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## MATHEMATICAL MODELLING OF TUMOR GROWTH

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*Abstract.* The carcinogenesis is a very complex multistage phenomenon, including a large number of variables with specific activities and interacting between them. This review intends to present very briefly the main stages in a tumor evolution. A model with three types of cells (proliferating, quiescent and dead cells) in a macroscopic tumor is presented in more detail. Their densities are satisfying partially differential equations of reaction-diffusion type, with coefficients depending on the nutrient concentration. The space and time evolution of the nutrient is governed by a diffusion equation. Free boundary conditions have to be considered, as the tumor radius is changing in time. For the very simplified model of a single component, the stationary state and the tumor radius are explicitly calculated.

*Key words:* mathematical physics, tumor modelling.

The revolution in the natural sciences, seen in the last two centuries, was in great extend based on the use of mathematics as a powerful tool to describe natural phenomena. The situation is very different in life sciences which are mostly based on experiments and a heuristic interpretation of experimental data. But the last decades of the 20th century have seen an emerging new trend of mathematical formalization of life sciences and many people are thinking that a similar revolution in living matter will take place in the next future.

There are several reasons why such a mathematical formalization is much more difficult. First, the living matter is characterized by essentially new properties like *survival, reproduction, functionality, purpose* and it is not clear and easy to find mathematical objects to describe them. Then, the complexity of living systems is several orders higher than that of the inert matter. For instance, even in a single cell we have millions of objects, each containing

thousands of different components, each with its specific activity, and all in interaction. Moreover we have to take into account the nonlinear character of these interactions, and the fact that biological systems are open systems for which the interaction with the surrounding medium plays an essential role. All these complete the image of the difficulties which a mathematical description of biological systems has to overcome. Progress in this direction requires a joined intellectual effort of multidisciplinary groups of mathematicians, physicists, chemists collaborating closely with biologists and clinicians. It is expected that mathematical modelling will be a useful testing tool to systemize the experimental facts. Iterating back and forth between experiment and theory, the models will become more and more realistic, leading to a deeper understanding of biological processes.

The cancer modelling is a highly challenging problem at the frontier of applied mathematics. The carcinogenesis is a very complex multi-step phenomenon. In each step, different variables are used to discuss the processes which are taking place, and consequently different mathematical models and tools are used. Although this separation in several steps of a tumor evolution is not very exact, processes present in the first stages being active also in the next ones, each step characterizes a certain stage of evolution and is described by specific quantities and interactions. Many such models were considered by several authors [1–11] (the list includes some review articles where more details can be found) having a more or less level of generality. Some authors are considering that a new branch of applied mathematics has born, MATHEMATICAL ONCOLOGY.

The first step is a sub-cellular one. It is generally accepted that cancer results from the accumulation of mutations in the genes that control cell birth and death [12, 11], although the specific mechanisms through which these mutations are produced are still under debate. This accumulation process is often described as *somatic evolution* and can be discussed using *evolutionary game theory*. Carcinogenesis is the result of some combinations of intracellular and micro environmental processes. Very briefly, one assumes that in a given tissue volume  $n_S$  cellular phenotypes can exist, comprising extent populations as well as other populations obtained from temporary or permanent gene mutations. Each population consists of  $x_i$  individuals using strategies  $u_i$ ,  $i = 1, \dots, n_S$ . We can define a population vector  $\vec{x}_i$  and a mean strategy vector  $\vec{u}$

$$\vec{x} = (x_1, \dots, x_S), \quad \vec{u} = (u_1, \dots, u_S).$$

The time evolutions of  $x_i(t)$  is governed by a differential equation

$$\frac{dx_i}{dt} = x_i G(v, \vec{u}, \vec{x}, R) \Big|_{v=u_i}, \quad (1)$$

where  $v$  is a virtual variable (equal to  $u_i$  for  $x_i$ ) and  $R(t)$  a quantity describing the substrate dynamics. In (1),  $G$  is a fitness generating function and the crucial point of the model is the determination of this function. Such a model is discussed in [11] and several results can be drawn concerning the dynamics of carcinogenesis, depending on phenotypic diversity and environmental conditions.

In the second stage, the cellular stage, the attention is focused on the proliferation of tumor cells in competition with the immune system, resulting either the destruction of tumor cells or the inhibition and depression of the immune system. No dependence on spatial variables is considered. In order to describe the evolution of a large number of cells we have to use kinetic equations for distribution functions. Denoting by  $f_i(t, u)$  the distribution function for the  $i$ -th population, it depends on the time  $t$  and on a scalar variable  $u$ , having a different meaning for each population, and indicating the level of ability to perform its purpose. For instance, considering three kinds of interacting populations, tumor cells, immune cells and environmental cells, for each of them  $u$  represents:

- $i = 1$ , tumor cells:  $u$  corresponds to proliferation;
- $i = 2$ , environmental cells:  $u$  corresponds to feeding ability;
- $i = 3$ , immune cells:  $u$  corresponds to defense ability.

A model with  $n > 3$  populations can arise from a division of the immune system into  $i = 3$  – polymorphonuclear leukocytes,  $i = 4$  – lymphocytes,  $i = 5$  – macrophages. The scalar  $u \in (0, \infty)$  and a small value of  $u$  for any population  $i$  corresponding to a weak value of its activity. The time evolution of each  $f_i$  is described by a kinetic equation [7, 13, 14]

$$\begin{aligned} \frac{\partial f_i(t, u)}{\partial t} + \frac{\partial}{\partial \varphi} \left\{ f_i(t, u) \sum_{k=1}^3 \int_0^\infty \varphi_{ik}(u, w) f_k(t, w) dw \right\} &= \quad (2) \\ &= f_i(t, u) \sum_{k=1}^3 \int_0^\infty \Psi_{ik}(u, w) f_k(t, w) dw. \end{aligned}$$

Here  $\varphi_{ik}(u, w)$  and  $\Psi_{ik}(u, w)$  describe the interaction between the population  $i$  in the state  $u$  and the population  $k$  in the state  $w$  (sometimes it is necessary to extend the integration over negative values of  $w$ ; a negative value corresponds to a negative activity – destruction). The two interacting terms in (2) are corresponding to conservative action, which modifies the state of the particles, but not their number, and a non-conservative action which generates birth or death processes. The key point is the determination of the functions  $\varphi_{ik}$  and  $\Psi_{ik}$  to describe adequately the interaction process between the populations.

After this very brief introduction into the problem of the first two stages, let us consider in more detail the last one, the macroscopic stage. This corresponds to the situation when the tumor cells are condensed into a macroscopic object of more or less a spherical form. The phenomena occurring in this stage can be described using the language of continuum systems, and the models are generally stated in terms of partial differential equations of parabolic type [1-9]. In the following we shall give the main ideas of such a model developed by Friedman and coworkers [8, 9, 4, 15, 16].

We consider an existing macroscopic tumor and denote by  $\Omega(t)$  and  $\partial\Omega(t)$  its volume and surface respectively. Inside the tumor the cells are in a living state or in a necrotic state, and the living cells can be in a proliferating or a quiescent state. We denote by  $P, Q$  and  $D$  the corresponding densities of proliferating, quiescent and dead cells, and we assume that the total density of cells in the volume  $\Omega$  is constant

$$P + Q + D = N = \text{const.} \quad (3)$$

These densities are time depending due to several processes, schematically represented in Fig. 1. Here different  $K_S$  are rate coefficients, governing the

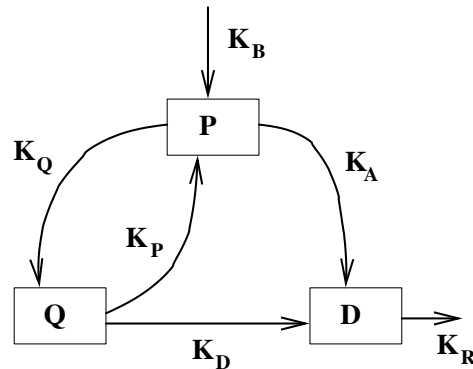


Fig. 1 – Rate diagram of  $P, Q, D$  changes for  $M_3$  model.

time evolution of different populations, and it is assumed to depend only on the nutrient concentration (only one component), denoted in the followings by  $C$ . The variation of  $P$  is due to the birth of cells from outside the volume  $\Omega$  (coeff.  $K_B$ ), to the dying mechanism by apoptosis (coeff.  $K_A$ ), to the transformation of  $Q$  cells into  $P$  cells (coeff.  $K_P$ ) and vice versa (coeff.  $K_Q$ ). The variation of  $Q$  is due to  $Q \rightarrow P$  mechanism mentioned above and to a dying mechanism (coeff.  $K_D$ ) partially through apoptosis but mainly through starvation. The variation of  $D$  is given by the  $P \rightarrow D$  and  $Q \rightarrow D$  mechanisms already discussed and to a mechanism by which the dead cells are removed

from the volume (coeff.  $K_R$ ). The rate coefficients are functions of the nutrient concentration except  $K_R$  which is independent. The general trend of this dependence is:

- $K_B, K_P$  are increasing when  $C$  increases;
- $K_A, K_D, K_Q$  are decreasing when  $C$  increases.

The simplest dependence is a linear one

$$\begin{aligned} K_A &= k_A(C_0 - C), & K_B &= k_B C, & K_D &= k_D(C_0 - C), \\ K_P &= k_P C, & K_Q &= k_Q(C_0 - C), \end{aligned} \quad (4)$$

where  $C_0$  is the value of  $C$  on  $\partial\Omega$ . More complicated dependences can be considered, but with the same monotonic behavior on  $C$ .

As regards the concentration, it satisfies a diffusion equation

$$\varepsilon_0 \frac{\partial C}{\partial t} = \nabla^2 C - \lambda C, \quad (5)$$

where  $\varepsilon_0$  is a small parameter, given by the ratio  $T_{diff}/T_{growth}$ . Here  $T_{diff}$  is a characteristic time for the diffusion process (of magnitude of 1 minute), while  $T_{growth}$  a characteristic time for the tumor growth (of order of 1 day) ( $\varepsilon_0 \sim 10^{-3}$ ). The continuous motion in the tumor is described by a vector field  $\vec{v}$ , which satisfies Darcy's law

$$\vec{v} = \nabla \sigma, \quad (6)$$

$\sigma$  being the inside pressure. On the surface it is determined by the surface tension  $\gamma$  and the curvature of the surface ( $\kappa$  the mean curvature)

$$\sigma = \gamma \kappa \quad \text{on } \partial\Omega. \quad (7)$$

Using scaled quantities

$$p = \frac{P}{N}, \quad q = \frac{Q}{N}, \quad d = \frac{D}{N}$$

the dead cells can be removed from the discussion because  $p + q + d = 1$ . Assuming  $C_0$  constant on the surface  $\partial\Omega$ , we can scale also the nutrient concentration ( $\frac{C_0}{C}$ ) and because  $\varepsilon_0 \ll 1$  we shall consider  $\varepsilon_0 = 0$ . Then the equations describing the tumor evolution are

$$\nabla^2 c - \lambda c = 0, \quad (8)$$

$$c = 1 \quad \text{on } \partial\Omega,$$

$$\frac{\partial p}{\partial t} + \operatorname{div}(p \nabla \sigma) = [K_B - K_Q - K_A] p + K_P q, \quad (9)$$

$$\frac{\partial q}{\partial t} + \operatorname{div}(q \nabla \sigma) = K_Q p - [K_P + K_D] q,$$

$$\nabla^2 \sigma = -K_R + [K_B + K_R] p + K_R q. \quad (10)$$

The motion of the free boundary is given by

$$\frac{\partial \sigma}{\partial n} = V_n, \quad \text{on } \partial\Omega, \quad (11)$$

where  $\vec{n}$  is the outward normal and  $V_n$  the velocity of the free boundary on the normal direction. Writing the surface equation as

$$\Phi(x, t) = 0 \quad \text{with } \nabla_x \Phi \neq 0$$

the relation (11) becomes

$$\frac{\partial \sigma}{\partial n} = \frac{\Phi_t}{|\Phi_x|}, \quad \text{on } \partial\Omega. \quad (12)$$

The set of equations (8)–(12) represents a complicated system of coupled non-linear equations (a free boundary  $M_3$  elliptic-hyperbolic problem) for which very few results are known (see [9]).

The  $M_3$  model can be simplified assuming that the removal rate is very large so that dead cells are instantly eliminated. Then  $p + q = 1$  and the  $q$  variable can be also eliminated from the equations. Taking also  $K_A = 0$  there remain the equations (8) and

$$\frac{\partial p}{\partial t} + \nabla \sigma \nabla p = K_P + [K_M - K_N]p + K_M p^2, \quad (13)$$

where

$$K_M = K_B + K_D, \quad K_N = K_P + K_Q \quad (14)$$

and

$$\nabla^2 \sigma = -K_D + K_M p. \quad (15)$$

The boundary conditions on  $\partial\Omega$  remain unchanged (Eqs. (7) and (11)). To these we have to add the initial condition  $p(x, 0) = p_0(x)$  in  $\Omega(0)$ , with  $\Omega(0)$  given. For a spherically symmetric  $M_2$  problem, denoting

$$\vec{v} = \frac{\vec{r}}{r} u(r, t) \quad (16)$$

the equations (8) become

$$\begin{aligned} c'' + \frac{2}{r} c' &= \lambda c, \quad 0 < r < R(t), \\ c'(0, t) &= 0, \quad c(R(t)) = 1, \end{aligned} \quad (17)$$

and equation (13) writes

$$\frac{\partial p}{\partial t} + u \frac{\partial p}{\partial r} = K_P + [K_M - K_N]p + K_M p^2. \quad (18)$$

For  $u(r, t)$ , using the relation (6) between the pressure  $\sigma$  and the velocity field  $\vec{v}$ , one obtains

$$\frac{\partial u}{\partial r} + \frac{2}{r} u = -K_D + K_M p, \quad u(0, t) = 0. \quad (19)$$

The time evolution of the tumor radius is given by the implicit equation

$$\frac{dR(t)}{dt} = u(R(t), t). \quad (20)$$

For this spherically symmetric  $M_2$  model, it has been proved [17] the existence of a unique stationary solution if the following inequality is satisfied

$$K'_B(c) + K'_D(c) > 0. \quad (21)$$

Assuming that all the cells are proliferating, we get the simplest model  $M_1$ . As  $p = 1$ , the only variable is the nutrient concentration and to study its time evolution we have to work with the general diffusion equation (5) and the corresponding equation for the pressure.

A spherically symmetric  $M_1$  model was studied in [8]. The nutrient concentration in the tumor satisfies the equation

$$\varepsilon_0 \frac{\partial c}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r} \left( r^2 \frac{\partial c}{\partial r} \right) + \Gamma(c_B - c) - \lambda_0 c, \quad 0 < r < R(t), \quad (22)$$

where we denoted by  $c_B$  the nutrient concentration in the vasculature,  $\Gamma$  is the ratio of blood-tissue transfer per unit length so that  $\Gamma(c_B - c)$  represents the transfer of nutrient by means of vasculature, and  $\lambda_0 c$  is the nutrient consumption rate. The external nutrient concentration is assumed constant (boundary condition)

$$c = c_0, \quad \text{on } r = R(t).$$

An expression for the rate of tumor growth is given by

$$\frac{d}{dt} \left( \frac{4\pi}{3} R^3(t) \right) = \iint \sin \theta \, d\theta \, d\varphi \int_0^{R(t)} S(c) r^2 \, dr, \quad (23)$$

where  $S(c)$  is the cell proliferating rate within the tumor

$$S(c) = \mu(c - c_A) \quad (24)$$

$\mu c$  being the cell birth rate and  $\mu c_A$  the death rate. With the change of variable

$$c - \frac{\Gamma c_B}{\Gamma + \lambda_0} \rightarrow c \quad (25)$$

and denoting

$$\lambda = \Gamma + \lambda_0, \quad c_A - \frac{\Gamma c_B}{\Gamma + \lambda_0} = \bar{c}_A, \quad c_0 - \frac{\Gamma c_B}{\Gamma + \lambda_0} = \bar{c}, \quad (26)$$

we get

$$\begin{aligned} \varepsilon_0 \frac{\partial c}{\partial t} &= \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial c}{\partial r} \right) - \lambda c, \quad 0 < r < R(t) \\ c &= \bar{c} \quad \text{on } r = R(t) \\ \frac{1}{\Gamma} R^2 \frac{dR}{dt} &= \int_0^{R(t)} (c - \bar{c}_A) r^2 \, dr, \end{aligned} \quad (27)$$

which has to be solved with the initial conditions

$$c(r, 0) = f(r), \quad \left( \frac{\partial c(r, 0)}{\partial r} \right)_{r=0} = 0. \quad (28)$$

It was proved [8] that for  $\varepsilon_0$  sufficiently small,  $R(t)$  is uniformly bounded and  $R(t) \rightarrow R_0$  exponentially as  $t \rightarrow \infty$ . The stationary solution is, globally, asymptotic stable and satisfies the equation

$$\frac{d^2 c}{dr^2} + \frac{2}{r} \frac{dc}{dr} - \lambda c = 0$$

and, taking the boundary conditions into account, has the form

$$c_S(r) = \bar{c} \frac{R_0}{\sinh \sqrt{\lambda} R_0} \frac{\sinh \sqrt{\lambda} r}{r}.$$

The value of  $R_0$  can be easily found from (23), namely

$$\frac{1}{3} \bar{c}_A R_0^3 = \int_0^{R_0} c_S(r) r^2 dr,$$

with  $c_S(r)$  given by the previous expression. The integration is straightforward. Introducing the notation

$$\eta = \sqrt{\lambda} R_0, \quad \Lambda = \frac{1}{3} \frac{\bar{\sigma}_A}{\bar{\sigma}}, \quad 0 < \Lambda < \frac{1}{3}$$

the value of  $R_0$  is found from the implicit relation

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

The only parameter which determines the tumor radius  $R_0$  is  $\Lambda$ . One sees that for  $\Lambda \rightarrow \frac{1}{3}$ ,  $\eta \rightarrow 0$ .

Few remarks are necessary at the end of this review. Due to the great complexity of carcinogenesis phenomenon any review has to select and present only few aspects of the problem. Moreover, the mathematical models are reflecting the reality only in an approximate way. Therefore, their results have to be carefully scrutinized to eliminate any artifacts not compatible with the experimental situation. But at the same time, they can be used to perform (numerical) *experiments* that are impractical in laboratory conditions. In the present review we focused mainly on few models used to describe the evolution of a macroscopic tumor. It would be very interesting to enlarge and optimize these models in order to include in a better way the activity of the immune system, or the angiogenesis phenomena. The effort to find analytical solutions has to be completed with numerical simulations. It is quite generally accepted that this new branch of applied mathematics, the mathematical oncology, will contribute to a better understanding of the carcinogenesis phenomenon, with the ultimate goal of modelling and optimize the therapeutical actions.

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