A MODEL OF THE TUMOUR SPHEROID RESPONSE TO RADIATION
Identifiability Analysis

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Abstract: A spatially uniform model of tumour growth after a single instantaneous radiative treatment is presented in this paper. The ordinary differential equation model presented may be obtained from an equivalent partial derivative equation model, by integration with respect to the radial distance. The main purpose of the paper is to study its identifiability properties. In fact, a preliminary condition, that is necessary to verify before performing the parameter identification, is the global identifiability of a model. A detailed study of the identifiability properties of the model is done pointing out that it is globally identifiable, provided that the responses to two different radiation doses are available.

1 INTRODUCTION

The mathematical literature on solid tumour growth is very wide. Looking through it, this evolution line can be recognized: the earliest models were focused on avascular tumour growth; then models of angiogenesis were developed; more recently, models of vascular tumour growth are starting to emerge (Byrne, 2003).

With reference to mathematical models of avascular tumour growth we can underline the presence of two different kinds of models: the spatially uniform models and the spatially structured models.

The first class of models concerns with models in which details of the spatial structure of the tumour are neglected and the attention is focused, for instance, on the tumour overall volume or on the total number of cells present within the tumour itself.

On the other hand, the second class concerns with models in which the spatial coordinates are taken into account, in order to investigate the role of rate limiting, diffusible *growth factors* on the tumour development.

In this paper a spatially uniform model of tumour growth, after a single instantaneous radiative treatment is presented, with the main purpose of studying its identifiability properties. This model comes from the integration with respect to the spatial coordinate of the partial derivative equations of a spatially structured model (Bertuzzi et al., 2009), when it is possible to neglect the distribution of oxygen concentration inside the tumour. In fact, the oxygen concentration is generally very important in such models because it influences the radiosensitivity of cells (Wouters and Brown, 1997) and it determines the cell death when its level is too low. Nevertheless, when the tumoral spheroid, during all its growth, remains smaller than a critical dimension at which an internal necrotic region starts to develop ('small spheroids'), then it can be assumed that:

1. the oxygen concentration is higher than the minimum value necessary to the cell life
2. the initial distribution of oxygen inside the spheroid is sufficiently uniform to be assumed constant

In view of 1. the cell death for insufficient oxygenation can be neglected and the radiation is the only cause of death. Moreover for 2. it can be assumed that the radiosensitivity coefficients are constant for all the tumoral cells inside the spheroid. With these two assumptions, the ODE model presented in this paper is completely equivalent to the original PDE model proposed by Bertuzzi et al. (2009), and it may be obtained from the latter by integration with respect to the radial distance, as mentioned above.

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2 AN ODE MATHEMATICAL MODEL OF THE TUMOUR SPHEROID RESPONSE TO RADIATION

Although quiescent cells have been evidenced in tumour spheroids (Freyer and Sutherland, 1986), (Sutherland, 1988), for simplicity we will assume that all viable cells proliferate with the same rate and this assumption is reasonable because the model is formulated under the assumption of 'small spheroids', where the oxygen level is sufficiently high and uniform. So in a spheroid we will distinguish: viable cells, lethally damaged cells and dead cells.

Under the hypothesis of 'small spheroids', let us consider the following ODE model (Papa, 2009), obtained by integrating the PDE equations of the model proposed by Bertuzzi et al. (2009):

$$\begin{cases} \dot{V}(t) = \chi V(t)\,, \\ \dot{V}_{D_1}(t) = (\chi_D - \mu_D) V_{D_1}(t)\,, \\ \dot{V}_{D_2}(t) = (\chi_D - \mu_D) V_{D_2}(t) + \mu_D V_{D_1}(t)\,, \\ \dot{V}_{D_3}(t) = (\chi_D - \mu_D) V_{D_3}(t) + \mu_D V_{D_2}(t)\,, \\ \dot{V}_{N_1}(t) = \mu_D V_{D_3}(t) - \mu_N V_{N_1}(t)\,, \\ \dot{V}_{N_2}(t) = \mu_N V_{N_1}(t) - \mu_N V_{N_2}(t)\,, \\ \dot{V}_{N_3}(t) = \mu_N V_{N_2}(t) - \mu_N V_{N_3}(t)\,, \end{cases} \tag{1}$$

where $V(t)$ is the volume of viable cells, $V_{D_1}(t)$, $V_{D_2}(t)$ and $V_{D_3}(t)$ are the volumes of three subcompartments of lethally damaged cells and $V_{N_1}(t)$, $V_{N_2}(t)$ and $V_{N_3}(t)$ are the volumes of three subcompartments of dead cells (Bertuzzi et al., 2009), (Papa, 2009); with χ and χ_D we denote the constant proliferation rates, respectively, of viable cells and of the three subcompartments of lethally damaged cells (that we suppose to progress across the cell cycle and to divide until they die), with μ_D and μ_N, respectively, the death rate of lethally damaged cells and the degradation rate of dead cells. All these dynamic parameters are positive and, since lethally damaged cells eventually die, it is necessary to assume that $\mu_D > \chi_D$. The output of the model is the total volume of the spheroid, obtained by summing the state variables:

$$y(t) = V(t) + \sum_{i=1}^{3} V_{D_i}(t) + \sum_{i=1}^{3} V_{N_i}(t)\,. \tag{2}$$

Without loss of generality, cells are assumed to occupy all the volume of the spheroid.

Considering only impulsive irradiations, both the direct action and the effect of binary misrepair will be considered instantaneous and described by a non linear relation named linear-quadratic (LQ) model (Bristow and Hill, 1987). Denoting by δ the surviving fraction of cells after a single impulsive irradiation, the LQ dose-response relation has the form:

$$\delta = e^{[-\alpha d - \beta d^2]}\,, \tag{3}$$

where d is the dose, α and β the radiosensitivity parameters related, respectively, to the direct action of radiation and to the binary misrepair of DSBs. Then the initial conditions for the basic model, according to (3), are:

$$\begin{cases} V(0^+) = e^{[-\alpha d - \beta d^2]} V(0^-)\,, \\ V_{D_1}(0^+) = (1 - e^{[-\alpha d - \beta d^2]}) V(0^-)\,, \\ V_{D_i}(0^+) = 0\,,\ \ i = 2,3\,, \\ V_{N_j}(0^+) = 0\,,\ \ j = 1,2,3\,, \end{cases} \tag{4}$$

where $V(0^-)$ is the spheroid volume before irradiation.

Equations (1), with their initial conditions (4), define a linear time-invariant dynamical system and (2) is the corresponding linear output equation.

3 PARAMETRIC IDENTIFIABILITY OF THE MODEL

There are different methods for studying the identifiability of dynamical systems. For the model presented above it has been used the similarity transformation method (Travis and Haddock, 1981), that can be only used for linear dynamical systems. In general, some parameters of a linear stationary dynamical system are not known. Therefore the similarity transformation method allows to determine the identifiability properties of system parameters when they correspond to the elements of the model matrices or when there is a univocal relationship between them. It is easy to understand, looking at the structure of the matrices given below, that a univocal relationship exists between the parameters $(\chi, \chi_D, \mu_D, \mu_N)$ and the elements of the system matrices whereas it does not happen for the radiological parameters (α, β). Considering the parameter δ, given by (3) and depending on the radiological parameters (α, β), even if it was identifiable, the parameters α and β would not be univocally determined from its value. It will be shown that α and β can be univocally identified by exploiting model responses to at least two different radiation doses.

Let us study the identifiability of the parameter vector

$$\theta = \begin{bmatrix} \chi & \chi_D & \mu_D & \mu_N & \delta \end{bmatrix}^T, \tag{5}$$

ranging in the admissible set $\Theta \subset R^5$, where

$$\Theta = \{\theta \in R^5 \mid \chi, \chi_D, \mu_D, \mu_N > 0,\ \ \mu_D > \chi_D \text{ and } 0 < \delta < 1\}\,. \tag{6}$$

Taking model equations (1) - (4) into account, let us denote by

$$x = \begin{bmatrix} V & V_{D_1} & V_{D_2} & V_{D_3} & V_{N_1} & V_{N_2} & V_{N_3} \end{bmatrix}^T \quad (7)$$

the state vector and by $A(\theta)$, $c^T(\theta)$ and $b(\theta)$ respectively the model dynamical matrix, the state-output matrix and the fraction of the initial state vector independent of the spheroid initial volume. In particular, for the elements of $A(\theta)$, $c^T(\theta)$, and $b(\theta)$ we have that:

$$\begin{cases} a_{11}(\theta) = \chi\,, \\ a_{22}(\theta) = a_{33}(\theta) = a_{44}(\theta) = \chi_D - \mu_D\,, \\ a_{55}(\theta) = a_{66}(\theta) = a_{77}(\theta) = -\mu_N\,, \\ a_{32}(\theta) = a_{43}(\theta) = a_{54}(\theta) = \mu_D\,, \\ a_{65}(\theta) = a_{76}(\theta) = \mu_N\,, \\ \text{all other elements of } A(\theta) \text{ are equal to zero}\,, \\ c_i(\theta) = 1,\ \ i = 1,\dots,7\,, \\ b_1(\theta) = \delta,\ b_2(\theta) = 1 - \delta\,, \\ b_i(\theta) = 0\,,\ i = 3,\dots,7\,. \end{cases} \quad (8)$$

Then the model (1) - (4) can be written in a compact form:

$$\begin{cases} \dot{x}(t;\theta) = A(\theta)x(t;\theta),\ \ x(0^+;\theta) = b(\theta)V(0^-), \\ y(t;\theta) = c^T(\theta)x(t;\theta). \end{cases} \quad (9)$$

It is useful to observe, at this point, that the output $y(t;\theta)$ obtained by the model (9), in which no input acts, is the same output obtainable by the following model:

$$\begin{cases} \dot{\bar{x}}(t;\theta) = A(\theta)\bar{x}(t;\theta) + b(\theta)u(t), \\ \bar{x}(0^-) = 0, \\ \bar{y}(t;\theta) = c^T(\theta)\bar{x}(t;\theta) \end{cases} \quad (10)$$

with $u(t) = u_0(t)V(0^-)$, where $u_0(t)$ is a Dirac unit pulse function. In fact:

$$y(t;\theta) = \bar{y}(t;\theta) = c^T(\theta)e^{A(\theta)t}b(\theta)V(0^-)\,. \quad (11)$$

Therefore, it is easy to understand from relation (11) that the identifiability problem of θ for the model (9) is the same one for the model (10). In particular we can talk about controllability of the couple $(A(\theta), b(\theta))$, since the role of the matrix $b(\theta)$ in the model (9) is equivalent to the one in the model (10).

The similarity transformation method is based on the following theorem (Papa, 2009):

Theorem 1 . Let the triples $(A(\theta), b(\theta), c^T(\theta))$ and $(A(\phi), b(\phi), c^T(\phi))$ be observable and controllable. Then

$$c^T(\theta)e^{A(\theta)t}b(\theta) = c^T(\phi)e^{A(\phi)t}b(\phi)\,, \quad t \in [0,T] \quad (12)$$

if and only if a nonsingular matrix P exists such that

$$\begin{cases} PA(\theta)P^{-1} = A(\phi)\,, \\ c^T(\theta)P^{-1} = c^T(\phi)\,, \\ Pb(\theta) = b(\phi)\,. \end{cases} \quad (13)$$

Proof . It is immediate to see that (13) implies (12) by taking into account the power expansion of the exponential. The inverse implication, that requires the controllability and observability properties, was proved by Kalman (Kalman, 1963), (Kalman et al., 1969).

□

From Theorem 1 it is easy to understand that given an indistinguishable couple $(\theta, \phi) \in \Theta$ for the system (9), if it exists, the corresponding system matrices, $(A(\theta), b(\theta), c^T(\theta))$ and $(A(\phi), b(\phi), c^T(\phi))$, have the same structure and are linked by the algebraic relations (13). It is easy also to see that if (13) have a unique solution (θ, I) then indistinguishable couples do not exist. So the following obvious lemma follows:

Lemma 1 . Let the triples $(A(\theta), b(\theta), c^T(\theta))$ and $(A(\phi), b(\phi), c^T(\phi))$ be observable and controllable. Then the system (9) is globally identifiable in Θ if and only if the equations (13), for all fixed vector $\theta \in \Theta$, have the unique solution $(\phi, P) = (\theta, I)$.

The observability and controllability properties of the triple $(A(\theta), b(\theta), c^T(\theta))$ of (9) have been proved by Papa (2009). Now we can prove the following result.

Theorem 2 . The model (1) - (4) is globally identifiable with respect to the unknown parameter vector θ given by (5) and ranging in the set Θ defined by (6). In fact $\forall\theta \in \Theta$ it does not exist in Θ another parameter vector ϕ that gives the same output.

Proof . Given $\theta \in \Theta$, let us consider a (1×5) vector $\phi = [\chi^* \ \chi_D^* \ \mu_D^* \ \mu_N^* \ \delta^*] \ \in \Theta$ and the (7×7) matrix P. From the first equation of (13) it is easy to obtain the following equation system:

$$\begin{aligned} &\begin{bmatrix} \mathfrak{r}_1 & \mathfrak{r}_2 & \mathfrak{r}_3 & \mathfrak{r}_4 & \mathfrak{r}_5 & \mathfrak{r}_6 & \mathfrak{r}_7 \end{bmatrix}^T = \\ &= \begin{bmatrix} \mathfrak{c}_1 & \mathfrak{c}_2 & \mathfrak{c}_3 & \mathfrak{c}_4 & \mathfrak{c}_5 & \mathfrak{c}_6 & \mathfrak{c}_7 \end{bmatrix}, \end{aligned} \quad (14)$$

where $\mathfrak{r}_i$ and $\mathfrak{c}_i$ are, respectively, a (1×7) row vector and (7×1) column vector:

$$\mathfrak{r}_i = \begin{bmatrix} p_{i1}\chi \\ p_{i2}(\chi_D - \mu_D) + p_{i3}\mu_D \\ p_{i3}(\chi_D - \mu_D) + p_{i4}\mu_D \\ p_{i4}(\chi_D - \mu_D) + p_{i5}\mu_D \\ -p_{i5}\mu_N + p_{i6}\mu_N \\ -p_{i6}\mu_N + p_{i7}\mu_N \\ -p_{i7}\mu_N \end{bmatrix}^T ,$$

$$\mathfrak{c}_i = \begin{bmatrix} p_{1i}\chi^* \\ p_{2i}(\chi_D^* - \mu_D^*) \\ p_{2i}\mu_D^* + p_{3i}(\chi_D^* - \mu_D^*) \\ p_{3i}\mu_D^* + p_{4i}(\chi_D^* - \mu_D^*) \\ p_{4i}\mu_D^* - p_{5i}\mu_N^* \\ p_{5i}\mu_N^* - p_{6i}\mu_N^* \\ p_{6i}\mu_N^* - p_{7i}\mu_N^* \end{bmatrix} , \ i = 1, \dots, 7 .$$

Furthermore, using the second and the third equation of (13) it is easy to obtain, respectively, the following relations:

$$p_{1i} + p_{2i} + \dots + p_{7i} = 1, \ \text{with} \ i = 1, \dots, 7, \tag{15}$$

$$\begin{cases} p_{11}\delta + p_{12}(1-\delta) = \delta^* , \\ p_{21}\delta + p_{22}(1-\delta) = (1-\delta^*) , \\ p_{i1}\delta + p_{i2}(1-\delta) = 0, \ \text{with} \ i = 3, \dots, 7 . \end{cases} \tag{16}$$

By solving equations (14) - (16), it can be shown that (13) admits only the trivial solution (θ, I). For details see the proof of Theorem 4 given by Papa (2009). Then, from Lemma 1, we can say that the model (1) - (4) is globally identifiable with respect to the five considered parameters. □

Theorem 2 does not establish the global identifiability of the model (1) - (4) with respect to the radiological parameters. In order to study the identifiability of the radiological parameters α and β it is necessary to consider two different doses d_1 and d_2 and the corresponding parameters δ_1 and δ_2:

$$\begin{cases} \delta_1 = e^{[-\alpha d_1 - \beta d_1^2]} , \\ \delta_2 = e^{[-\alpha d_2 - \beta d_2^2]} . \end{cases} \tag{17}$$

It is easy to verify that the relation between (δ_1, δ_2) and (α, β) is one to one if $d_1 \neq d_2$. Therefore, let us consider two different initial states $x^{(1)}(0^+;\theta)$ and $x^{(2)}(0^+;\theta)$ related to two different doses and let us observe parallely the two corresponding system responses. Let us define a new parameter vector

$$\theta = \begin{bmatrix} \chi & \chi_D & \mu_D & \mu_N & \delta_1 & \delta_2 \end{bmatrix}^T \tag{18}$$

ranging in the admissible set $\Theta \subset R^6$, where

$$\begin{aligned} \Theta = \{ \theta \in R^6 \mid \chi, \chi_D, \mu_D, \mu_N > 0, \ \mu_D > \chi_D, \\ 0 < \delta_1 < 1 \ \text{and} \ 0 < \delta_2 < 1 \} . \end{aligned} \tag{19}$$

Let us define by $x_T \in R^{14}$ the total state vector

$$x_T = \begin{bmatrix} x^{(1)} \\ x^{(2)} \end{bmatrix} , \tag{20}$$

that is the union of two state vectors of the type (7), $x^{(1)}$ and $x^{(2)}$, related to the two different initial states, and the block matrices

$$\begin{aligned} A_T(\theta) &= \begin{bmatrix} A(\theta) & 0 \\ 0 & A(\theta) \end{bmatrix} , \\ C_T(\theta) &= \begin{bmatrix} c^T(\theta) & 0 \\ 0 & c^T(\theta) \end{bmatrix} , \\ B_T(\theta) &= \begin{bmatrix} b^{(1)}(\theta) & 0 \\ 0 & b^{(2)}(\theta) \end{bmatrix} , \end{aligned} \tag{21}$$

where $A(\theta)$ and $c^T(\theta)$ are the same matrices defined in (8), $b^{(1)}(\theta)$ and $b^{(2)}(\theta)$ are such that

$$\begin{aligned} b^{(1)}(\theta) &= \begin{bmatrix} \delta_1 & (1-\delta_1) & 0 & \dots & 0 \end{bmatrix}^T , \\ b^{(2)}(\theta) &= \begin{bmatrix} \delta_2 & (1-\delta_2) & 0 & \dots & 0 \end{bmatrix}^T . \end{aligned} \tag{22}$$

Obviously, $A_T(\theta)$, $C_T(\theta)$ and $B_T(\theta)$ are, respectively, (14×14), (2×14) and (14×2) matrices and the model (1) - (4) can be written as:

$$\begin{cases} \dot{x}_T(t;\theta) = A_T(\theta) x_T(t;\theta) , \\ x_T(0^+;\theta) = B_T(\theta) \begin{pmatrix} V(0^-) \\ V(0^-) \end{pmatrix} , \\ y_T(t;\theta) = C_T(\theta) x_T(t;\theta) , \end{cases} \tag{23}$$

where $y_T(t;\theta) \in R^2$ is the union of the two outputs related to the two different initial states.

Using the observability and the controllability properties of (9), it can be easily shown that the system (23) is observable and controllable too (Papa, 2009).

Now we can prove the following result.

Theorem 3 . The model (1) - (4) is globally identifiable with respect to the unknown parameter vector θ given by (18) and ranging in the set Θ defined by (19), exploiting the outputs of the model obtained from two different radiation doses.

Proof . Given $\theta \in \Theta$, let us consider a (1×6) vector $\phi = [\chi^* \ \chi_D^* \ \mu_D^* \ \mu_N^* \ \delta_1^* \ \delta_2^*] \in \Theta$ and the (14×14) matrix P. Dividing the P matrix into four (7×7) blocks

$$P = \begin{bmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{bmatrix} \tag{24}$$

it is easy to show that from the matrix equations (13), developing the block products, the following subsystems are obtained:

$$\begin{aligned} &\begin{cases} P_{ii}A(\theta) = A(\phi)P_{ii} \\ c^T(\theta) = c^T(\phi)P_{ii} \\ P_{ii}b^{(1)}(\theta) = b^{(1)}(\phi) \end{cases} \quad \text{with } i = 1, 2 , \\ &\begin{cases} P_{ij}A(\theta) = A(\phi)P_{ij} \\ 0 = c^T(\phi)P_{ij} \\ P_{ij}b^{(2)}(\theta) = 0 \end{cases} \quad \text{with } i, j = 1, 2, \ i \neq j . \end{aligned} \tag{25}$$

The first two subsystems of (25) are similar to the one studied in the proof of theorem 1. So both the subsystems have only the trivial solution (θ, I). Therefore it results that

$$\begin{aligned} &\chi^* = \chi,\ \chi_D^* = \chi_D,\ \mu_D^* = \mu_D,\ \mu_N^* = \mu_N, \\ &\delta_1^* = \delta_1,\ \delta_2^* = \delta_2 \text{ and } P_{11} = P_{22} = I. \end{aligned} \tag{26}$$

It is simple to verify that, with the results (26), the latter two subsystems of (25) give the solutions $P_{12} = P_{21} = 0$.

Therefore we have that system (13) admits only the trivial solution (θ, I). Thus, from Lemma 1, we can say that the model (1) - (4) is globally identifiable by exploiting the model response $y_T(t;\theta)$ to at least two different doses d_1 and d_2. □

4 CONCLUDING REMARKS

In this paper we have considered a spatially uniform dynamical model of tumour growth after a single instantaneous radiative treatment. In this model the details of the spatial structure of the tumour are neglected and the attention is focused on the temporal evolution of tumour overall volume after the radiative treatment. The model can be used for different applications. For instance, to asses the efficiency of the radiotherapeutic treatment, but for this application it is necessary to identify the unknown parameters. A preliminary condition, that is necessary to verify before performing the parameter estimation, is the global identifiability of the model.

In this paper a detailed study of the identifiability properties of the model is done, pointing out that it is globally identifiable, provided that the responses to two different radiation doses are considered. This important property assures a correct formulation of the parametric identification problem. The parametric identification of the model and the corresponding validation, with respect to both the fitting and the prediction capability of the experimental data, are treated by Bertuzzi et al. (2009).

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