recapitulates the main points as a brief conclusion.

II. Statement of the Problem

Let us consider a fully developed avascular tumour that grows maintaining all its boundary surfaces as confocal prolate spheroids. Therefore, given the fixed positive number $c > 0$, which denotes the semifocal distance of the prolate spheroidal system, we set the transformed prolate spheroidal coordinates (τ, ζ, ϕ) with semi–axes $a_1(\tau) = a_2(\tau) = c\sqrt{\tau^2 - 1} < a_3(\tau) = c\tau$, which yield $c = \sqrt{a_3^2(\tau) - a_1^2(\tau)} = \sqrt{a_3^2(\tau) - a_2^2(\tau)}$. Those are connected to the Cartesian coordinates $\mathbf{r} = (x_1, x_2, x_3)$ via the relations [15]

$$x_1 = c\sqrt{\tau^2 - 1}\sqrt{1 - \zeta^2}\cos\phi, \tag{1}$$

$$x_2 = c\sqrt{\tau^2 - 1}\sqrt{1 - \zeta^2}\sin\phi \tag{2}$$

and

$$x_3 = c\tau\zeta, \tag{3}$$

where the corresponding variables run within the intervals $\tau \geq 1$, $\zeta \in [-1, 1]$ and $\phi \in [0, 2\pi)$.

For such ζ and ϕ, the tumour's compartments are defined so as to correspond to successive intervals of the prolate variable τ. In such terms, the tumour consists of a necrotic core Ω_n, defined for every $\tau \in [1, \tau_n)$, where $0 < \sigma < \sigma_n^*$, surrounded by a quiescent layer Ω_q, where $\tau \in (\tau_n, \tau_q)$ that is

occupied by hypoxic cells, which are alive, but are not able to proliferate, since $0<\sigma_n^*<\sigma<\sigma_p^*$. In the subsequent layer there is enough nutrient to support proliferation but there is too much inhibitor concentration present to allow division, namely Ω_{p_-}, for $\tau\in\left(\tau_q,\tau_{p_-}\right)$. In the next confocal layer denoted as Ω_{p_+}, for $\tau\in\left(\tau_{p_-},\tau_{p_+}\right)$ cell proliferation takes place, since $\sigma>\sigma_p^*$ and $\beta<\beta^*$. Finally, the compartment of the normal host tissue Ω_e with $\tau\in\left(\tau_{p_+},\tau_e\right)$ is strongly affected by the cancerous mass growth. The interfaces between the successive compartments are denoted by S_j for $j=n,q,p-,p+$. On the exterior surface S_e, the surrounding provides nutrient in the general form

$$\sigma_\infty\left(\mathbf{r}_e\right)=\sum_{l=0}^{\infty}\sigma_{\infty,l}\left(\tau_e\right)P_l\left(\zeta\right)\ \text{for every}\ \zeta\in\left[-1,1\right] \tag{4}$$

and impose a pressure field

$$\mathrm{P}_\infty\left(\mathbf{r}_e\right)=\mathrm{p}_\infty\left(\tau_e\right)\left[1+a\left(1-\zeta^2\right)\right]\ \text{for every}\ \zeta\in\left[-1,1\right], \tag{5}$$

where the nutrient parameters $\sigma_{\infty,l}\left(\tau_e\right)$ for $l\geq 0$ and the pressure parameter $\mathrm{p}_\infty\left(\tau_e\right)$ are subject to the exterior conditions. The constant $a>0$ adapts the exterior pressure in a form that attributes the special characteristics of the prolate spheroidal tumour. Functions P_l for $l\geq 0$, stand for Legendre functions of the first kind [16] in terms of polynomials [16].

Our goal is the solution of proper boundary value problems within the aforementioned domains, in order to obtain the basic fields, i.e. the nutrient and the inhibitor concentration, as well as the pressure field in a closed analytical form in terms of the data (4) and (5). Once done, we proceed to the evolution equation of the tumour's exterior boundary.

III. Nutrient and Inhibitor Concentration

As both the nutrient and the inhibitor diffuse inward to or outward from the tumour, respectively, their distribution is described by standard parabolic partial differential equations, as it is shown in details in [12]. Though, it is a common assumption [5,6] that as the diffusion time scale is significantly shorter than the growth time scale, the chemicals maintain a permanent diffusive equilibrium state [14]. Therein, the partial differential equations for the nutrient and for the inhibitor concentration, become

$$\Delta\sigma\left(\mathbf{r}\right)=\gamma_j\ \text{for every}\ \mathbf{r}\in\Omega_j,\ \ j=n,q,p_-,p_+,e \tag{6}$$

and

$$\Delta\beta\left(\mathbf{r}\right)=p_j\ \text{for every}\ \mathbf{r}\in\Omega_j,\ \ j=n,q,p_-,p_+,e, \tag{7}$$

respectively, where each physical constant γ_j and p_j denotes the consumption rate, or production rate, as the case may be, normalized by the well–known diffusion constants k_σ and k_β, respectively, at the corresponding region.

Here, we have assumed that as long as the cell remains in a certain phase of its cycle, its needs in nutrients are unaltered, no matter the availability on them. Therefore, we may suggest that all cells occupying the same tumour region have the same constant consumption rate, while the transmission from one region to another results to a discontinuous and instant change in the consumption rate, modeled by means of a step function. The same argumentation is followed for the inhibitor.

In particular, the nutrient diffuses inward to the tumour and it is consumed at a rate γ_j that depends on the vital state of the cells and reflects the corresponding phase of the cell cycle, while, on the contrary, the inhibitor diffuses outward to the tumour and it is produced at a rate p_j. Obviously, $\gamma_n=0$ as Ω_n is occupied by necrotic debris and $\gamma_q\neq 0$, since the cells in Ω_q are quiescent but alive. On the other hand, it is valid that $\gamma_{p_-}=\gamma_{p_+}:=\gamma_p\geq\gamma_q$, since the cells in both Ω_{p_-} and Ω_{p_+} are in a more active state and, finally, $\gamma_e\geq\gamma_q$ but γ_e can be either grater or lower than γ_p depending on the kind of the healthy tissue in which the tumour grows. Probably, the suggestion of $\gamma_e\leq\gamma_p$ has a physical reasoning due to the greater demands of the much longer proliferation phase of the cancerous cell cycle compared to the normal cell cycle. However, without loss of generality and in order to make our calculations simpler, we assume that $\gamma_e=0$. Under similar physical considerations as previously stated, we may refer to the inhibitor's physical constants and claim that $p_n\neq 0$ and $p_q=p_{p_-}=p_{p_+}:=p_L$, while $p_e=0$. Here, we complete with the position of the partial differential equations.

Both the nutrient and the inhibitor fields are regular at zero and continuous on each S_j for $j=n,q,p_-,p_+,e$ as well. Their normal derivatives must be also continuous on each boundary [12]. In terms of the outward unit normal vector $\hat{\boldsymbol{\tau}}$ and by definition [15] of the $\hat{\boldsymbol{\tau}}$–directional derivative in the prolate spheroidal coordinates, which reads as

$$\hat{\boldsymbol{\tau}}\cdot\nabla=\frac{\sqrt{\tau^2-1}}{c\sqrt{\tau^2-\zeta^2}}\frac{\partial}{\partial\tau}\ \text{for}\ \tau\in\left[1,\tau_e\right]\ \text{and}\ \zeta\in\left[-1,1\right], \tag{8}$$

it is readily seen that the boundary conditions to be satisfied for every $\zeta\in\left[-1,1\right]$ and $\phi\in\left[0,2\pi\right)$ yield

$$\sigma\left(\tau_i,\zeta,\phi\right)=\sigma\left(\tau_j,\zeta,\phi\right)\ \text{with}\ i,j=n,q,p_-,p_+,e \tag{9}$$

and

$$\frac{\partial\sigma\left(\tau_i,\zeta,\phi\right)}{\partial\tau}=\frac{\partial\sigma\left(\tau_j,\zeta,\phi\right)}{\partial\tau}\ \text{with}\ i,j=n,q,p_-,p_+,e \tag{10}$$

for the nutrient concentration, while

$$\beta\left(\tau_i,\zeta,\phi\right)=\beta\left(\tau_j,\zeta,\phi\right)\ \text{with}\ i,j=n,q,p_-,p_+,e \tag{11}$$

and

$$\frac{\partial\beta\left(\tau_i,\zeta,\phi\right)}{\partial\tau}=\frac{\partial\beta\left(\tau_j,\zeta,\phi\right)}{\partial\tau}\ \text{with}\ i,j=n,q,p_-,p_+,e \tag{12}$$

for the inhibitor concentration, provided that always $\tau_j>\tau_i$. Conditions (9) and (10) are supplemented by the nutrient supply (4), i.e.,

$$\sigma\left(\tau_e,\zeta,\phi\right)=\sum_{l=0}^{\infty}\sigma_{\infty,l}\left(\tau_e\right)P_l\left(\zeta\right)\ \text{for every}\ \zeta\in\left[-1,1\right]. \tag{13}$$

Moreover, on the boundaries S_n and S_q the critical values of the nutrient and the inhibitor concentrations are met, a fact that will be especially useful in section V.

Applying the standard method of separation of variables in every compartment Ω_j for $j = n, q, p-, p+, e$, we solve the Laplace's and the Poisson's equations (6)–(7) and we perform some tedious but straightforward calculations, which are based on the proper application of the aforementioned boundary conditions (9)–(13). The analytical results are obtained in a closed compact fashion in terms of the well–known Heaviside function

$$H(\tau-\tau_j)=\begin{cases}1, & \tau\geq\tau_j\\ 0, & \tau<\tau_j\end{cases} \text{ with } j=n,q,p_-,p_+ \tag{14}$$

and accordingly to the following convenient notation for any $j,k = n, q, p_-, p_+, e$ and every $l,m = 0,1,2,\ldots$, which is provided by

$$E_{0,k}^{l,m} \coloneqq E_{0,k}^{l,m}(\tau) = P_l(\tau)Q_m'(\tau_k) - Q_l(\tau)P_m'(\tau_k) \tag{15}$$

and

$$W_{0,k}^{l,m} \coloneqq W_{0,k}^{l,m}(\tau) = P_l(\tau)Q_m'(\tau_k) - P_l'(\tau)Q_m(\tau_k), \tag{16}$$

where

$$E_{j,k}^{l,m} \coloneqq E_{0,k}^{l,m}(\tau_j) \text{ and } W_{j,k}^{l,m} \coloneqq W_{0,k}^{l,m}(\tau_j), \tag{17}$$

written in view of the Legendre functions of the first P_l and of the second Q_l kind [16]. Let us notice that the prime denotes derivation with respect to the argument, while all the fields are taken at $\mathbf{r} = (\tau, \zeta, \phi)$ provided that $\tau \in [1, \tau_e)$, $\zeta \in [-1,1]$ and $\phi \in [0, 2\pi)$.

Then, the nutrient concentration, which solves the elliptic equations (6), yields

$$\begin{aligned}\sigma(\mathbf{r}) = \frac{c^2}{9}\Bigg\{&\gamma_q\left[\frac{W_{n,n}^{2,0}}{Q_0'(\tau_n)} - \frac{W_{q,q}^{2,0}}{Q_0'(\tau_q)} + Q_0(\tau_e)\left(\frac{P_2'(\tau_n)}{Q_0'(\tau_n)} - \frac{P_2'(\tau_q)}{Q_0'(\tau_q)}\right)\right]\\ &+\gamma_p\left[\frac{W_{q,q}^{2,0}}{Q_0'(\tau_q)} - \frac{W_{p_+,p_+}^{2,0}}{Q_0'(\tau_{p_+})} + Q_0(\tau_e)\left(\frac{P_2'(\tau_q)}{Q_0'(\tau_q)} - \frac{P_2'(\tau_{p_+})}{Q_0'(\tau_{p_+})}\right)\right]\Bigg\}\\ &-\frac{c^2}{9}\left[-\gamma_q\frac{E_{e,n}^{2,2}}{W_{n,n}^{2,2}} + (\gamma_q-\gamma_p)\frac{E_{e,q}^{2,2}}{W_{q,q}^{2,2}} + \gamma_p\frac{E_{e,p_+}^{2,2}}{W_{p_+,p_+}^{2,2}}\right]\frac{P_2(\tau)}{P_2(\tau_e)}P_2(\zeta)\\ &+\sum_{l=0}^{\infty}\sigma_{\infty,l}(\tau_e)\frac{P_l(\tau)}{P_l(\tau_e)}P_l(\zeta)\\ &+H(\tau-\tau_n)\frac{c^2}{9}\gamma_q\left[P_2(\tau)-P_2(\tau_n)-\frac{P_2'(\tau_n)}{Q_0'(\tau_n)}\left(Q_0(\tau)-Q_0(\tau_n)\right)\right.\\ &\left.+\left(1-\frac{E_{0,n}^{2,2}}{W_{n,n}^{2,2}}\right)P_2(\zeta)\right]\\ &-H(\tau-\tau_q)\frac{c^2}{9}(\gamma_q-\gamma_p)\left[P_2(\tau)-P_2(\tau_q)-\frac{P_2'(\tau_q)}{Q_0'(\tau_q)}\left(Q_0(\tau)-Q_0(\tau_q)\right)\right.\\ &\left.+\left(1-\frac{E_{0,q}^{2,2}}{W_{q,q}^{2,2}}\right)P_2(\zeta)\right]\end{aligned}$$

$$\begin{aligned}&-H(\tau-\tau_{p_+})\frac{c^2}{9}\gamma_p\left[P_2(\tau)-P_2(\tau_{p_+})-\frac{P_2'(\tau_{p_+})}{Q_0'(\tau_{p_+})}\left(Q_0(\tau)-Q_0(\tau_{p_+})\right)\right.\\ &\left.+\left(1-\frac{E_{0,p_+}^{2,2}}{W_{p_+,p_+}^{2,2}}\right)P_2(\zeta)\right]. \quad (18)\end{aligned}$$

Similarly, for the inhibitor concentration that it is the solution of the corresponding elliptic relations (7), we derive

$$\begin{aligned}\beta(\mathbf{r}) = &\frac{c^2}{9}\left[(p_L-p_n)\frac{W_{n,n}^{2,0}}{Q_0'(\tau_n)} - p_L\frac{W_{p_+,p_+}^{2,0}}{Q_0'(\tau_{p_+})} + p_nP_2(\tau)\right]\\ &+\frac{c^2}{9}\left\{\left[(p_L-p_n)\frac{Q_2'(\tau_n)}{W_{n,n}^{2,2}} - p_L\frac{Q_2'(\tau_{p_+})}{W_{p_+,p_+}^{2,2}}\right]P_2(\tau) + p_n\right\}P_2(\zeta)\\ &+H(\tau-\tau_n)\frac{c^2}{9}(p_L-p_n)\left[P_2(\tau)-P_2(\tau_n)-\frac{P_2'(\tau_n)}{Q_0'(\tau_n)}\left(Q_0(\tau)-Q_0(\tau_n)\right)\right.\\ &\left.+\left(1-\frac{E_{0,n}^{2,2}}{W_{n,n}^{2,2}}\right)P_2(\zeta)\right]\\ &-H(\tau-\tau_{p_+})\frac{c^2}{9}p_L\left[P_2(\tau)-P_2(\tau_{p_+})-\frac{P_2'(\tau_{p_+})}{Q_0'(\tau_{p_+})}\left(Q_0(\tau)-Q_0(\tau_{p_+})\right)\right.\\ &\left.+\left(1-\frac{E_{0,p_+}^{2,2}}{W_{p_+,p_+}^{2,2}}\right)P_2(\zeta)\right], \quad (19)\end{aligned}$$

where it is verified that both (18) and (19), satisfy (6) and (7), respectively and boundary conditions (9)–(13), as well.

IV. Pressure Field

The pressure field is imposed by the host boundary, along with the net cell gain. By combination of previous assumptions [3,6], which attribute the cells to the pressure gradient, as it is dictated by the Darcy law, we further assume that cells exhibit an active chemotactic movement [12] and move towards the direction of the nutrient gradient and opposite to the direction of the pressure and of the inhibitor gradients. In other words, we assume that the velocity of the tumour cells inside Ω_j with $j = n, q, p-, p+, e$ is given by

$$\mathbf{v}_j(\mathbf{r}) = -\mu_P\nabla\mathrm{P}(\mathbf{r}) + \mu_\sigma\nabla\sigma(\mathbf{r}) - \mu_\beta\nabla\beta(\mathbf{r}) \text{ for } \mathbf{r}\in\Omega_j, \tag{20}$$

where μ_P, μ_σ and μ_β are proportionality constants, which characterize the motility of the cell. Applying the divergence operator on both sides of (20) and implying (6) and (7) we obtain

$$\Delta\mathrm{P}(\mathbf{r}) = F_j \text{ for } \mathbf{r}\in\Omega_j \text{ with } j = n, q, p-, p+, e, \tag{21}$$

where

$$F_j \coloneqq -G_j/\mu_P + \mu_\sigma\gamma_j/\mu_P - \mu_\beta p_j/\mu_P, \tag{22}$$

while $G_j \coloneqq \nabla\cdot\mathbf{v}_j$ denote the mass per unit volume, per unit time that is produced or lost in the region Ω_j and normalized by the tissue's density [12]. Easy physical argumentations allow us to consider that $F_n \neq 0$, $F_q = F_{p_-}$, $F_{p_+} \coloneqq F_p$ and $F_e = 0$.

The boundary conditions that will complement the partial differential equations (21) with (22) and provide uniqueness to the corresponding Boundary Value Problems–follow from the consideration that the pressure and its normal derivative must be regular at the origin and, moreover, they definitely should be continuous on the boundaries S_j for $j = n, q, p_-$, that is for $\zeta \in [-1,1]$ and $\phi \in [0, 2\pi)$

$$\mathrm{P}(\tau_i, \zeta, \phi) = \mathrm{P}(\tau_j, \zeta, \phi) \text{ with } i, j = n, q, p_- \tag{23}$$

and

$$\frac{\partial \mathrm{P}(\tau_i, \zeta, \phi)}{\partial \tau} = \frac{\partial \mathrm{P}(\tau_j, \zeta, \phi)}{\partial \tau} \text{ with } i, j = n, q, p_-, \tag{24}$$

provided that $\tau_j > \tau_i$. On the other hand, since the tumour, the affected compartment and the host tissue are considered to be fluids of different phase, then the corresponding boundary conditions on S_{p_+} and S_e follow the Young–Laplace law for the case of two–face incompressible fluids. Thus,

$$\lim_{\tau \to \tau_j^-} \mathrm{P}(\mathbf{r}) - \lim_{\tau \to \tau_j^+} \mathrm{P}(\mathbf{r}) = \alpha_j J(\mathbf{r}_j) \text{ with } j = p_+, e, \tag{25}$$

where J stands for the prolate spheroid's mean curvature and $\alpha_{p_+}, \alpha_e \in \mathbb{R}$, while the pressure field's trace on the exterior surface at S_e is provided via (5), in the form

$$\lim_{\tau \to \tau_e^+} \mathrm{P}(\tau, \zeta, \phi) = \mathrm{P}_\infty(\tau_e, \zeta, \phi) = \mathrm{p}_\infty(\tau_e)\left[1 + a\left(1 - \zeta^2\right)\right] \tag{26}$$

for every $\zeta \in [-1,1]$ and $\phi \in [0, 2\pi)$. In order to apply the boundary conditions (25), we expand function J in Legendre series. Hence, by virtue of a geometrical analysis of our system, the definition of the mean curvature in the prolate geometry results to

$$J(\tau, \zeta, \phi) = -\frac{\tau}{2c\sqrt{\tau^2 - 1}} \frac{1 - 2\tau^2 + \zeta^2}{\sqrt{\left(\tau^2 - \zeta^2\right)^3}} = \sum_{l=0}^{\infty} j_l(\tau) P_l(\zeta), \tag{27}$$

evaluated at $\tau = \tau_{p_+}, \tau_e$ for every $\zeta \in [-1,1]$ and $\phi \in [0, 2\pi)$. It can be easily verified after some trivial and straightforward calculations for $l \geq 0$,

$$j_{2l}(\tau) = \frac{\tau}{2c\sqrt{\tau^2 - 1}}\left[\left(2\tau^2 - 1\right) a_{2l}(\tau) - b_{2l}(\tau)\right], \tag{28}$$

corresponding to the even part and

$$j_{2l+1}(\tau) = 0 \tag{29}$$

for the odd part, in terms of the complicated practical notations

$$a_{2l}(\tau) = \frac{4l+1}{2^l\sqrt{\tau^2 - 1}} \sum_{k=0}^{l} \frac{(-1)^k (2l - 2k - 1)!!}{k!(l-k)!(2l - 2k - 2)!!} \times \left[\tau^{2l-2k} + \sum_{m=0}^{l-k-2} \tau^{2m} \frac{(2l - 2k - 2m)!!}{(2l - 2k - 2m - 1)!!}\right] \tag{30}$$

and

$$b_{2l}(\tau) = \frac{4l+1}{2^l\sqrt{\tau^2 - 1}} \sum_{k=0}^{l} \frac{(-1)^k (2l - 2k + 1)!!}{k!(l-k)!(2l - 2k)!!} \times \left[\tau^{2l-2k} + \sum_{m=0}^{l-k-1} \tau^{2m} \frac{(2l - 2k - 2m)!!}{(2l - 2k - 2m + 3)!!}\right]. \tag{31}$$

Therefore, the pressure field that solves the boundary value problem (21)–(26) with the aid of definitions (26)–(31) at $\mathbf{r} = (\tau, \zeta, \phi)$ with $\tau \in [1, \tau_e)$, $\zeta \in [-1,1]$ and $\phi \in [0, 2\pi)$ as usual, is obtained after a cumbersome mathematical analysis, which leads us to the following complicated but closed analytical form

$$\begin{aligned}
\mathrm{P}(\mathbf{r}) = \frac{2}{3}\mathrm{p}_\infty(\tau_e)\Bigg[\left(a + \frac{3}{2}\right) - a\frac{P_2(\tau)}{P_2(\tau_e)}P_2(\zeta)\Bigg] + \frac{c^2}{9}\Bigg\{ & F_n\left(P_2(\tau) + P_2(\zeta)\right) \\
& - \left(F_n - F_q\right)\frac{E^{2,0}_{n,n} + P_2'(\tau_n)\left(Q_0(\tau_e) - Q_0(\tau_n)\right)}{Q_0'(\tau_n)} \\
& - \left(F_q - F_p\right)\frac{E^{2,0}_{p_-,p_-} + P_2'(\tau_{p_-})\left(Q_0(\tau_e) - Q_0(\tau_{p_-})\right)}{Q_0'(\tau_{p_-})} \\
& - F_p\frac{E^{2,0}_{p_+,p_+} + P_2'(\tau_{p_+})\left(Q_0(\tau_e) - Q_0(\tau_{p_+})\right)}{Q_0'(\tau_{p_+})}\Bigg\} \\
- \frac{c^2}{9}\Bigg[\left(F_n - F_q\right)\frac{E^{2,2}_{e,n}}{W^{2,2}_{n,n}} + \left(F_q - F_p\right)\frac{E^{2,2}_{e,p_-}}{W^{2,2}_{p_-,p_-}} + F_p\frac{E^{2,2}_{e,p_+}}{W^{2,2}_{p_+,p_+}}\Bigg]\frac{P_2(\tau)}{P_2(\tau_e)}P_2(\zeta) & \\
+ \sum_{l=0}^{\infty}\Bigg[\alpha_e j_l(\tau_e) + \alpha_{p_+} j_l(\tau_{p_+})\frac{E^{l,l}_{e,p_+}}{W^{l,l}_{p_+,p_+}}\Bigg]\frac{P_l(\tau)}{P_l(\tau_e)}P_l(\zeta) & \\
- H(\tau - \tau_n)\frac{c^2}{9}\left(F_n - F_q\right)\Bigg[P_2(\tau) - P_2(\tau_n) - \frac{P_2'(\tau_n)}{Q_0'(\tau_n)}\left(Q_0(\tau) - Q_0(\tau_n)\right) & \\
+ \left(1 - \frac{E^{2,2}_{0,n}}{W^{2,2}_{n,n}}\right)P_2(\zeta)\Bigg] & \\
- H(\tau - \tau_{p_-})\frac{c^2}{9}\left(F_q - F_p\right)\Bigg[P_2(\tau) - P_2(\tau_{p_-}) - \frac{P_2'(\tau_{p_-})}{Q_0'(\tau_{p_-})}\left(Q_0(\tau) - Q_0(\tau_{p_-})\right) & \\
+ \left(1 - \frac{E^{2,2}_{0,p_-}}{W^{2,2}_{p_-,p_-}}\right)P_2(\zeta)\Bigg] & \\
- H(\tau - \tau_{p_+})\Bigg\{\frac{c^2}{9}F_p\Bigg[P_2(\tau) - P_2(\tau_{p_+}) - \frac{P_2'(\tau_{p_+})}{Q_0'(\tau_{p_+})}\left(Q_0(\tau) - Q_0(\tau_{p_+})\right) & \\
+ \left(1 - \frac{E^{2,2}_{0,p_+}}{W^{2,2}_{p_+,p_+}}\right)P_2(\zeta)\Bigg] & \\
+ \alpha_{p_+}\sum_{l=0}^{\infty} j_l(\tau_{p_+})\frac{E^{l,l}_{0,p_+}}{W^{l,l}_{p_+,p_+}}P_l(\zeta)\Bigg\}. &
\end{aligned} \tag{32}$$

It is easily verified that, after some trivial calculations, expression (32), satisfies (21) and the boundary conditions (23)–(26), as well.

V. Evolution Equation

The aim of this work is to determine the evolution of the tumour's exterior boundary S_{p_+} under the assumption that it evolves normally to itself, so as to remain a confocal prolate spheroid throughout the tumour's development. Considering

that the velocity of the cells on the exterior boundary is set as

$$\mathbf{v}_{p_+}\left(\mathbf{r}_{p_+}\right)=\frac{d\mathbf{r}_{p_+}}{dt}, \tag{33}$$

then equation (20) results to the following relationship in terms of $\hat{\boldsymbol{\tau}}$ [15], i.e.,

$$\hat{\boldsymbol{\tau}}\cdot\frac{d\mathbf{r}_{p_+}}{dt}=\hat{\boldsymbol{\tau}}\cdot\left[-\mu_P\nabla \mathrm{P}\left(\mathbf{r}_{p_+}\right)+\mu_\sigma\nabla\sigma\left(\mathbf{r}_{p_+}\right)-\mu_\beta\nabla\beta\left(\mathbf{r}_{p_+}\right)\right]. \tag{34}$$

Then, since $\mathbf{r}_{p_+}=\left(\tau_{p_+},\zeta,\phi\right)$ for $\zeta\in[-1,1]$, $\phi\in[0,2\pi)$ and in view of (8), we obtain

$$c^2\frac{\tau_{p_+}^2-\zeta^2}{\tau_{p_+}^2-1}\frac{d\tau_{p_+}}{dt}=\frac{\partial}{\partial\tau}\left(-\mu_P \mathrm{P}\left(\mathbf{r}_{p_+}\right)+\mu_\sigma\sigma\left(\mathbf{r}_{p_+}\right)-\mu_\beta\beta\left(\mathbf{r}_{p_+}\right)\right). \tag{35}$$

We, now, proceed by substituting the results (18), (19) and (32) evaluated on $S_{p_+}:\tau=\tau_{p_+}$, in (35) and we expand both its sides in Legendre series. Next, we use standard orthogonality properties of Legendre functions [16] to arrive at a system of equations with two outcomes.

Firstly, the system is self–consistent for every $\zeta\in[-1,1]$ and $\phi\in[0,2\pi)$ if the externally supplied nutrient has the form

$$\sigma\left(\tau_e,\zeta,\phi\right)=\sigma_{\infty,0}\left(\tau_e\right)+\sigma_{\infty,2}\left(\tau_e\right)P_2\left(\zeta\right)+\sum_{\substack{l=1\\ l\neq 2}}^{\infty}\frac{\mu_P}{\mu_\sigma}\left(\alpha_e j_l\left(\tau_e\right)+\alpha_{p_+} j_l\left(\tau_{p_+}\right)\frac{E_{e,p_+}^{l,l}}{W_{p_+,p_+}^{l,l}}\right)P_l\left(\zeta\right), \tag{36}$$

where the term $\sigma_{\infty,0}\left(\tau_e\right)$ is arbitrary and it is conveniently chosen accordingly to the particular physical requirements of every problem, while

$$\sigma_{\infty,2}\left(\tau_e\right)=\frac{\mu_P}{\mu_\sigma}\frac{2a}{3}\mathrm{p}_\infty\left(\tau_e\right)-\frac{\mu_P}{\mu_\sigma}\left(\alpha_e j_2\left(\tau_e\right)+\alpha_{p_+} j_2\left(\tau_{p_+}\right)\frac{E_{e,p_+}^{2,2}}{W_{p_+,p_+}^{2,2}}\right)+\frac{c^2}{9}f\left(\tau_n,\tau_q,\tau_{p_-},\tau_{p_+},\tau_e\right) \tag{37}$$

and by definition

$$\begin{aligned}f\left(\tau_n,\tau_q,\tau_{p_-},\tau_{p_+},\tau_e\right)=&\left(\mu_P\left(F_n-F_q\right)+\mu_\sigma\gamma_q\right.\\&\left.-\mu_\beta\left(p_L-p_n\right)\right)\left[\frac{E_{e,p_+}^{2,2}}{E_{n,n}^{2,2}}-\frac{E_{e,p_+}^{2,0}}{E_{p_+,n}^{2,0}}\right]\frac{P_2'\left(\tau_n\right)}{P_2'\left(\tau_{p_+}\right)}\\&-\mu_\sigma\left(\gamma_q-\gamma_p\right)\left[\frac{E_{e,p_+}^{2,2}}{E_{q,q}^{2,2}}-\frac{E_{e,p_+}^{2,0}}{E_{p_+,q}^{2,0}}\right]\frac{P_2'\left(\tau_q\right)}{P_2'\left(\tau_{p_+}\right)}\\&+\mu_P\left(F_q-F_p\right)\left[\frac{E_{e,p_+}^{2,2}}{E_{p_-,p_-}^{2,2}}-\frac{E_{e,p_+}^{2,0}}{E_{p_+,p_-}^{2,0}}\right]\frac{P_2'\left(\tau_{p_-}\right)}{P_2'\left(\tau_{p_+}\right)}\\&+\left(\mu_P F_p-\mu_\sigma\gamma_p+\mu_\beta p_L\right)\left[\frac{E_{e,p_+}^{2,2}}{E_{p_+,p_+}^{2,2}}-\frac{E_{e,p_+}^{2,0}}{E_{p_+,p_+}^{2,0}}\right]\\&-\mu_\beta\left[\left(p_L-p_n\right)\frac{P_2'\left(\tau_n\right)}{P_2'\left(\tau_{p_+}\right)}-p_L\frac{E_{n,n}^{2,2}}{E_{p_+,p_+}^{2,2}}\right]\frac{Q_2\left(\tau_e\right)P_2'\left(\tau_{p_+}\right)}{E_{n,n}^{2,2}}\Bigg\}.\end{aligned} \tag{38}$$

Secondly, we derive the evolution equation of the exterior tumour boundary S_{p_+} at $\tau=\tau_{p_+}$, that is

$$\begin{aligned}\frac{d\tau_{p_+}}{dt}=&\frac{1}{\left(3\tau_{p_+}^2-1\right)}\left[\left(-\mu_P\left(F_n-F_q\right)-\mu_\sigma\gamma_q+\mu_\beta\left(p_L-p_n\right)\right)\tau_n\left(\tau_n^2-1\right)\right.\\&+\mu_\sigma\left(\gamma_q-\gamma_p\right)\tau_q\left(\tau_q^2-1\right)-\mu_P\left(F_q-F_p\right)\tau_{p_-}\left(\tau_{p_-}^2-1\right)\\&\left.+\left(-\mu_P F_p+\mu_\sigma\gamma_p-\mu_\beta p_L\right)\tau_{p_+}\left(\tau_{p_+}^2-1\right)\right].\end{aligned} \tag{39}$$

Relationship (39) is an ordinary differential equation with respect to $\tau_{p_+}=\tau_{p_+}\left(t\right)$, where the uniqueness of its solution is secured by the initial condition $\tau_{p_+}\left(0\right)=T_{p_+}$, T_{p_+} being the initial radial prolate spheroidal variable of the S_{p_+} boundary. Its right hand–side depends on the time dependent boundaries at $\tau_n\left(t\right)$, $\tau_q\left(t\right)$, $\tau_{p_-}\left(t\right)$ and $\tau_{p_+}\left(t\right)$. Hence, equation (39) is solvable under constraints, which interrelate these boundaries and secure that (39) is dependent only on $\tau_{p_+}\left(t\right)$.

These constraints are provided by the critical values of the nutrient and inhibitor concentrations. In particular, the critical nutrient value σ_n^* determines if a cell dies out of starvation or not, so this value is met on the surface S_n, that is

$$\sigma_q\left(\mathbf{r}_n\right)=\sigma_n\left(\mathbf{r}_n\right)=\sigma_n^* \text{ with } \mathbf{r}_n=\left(\tau_n,\zeta,\phi\right) \tag{40}$$

for every $\zeta\in[-1,1]$ and $\phi\in[0,2\pi)$. The nutrient σ_p^* and the inhibitor β^* value determine if a cell proliferates or not, so these critical values are met on surfaces S_q and S_{p_-} i.e.,

$$\sigma_q\left(\mathbf{r}_q\right)=\sigma_{p_-}\left(\mathbf{r}_q\right)=\sigma_p^* \text{ with } \mathbf{r}_q=\left(\tau_q,\zeta,\phi\right) \tag{41}$$

and

$$\beta_q\left(\mathbf{r}_{p_-}\right)=\beta_{p_-}\left(\mathbf{r}_{p_-}\right)=\beta^* \text{ with } \mathbf{r}_{p_-}=\left(\tau_{p_-},\zeta,\phi\right), \tag{42}$$

whereas $\zeta\in[-1,1]$ and $\phi\in[0,2\pi)$. Such kind of formulae can be obtained by integration of σ and β, given by (18)–(19), on the boundary surfaces $S_n:\tau=\tau_n$, $S_q:\tau=\tau_q$ and $S_{p_-}:\tau=\tau_{p_-}$, respectively, providing the critical values σ_n^*, σ_p^* and β^* as average values on these boundaries. This procedure implies

$$\sigma_n^*-\sigma_p^*=\frac{c^2}{9}\gamma_q\left[P_2\left(\tau_n\right)-P_2\left(\tau_q\right)-\frac{P_2'\left(\tau_n\right)}{Q_0'\left(\tau_n\right)}\left(Q_0\left(\tau_n\right)-Q_0\left(\tau_q\right)\right)\right], \tag{43}$$

while

$$\begin{aligned}\sigma_{\infty,0}\left(\tau_e\right)=\sigma_n^*&-\frac{c^2}{9}\gamma_q\left[\frac{W_{n,n}^{2,0}}{Q_0'\left(\tau_n\right)}-\frac{W_{q,q}^{2,0}}{Q_0'\left(\tau_q\right)}\right.\\&\left.+Q_0\left(\tau_e\right)\left(\frac{P_2'\left(\tau_n\right)}{Q_0'\left(\tau_n\right)}-\frac{P_2'\left(\tau_q\right)}{Q_0'\left(\tau_q\right)}\right)\right]\\&-\frac{c^2}{9}\gamma_p\left[\frac{W_{q,q}^{2,0}}{Q_0'\left(\tau_q\right)}-\frac{W_{p_+,p_+}^{2,0}}{Q_0'\left(\tau_{p_+}\right)}\right.\\&\left.+Q_0\left(\tau_e\right)\left(\frac{P_2'\left(\tau_q\right)}{Q_0'\left(\tau_q\right)}-\frac{P_2'\left(\tau_{p_+}\right)}{Q_0'\left(\tau_{p_+}\right)}\right)\right],\end{aligned} \tag{44}$$

concerning the nutrient's critical values and

$$\beta^* = -\frac{c^2}{9}\left[p_L\left(P_2\left(\tau_{p_+}\right) - P_2\left(\tau_{p_-}\right) - \frac{P_2'\left(\tau_{p_+}\right)}{Q_0'\left(\tau_{p_+}\right)} Q_0\left(\tau_{p_+}\right)\right) + \left(p_L - p_n\right)\frac{P_2'\left(\tau_n\right)}{Q_0'\left(\tau_n\right)} Q_0\left(\tau_{p_-}\right)\right] \quad (45)$$

for the inhibitor's critical value. On the other hand, the healthy stromal compartment Ω_e follows passively the volume changes of the growing tumour mass. Consequently, both the tumour and Ω_e enjoy the same time variation rate of their volumes. In terms of the prolate spheroidal geometry [15], this leads to

$$\tau_e\left(\tau_e^2 - 1\right) - 2\tau_{p_+}\left(\tau_{p_+}^2 - 1\right) = T_e\left(T_e^2 - 1\right) - 2T_{p_+}\left(T_{p_+}^2 - 1\right), \quad (46)$$

in view of the initial conditions T_{p_+} and $T_e = \tau_e\left(0\right)$. The above expressions (43)–(46) form a non–linear system of four equations with four unknowns τ_n, τ_q, τ_{p_-} and τ_e, which can be solved to provide them as a function of τ_{p_+}. Therein, this set of solutions is substituted to the evolution equation (39) and, finally, the last one is solved with respect to $\tau_{p_+} = \tau_{p_+}\left(t\right)$ in order to obtain the outer boundary's evolution.

Concluding, a transversally isotropic pressure field alone cannot result to a prolate spheroidal tumour growth, but a specific nutrient supply given via (36) is also needed. This result could be interpreted in terms of the specific energy needed for the adhesion bonds between cells to preserve the lack of symmetry.

VI. Special Cases – Spherical Model

In this section, we are initially involved with the recovering of special geometrical cases. Consequently, the corresponding results for the oblate spheroidal geometry are obtained through the simple transformation [15]

$$\tau \to i\lambda \text{ and } c \to -i\overline{c}\,, \quad (47)$$

where $0 \le \lambda < +\infty$ and $\overline{c} > 0$ are the new characteristic variables. Hence, all the corresponding fields described during our previous analysis, are readily obtained in oblate spheroidal coordinates, providing us with the results drawn in [13]. The asymptotic case of the needle can be reached by a prolate spheroid, where it holds $0 < a_1\left(\tau\right) = a_2\left(\tau\right) << a_3\left(\tau\right) < +\infty$, while in the case where $0 < a_3\left(\tau\right) << a_1\left(\tau\right) = a_2\left(\tau\right) < +\infty$ the oblate spheroid takes the shape of a circular disk. Those comprise some interesting limiting cases with physical importance.

On the other hand, the spheroidal geometry degenerates to the spherical one [15] in the limit, as the semifocal distance tends to zero, that is $c \to 0$. For the corresponding analytical reduction, the limiting process is complicated and involves an appropriate combination of c with the coordinate variables such as $r \equiv \left\|\mathbf{r}\right\| = c\sqrt{\tau^2 + \zeta^2 - 1}$ for $\tau \ge 1$ and $\left|\zeta\right| \le 1$, as well as the following limits,

$$\lim_{c\to 0}\left(c\tau\right) = r \text{ and } \lim_{c\to 0}\left(\frac{1}{2c}\ln\frac{\tau+1}{\tau-1}\right) = \frac{1}{r}. \quad (48)$$

That way we recover the radial component r (as well as $\frac{1}{r}$) of the spherical coordinate system $\left(r,\zeta,\phi\right)$ for $r \in \left[0,+\infty\right)$ (here $0 \le r < r_e$) and the variables ζ, ϕ as usual [15], yielding

$$\mathbf{r} = \sum_{i=1}^{3} x_i \hat{\mathbf{x}}_i = r\sqrt{1-\zeta^2}\cos\varphi\hat{\mathbf{x}}_1 + r\sqrt{1-\zeta^2}\sin\varphi\hat{\mathbf{x}}_2 + r\zeta\hat{\mathbf{x}}_3, \quad (49)$$

where it is obvious that the spherical normal unit vector on the surface of every sphere is given by [15]

$$\lim_{c\to 0}\hat{\boldsymbol{\tau}} = \hat{\boldsymbol{r}} = \frac{\mathbf{r}}{r}. \quad (50)$$

The corresponding mathematical forms for the spherical case are taken via the definitions of the associated Legendre functions of the first P_l^m and of the second Q_l^m kind [16] of degree $l = 0,1,2,...$ and of order $m = 0,1,2,...,l$, which lead to

$$\lim_{c\to 0}\left[c^l P_l^m\left(\tau\right)\right] = d_l\frac{l!}{\left(l-m\right)!}r^l \quad (51)$$

and

$$\lim_{c\to 0}\left[c^{-(l+1)}Q_l^m\left(\tau\right)\right] = q_l\left(-1\right)^m\frac{\left(l+m\right)!}{l!}r^{-(l+1)} \quad (52)$$

for every $\tau \ge 1$ and $r \in \left[0,+\infty\right)$ with the aim of the reduction formulae (48). Moreover,

$$d_l = \frac{\left(2l\right)!}{2^l\left(l!\right)^2} \quad (53)$$

and

$$q_l = \frac{1}{2^l}\sum_{k=0}^{[l/2]}\frac{\left(-1\right)^k\left(2l-2k\right)!}{k!\left(l-k\right)!\left(l-2k\right)!\left(2l-2k+1\right)} \quad (54)$$

with $\left(2l+1\right)d_l q_l = 1$, while the relationships (51) and (52) are utilized for the zero order ($m = 0$) in our case.

Therefore, as the spheroidal geometry degenerates to the spherical one in the limit where $c \to 0$, then a mathematical treatment upon our final results (18), (19), (32) and (39), leads to the recovering of the corresponding expressions for the sphere problem. Hence, using the standard reduction relations, described earlier, i.e., expressions (48)–(54), we proceed to the mathematical treatment for the calculation of the spherical fields in terms of the spherical position vector (49). To that end, the nutrient concentration (18) reduces to

$$\begin{aligned}\sigma_s\left(\mathbf{r}\right) = {} & \gamma_q\left[-\frac{r_q^2 - r_n^2}{2} + \frac{1}{3r_e}\left(r_q^3 - r_n^3\right)\right] + \gamma_p\left[-\frac{r_{p_+}^2 - r_q^2}{2} + \frac{1}{3r_e}\left(r_{p_+}^3 - r_q^3\right)\right] \\ & + H\left(r - r_n\right)\frac{\gamma_q}{3}\left[\frac{r^2 - r_n^2}{2} + r_n^3\left(\frac{1}{r} - \frac{1}{r_n}\right)\right] \\ & - H\left(r - r_q\right)\frac{\gamma_q - \gamma_p}{3}\left[\frac{r^2 - r_q^2}{2} + r_q^3\left(\frac{1}{r} - \frac{1}{r_q}\right)\right] \\ & - H\left(r - r_{p_+}\right)\frac{\gamma_p}{3}\left[\frac{r^2 - r_{p_+}^2}{2} + r_{p_+}^3\left(\frac{1}{r} - \frac{1}{r_{p_+}}\right)\right] \\ & + \sum_{l=0}^{\infty}\sigma_{\infty,l}\left(r_e\right)\left(\frac{r}{r_e}\right)^l P_l\left(\zeta\right) \text{ for every } \mathbf{r} = \left(r,\zeta,\phi\right), \end{aligned} \quad (55)$$

where the corresponding boundaries of the spherical tumour's structure, as well as the physical spherical quantities appearing within (55), represent the prolate spheroidal analogous. Under the same consideration the inhibitor concentration (19) has the spherical limiting expression

$$\begin{aligned}\beta_s(\mathbf{r}) &= \frac{p_L-p_n}{2}r_n^2-\frac{p_L}{2}r_{p_+}^2+\frac{p_n}{6}r^2\\ &+H(r-r_n)\frac{p_L-p_n}{3}\left[\frac{r^2-r_n^2}{2}+r_n^3\left(\frac{1}{r}-\frac{1}{r_n}\right)\right]\\ &-H\left(r-r_{p_+}\right)\frac{p_L}{3}\left[\frac{r^2-r_{p_+}^2}{2}+r_{p_+}^3\left(\frac{1}{r}-\frac{1}{r_{p_+}}\right)\right],\ \mathbf{r}=(r,\zeta,\phi)\end{aligned} \quad (56)$$

with this form being less complicated compared to (55). In a similar way, the pressure field in spherical coordinates is taken from the appropriate limiting procedure via (32) as

$$\begin{aligned}\mathrm{P}_s(\mathbf{r}) &= \mathrm{p}_\infty(r_e)\left[1+\frac{2a}{3}\left(1-P_2(\zeta)\right)\right]+\frac{\alpha_e}{r_e}+\frac{\alpha_{p_+}}{r_{p_+}}\left(1-H\left(r-r_{p_+}\right)\right)\\ &+\frac{1}{6}\left\{F_n r^2+\left(F_n-F_q\right)r_n^2\left[1+2r_n\left(\frac{1}{r_e}-\frac{1}{r_n}\right)\right]\right.\\ &\quad+\left(F_q-F_p\right)r_{p_-}^2\left[1+2r_{p_-}\left(\frac{1}{r_e}-\frac{1}{r_{p_-}}\right)\right]\\ &\quad\left.+F_p r_{p_+}^2\left[1+2r_{p_+}\left(\frac{1}{r_e}-\frac{1}{r_{p_+}}\right)\right]\right\}\\ &-H(r-r_n)\frac{F_n-F_q}{3}\left[\frac{r^2-r_n^2}{2}+r_n^3\left(\frac{1}{r}-\frac{1}{r_n}\right)\right]\\ &-H\left(r-r_{p_-}\right)\frac{F_q-F_p}{3}\left[\frac{r^2-r_{p_-}^2}{2}+r_{p_-}^3\left(\frac{1}{r}-\frac{1}{r_{p_-}}\right)\right]\\ &-H\left(r-r_{p_+}\right)\frac{F_p}{3}\left[\frac{r^2-r_{p_+}^2}{2}+r_{p_+}^3\left(\frac{1}{r}-\frac{1}{r_{p_+}}\right)\right]\end{aligned} \quad (57)$$

for every $\mathbf{r}=(r,\zeta,\phi)$, whereas relations (55)–(57) hold true when the spherical variables run within the intervals $r\in[0,r_e)$, $\zeta\in[-1,1]$ and $\phi\in[0,2\pi)$, while those expressions comprise part of the results of [12].

Finally, the evolution equation (39), after some trivial and straightforward manipulation, assumes the spherical form

$$\begin{aligned}\frac{dr_{p_+}}{dt} &= \frac{1}{3r_{p_+}^2}\left[\left(-\mu_P\left(F_n-F_q\right)-\mu_\sigma\gamma_q+\mu_\beta\left(p_L-p_n\right)\right)r_n^3\right.\\ &\quad+\mu_\sigma\left(\gamma_q-\gamma_p\right)r_q^3-\mu_P\left(F_q-F_p\right)r_{p_-}^3\\ &\quad\left.+\left(-\mu_P F_p+\mu_\sigma\gamma_p-\mu_\beta p_L\right)r_{p_+}^3\right],\end{aligned} \quad (58)$$

which is the corresponding spherical form of a fully non–linear ordinary differential equation with respect to the tumour outer boundary r_{p_+} and initial condition $r_{p_+}(0)=R_{p_+}$, since, in view of the critical values (43)–(45) and (46) with corresponding initial condition $r_e(0)=R_e$, we obtain

$$\sigma_n^*-\sigma_p^*=\frac{\gamma_q}{3}\left[\frac{r_n^2-r_q^2}{2}+r_n^3\left(\frac{1}{r_n}-\frac{1}{r_q}\right)\right], \quad (59)$$

$$\begin{aligned}\sigma_{\infty,0}(r_e) &= \sigma_n^*-\gamma_q\left[-\frac{r_q^2-r_n^2}{2}+\frac{1}{3r_e}\left(r_q^3-r_n^3\right)\right]\\ &\quad-\gamma_p\left[-\frac{r_{p_+}^2-r_q^2}{2}+\frac{1}{3r_e}\left(r_{p_+}^3-r_q^3\right)\right],\end{aligned} \quad (60)$$

$$\beta^*=\frac{1}{3}\left[-p_L\frac{3r_{p_+}^2-r_{p_-}^2}{2}+\left(p_L-p_n\right)\frac{r_n^3}{r_{p_-}}\right] \quad (61)$$

and

$$r_e^3-2r_{p_+}^3=R_e^3-2R_{p_+}^3. \quad (62)$$

Once (59)–(62) are readily solved to obtain r_n, r_q, r_{p_-} and r_e as a function of r_{p_+}, then we can evaluate r_{p_+} as a function of time via relationship (58) and therefore to predict the evolution of the tumour's exterior boundary, which is our final goal.

VII. Numerical Implementation

The spheroidal coordinate system (prolate or oblate) yields an appropriate environment for solving classical boundary value problems involving cancerous tumour growth. However, this is true only if we impose particular conditions as we have already discussed extensively in the previous sections or if we work within the frame of simple orthogonal geometries. For this reason, problems similar to our case adopt this fitting system to obtain analytical results for the corresponding fields of the nutrient, the inhibitor and the pressure.

Nevertheless, it not always easy and feasible to pursue fully analytical solutions in closed forms because either the derived formulae do not have the required accuracy or it is difficult to manipulate such solutions. Even in simple geometries as the spherical or the spheroidal one, where the Laplace's and the Poisson's partial differential equations admit separation of variables, the semi–analytical approach is inherited. Indeed, the derivation of the ordinary differential equation describing the evolution of the tumour's exterior boundary is highly non–linear and as already seen its solution needs several physically explained constrains and numerical implementation.

To this purpose, there is always room for purely numerical analysis or better for computational treatment of our analytical results. Under this useful aspect, we inherit the semi–analytical terminology and character to our method. Then, in order to crosscheck our analytical formulae with the experimental data and predict the behavior of our fields, we plot the nutrient and the inhibitor concentrations, as well as the pressure field given via expressions (18) and (19), as well as (32), respectively as the tumour evolves in the τ–direction, so as to confirm that our results comply with the hypotheses.

The numerical treatment of the aforementioned fields needs the definitions of various parameters and constants, mostly taken from the bibliography [1–9]. Initially, we must confine the boundaries of the compartments of the tumour with respect to the prolate spheroidal variable $\tau\in[1,\tau_e)$, while each field is going to be plotted for $\zeta=0$, $\zeta=0.25$ and $\zeta=0.5$ for

every $\phi \in [0, 2\pi)$. To achieve that, we inherit from spherical models the corresponding already known from measurements spherical boundaries with respect to the spherical variable $r \in [0, r_e)$, at $r_n = 0.7\text{m}$, $r_q = 0.75\text{m}$, $r_{p_-} = 0.8\text{m}$, $r_{p_+} = 0.9\text{m}$ and $r_e = 0.91\text{m}$. Therein, we utilize a very useful geometrical condition that connects the two systems [15,16] to recover the prolate spheroidal boundaries at $\tau_n = 1.4114$, $\tau_q = 1.4311$, $\tau_{p_-} = 1.4503$, $\tau_{p_+} = 1.4868$ and $\tau_e = 1.4904$, respectively. In addition, we assume that our system is provided given the fixed semifocal distance $c = 0.5\text{m}$. In the sequel, we provide the basic physical parameters that appear in every field and have been already discussed extensively. For the nutrient field $\sigma[=]\text{kg/m}^3$ we need $\gamma_q = 20\text{kg/m}^5$ and $\gamma_p = 50\text{kg/m}^5$, for the inhibitor field $\beta[=]\text{kg/m}^3$ it is adequate $p_n = -40\text{kg/m}^5$ and $p_L = -20\text{kg/m}^5$, while for the pressure field $\text{P}[=]\text{kg/ms}^2$ we take the values as $F_n = 20\text{kg/m}^3\text{s}^2$, $F_q = 30\text{kg/m}^3\text{s}^2$ and $F_p = 40\text{kg/m}^3\text{s}^2$. A detailed dimensionless analysis secures the validity of the above values. Based on the same analysis, we are obliged to provide the following constants, i.e., $a = 1$, $\alpha_{p_+} = 1.0\text{kg/s}^2$ and $\alpha_e = 1.4\text{kg/s}^2$. Moreover, if we refer to the nutrient and the pressure filed given by (18) and (32), respectively, we have to evaluate the series term up to a certain order. Some physical argumentation, in view of our analysis, leads us to assume that convergence is obtained with $l = 0,1,2$ to the series terms. In view of that, for the pressure we obtain $j_l(\tau_e)[=]1/\text{m}$ and $j_l(\tau_{p_+})[=]1/\text{m}$ via (28) and (29), while we impose a reference pressure $\text{p}_\infty(\tau_e) = 15\text{kg/ms}^2$ and for the nutrient we provide the necessary external conditions as $\sigma_{\infty,0}(\tau_e) = \sigma_{\infty,2}(\tau_e) = 0.5\text{kg/m}^3$, since $\sigma_{\infty,0}(\tau_e) = 0.0\text{kg/m}^3$. For the sake of completeness, we invoke the dimensions of the physical parameters into the evolution equation, those are $\mu_P[=]\text{m}^3\text{s/kg}$, $\mu_\sigma[=]\text{m}^5/\text{kgs}$ and $\mu_\beta[=]\text{m}^5/\text{kgs}$.

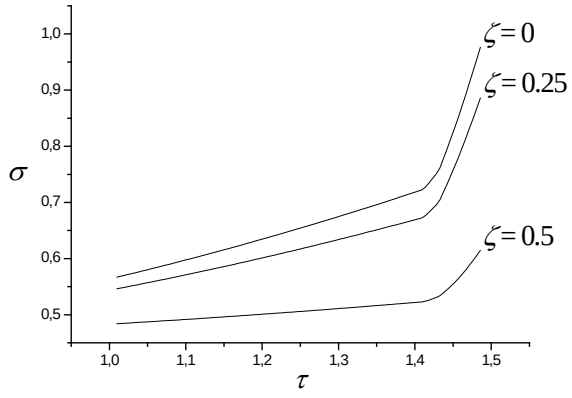

Fig. 1 The nutrient concentration.

The nutrient concentration field (18) is shown in figure 1, where one can observe, as expected, that it is increasing as we move outwards the tumour, while the critical values σ_n^* and σ_p^* in kg/m^3 at $\tau_n = 1.4114$ and $\tau_q = 1.4311$ can be easily verified through (40) and (41), respectively.

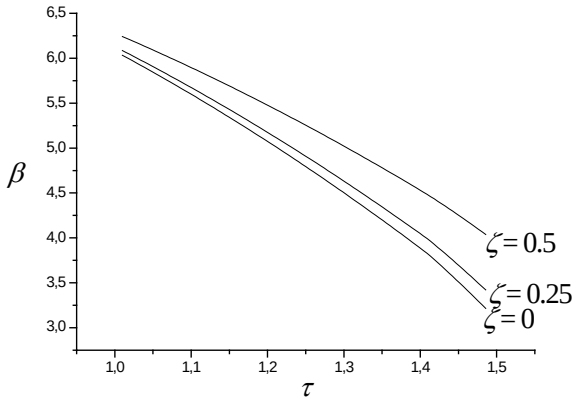

Fig. 2 The inhibitor concentration.

Similarly, the inhibitor concentration field (19) follows the behavior depicted in figure 2, where obviously it is revealed that this field, on the contrary to the nutrient, decreases as we move outwards to the tumour's structure. The inhibitor's critical value β^* in kg/m^3 yielded in (42), is calculated at $\tau_{p_-} = 1.4503$ within figure 2.

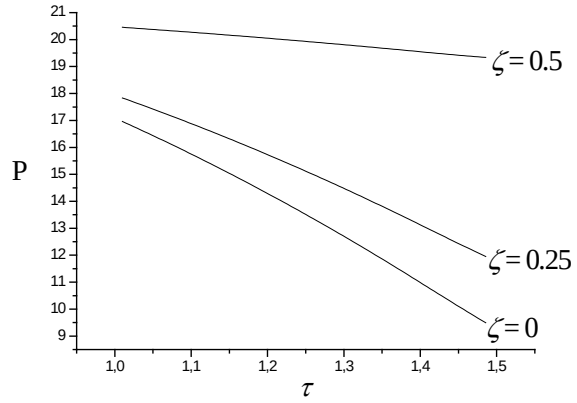

Fig. 3 The pressure field.

Finally, the plotted pressure field (32) appears in figure 3, where its predicted behavior is confirmed, provided the fact that, as we move inwards the tumour, the compartments exert an additional pressure to the tumour, hence the pressure field is increasing.

VIII. Conclusion

In the present work we analyzed a continuous non symmetrical model of avascular tumour growth that evolves maintaining a prolate spheroidal multilayer structure, lying inside a finite confocal prolate spheroidal host microenvironment. Its evolution is regulated by the diffusion of an inhomogeneous nutrient field, and of an internally produced inhibitory agent.

Moreover the evolution is affected by a pressure field, generated from the compensation of cell proliferation and disintegration and the transversally isotropic pressure imposed from the surrounding medium.

Hence, the model is formulated in three boundary value problems that hold true as the tumour evolves and provide the nutrient field, the internally produced inhibitor field and the pressure field throughout the spheroidal tumour, as well as the host surrounding. The model predicts the evolution of the tumour's compartments in terms of a non–linear ordinary differential equation with respect to the tumour's exterior boundary and it also includes the three aforementioned main fields, calculated on the exterior prolate spheroidal boundary. Connection formulae between all the other boundaries with respect to the tumour's exterior one are provided in analytical expressions.

It turns out that a concentric prolate spheroidal multilayer development under an externally imposed transversally isotropic pressure field could be secured only under a particular type of nutrient supply that in the same time specifies the way the exterior boundary evolves.

Our final step involved a numerical implementation of the derived analytical forms. On the other hand, the numerical implementation of the evolution equation and alternative evolution approaches for the same spheroidal structure in avascular tumour development, as well as alternative geometrical structure of the development, which is much more applicable to cancer growing in humans, is under our current investigation.

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