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MATHEMATICAL MODELLING OF A NON-NECROTIC TUMOR GROWTH. ONE COMPONENT SPHERICALLY SIMETRIC MODEL

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Abstract
A spherically symmetric model, proposed several years ago by Byrne and Chaplain for a non-necrotic vascularized tumor is reviewed. The nutrient and inhibitor are satisfying reaction-diffusion equations, while the tumor radius is determined from a very simple integro-differential equation resulting from a balance of cell proliferation and cell death. In principle the coefficients characterizing the model together with the boundary and initial conditions can be space and time dependent, but explicit calculations are done when these are constant. A special attention was given to the stationary state of the inhibitor-free model. The tumor radius is determined graphically from a very simple implicit equation, and it depends only on one parameters Λ. Stationary states exist if $\Lambda \in (\Lambda_{crit.}, 1/3)$. The model was extended assuming a space dependence (two regions, one near the surface and the rest of the tumor) for a concentration c_B of the nutrient in the vasculature. The implicit relation determining the radius is found.

The carcinogenesis is a very complex, multistage phenomenon involving the space and time evolution of a large number of variables, each with specific activity and strongly interacting between them. Therefore the mathematical modelling of a tumor evolution is a highly challenging problem at the frontier of applied mathematics. In each stage specific variables are characterizing the tumor evolution and specific mathematical models are used. Although this separation in several stages is only partial true, the mechanisms working in a previous stage being present also in the next ones, it is a convenient way to tackle the problem. As mentioned before, this approach allows to identify the main processes which are considered to be characteristic to the respective stage, and to introduce proper variables that describe them.

It is generally accepted that cancer results from the accumulation of mutations in the genes controlling the birth and death of cells. Therefore the first stage is a sub-cellular one and this

accumulation process is usually described as a somatic evolution. It can be discussed mathematically using the evolutionary game theory **Error! Reference source not found.**-**Error! Reference source not found.**. In the second stage, which can be called the cellular stage, the attention is concentrated on the proliferation of tumor cells in competition with the immune system, resulting either the inhibition and depression of the immune system, or the destruction of the tumor cells. One write kinetic equations for the distribution functions of different populations (tumor cells, environmental cells, immune cells), depending on time and on a scalar variable describing the ``ability'' of each population to perform its purpose (proliferation for tumor cells, feeding for the environmental cells, defense for the immune ones). The key point is to properly describe the interaction between these populations. Such models have been considered by several authors **Error! Reference source not found.**-**Error! Reference source not found.**.

The last stage is a macroscopic one, when the tumor cells are constituted into a macroscopic object of more or less spherical form. Over the last 30 years many such models appeared and have been discussed **Error! Reference source not found.**-**Error! Reference source not found.**. Recently a model with three types of cancerous cells, proliferating, quiescent and dead cells, was discussed by Friedman and coworkers **Error! Reference source not found.** - **Error! Reference source not found.**. The densities of each type of cells are satisfying a coupled set of reaction-diffusion equations with coefficients depending on the nutrient concentration. The nutrient concentration satisfies a diffusion equation and consequently the problem becomes nonlinear. The situation is even more complicated because the tumor boundary changes in time. In certain conditions, for spherically symmetric models a unique stationary solution exists.

In this paper we shall consider the simplest situation of a spherically symmetric model of a non necrotic tumor. It was proposed by Byrne and Chaplain **Error! Reference source not found.** and exact results were obtained by Friedman and Reitich **Error! Reference source not found.**.

One considers a spherically symmetric tumor of radius $R(t)$. Two reaction-diffusion equations are describing the distribution of the external supplied nutrient $c(t)$, and the inhibitor, $\beta(t)$, and an integro-differential equation governs the evolution of the tumor's radius. Denoting by (r,t) the spatial and temporal variables, the equation satisfied by the nutrient concentration is given by

$$\frac{\partial c}{\partial t} = \frac{D_1}{r^2}\partial\partial r\left(r^2\frac{\partial c}{\partial r}\right) + \Gamma(c_B - c) - \lambda c - g_1(c,\beta) \qquad (1)$$

The first term in the right-hand side describes the diffusion of the nutrient in the tumor region, while the second describes the nourishment by blood-tissue transfer, and his presence stems from angiogenesis (the tumor generates its own blood supply) **Error! Reference source not found.**. Here D_1 is the diffusion constant (assumed constant), c_B is the nutrient concentration in the vasculature and Γ the rate of blood-tissue transfer per unit length. For $\Gamma = 0$ we get the avascular case. The nutrient is consumed at the rate λc. The presence of the inhibitor β acts as second sink for the nutrient and it is described by the term $g_1(c,\beta)$ in the r.h.s. of (**Error! Reference source not found.**). In this model the tumor comprises only one type of proliferating cells, and due to the fact that their density is constant (no constant densities exist in the model with more species of cancerous cells), they can be eliminated from discussion. The only factors which influence the tumor growth are the supply of nutrient and inhibitor. Although in the model one assumes constant values for $D_1, \Gamma, c_B, \lambda$, this assumption can be enlarged by considering reasonable and simple spatially varying expressions for these coefficients. Actually we shall consider also a case when c_B in the proximity of the tumor surface is greater than the value inside the tumor, reflecting a greater tumor angiogenetic factor near the surface. The model describes a non-necrotic tumor, but can be used to study also the beginning of the necrotic case, assuming that this new situation is starting when the nutrient concentration decreases below a certain critical value c_N (the cancerous cells die by starvation when they are not properly nourished).

As concerns the inhibitor, it satisfies a similar reaction-diffusion equation

$$\frac{\partial \beta}{\partial t} = \frac{D_2}{r^2}\partial\partial r\left(r^2\frac{\partial \beta}{\partial r}\right) - g_2(c,\beta) \qquad (2)$$

where D_2 is the diffusion constant (usually $D_2 < D_1$) and all the sinks and sources of inhibitor are included for simplicity in the single term $g_2(c,\beta)$ (its form depends on the scenario by which the inhibitor is delivered to the tumor).

The rate of growth of the tumor depends on the number of proliferating cells inside it, whose density is a function of nutrient and inhibitor concentration. In this case of a single type of active cells inside the tumor, it is necessary to give an expression for the cell proliferating rate.

Denoting this rate by $S(c,\beta)$, the time evolution of the tumor volume (radius) is given by

$$\frac{d}{dt}\left(4\pi 3R^3\right) = 4\pi\int_{tumor} S(c,\beta)r^2 dr$$

$$\frac{dR}{dt} = 1R^2\int_0^{R(t)} S(c,\beta)r^2 dr \tag{3}$$

Several expressions for $S(c,\beta)$ can be used. Any of them have to express the balance between the creation and the death of cells. In the absence of inhibitors the simplest form is

$$S(c) = s(c-\bar{c}) \tag{4}$$

where s and $\bar{c}$ are constants. Here sc is the birth rate, proportional with the nutrient concentration , and $s\bar{c}$ is the constant death rate of the cells inside the tumor. Another expression uses a second order death rate $\frac{sc^2}{\hat{c}}$ and the following logistic expression for $S(c,\beta)$ is obtained

$$S(c) = sc\left(1-\frac{c}{\hat{c}}\right) \tag{5}$$

In (**Error! Reference source not found.**) the situation $c < \bar{c}$ is excluded (in (**Error! Reference source not found.**) $c > \hat{c}$) as being physically unrealistic. Assuming that the inhibitor acts in a similar way in reducing the proliferation rate, the expression (**Error! Reference source not found.**) can be completed with a similar linear term in β

$$S(c,\beta) = s(c-\bar{c})\left(1-\frac{\beta}{\hat{\beta}}\right) \tag{6}$$

or

$$S(c,\beta) = s(c-\bar{c})11+\beta\hat{\beta} \tag{7}$$

Similar extensions can be considered starting from the logistic expression (**Error! Reference source not found.**). In (**Error! Reference source not found.**) the situation $\beta > \hat{\beta}$ is excluded as being unrealistic.

We have to prescribe the boundary and the initial conditions. The boundary conditions are

$$\frac{\partial c(r=0,t)}{\partial r} = \frac{\partial \beta(r=0,t)}{\partial r} = 0 \tag{8}$$

$$c(R(t),t) = c_R(t), \quad \beta(R(t),t) = \beta_R(t)$$

where $c_R(t)$ and $\beta_R(t)$ are the nutrient and the inhibitor concentration at the tumor surface (usually they are taken constants, but can be also considered as depending on time in a given way), while the initial conditions are given by

$$c(r,0) = c_0(r), \quad \beta(r,0) = \beta_0(r) \tag{9}$$

$$R(0) = R_0$$

Here $c_0(r), \beta_0(r), R_0$ are known.

The last step is to give functional forms for the interaction terms g_1 and g_2. Very few experimental informations about how an inhibitor operates, are known, and insufficient to determine these expressions. Therefore several mechanisms can be considered, namely:

• inhibitor free case:

$$\beta \equiv 0, \quad g_1 = g_2 = 0, \quad S = s(c - \bar{c}); \tag{10}$$

• inhibitor affects cell proliferation rate, but not the nutrient concentration

$$g_1 = 0, \quad g_2 = \gamma_2\beta, \quad S = s(c - \bar{c})\left(1 - \frac{\beta}{\hat{\beta}}\right); \tag{11}$$

• inhibitor affects nutrient concentration but not the proliferation rate

$$g_1 = \gamma_1\beta, \quad g_2 = \gamma_2\beta, \quad S = s(c - \bar{c}) \tag{12}$$

• inhibitor affects both nutrient concentration and the cell proliferation rate

$$g_1 = \gamma_1\beta, \quad g_2 = \gamma_2\beta, \quad S = s(c - \bar{c})\left(1 - \beta\hat{\beta}\right) \tag{13}$$

These are very simple expressions depending only on the inhibitor concentration β, but other more complicated expressions can be considered.

In the process of tumor growth two time-scales can be identified. The first is related to the nutrient diffusion inside the tumor. We can define a characteristic diffusion time τ_DÇlL²D, where L is a typical length scale and D a typical diffusion coefficient. With LÇl0⁻² cm and DÇl0⁻⁶ cm² s⁻¹, we have τ_DÇlminute. The second is related to the growth rate of the tumor which is of order 0.5 mm/day. Therefore the ratio $\varepsilon = \tau_0/T$, where T is a characteristic tumor-doubling time, TÇl day, is a small quantity. It is convenient to introduce space and time dimensionless variables

$$\bar{r} = rR_0, \qquad \bar{t} = tT \tag{14}$$

We shall rescale the dependent variables and the parameters

$$\bar{c}(\bar{r},\bar{t}) = \frac{c(r,t)}{\Sigma}, \quad \bar{\beta}(\bar{r},\bar{t}) = \frac{\beta(r,t)}{B}, \quad \bar{R}(\bar{t}) = \frac{R(t)}{R_0}$$

$$\left(\bar{c}_B, \bar{\bar{c}}, \bar{c}_0, \bar{c}_R\right) = \frac{\left(c_B, \bar{c}, c_0, c_R\right)}{\Sigma}, \qquad \left(\bar{\hat{\beta}}, \bar{\beta}_0, \bar{\beta}_R\right) = \frac{\left(\hat{\beta}, \beta_0, \beta_R\right)}{B}$$

$$\bar{D} = D_2 D, \quad \bar{\Gamma} = \frac{\Gamma R_0^2}{D_1}, \quad \bar{\lambda} = \frac{\lambda R_0^2}{D_1}, \tag{15}$$

$$\bar{\gamma}_1 = \frac{\gamma_1 R_0^2 B}{D_1 \Sigma}, \quad \bar{\gamma}_2 = \frac{\gamma_2 R_0^2}{D_1}, \quad \bar{S}(\bar{c},\bar{\beta}) = S(c,\beta)T$$

Here Σ and B are typical nutrient and inhibitor concentrations(as the maximum values inside the tumor $0 < r < 1$). Dropping the bars the equations governing the tumor growth are

$$\varepsilon \frac{\partial c}{\partial t} = 1 r^2 \partial\partial r\left(r^2 \frac{\partial c}{\partial r}\right) + \Gamma(c_B - c) - \lambda c - \gamma_1 \beta$$

$$\varepsilon \frac{\partial \beta}{\partial t} = D r^2 \partial\partial r\left(r^2 \frac{\partial \beta}{\partial r}\right) - \gamma_2 \beta \tag{16}$$

$$\frac{dR}{dt} = sR^2 \int_0^R (c - \bar{c})\left(1 - \beta\hat{\beta}\right) r^2 dr$$

subjected to the following boundary and initial conditions

$$\frac{\partial c(0,t)}{\partial r} = 0 \quad c(R,t) = c_R(t) \quad c(r,0) = c_0(r)$$
$$\frac{\partial \beta(0,t)}{\partial r} = 0 \quad \beta(R,t) = \beta_R(t) \quad \beta(r,0) = \beta_0(r) \tag{17}$$
$$R(0) = 1$$

Numerical solutions have been obtained assuming different inhibitory mechanisms **Error! Reference source not found.**. The free-inhibitor simulations indicate the existence of a non-trivial stationary state. Further on we shall discuss only this situation **Error! Reference source not found.**,**Error! Reference source not found.**. In this case $\beta \equiv 0, S(c,\beta) = s(c - \bar{c})$, and the set of equations (**Error! Reference source not found.**), (**Error! Reference source not found.**) becomes

$$1 r^2 \frac{d}{dr}\left(r^2 \frac{dc}{dr}\right) + \Gamma(c_B - c) - \lambda c = 0$$

$$\frac{dc(0)}{dr} = 0, \qquad c(R) = c_R \tag{18}$$

Here we assume a constant nutrient concentration at the tumor boundary, and a constant c_B value inside the tumor. Denoting

$$c(r) = \frac{\Gamma c_B}{\Gamma + \lambda} + y(r), \qquad c_R = \frac{\Gamma c_B}{\Gamma + \lambda} + y_R \tag{19}$$

the eqs (**Error! Reference source not found.**) can be written

$$1r^2 \frac{d}{dr}\left(r^2 \frac{dy}{dr} \right) - (\Gamma + \lambda) y = 0 \tag{20}$$

$$\frac{dy(0)}{dr} = 0, \qquad y(R) = y_R$$

whose solution is

$$y(r) = y_R \frac{R}{\sinh\left(R\sqrt{\Gamma + \lambda}\right)} \frac{\sinh\left(r\sqrt{\Gamma + \lambda}\right)}{r} \tag{21}$$

From the last eq (**Error! Reference source not found.**), as $dR/dt \equiv 0$, we obtain

$$\int_0^R c(r) r^2 dr = 13\bar{c}R^3 \tag{22}$$

and using (**Error! Reference source not found.**) and (**Error! Reference source not found.**) one gets

$$13\left(\bar{c} - \frac{\Gamma c_B}{\Gamma + \lambda} \right) R^2 = \left(c_R - \frac{\Gamma c_B}{\Gamma + \lambda} \right) \left\{ R\sqrt{\Gamma + \lambda} \coth(R\sqrt{\Gamma + \lambda}) - 1\Gamma + \lambda \right\}$$

Denoting

$$\Lambda = 13 \frac{(\Gamma + \lambda)\bar{c} - \Gamma c_B}{(\Gamma + \lambda) c_R - \Gamma c_B}, \quad \eta = R\sqrt{\Gamma + \lambda} \tag{23}$$

the value of the tumor radius is determined by the implicit equation

$$\tanh \eta = \frac{\eta}{1 + \Lambda \eta^2} \tag{24}$$

In order to have a positive Λ, the coefficient c_B has to satisfy the inequality

$$\frac{\Gamma}{\Gamma + \lambda} c_B < \bar{c} < c_R \tag{25}$$

the last inequality being a reasonable assumption. Then from the definition (**Error! Reference source not found.**) of Λ, we have

$$0 < \Lambda < 13 \tag{26}$$

and in this case eq. (**Error! Reference source not found.**) has a unique solution which can be obtained graphically **Error! Reference source not found.**. As mentioned previously a necrotic stage starts to develop when the nutrient concentration lowers below a certain value c_N. As this case happens for $r \to 0$, using (**Error! Reference source not found.**) and (**Error! Reference source not found.**) another restriction results, namely

$$c_N < \frac{\Gamma c_B}{\Gamma + \lambda} + \left(c_R - \frac{\Gamma c_B}{\Gamma + \lambda} \right) \frac{\eta}{\sinh \eta} \tag{27}$$

where η is the solution of (**Error! Reference source not found.**).

Now we shall extend the present model relaxing the assumption of a constant c_B inside the tumor. We shall assume that near the tumor boundary in a layer of thickness δ, c_B is greater than in the rest of the tumor

$$c_B(r) = \begin{cases} c_B(1+\Delta), & R - \delta < r < R c_B, \\ r < R - \delta \end{cases} \tag{28}$$

This is corresponding to a greater tumor angiogenesis factor in the outer region of the tumor. The solution of (**Error! Reference source not found.**) in the first region $r < R - \delta$ is of the form

$$c(r) = \frac{\Gamma c_B}{\Gamma + \lambda} + K \frac{\sinh(r\sqrt{\Gamma + \lambda})}{r} \tag{29}$$

Here we used only the condition $\frac{dc(0)}{dr} = 0$, and K is an integration constant to be determined from the matching conditions at the boundary between the two regions. In the second region $R(1-\delta) < r < R$, the solution of (**Error! Reference source not found.**) is

$$c(r) = \frac{\Gamma c_B (1+\Delta)}{\Gamma + \lambda} + K_1 2 \frac{\exp\left(-r\sqrt{\Gamma + \lambda}\right)}{r} + K_2 2 \frac{\exp\left(+r\sqrt{\Gamma + \lambda}\right)}{r} \tag{30}$$

with K_1 and K_2 two integration constants to be determined from the boundary condition $c(R) = c_R$ and the matching conditions at the boundary between the two regions. The first condition gives

$$c_R - \frac{\Gamma c_B}{\Gamma + \lambda}(1+\Delta) = 12R\left(K_1 \mathrm{e}^{-R\sqrt{\Gamma+\lambda}} + K_2 \mathrm{e}^{R\sqrt{\Gamma+\lambda}}\right) \tag{31}$$

From the continuity of the solution $c(r)$ and its derivative $\frac{dc(r)}{dr}$ at the point $r = R - \delta$ one obtains

$$-12(K+K_1)\frac{\mathrm{e}^{-(R-\delta)\sqrt{\Gamma+\lambda}}}{R-\delta}+12(K-K_2)\frac{\mathrm{e}^{(R-\delta)\sqrt{\Gamma+\lambda}}}{R-\delta}=\Gamma c_B\Gamma+\lambda\Delta \tag{32}$$

and

$$12(K+K_1)\sqrt{\Gamma+\lambda}\,\frac{\mathrm{e}^{-(R-\delta)\sqrt{\Gamma+\lambda}}}{R-\delta}+12(K-K_2)\sqrt{\Gamma+\lambda}\,\frac{\mathrm{e}^{(R-\delta)\sqrt{\Gamma+\lambda}}}{R-\delta}= \tag{33}$$

$$=-12(K+K_1)\frac{\mathrm{e}^{-(R-\delta)\sqrt{\Gamma+\lambda}}}{(R-\delta)^2}+12(K-K_2)\sqrt{\Gamma+\lambda}\,\frac{\mathrm{e}^{-(R-\delta)\sqrt{\Gamma+\lambda}}}{(R-\delta)^2}$$

The equations (**Error! Reference source not found.**) - ((33)) represent a linear system from which constants K, K_1 and K_2 are completely determined. Using the solutions (**Error! Reference source not found.**) and (**Error! Reference source not found.**), the relation (**Error! Reference source not found.**) becomes

$$K\int_0^{R-\delta} r\sinh(r\sqrt{\Gamma+\lambda})dr+K_1 2\int_{R-\delta}^{R} r\,\mathrm{e}^{-r\sqrt{\Gamma+\lambda}}dr+K_2 2\int_{R-\delta}^{R} r\,\mathrm{e}^{r\sqrt{\Gamma+\lambda}}dr= \tag{34}$$

$$=13\left[\bar{c}-(1+\Delta)\frac{\Gamma c_B}{\Gamma+\lambda}\right]R^3+13\Delta\frac{\Gamma c_B}{\Gamma+\lambda}(R-\delta)^3$$

The integrals in the r.h.s of (**Error! Reference source not found.**) are straightforward and the following relation results

$$\begin{aligned}
&K\frac{R-\delta}{\sqrt{\Gamma+\lambda}}\cosh\left[(R-\delta)\sqrt{\Gamma+\lambda}\right]-K\Gamma+\lambda\sinh\left[(R-\delta)\sqrt{\Gamma+\lambda}\right]-\\
&-K_1 2\sqrt{\Gamma+\lambda}\left(R\,\mathrm{e}^{-R\sqrt{\Gamma+\lambda}}-(R-\delta)\,\mathrm{e}^{-(R-\delta)\sqrt{\Gamma+\lambda}}\right)+\\
&+K_2 2\sqrt{\Gamma+\lambda}\left(R\,\mathrm{e}^{R\sqrt{\Gamma+\lambda}}-(R-\delta)\,\mathrm{e}^{(R-\delta)\sqrt{\Gamma+\lambda}}\right)+\\
&+K_1 2(\Gamma+\lambda)\,\mathrm{e}^{-R\sqrt{\Gamma+\lambda}}\left(\mathrm{e}^{\delta\sqrt{\Gamma+\lambda}}-1\right)-\\
&-K_2 2(\Gamma+\lambda)\,\mathrm{e}^{R\sqrt{\Gamma+\lambda}}\left(1-\mathrm{e}^{-\delta\sqrt{\Gamma+\lambda}}\right)=\\
&=13\left(\bar{c}-\frac{\Gamma c_B}{\Gamma+\lambda}\right)R^3-13\Delta\frac{\Gamma c_B}{\Gamma+\lambda}\left[R^3-(R-\delta)^3\right].
\end{aligned} \tag{35}$$

With the constants K, K_1, K_2 determined from (**Error! Reference source not found.**)-

((33)), the equation (**Error! Reference source not found.**) is an implicit relation giving the tumor radius (and the conditions which have to be satisfied by the constants $\bar{c}, c_R, c_B$, Γ, λ, Δ, δ in order to have a stationary solution). The analysis is much more complex and work on this direction is in progress.

The model besides its simplicity has the merit to introduce in a simple way a feeding mechanism by a blood-tissue transfer, not only via diffusion. Also the influence of inhibitors is considered in a very simple and natural way. The reaction-diffusion equations governing the space and time evolution of the nutrient and inhibitor and the equation giving the rate of growth of the spherically symmetric tumor are simple enough and numerical simulations can be done. A special attention was given to the stationary state, when an analytical solution is easily found for an inhibitor free model. A free- inhibitor model with a nutrient concentration c_B in the vasculature near the surface different from the value inside the tumor was also considered. This case arises from a higher tumor angiogenesis factor at the surface of an aggressive tumor. More improved models will be considered in the future.

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