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A PARAMETER ESTIMATION PROBLEM FOR A TUMOUR GROWTH MODEL

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A parameter estimation problem for a tumour growth model .

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Abstract

In this paper we present a method for estimating unknown parameters that appear on an avascular, spheric tumour growth model. The model for the tumour is based on nutrient driven growth of a continuum of live cells, whose birth and death generate volume changes described by a velocity field. The drug is applied externally, and is assumed to be a diffusible substance capable of killing cells.

The model consists on a coupled system of partial differential equations which is solved numerically. As the domain on which the equations are defined is the tumour, that changes in size over time, the problem can be formulated as a moving boundary one.

After solving the forward problem properly, we are concerned in using the model for the estimation of parameters, by fitting the numerical solution with real data. We define a functional to compare both of them and we use the pattern search method for minimizing it, obtaining good accuracy for the recovery of a few parameters.

Keywords: avascular tumour, constrained optimization, inverse problem, mathematical modeling.

1 Introduction.

The interest for research in modeling cancer has grown enormously over the last decades, [1, 2]. Pioneers have been, for example, [11, 15], where the first spatio-temporal models of an avascular multicellular spheroid's (MCS) growth have been developed. The study of MCS is interesting because they provide the best insight into the effectiveness of chemotherapeutic drugs on tumours in vivo, and their behaviour can be studied experimentally (in vitro) by controlling environmental conditions in which they grow: for example, the radii of the tumour can be monitored by changing the chemotherapeutic drug or oxygen levels.

In addition, another variables can be measured. If possible, experimentalists can get information about the distribution of substances within the tumour. Moreover, via medical imaging or histological cuts, they can also get data about the density of the different kind of cells conforming it: proliferating, quiescent, necrotic.

That is why in this general approach of modeling the key variables are the tumour size (radius) and the concentration within the tumour of growth-rate limiting diffusible chemicals (nutrients such as oxygen or glucose or a chemotherapeutic drug). Since the tumour changes in size over time, the domain on which the models are formulated must be determined as part of the solution process, giving a vast class of moving boundary problems, [6, 7].

In this article, we propose a framework for estimating unknown parameters via PDE-constrained optimization, following the PDE-based model by Ward and King, [16]. In this approach, avascular

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tumour growth is modeled via a coupled nonlinear system of differential equations, which make the numerical solution procedure quite challenging.

We are concerned with developing a robust PDE-constrained formulation that let us find the best set of parameters of a tumour growth model that fits patient or experimental data. We choose the parameters that should be of applied interest and try to obtain them by defining a functional to be minimized.

The paper is organized as follows: section 2 introduces the tumour growth model (forward problem). Section 3 shows the numerical solution of the forward problem and checks its accuracy by proving some theoretical results. Section 4 introduces the inverse problem approach, by defining the functional to be minimized. Finally, in section 5 the numerical procedure to solve the inverse problem is discussed.

2 Mathematical model.

We consider the model proposed by Ward and King in [16]. The tumour is a spheroid which consists of a continuum of living cells, in one of two states: live or dead. The rates of birth and death depend on the nutrient and chemotherapeutic drug concentration. It is supposed that those processes generate volume changes, leading to cell movement described by a velocity field. The system of equations to be studied is:

$$\frac{\partial n}{\partial t}+\frac{1}{r^2}\frac{\partial(r^2vn)}{\partial r}=[k_m(c)-k_d(c)-KG(k_m(c))w]n, \tag{2.1}$$

$$\frac{\partial c}{\partial t}+\frac{1}{r^2}\frac{\partial(r^2vc)}{\partial r}=\frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right)-\beta k_m(c)n, \tag{2.2}$$

$$\frac{1}{r^2}\frac{\partial(r^2v)}{\partial r}=[V_Lk_m(c)-(V_L-V_D)\{k_d(c)+KG(k_m(c))w\}]n, \tag{2.3}$$

$$\frac{\partial w}{\partial t}+\frac{1}{r^2}\frac{\partial(r^2vw)}{\partial r}=\frac{D_w}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial w}{\partial r}\right)-\frac{K}{\omega}G(k_m(c))wn, \tag{2.4}$$

where the dependent variables n, c, v and w are the live cell density (cells/unit volume), nutrient concentration, velocity and drug concentration, respectively. As it is described in [16], equation (2.1) states that the rate of change of n is dependent on the difference between the birth $k_m(c)$ and death $k_d(c)$ rates, where this one is either natural (as described in [17]) or due to the drug effects, at a rate $KG(k_m(c))w$. The functons k_m and k_d are taken to be generalised Michaelis-Menten kinetics with exponent 1, i.e.

$$k_m(c)=A\left(\frac{c}{c_c+c}\right), \tag{2.5}$$

$$k_d(c)=B\left(1-\sigma\frac{c}{c_d+c}\right). \tag{2.6}$$

The constant K is the maximum possible rate of drug induced cell death. The constants A, B and σ are positive parameters of the Michaelis-Menten kinetics, while c_c and c_d are critical concentrations. $G(k_m(c))$ is a function that represents the dependence between drug action and cell-cycle. As it is considered in [16] it is a good idea to choose a linear dependence, giving

$$G(k_m(c))=k_m(c)/A.$$

Equation (2.2) states that the nutrient is consumed at a rate proportional to the rate of mitosis, and its diffusion is described by Ficks law. Equation (2.3) states that the rate of volume change is given by the difference in volume generated via birth from that lost by death (it is assumed that a live cell occupies a volume V_L that is twice the volume of a death cell V_D). The diffusion of the drug is described also by Ficks law, and it is assumed that it is degraded only when it attacks a living cell, giving a maximum degradation rate K/ω. ω is a dimensionless constant that can be interpreted as a measure of the drugs effectiveness, as explained in [16], with increasing ω implying that less drug is consumed to produce the same effects during the killing process. These considerations lead to equation (2.4).

2.1 Moving boundary problem

As it has been mentioned, the tumour is assumed to be a spheroid that exhibits radial simmetry. That is why, not only the state variables n, c, v and w are important, but the outer tumour radius is also a key variable to be determined. Since the tumour changes in size over time, the domains on which the models are formulated (and the PDEs are valid) must be determined as part of the solution.

Let $S(t)$ be the tumour radius at time t. So, if we suppose that the treatment begins at time $t = 0$, in which the tumour has a radius S_I, with living cell density and nutrient concentration distributions $n_I(r)$ and $c_I(r)$, respectively, then the initial conditions of the problem can be formulated as

$$n(r,0) = n_I(r), \tag{2.7}$$
$$c(r,0) = c_I(r), \tag{2.8}$$
$$w(r,0) = 0, \tag{2.9}$$
$$S(0) = S_I. \tag{2.10}$$

Because symmetry is assumed about the tumour center, there is no flux there. That is why, as boundary conditions about $r = 0$, are taken:

$$\frac{\partial c}{\partial r}(0,t) = 0, \tag{2.11}$$
$$v(0,t) = 0, \tag{2.12}$$
$$\frac{\partial w}{\partial r}(0,t) = 0. \tag{2.13}$$

Moreover, on the external boundary (which is also the boundary of the complement of the tumour as a subset of the body), the following conditions are taken:

$$c(S(t),t) = c_0, \tag{2.14}$$
$$\frac{dS}{dt} = v(S(t),t), \tag{2.15}$$
$$w(S(t),t) = w_0(t), \tag{2.16}$$

where c_0 and $w_0(t)$ are external nutrient and drug concentrations, respectively. The function $w_0(t)$ depends on the chemotherapeutic protocol. In our simulations it will be considered as a constant that does not depend on t. However, other functions may be adopted, for example in section 3 we show an example in which drug is provided for some intervals of time, but not for other ones.

2.2 Nondimensionalisation

Before analysing the model equations, we re-scale the mathematical model in the following way, denoting non-dimensional variables with bars:

$$\overline{n} = V_L n; \qquad \overline{c} = c/c_0; \qquad \overline{v} = v/r_0 A; \qquad \overline{t} = At \qquad \overline{r} = r/r_0; \qquad \overline{S} = S/r_0; \qquad \overline{w} = w/W_0$$

where $r_0 = (3V_L/4\pi)^{1/3}$ is the radius of a single cell and W_0 is a suitable reference drug concentration (typically $W_0 = max(w_0(t))$).

It is important to remark that inherent in this problem are two timescales: the tumour growth timescale ($\approx$ 1 day) and the much shorter drug and nutrient diffusions ($\approx$ 1 min). That is why, following [2, 1, 16, 6] we adopt a quasi-steady assumption in the nutrient and drug equations.

Following [16], and relabeling the variables with bar again without it, these rescalings lead to the following system of differential equations:

$$\frac{\partial n}{\partial t} + v\frac{\partial n}{\partial r} = [a(c,w) - b(c,w)n]n, \tag{2.17}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) = k(c)n, \tag{2.18}$$

$$\frac{1}{r^2}\frac{\partial (r^2 v)}{\partial r} = b(c,w)n, \tag{2.19}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial w}{\partial r}\right) = \frac{\widehat{K}}{\alpha}k_m(c)wn, \tag{2.20}$$

where

$$\alpha = \omega D_w V_L W_0/Ar_0^2, \tag{2.21}$$

$$\widehat{K} = KW_0/A,$$

$$a(c,w) = \frac{1}{A}[k_m(c) - k_d(c) - KG(k_m(c))w],$$

$$b(c,w) = \frac{1}{A}\{k_m(c) - (1-\delta)[k_d(c) - KG(k_m(c))w]\},$$

$$k(c) = \widehat{\beta}k_m(c)/A,$$

with $\delta = V_D/V_L$ and $\widehat{(\beta)} = r_0^2\beta A/V_L c_0 D$.

We note that the *constant* α defined above comprises many model parameters that should be interesting to know exactly. It will be of great importance in the next sections, where α will be considered as a key parameter of the problem.

Also, it is worth saying that rigorous mathematical analysis including existence, uniqueness, and stability theorems, as well as properties of the free boundaries for similar tumour growth models in which different kind of PDEs are combined, have been obtained, [4] and [8].

3 Numerical solution of the forward problem

After the assumptions made in the previous section, we have to solve the following system of PDEs:

$$n_t + v n_r = [a(c,w) - b(c,w)n]n \qquad 0 < r \leq S(t), \qquad t > 0, \tag{3.1}$$

$$v_r + \frac{2}{r}v = b(c,w)n \qquad 0 < r \leq S(t), \qquad t > 0, \tag{3.2}$$

$$c_{rr} + \frac{2}{r}c_r = k(c)n \qquad 0 < r \leq S(t), \qquad t > 0, \tag{3.3}$$

$$w_{rr} + \frac{2}{r}w_r = \frac{\widehat{K}}{\alpha}k_m(c)w \qquad 0 < r \leq S(t), \qquad t > 0. \tag{3.4}$$

The initial conditions at $t = 0$ are

$$n(r,0) = n_I(r), \tag{3.5}$$

$$S(0) = S_I, \tag{3.6}$$

$$w(r,0) = 0, \tag{3.7}$$

and the boundary conditions are

$$v(0,t) = 0, \tag{3.8}$$

$$c_r(0,t) = 0, \tag{3.9}$$

$$w_r(0,t) = 0, \tag{3.10}$$

$$c(S(t),t) = 1, \tag{3.11}$$

$$w(S(t),t) = 1, \tag{3.12}$$

$$\dot{S}(t) = v(S(t),t). \tag{3.13}$$

It is important to remark that the density of living cells in the boundary, $n(S(t),t)$, can be calculated explicitly. Indeed, consider equation (3.1) and note that, using the chain rule, the total variation of n in time is

$$\frac{dn}{dt} = \frac{\partial n}{\partial t} + \frac{\partial n}{\partial r}\frac{dr}{dt}. \tag{3.14}$$

At the point $(S(t),t)$ the expression $\frac{dr}{dt}$ is equal to $v(S(t),t)$. So, substitution in (3.1) gives

$$\frac{dn}{dt}(S(t),t) = [a(1,1) - b(1,1)n(S(t),t)]n(S(t),t),$$

where $a(1,1)$ and $b(1,1)$ are the corresponding values of the functions a and b on the boundary at any time. The last equation is a separable ODE, that can be transformed into

$$\frac{dn^*}{[a^* - b^*n^*]n^*} = dt, \tag{3.15}$$

where for simplicity we wrote $a^* = a(1,1)$, $b^* = b(1,1)$ and $n^* = n(S(t),t)$.

Now, we use expansion into simple fractions:

$$\frac{1}{(a^*-b^*n^*)n^*} = \frac{b^*}{a^*}\frac{1}{a^*-b^*n^*} + \frac{1}{a^*}\frac{1}{n^*}. \tag{3.16}$$

Combining equations (3.15) and (3.16) and integrating over time we get

$$\int_0^t dt = \int_1^{n(S(t),t)} \frac{dn^*}{(a^*-b^*n^*)n^*} = \ln\left(\frac{(a^*-b^*)n(S(t),t)}{a^*-b^*n(S(t),t)}\right). \tag{3.17}$$

Finally, solving for n on the boundary, we obtain

$$n(S(t),t) = \frac{a^*e^{a^*t}}{a^*-b^*+b^*e^{a^*t}}. \tag{3.18}$$

Equation (3.18) is not only an elegant analytical result, but also it will become of really importance when calculating numerically the value of n in the boundary. As we shall see, when defining the spatial grid to solve equation (3.1) with a forward finite difference scheme, for each point r_j of the grid we will need to take also the point r_{j+1} but that is impossible in the last point of the grid, say $S(t)$

3.1 Fixed domain method

The first step for solving this moving boundary problem will be transforming the original domain to a fixed one, i.e., re-writing the whole system for the change of coordinates $y = r/S(t)$. In this way, the spatial domain will be the interval $[0,1]$.

Observation 3.1 *If $r = yS(t)$, then $\frac{dr}{dy} = S(t)$ and $\frac{dr}{dt} = y\dot{S}(t)$.*

We briefly illustrate the way in which the new equations are obtained, using (3.1).
Let $N(y,t) \doteq n(r,t) = n(yS(t),t)$. Differentiating this expression respect to y, we obtain

$$N_y = n_r r_y + n_t t_y = n_r S(t),$$

and then $n_r = \frac{N_y}{S}$.
And differentiation respect to t gives

$$N_t = n_r \frac{dr}{dt} + n_t,$$

and so we deduce that $n_t = N_t - \frac{N_y}{S}y\dot{S}$.
Substitution in (3.1) gives

$$N_t - \frac{\dot{S}}{S}yN_y + \frac{V}{S}N_y = N[a(C) - b(C)N]N \qquad 0 < r \leq 1, \qquad t > 0. \tag{3.19}$$

The same procedure is applied to the other equations, and we obtain

$$C_{yy} + \frac{2}{y}C_y = k(C)S^2N, \tag{3.20}$$

$$V_y + \frac{2}{y}V = b(C)NS, \tag{3.21}$$

$$W_{yy} + \frac{2}{y}W_y = \frac{\hat{K}}{\alpha}k_m(C)S^2WN. \tag{3.22}$$

The initial conditions for the transformed problem are

$$N(y,0) = N_I(y), \qquad 0 \le y \le 1, \tag{3.23}$$
$$S(0) = S_I, \tag{3.24}$$
$$W(y,0) = 0, \qquad 0 \le y \le 1, \tag{3.25}$$

and the boundary conditions are

$$V(0,t) = 0, \qquad t > 0, \tag{3.26}$$
$$C_y(0,t) = 0, \qquad t > 0, \tag{3.27}$$
$$W_y(0,t) = 0, \qquad t > 0, \tag{3.28}$$
$$C(1,t) = 1, \qquad t > 0, \tag{3.29}$$
$$W(1,t) = 1, \qquad t > 0, \tag{3.30}$$
$$\dot{S}(t) = V(1,t), \qquad t > 0. \tag{3.31}$$

3.2 Numerical procedure

The drug is first applied at $t = 0$, by which time the tumour has grown following the model without drug, [17]. Originally, at $t \approx -500$, a single cell started to take nutrients from the environment, letting it grow up to a dimensionless size of $S_I \approx 202$. The solution for the variables N, C and V is taken as the initial distribution of them for the drug treatment case.

All the simulations described in this section use the following parameter values, as suggested in [16]:

$$B/A = 1, \qquad \sigma = 0.9, \qquad \delta = 0.5, \qquad \beta = 0.005, \qquad c_c = 0.1, \qquad c_d = 0.05, \qquad K = 50.$$

The problem (3.19)-(3.22) subject to the initial and boundary conditions is solved in the following way:

1. Given the distributions of N, V, C and W at time k we solve (3.19) using a finite-difference scheme to obtain N at time $k+1$. The value of N at the boundary is updated directly by solving equation (3.18).

2. The ODEs system (3.20)-(3.22) is solved using the `MATLAB`'s package `bbvp4c` to obtain C, V and W at time $k+1$.

3. Using the value $V(1,k+1)$ we solve equation (3.31) for S at time $k+1$ using Eulers method.

We remark that solving the system (3.20)-(3.22) is challenging in the sense that there is a singularity at $r = 0$. The package `bbvp4c` let us deal with this singularity by using a *Singular Term* tool.

3.3 Numerical results

The numerical solution for this problem is very well discussed and analized in many aspects by Ward and King, [16]. The parameter α is taken as a variable in the sense that we are interested in studying how the solution behaves when α is changed.

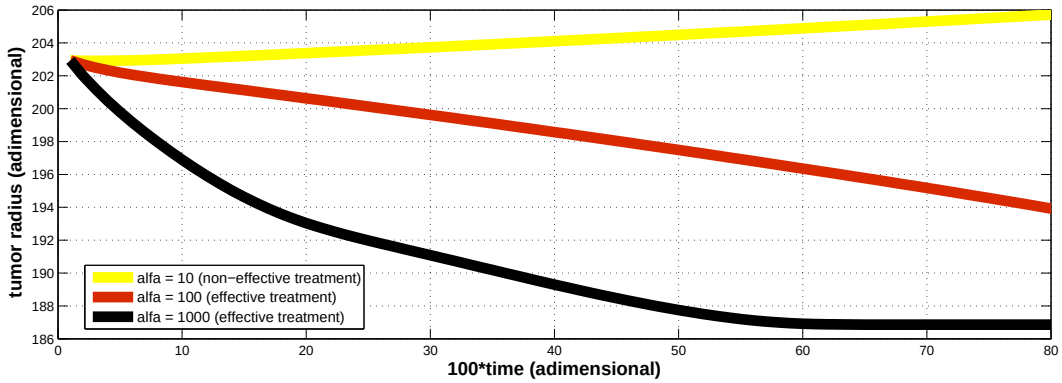

Figure 1: Evolution of the tumour radius for different values of α.

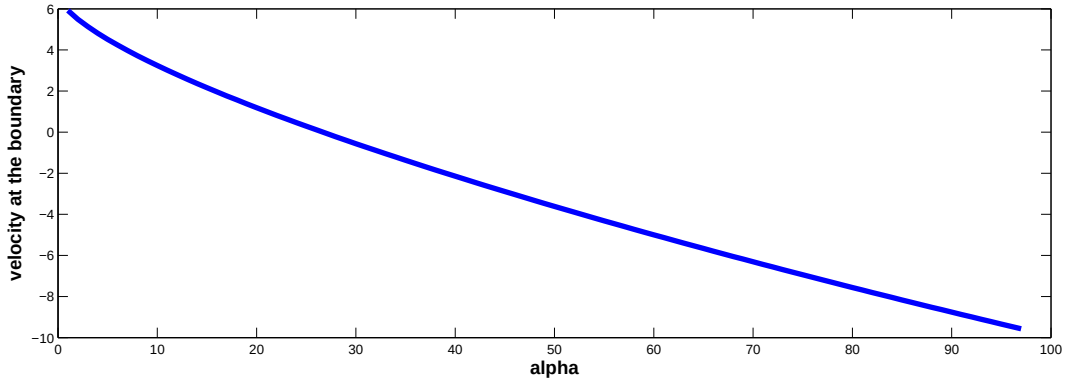

Figure 2: Velocity at the tumour's boundary for a fixed time ($t = 10$) for different values of α.

We are able to confirm that α can, indeed, be considered a *measure of the treatment effectiveness*. We plot how the radius of the tumour evolves in time when varying this parameter, as showed in figure 1.

We can observe that a value $\alpha = 10$ does not stop the growth of the tumour, although there is a killing cell process. However, if $\alpha = 100$ or $\alpha = 1000$ the radius of the tumour decreases (of course the mass could never disappear because the drug does not act over the already formed necrotic core).

An interesting question to answer is: *for which value of* α *can be stated that tumour will decrease in size?* That should be helpful, for example, w hen choosing some dose when the drug coefficient diffusion and the initial spheroid size are known. To determine this value we take into account the velocity in the boundary at a fixed time for different values of α. For example, in figure 2 we can see that if we fix the non-dimensional time $t = 10$, the function $v(S(t),t)$ has a root in $\alpha \approx 25$.

The problem has also be solved for a different treatment protocol. We took a drug with $\alpha = 1000$ and provided it for some time intervals, so that the boundary condition is the following:

$$\begin{aligned} w_0(t) &= 1, \quad t \in [0,20), \\ w_0(t) &= 0, \quad t \in [20,50), \\ w_0(t) &= 1, \quad t \geq 50. \end{aligned}$$

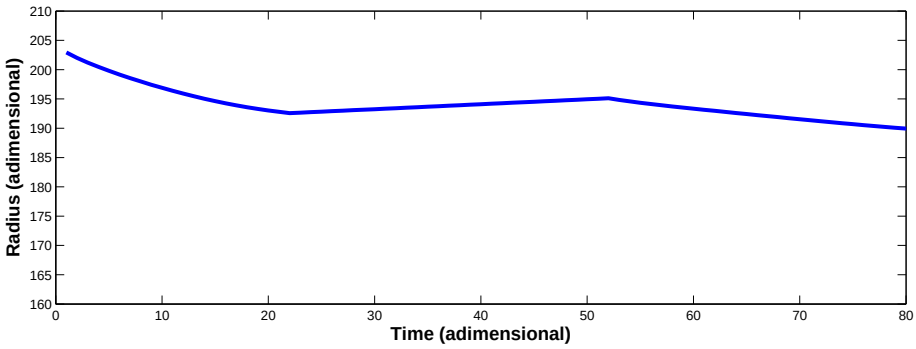

Figure 3: Evolution of the tumour radius for a pulse-type drug provision.

In [16] the surviving fraction is plotted for a boundary condition similar to this one. In contrast, in figure 3 we plot the evolution of the tumour radius for this situation, which should be considered when designing a treatment, because it is really important in the effectiveness-toxicity balance.

4 Inverse problem

The main idea of this section is to recover some of the parameters which appear in the mathematical model, motivated in the lack of references that exist in literature. In reality, some of them are unknown, especially in vivo.

We consider that the parameter α defined above is important because it provides a measure of the treatment effectiveness. In particular, it can provide information about the drug diffusion coefficient, the optimal dose to get a desired effect or, eventually, Michaelis-Menten kinetics, see equation (2.21).

Thus, we are interested in the recovery of this parameter using available scans (MR images from real patients that could let us follow the tumour size evolution over time) or reliable measurements such as histological studies (obtained experimentally for in vitro cases). The data should be obtained at different moments in time over a time interval of lenght T. The inverse problem can be formulated as follows:

Find a parameter value able to generate data that best match the available information over time $0 \leq t \leq T$.

Because of the nature of the mathematical model, we have to solve a PDE constrained optimization problem. The constraints are given by the model equations (2.1)-(2.14), which can be written in a short way as $\mathcal{P}(\phi) = 0$, where $\mathcal{P}$ is the differential operator given by the set of equations and $\phi = (N, C, V, W)$.

4.1 The objective functional

We should construct an objective functional which gives us some *distance* between the experimental (real) data and the solution of the system of PDEs for each value of α.

First of all, it is important to decide which variables are capable to be measured experimentally. For instance, it is clear that the tumour radius $S(t)$ can be known at certain times t_k, $k = 1, ..., M$. So, the first possibility for defining a functional could be

$$J(S;\alpha) = \int_0^T [S_\alpha(t) - S^*(t)]^2 dt, \tag{4.1}$$

where $S_\alpha(t)$ is the radius evolution obtained solving the direct problem for a certain value of α and $S^*(t)$ is the evolution measured experimentally (real data).

Other variable that could be measured is the concentration of living cells, via biomedical imaging. Thus, we are motivated to define a functional that reproduces in a better way the knowledge we have about the process, i.e.

$$J(N,S;\alpha) = \int_0^1 \int_0^T [N_\alpha(y,t) - N^*(y,t)]^2 dt dy + \mu \int_0^T [S_\alpha(t) - S^*(t)]^2 dt, \tag{4.2}$$

where $N_\alpha(y,t)$ and $N^*(y,t)$ are the living cell concentration for the direct problem solved with the value α and the real data, respectively (both of them in the domain $[0,1] \times [0,T]$). The positive constant μ is introduced, as we shall see, to take into account the different order of magnitude between N and S.

So, the constrained optimization problem can be formulated as

$$\min_{\alpha \in \mathcal{C}} J(\alpha),$$

$$s.t. \mathcal{P}(\phi) = 0,$$

where $\mathcal{C}$ denotes the set of *admissible values* of α.

We remark that, in general, there is a fundamental difference between the direct and the inverse problems. In fact, the latter is usually ill-posed in the sense of existence, uniqueness and stability of the solution. This inconvenient is often treated by using some regularization techniques, [12, 10].

4.2 Discretization of the objective functional

Even if the functions $S(t)$ and $N(y,t)$ are not known in their whole domains, it is sufficient to know the values that they take at several points (defining a convenient grid mesh for y and t).

First of all, suppose that we have experimental measurements of N and S at different times t_k, $k = 1,...,M$. That would give us temporal information about the variables.

On the other hand, the distribution of living cells depends also on the position along the tumour. A common techniche in medical imaging is *landmark registration*: landmarks are points placed at meaningful parts of the tumour, with the intention of representing it as good as possible with a few isolated points. Let y_j, $j = 1,...,Q$ denote a set of points in the interval $[0,1]$ that are chosen by an expert. Note that the points should be chosen in the interval $[0,S(t)]$, but for simplicity we will assume that they are fixed in time.

Then, the objective functional (4.2) can be discretized as

$$J(N,S;\alpha) = \sum_{j=1}^{Q} \sum_{k=1}^{M} [N_\alpha(y_j,t_k) - N^*(y_j,t_k)]^2 + \mu \sum_{k=1}^{M} [S_\alpha(t_k) - S^*(t_k)]^2 dt. \tag{4.3}$$

5 Numerical experiments

The pattern search method, [9]-[13], was employed to estimate the parameter of interest by minimizing the objective functional. It is a direct method, i.e. a method that neither compute nor explicitly approximate derivatives of J. For this purpose we use the function **pattern search** of MATLAB.

We study the functionals behaviour by solving some test cases. The living cell density and the tumour radius are generated via the forward problem. We show here the results obtained by assuming a *standard value* $\alpha = 1000$. It seems that this value is quite reasonable, see [16], although in a next step we are trying to determine whether or not the dose considered is tolerable for a patient.

1. *Model-generated data*

   Consider first an optimization problem that consist in minimizing the functional (4.3), where $N^*(y,t)$ and $S^*(t)$ are generated via the forward model, for a choice of the model parameter $\alpha = 1000$.

   Working with the functional (4.3) requires to define the landmark points y_j and the times t_k where the measurements are made. For simplicity, and to be consistent with the way we solved the direct problem, we took the same spatial grid for the landmarks, i.e. 30 equidistant points $0 = y_1 < ... < y_{30} = 1$. Regarding to the time selection, it is apparent from the experiments that 20 time steps are enough to obtain the desired results, so we take 20 equidistant points $t_1 < ... < t_{20}$. The factor μ is taken to be 1.

   The idea of this test case is to investigate how close the original value of the parameter can be retrieved. However, it is not a trivial one, because we do not know, for instance, if the optimization problem has a solution or, in that case, if it is unique or if the method converges to another local minima.

   We emphasize we have run the algorithm several times using different initial random conditions and in all cases the results were similar. They can be summarized in the following table:

   - Stopping criteria: *difference between two consecutive iterations lower than* 10^{-5}
   - Iterations/elapsed time: *25/45 min*
   - Final point: $\alpha = 1001$
   - Functional final value: $J(\alpha) = 1.8871.10^{-4}$

2. *Model-generated data with* 5% *of random noise*

   It is well known that the presence of noise in the data may imply the appearance of strong numerical instabilities in the solution of an inverse problem, [5].

   The outputs of the detectors and the experimental equipment where the variables N^* and S^* are measured are often affected by perturbations, usually random ones. As stated in [3], it is in general valid to consider a 5% of random noise.

   The functional (4.3) is the same used for case 1, except from the constant μ. It was clear from numerical experiments that the factor $\mu = 1$ was not suitable for this case, as it is showed in figures 4 and 5, where we can see that the order of magnitude between both terms in the objective functional is different. Indeed, in the case of the living cell density, we can see that both lines are almost indistinguishable. By a trial and error procedure, we determined that $\mu = 10^{-4}$ is a suitable factor.

   Again, starting with different points, the results of the procedure are the following:

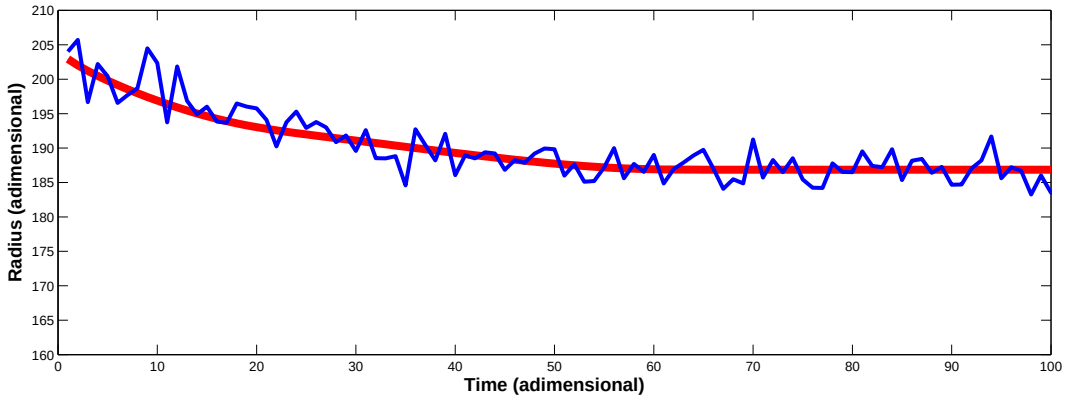

Figure 4: Evolution of the tumour radius without (red line) and with 5% random noise (blue line).

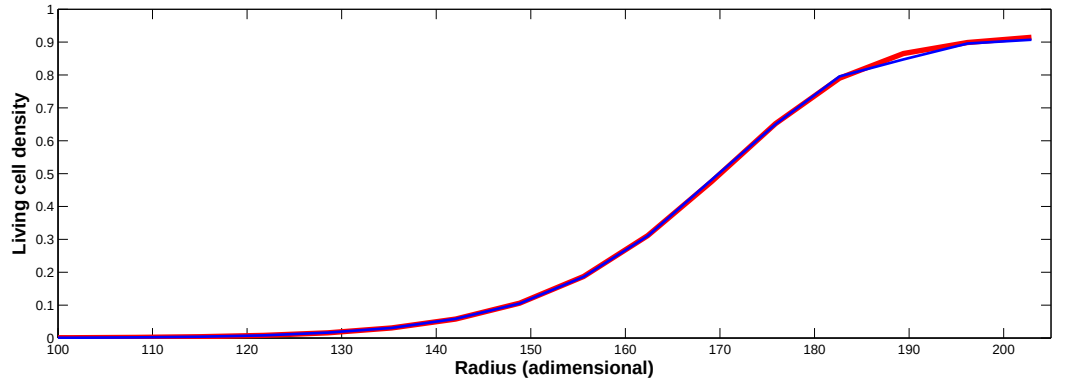

Figure 5: Living cell distribution without (red line) and with 5% random noise (blue line), for the initial time.

- Stopping criteria: *difference between two consecutive iterations lower than* 10^{-5}
- Iterations/elapsed time: *24/36 min*
- Final point: $\alpha = 992.97$
- Functional final value: $J(\alpha) = 0.100886$

6 Conclusions and future work

A simple methodology was developed for the estimation of biochemical parameters involved in the growth of an avascular tumour using data that could be obtained from medical imaging. The inverse problem has been solved using the Pattern Search algorithm, coupled with a finite different scheme and a boundary value problem solver for the resolution of the direct problem. The presented results demonstrate the feasibility of the proposed methodology. Even in the case when 5% of noise was added to the input data the methodology estimates the desired parameter with very good accuracy

According to the results, this methodology can help to estimate several chemical/biological parameters involved in the process (diffusion coefficient, mitosis and death rates, Michaelis-Menten constants, etc.) that could be useful and important to study for the design of a treatment procedure. As future work we plan to recover more parameters involved in the model, and focus on the regularization of the problem considering different regularization methods and iterative algorithms. In order to solve the optimization problem, we will use an algorithm that take into account the derivative of the functional like the conjugate gradient method.

In addition, we are trying to use these optimization ideas to work with vascular tumour's model. That will surely give a more realistic idea of a chemotherapeutic treatment and its protocol.

Acknowledgments

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A parameter estimation problem for a tumour growth model .

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Abstract

In this paper we present a method for estimating unknown parameters that appear on an avascular, spheric tumour growth model. The model for the tumour is based on nutrient driven growth of a continuum of live cells, whose birth and death generate volume changes described by a velocity field. The drug is applied externally, and is assumed to be a diffusible substance capable of killing cells.

The model consists on a coupled system of partial differential equations which is solved numerically. As the domain on which the equations are defined is the tumour, that changes in size over time, the problem can be formulated as a moving boundary one.

After solving the forward problem properly, we are concerned in using the model for the estimation of parameters, by fitting the numerical solution with real data. We define a functional to compare both of them and we use the pattern search method for minimizing it, obtaining good accuracy for the recovery of a few parameters.

Keywords: avascular tumour, constrained optimization, inverse problem, mathematical modeling.

1 Introduction.

The interest for research in modeling cancer has grown enormously over the last decades, [1, 2]. Pioneers have been, for example, [11, 15], where the first spatio-temporal models of an avascular multicellular spheroid's (MCS) growth have been developed. The study of MCS is interesting because they provide the best insight into the effectiveness of chemotherapeutic drugs on tumours in vivo, and their behaviour can be studied experimentally (in vitro) by controlling environmental conditions in which they grow: for example, the radii of the tumour can be monitored by changing the chemotherapeutic drug or oxygen levels.

In addition, another variables can be measured. If possible, experimentalists can get information about the distribution of substances within the tumour. Moreover, via medical imaging or histological cuts, they can also get data about the density of the different kind of cells conforming it: proliferating, quiescent, necrotic.

That is why in this general approach of modeling the key variables are the tumour size (radius) and the concentration within the tumour of growth-rate limiting diffusible chemicals (nutrients such as oxygen or glucose or a chemotherapeutic drug). Since the tumour changes in size over time, the domain on which the models are formulated must be determined as part of the solution process, giving a vast class of moving boundary problems, [6, 7].

In this article, we propose a framework for estimating unknown parameters via PDE-constrained optimization, following the PDE-based model by Ward and King, [16]. In this approach, avascular

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tumour growth is modeled via a coupled nonlinear system of differential equations, which make the numerical solution procedure quite challenging.

We are concerned with developing a robust PDE-constrained formulation that let us find the best set of parameters of a tumour growth model that fits patient or experimental data. We choose the parameters that should be of applied interest and try to obtain them by defining a functional to be minimized.

The paper is organized as follows: section 2 introduces the tumour growth model (forward problem). Section 3 shows the numerical solution of the forward problem and checks its accuracy by proving some theoretical results. Section 4 introduces the inverse problem approach, by defining the functional to be minimized. Finally, in section 5 the numerical procedure to solve the inverse problem is discussed.

2 Mathematical model.

We consider the model proposed by Ward and King in [16]. The tumour is a spheroid which consists of a continuum of living cells, in one of two states: live or dead. The rates of birth and death depend on the nutrient and chemotherapeutic drug concentration. It is supposed that those processes generate volume changes, leading to cell movement described by a velocity field. The system of equations to be studied is:

$$\frac{\partial n}{\partial t}+\frac{1}{r^2}\frac{\partial(r^2vn)}{\partial r}=[k_m(c)-k_d(c)-KG(k_m(c))w]n, \tag{2.1}$$

$$\frac{\partial c}{\partial t}+\frac{1}{r^2}\frac{\partial(r^2vc)}{\partial r}=\frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right)-\beta k_m(c)n, \tag{2.2}$$

$$\frac{1}{r^2}\frac{\partial(r^2v)}{\partial r}=[V_Lk_m(c)-(V_L-V_D)\{k_d(c)+KG(k_m(c))w\}]n, \tag{2.3}$$

$$\frac{\partial w}{\partial t}+\frac{1}{r^2}\frac{\partial(r^2vw)}{\partial r}=\frac{D_w}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial w}{\partial r}\right)-\frac{K}{\omega}G(k_m(c))wn, \tag{2.4}$$

where the dependent variables n, c, v and w are the live cell density (cells/unit volume), nutrient concentration, velocity and drug concentration, respectively. As it is described in [16], equation (2.1) states that the rate of change of n is dependent on the difference between the birth $k_m(c)$ and death $k_d(c)$ rates, where this one is either natural (as described in [17]) or due to the drug effects, at a rate $KG(k_m(c))w$. The functons k_m and k_d are taken to be generalised Michaelis-Menten kinetics with exponent 1, i.e.

$$k_m(c)=A\left(\frac{c}{c_c+c}\right), \tag{2.5}$$

$$k_d(c)=B\left(1-\sigma\frac{c}{c_d+c}\right). \tag{2.6}$$

The constant K is the maximum possible rate of drug induced cell death. The constants A, B and σ are positive parameters of the Michaelis-Menten kinetics, while c_c and c_d are critical concentrations. $G(k_m(c))$ is a function that represents the dependence between drug action and cell-cycle. As it is considered in [16] it is a good idea to choose a linear dependence, giving

$$G(k_m(c))=k_m(c)/A.$$

Equation (2.2) states that the nutrient is consumed at a rate proportional to the rate of mitosis, and its diffusion is described by Ficks law. Equation (2.3) states that the rate of volume change is given by the difference in volume generated via birth from that lost by death (it is assumed that a live cell occupies a volume V_L that is twice the volume of a death cell V_D). The diffusion of the drug is described also by Ficks law, and it is assumed that it is degraded only when it attacks a living cell, giving a maximum degradation rate K/ω. ω is a dimensionless constant that can be interpreted as a measure of the drugs effectiveness, as explained in [16], with increasing ω implying that less drug is consumed to produce the same effects during the killing process. These considerations lead to equation (2.4).

2.1 Moving boundary problem

As it has been mentioned, the tumour is assumed to be a spheroid that exhibits radial simmetry. That is why, not only the state variables n, c, v and w are important, but the outer tumour radius is also a key variable to be determined. Since the tumour changes in size over time, the domains on which the models are formulated (and the PDEs are valid) must be determined as part of the solution.

Let $S(t)$ be the tumour radius at time t. So, if we suppose that the treatment begins at time $t = 0$, in which the tumour has a radius S_I, with living cell density and nutrient concentration distributions $n_I(r)$ and $c_I(r)$, respectively, then the initial conditions of the problem can be formulated as

$$n(r,0) = n_I(r), \tag{2.7}$$
$$c(r,0) = c_I(r), \tag{2.8}$$
$$w(r,0) = 0, \tag{2.9}$$
$$S(0) = S_I. \tag{2.10}$$

Because symmetry is assumed about the tumour center, there is no flux there. That is why, as boundary conditions about $r = 0$, are taken:

$$\frac{\partial c}{\partial r}(0,t) = 0, \tag{2.11}$$
$$v(0,t) = 0, \tag{2.12}$$
$$\frac{\partial w}{\partial r}(0,t) = 0. \tag{2.13}$$

Moreover, on the external boundary (which is also the boundary of the complement of the tumour as a subset of the body), the following conditions are taken:

$$c(S(t),t) = c_0, \tag{2.14}$$
$$\frac{dS}{dt} = v(S(t),t), \tag{2.15}$$
$$w(S(t),t) = w_0(t), \tag{2.16}$$

where c_0 and $w_0(t)$ are external nutrient and drug concentrations, respectively. The function $w_0(t)$ depends on the chemotherapeutic protocol. In our simulations it will be considered as a constant that does not depend on t. However, other functions may be adopted, for example in section 3 we show an example in which drug is provided for some intervals of time, but not for other ones.

2.2 Nondimensionalisation

Before analysing the model equations, we re-scale the mathematical model in the following way, denoting non-dimensional variables with bars:

$$\overline{n} = V_L n; \qquad \overline{c} = c/c_0; \qquad \overline{v} = v/r_0 A; \qquad \overline{t} = At \qquad \overline{r} = r/r_0; \qquad \overline{S} = S/r_0; \qquad \overline{w} = w/W_0$$

where $r_0 = (3V_L/4\pi)^{1/3}$ is the radius of a single cell and W_0 is a suitable reference drug concentration (typically $W_0 = max(w_0(t))$).

It is important to remark that inherent in this problem are two timescales: the tumour growth timescale ($\approx$ 1 day) and the much shorter drug and nutrient diffusions ($\approx$ 1 min). That is why, following [2, 1, 16, 6] we adopt a quasi-steady assumption in the nutrient and drug equations.

Following [16], and relabeling the variables with bar again without it, these rescalings lead to the following system of differential equations:

$$\frac{\partial n}{\partial t} + v\frac{\partial n}{\partial r} = [a(c,w) - b(c,w)n]n, \tag{2.17}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) = k(c)n, \tag{2.18}$$

$$\frac{1}{r^2}\frac{\partial (r^2 v)}{\partial r} = b(c,w)n, \tag{2.19}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial w}{\partial r}\right) = \frac{\widehat{K}}{\alpha}k_m(c)wn, \tag{2.20}$$

where

$$\alpha = \omega D_w V_L W_0/Ar_0^2, \tag{2.21}$$

$$\widehat{K} = KW_0/A,$$

$$a(c,w) = \frac{1}{A}[k_m(c) - k_d(c) - KG(k_m(c))w],$$

$$b(c,w) = \frac{1}{A}\{k_m(c) - (1-\delta)[k_d(c) - KG(k_m(c))w]\},$$

$$k(c) = \widehat{\beta}k_m(c)/A,$$

with $\delta = V_D/V_L$ and $\widehat{(\beta)} = r_0^2\beta A/V_L c_0 D$.

We note that the *constant* α defined above comprises many model parameters that should be interesting to know exactly. It will be of great importance in the next sections, where α will be considered as a key parameter of the problem.

Also, it is worth saying that rigorous mathematical analysis including existence, uniqueness, and stability theorems, as well as properties of the free boundaries for similar tumour growth models in which different kind of PDEs are combined, have been obtained, [4] and [8].

3 Numerical solution of the forward problem

After the assumptions made in the previous section, we have to solve the following system of PDEs:

$$n_t + v n_r = [a(c,w) - b(c,w)n]n \qquad 0 < r \leq S(t), \qquad t > 0, \tag{3.1}$$

$$v_r + \frac{2}{r}v = b(c,w)n \qquad 0 < r \leq S(t), \qquad t > 0, \tag{3.2}$$

$$c_{rr} + \frac{2}{r}c_r = k(c)n \qquad 0 < r \leq S(t), \qquad t > 0, \tag{3.3}$$

$$w_{rr} + \frac{2}{r}w_r = \frac{\widehat{K}}{\alpha}k_m(c)w \qquad 0 < r \leq S(t), \qquad t > 0. \tag{3.4}$$

The initial conditions at $t = 0$ are

$$n(r,0) = n_I(r), \tag{3.5}$$

$$S(0) = S_I, \tag{3.6}$$

$$w(r,0) = 0, \tag{3.7}$$

and the boundary conditions are

$$v(0,t) = 0, \tag{3.8}$$

$$c_r(0,t) = 0, \tag{3.9}$$

$$w_r(0,t) = 0, \tag{3.10}$$

$$c(S(t),t) = 1, \tag{3.11}$$

$$w(S(t),t) = 1, \tag{3.12}$$

$$\dot{S}(t) = v(S(t),t). \tag{3.13}$$

It is important to remark that the density of living cells in the boundary, $n(S(t),t)$, can be calculated explicitly. Indeed, consider equation (3.1) and note that, using the chain rule, the total variation of n in time is

$$\frac{dn}{dt} = \frac{\partial n}{\partial t} + \frac{\partial n}{\partial r}\frac{dr}{dt}. \tag{3.14}$$

At the point $(S(t),t)$ the expression $\frac{dr}{dt}$ is equal to $v(S(t),t)$. So, substitution in (3.1) gives

$$\frac{dn}{dt}(S(t),t) = [a(1,1) - b(1,1)n(S(t),t)]n(S(t),t),$$

where $a(1,1)$ and $b(1,1)$ are the corresponding values of the functions a and b on the boundary at any time. The last equation is a separable ODE, that can be transformed into

$$\frac{dn^*}{[a^* - b^*n^*]n^*} = dt, \tag{3.15}$$

where for simplicity we wrote $a^* = a(1,1)$, $b^* = b(1,1)$ and $n^* = n(S(t),t)$.

Now, we use expansion into simple fractions:

$$\frac{1}{(a^*-b^*n^*)n^*} = \frac{b^*}{a^*}\frac{1}{a^*-b^*n^*} + \frac{1}{a^*}\frac{1}{n^*}. \tag{3.16}$$

Combining equations (3.15) and (3.16) and integrating over time we get

$$\int_0^t dt = \int_1^{n(S(t),t)} \frac{dn^*}{(a^*-b^*n^*)n^*} = \ln\left(\frac{(a^*-b^*)n(S(t),t)}{a^*-b^*n(S(t),t)}\right). \tag{3.17}$$

Finally, solving for n on the boundary, we obtain

$$n(S(t),t) = \frac{a^*e^{a^*t}}{a^*-b^*+b^*e^{a^*t}}. \tag{3.18}$$

Equation (3.18) is not only an elegant analytical result, but also it will become of really importance when calculating numerically the value of n in the boundary. As we shall see, when defining the spatial grid to solve equation (3.1) with a forward finite difference scheme, for each point r_j of the grid we will need to take also the point r_{j+1} but that is impossible in the last point of the grid, say $S(t)$

3.1 Fixed domain method

The first step for solving this moving boundary problem will be transforming the original domain to a fixed one, i.e., re-writing the whole system for the change of coordinates $y = r/S(t)$. In this way, the spatial domain will be the interval $[0,1]$.

Observation 3.1 *If $r = yS(t)$, then $\frac{dr}{dy} = S(t)$ and $\frac{dr}{dt} = y\dot{S}(t)$.*

We briefly illustrate the way in which the new equations are obtained, using (3.1).
Let $N(y,t) \doteq n(r,t) = n(yS(t),t)$. Differentiating this expression respect to y, we obtain

$$N_y = n_r r_y + n_t t_y = n_r S(t),$$

and then $n_r = \frac{N_y}{S}$.
And differentiation respect to t gives

$$N_t = n_r \frac{dr}{dt} + n_t,$$

and so we deduce that $n_t = N_t - \frac{N_y}{S}y\dot{S}$.
Substitution in (3.1) gives

$$N_t - \frac{\dot{S}}{S}yN_y + \frac{V}{S}N_y = N[a(C) - b(C)N]N \qquad 0 < r \leq 1, \qquad t > 0. \tag{3.19}$$

The same procedure is applied to the other equations, and we obtain

$$C_{yy} + \frac{2}{y}C_y = k(C)S^2N, \tag{3.20}$$

$$V_y + \frac{2}{y}V = b(C)NS, \tag{3.21}$$

$$W_{yy} + \frac{2}{y}W_y = \frac{\hat{K}}{\alpha}k_m(C)S^2WN. \tag{3.22}$$

The initial conditions for the transformed problem are

$$N(y,0) = N_I(y), \qquad 0 \le y \le 1, \tag{3.23}$$
$$S(0) = S_I, \tag{3.24}$$
$$W(y,0) = 0, \qquad 0 \le y \le 1, \tag{3.25}$$

and the boundary conditions are

$$V(0,t) = 0, \qquad t > 0, \tag{3.26}$$
$$C_y(0,t) = 0, \qquad t > 0, \tag{3.27}$$
$$W_y(0,t) = 0, \qquad t > 0, \tag{3.28}$$
$$C(1,t) = 1, \qquad t > 0, \tag{3.29}$$
$$W(1,t) = 1, \qquad t > 0, \tag{3.30}$$
$$\dot{S}(t) = V(1,t), \qquad t > 0. \tag{3.31}$$

3.2 Numerical procedure

The drug is first applied at $t = 0$, by which time the tumour has grown following the model without drug, [17]. Originally, at $t \approx -500$, a single cell started to take nutrients from the environment, letting it grow up to a dimensionless size of $S_I \approx 202$. The solution for the variables N, C and V is taken as the initial distribution of them for the drug treatment case.

All the simulations described in this section use the following parameter values, as suggested in [16]:

$$B/A = 1, \qquad \sigma = 0.9, \qquad \delta = 0.5, \qquad \beta = 0.005, \qquad c_c = 0.1, \qquad c_d = 0.05, \qquad K = 50.$$

The problem (3.19)-(3.22) subject to the initial and boundary conditions is solved in the following way:

1. Given the distributions of N, V, C and W at time k we solve (3.19) using a finite-difference scheme to obtain N at time $k+1$. The value of N at the boundary is updated directly by solving equation (3.18).

2. The ODEs system (3.20)-(3.22) is solved using the `MATLAB`'s package `bbvp4c` to obtain C, V and W at time $k+1$.

3. Using the value $V(1,k+1)$ we solve equation (3.31) for S at time $k+1$ using Eulers method.

We remark that solving the system (3.20)-(3.22) is challenging in the sense that there is a singularity at $r = 0$. The package `bbvp4c` let us deal with this singularity by using a *Singular Term* tool.

3.3 Numerical results

The numerical solution for this problem is very well discussed and analized in many aspects by Ward and King, [16]. The parameter α is taken as a variable in the sense that we are interested in studying how the solution behaves when α is changed.

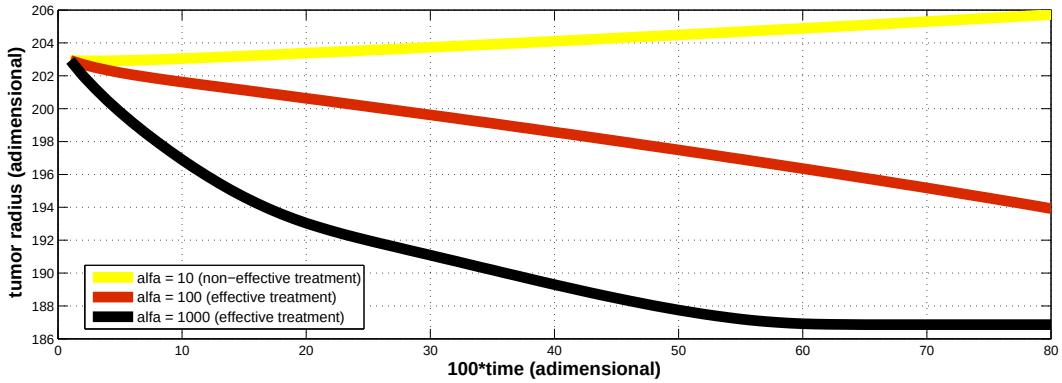

Figure 1: Evolution of the tumour radius for different values of α.

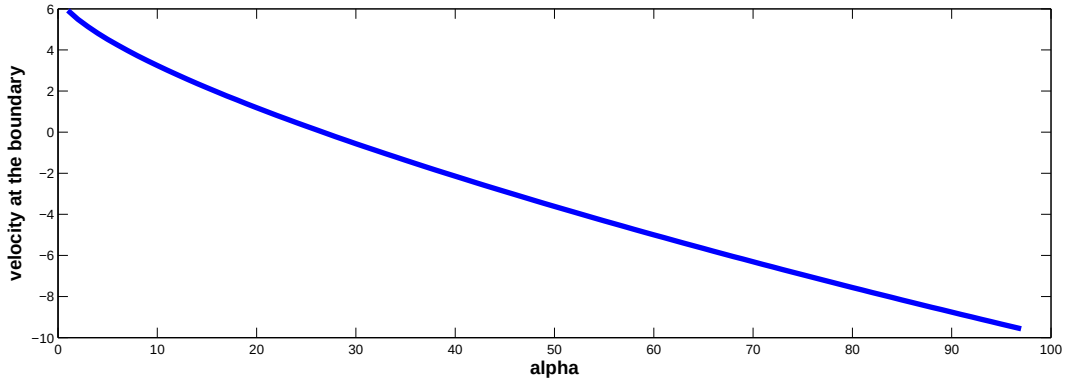

Figure 2: Velocity at the tumour's boundary for a fixed time ($t = 10$) for different values of α.

We are able to confirm that α can, indeed, be considered a *measure of the treatment effectiveness*. We plot how the radius of the tumour evolves in time when varying this parameter, as showed in figure 1.

We can observe that a value $\alpha = 10$ does not stop the growth of the tumour, although there is a killing cell process. However, if $\alpha = 100$ or $\alpha = 1000$ the radius of the tumour decreases (of course the mass could never disappear because the drug does not act over the already formed necrotic core).

An interesting question to answer is: *for which value of* α *can be stated that tumour will decrease in size?* That should be helpful, for example, w hen choosing some dose when the drug coefficient diffusion and the initial spheroid size are known. To determine this value we take into account the velocity in the boundary at a fixed time for different values of α. For example, in figure 2 we can see that if we fix the non-dimensional time $t = 10$, the function $v(S(t),t)$ has a root in $\alpha \approx 25$.

The problem has also be solved for a different treatment protocol. We took a drug with $\alpha = 1000$ and provided it for some time intervals, so that the boundary condition is the following:

$$\begin{aligned} w_0(t) &= 1, \quad t \in [0,20), \\ w_0(t) &= 0, \quad t \in [20,50), \\ w_0(t) &= 1, \quad t \geq 50. \end{aligned}$$

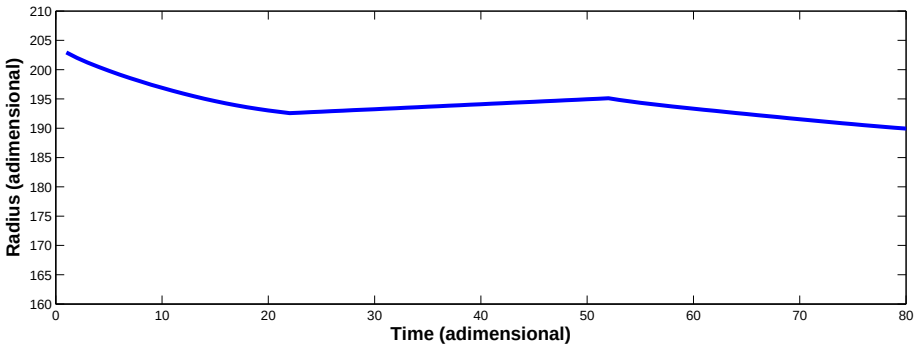

Figure 3: Evolution of the tumour radius for a pulse-type drug provision.

In [16] the surviving fraction is plotted for a boundary condition similar to this one. In contrast, in figure 3 we plot the evolution of the tumour radius for this situation, which should be considered when designing a treatment, because it is really important in the effectiveness-toxicity balance.

4 Inverse problem

The main idea of this section is to recover some of the parameters which appear in the mathematical model, motivated in the lack of references that exist in literature. In reality, some of them are unknown, especially in vivo.

We consider that the parameter α defined above is important because it provides a measure of the treatment effectiveness. In particular, it can provide information about the drug diffusion coefficient, the optimal dose to get a desired effect or, eventually, Michaelis-Menten kinetics, see equation (2.21).

Thus, we are interested in the recovery of this parameter using available scans (MR images from real patients that could let us follow the tumour size evolution over time) or reliable measurements such as histological studies (obtained experimentally for in vitro cases). The data should be obtained at different moments in time over a time interval of lenght T. The inverse problem can be formulated as follows:

Find a parameter value able to generate data that best match the available information over time $0 \leq t \leq T$.

Because of the nature of the mathematical model, we have to solve a PDE constrained optimization problem. The constraints are given by the model equations (2.1)-(2.14), which can be written in a short way as $\mathcal{P}(\phi) = 0$, where $\mathcal{P}$ is the differential operator given by the set of equations and $\phi = (N, C, V, W)$.

4.1 The objective functional

We should construct an objective functional which gives us some *distance* between the experimental (real) data and the solution of the system of PDEs for each value of α.

First of all, it is important to decide which variables are capable to be measured experimentally. For instance, it is clear that the tumour radius $S(t)$ can be known at certain times t_k, $k = 1, ..., M$. So, the first possibility for defining a functional could be

$$J(S;\alpha) = \int_0^T [S_\alpha(t) - S^*(t)]^2 dt, \tag{4.1}$$

where $S_\alpha(t)$ is the radius evolution obtained solving the direct problem for a certain value of α and $S^*(t)$ is the evolution measured experimentally (real data).

Other variable that could be measured is the concentration of living cells, via biomedical imaging. Thus, we are motivated to define a functional that reproduces in a better way the knowledge we have about the process, i.e.

$$J(N,S;\alpha) = \int_0^1 \int_0^T [N_\alpha(y,t) - N^*(y,t)]^2 dt dy + \mu \int_0^T [S_\alpha(t) - S^*(t)]^2 dt, \tag{4.2}$$

where $N_\alpha(y,t)$ and $N^*(y,t)$ are the living cell concentration for the direct problem solved with the value α and the real data, respectively (both of them in the domain $[0,1] \times [0,T]$). The positive constant μ is introduced, as we shall see, to take into account the different order of magnitude between N and S.

So, the constrained optimization problem can be formulated as

$$\min_{\alpha \in \mathcal{C}} J(\alpha),$$

$$s.t. \mathcal{P}(\phi) = 0,$$

where $\mathcal{C}$ denotes the set of *admissible values* of α.

We remark that, in general, there is a fundamental difference between the direct and the inverse problems. In fact, the latter is usually ill-posed in the sense of existence, uniqueness and stability of the solution. This inconvenient is often treated by using some regularization techniques, [12, 10].

4.2 Discretization of the objective functional

Even if the functions $S(t)$ and $N(y,t)$ are not known in their whole domains, it is sufficient to know the values that they take at several points (defining a convenient grid mesh for y and t).

First of all, suppose that we have experimental measurements of N and S at different times t_k, $k = 1,...,M$. That would give us temporal information about the variables.

On the other hand, the distribution of living cells depends also on the position along the tumour. A common techniche in medical imaging is *landmark registration*: landmarks are points placed at meaningful parts of the tumour, with the intention of representing it as good as possible with a few isolated points. Let y_j, $j = 1,...,Q$ denote a set of points in the interval $[0,1]$ that are chosen by an expert. Note that the points should be chosen in the interval $[0,S(t)]$, but for simplicity we will assume that they are fixed in time.

Then, the objective functional (4.2) can be discretized as

$$J(N,S;\alpha) = \sum_{j=1}^{Q} \sum_{k=1}^{M} [N_\alpha(y_j,t_k) - N^*(y_j,t_k)]^2 + \mu \sum_{k=1}^{M} [S_\alpha(t_k) - S^*(t_k)]^2 dt. \tag{4.3}$$

5 Numerical experiments

The pattern search method, [9]-[13], was employed to estimate the parameter of interest by minimizing the objective functional. It is a direct method, i.e. a method that neither compute nor explicitly approximate derivatives of J. For this purpose we use the function **pattern search** of MATLAB.

We study the functionals behaviour by solving some test cases. The living cell density and the tumour radius are generated via the forward problem. We show here the results obtained by assuming a *standard value* $\alpha = 1000$. It seems that this value is quite reasonable, see [16], although in a next step we are trying to determine whether or not the dose considered is tolerable for a patient.

1. *Model-generated data*

   Consider first an optimization problem that consist in minimizing the functional (4.3), where $N^*(y,t)$ and $S^*(t)$ are generated via the forward model, for a choice of the model parameter $\alpha = 1000$.

   Working with the functional (4.3) requires to define the landmark points y_j and the times t_k where the measurements are made. For simplicity, and to be consistent with the way we solved the direct problem, we took the same spatial grid for the landmarks, i.e. 30 equidistant points $0 = y_1 < ... < y_{30} = 1$. Regarding to the time selection, it is apparent from the experiments that 20 time steps are enough to obtain the desired results, so we take 20 equidistant points $t_1 < ... < t_{20}$. The factor μ is taken to be 1.

   The idea of this test case is to investigate how close the original value of the parameter can be retrieved. However, it is not a trivial one, because we do not know, for instance, if the optimization problem has a solution or, in that case, if it is unique or if the method converges to another local minima.

   We emphasize we have run the algorithm several times using different initial random conditions and in all cases the results were similar. They can be summarized in the following table:

   - Stopping criteria: *difference between two consecutive iterations lower than* 10^{-5}
   - Iterations/elapsed time: *25/45 min*
   - Final point: $\alpha = 1001$
   - Functional final value: $J(\alpha) = 1.8871.10^{-4}$

2. *Model-generated data with* 5% *of random noise*

   It is well known that the presence of noise in the data may imply the appearance of strong numerical instabilities in the solution of an inverse problem, [5].

   The outputs of the detectors and the experimental equipment where the variables N^* and S^* are measured are often affected by perturbations, usually random ones. As stated in [3], it is in general valid to consider a 5% of random noise.

   The functional (4.3) is the same used for case 1, except from the constant μ. It was clear from numerical experiments that the factor $\mu = 1$ was not suitable for this case, as it is showed in figures 4 and 5, where we can see that the order of magnitude between both terms in the objective functional is different. Indeed, in the case of the living cell density, we can see that both lines are almost indistinguishable. By a trial and error procedure, we determined that $\mu = 10^{-4}$ is a suitable factor.

   Again, starting with different points, the results of the procedure are the following:

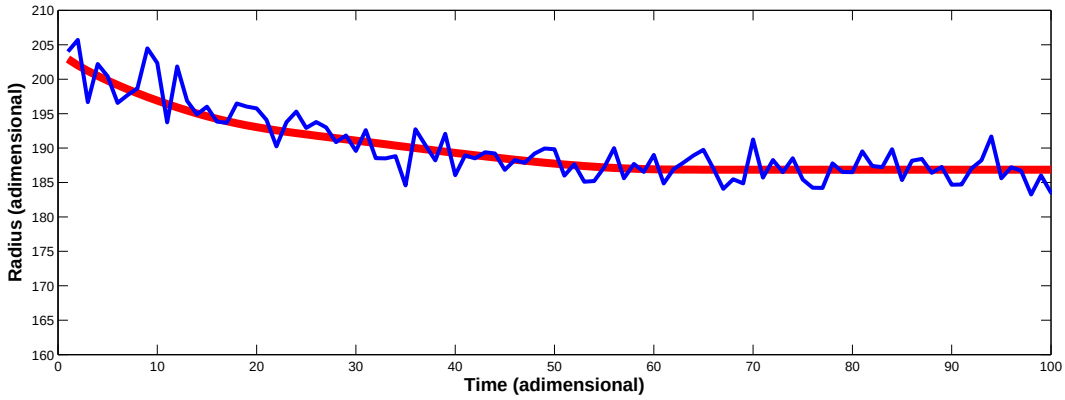

Figure 4: Evolution of the tumour radius without (red line) and with 5% random noise (blue line).

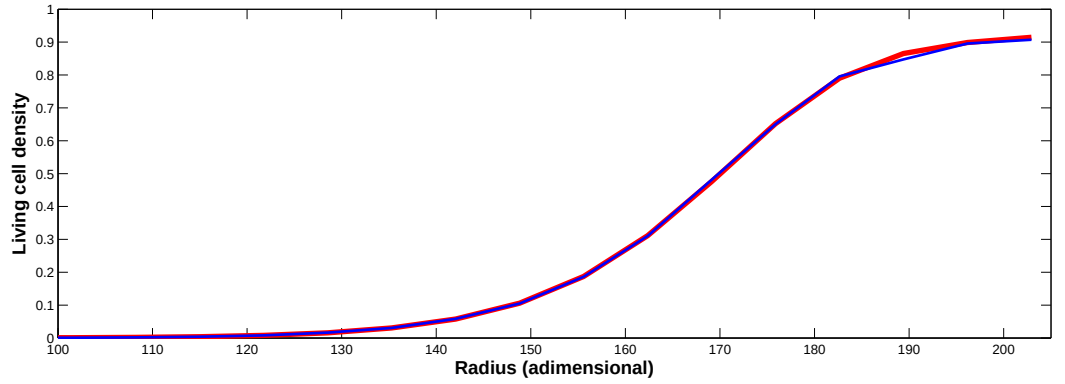

Figure 5: Living cell distribution without (red line) and with 5% random noise (blue line), for the initial time.

- Stopping criteria: *difference between two consecutive iterations lower than* 10^{-5}
- Iterations/elapsed time: *24/36 min*
- Final point: $\alpha = 992.97$
- Functional final value: $J(\alpha) = 0.100886$

6 Conclusions and future work

A simple methodology was developed for the estimation of biochemical parameters involved in the growth of an avascular tumour using data that could be obtained from medical imaging. The inverse problem has been solved using the Pattern Search algorithm, coupled with a finite different scheme and a boundary value problem solver for the resolution of the direct problem. The presented results demonstrate the feasibility of the proposed methodology. Even in the case when 5% of noise was added to the input data the methodology estimates the desired parameter with very good accuracy

According to the results, this methodology can help to estimate several chemical/biological parameters involved in the process (diffusion coefficient, mitosis and death rates, Michaelis-Menten constants, etc.) that could be useful and important to study for the design of a treatment procedure. As future work we plan to recover more parameters involved in the model, and focus on the regularization of the problem considering different regularization methods and iterative algorithms. In order to solve the optimization problem, we will use an algorithm that take into account the derivative of the functional like the conjugate gradient method.

In addition, we are trying to use these optimization ideas to work with vascular tumour's model. That will surely give a more realistic idea of a chemotherapeutic treatment and its protocol.

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