Energetic model of tumor growth

Paolo Castorina$^1$ and Dario Zappalà$^1$

$^1$INFN, Sezione di Catania, and Dept. of Physics, University of Catania,
Via S. Sofia 64, I-95123, Catania, Italy

(Dated: December 1, 2013)

Abstract

A macroscopic model of the tumor Gompertzian growth is proposed. This approach is based on the energetic balance among the different cell activities, described by methods of statistical mechanics and related to the growth inhibitor factors. The model is successfully applied to the multicellular tumor spheroid data.
I. INTRODUCTION

A microscopic model of tumor growth in vivo is still an open problem. However, in spite of the large set of potential parameters due to the variety of the in situ conditions, tumors have a peculiar growth pattern that is generally described by a Gompertzian curve \[1\], often considered as a pure phenomenological fit of the data. More precisely there is an initial exponential growth (until 1-3 mm in diameter) followed by the vascular Gompertzian phase\[2\]. Then it seems reasonable to think that cancer growth follows a general pattern that one can hope to describe by macroscopic variables and following this line of research, for example, the universal model proposed in \[3\] has been recently applied to cancer\[4\]. In this talk we present a macroscopic model of tumor growth, proposed in \[5\], that: i) gives an energetic basis to the Gompertzian law; ii) clearly distinguishes between the general evolution patterns, which include the internal feedback effects, and the external constraints; iii) can give indications on the different tumor phases during its evolution. The proposed macroscopic approach is not in competition with microscopic models \[6\], but it is a complementary instrument for the description of the tumor growth.

II. CELLULAR ENERGETIC BALANCE AND GOMPERTZIAN GROWTH

The Gompertzian curve is solution of the equation

\[
\frac{dN}{dt} = N \gamma \ln \left( \frac{N_{\text{max}}}{N} \right)
\]

where \(N(t)\) is the cell number at time \(t\), \(\gamma\) is a constant and \(N_{\text{max}}\) is the theoretical saturation value for \(t \to \infty\).

It is quite natural to identify the right hand side of Eq. (1) as the number of proliferating cells at time \(t\) and then to consider \(f_p(N) = \gamma \ln \left( \frac{N_{\text{max}}}{N} \right)\) as the fraction of proliferating cells and \(1 - f_p(N) = f_{np}\) the fraction of non proliferating cells. Since \(f_p(N)\) depends on \(N(t)\), there is a feedback mechanism usually described by introducing some growth inhibitor factors which increase with the number of non-proliferating cells and are responsible for the saturation of the tumor size. The concentration of inhibitor factors should be proportional to the number of non-proliferating cells which is maximum at \(N = N_{\text{max}}\) \[7\]. If one considers that, during the growth, each cell shares out its available energy at time \(t\), in the average, among its metabolic activities, the mechanical work (associated with the change of the
tumor size and shape) and the increase of the number of cells, it is conceivable to translate
the previous cellular feedback effect in terms of energy content. Indeed, as shown in [5], the
specific energy for the growth should be proportional to $f_{np}$ and the average metabolic plus
mechanical energy per cell, $M_e$, is proportional to $f_p$. As we shall see this reproduces the
observed cellular feedback.

The model [5], based on an analogy with statistical mechanics, assumes that in a larger
system $B$, the body, there is a subsystem $A$, the tumor, made of $N(t)$ cells at time $t$, with
total energy $U$, which has specific distributive mechanisms for providing, in the average,
the amount of energy $U/N$ to each cell. Then we indicate with $E_M$ the energy needed
for the metabolic activities of $A$, with $\Omega$ the energy associated with the mechanical work
required for any change of size and shape of $A$, and with $\mu$ the specific energy (i.e. per
cell) correlated to the change in the number of cells $N$, and, by assuming that these three
processes summarize the whole cellular activity, we have $U = E_M + \Omega + \mu N$. Let us assume
that the system $A$ slowly evolves through states of equilibrium with the system $B$, defined
by macroscopic variables, analogous for instance to the inverse temperature $\beta$, that have the
same value for the two systems, although it should be clear that in our case we do not have
real thermodynamical equilibrium because the system $B$ supplies the global energy for the
slow evolution of the subsystem $A$. Within this scheme, there are many microscopic states
of the system $A$, compatible with the macroscopic state, defined by $\beta$, $\mu$ and $V$, which are
built by a large number of states of each single cell. These microscopic states of each cell
have minimum total energy $\epsilon$ and in an extremely simplified picture, we assume an energy
spectrum of the form $\epsilon_l = \epsilon + l\delta$, where $l$ is an integer and $\delta$ is the minimum energy gap
between two states. With this spectrum the grand partition function $Z$ is given by the
following product $Z(\beta, V, \mu) = \prod_{l=0}^{\infty} \exp \left( e^{-\beta(\epsilon_l-\mu)} \right)$ and the corresponding grand potential,
which is natural to associate to the energy $\Omega$ related to the mechanical work in our problem,
is given by $\Omega(\beta, V, \mu) = -(R/\beta) \exp[-\beta(\epsilon - \mu)]$ where $R = 1/(1-e^{-\beta\delta})$. The average value
of $N$, defined for constant $V$ and $\beta$, turns out to be $N = -\beta\Omega$. According to the basic rules
of statistical mechanics, the product of the “entropy times the temperature”, which in our
system corresponds to $E_M$ introduced above, is

$$E_M = \left( \frac{\partial \Omega}{\partial \beta} \right)_{V,\mu} = \frac{N}{\beta} \left( 1 + C + \ln \left( \frac{R}{N} \right) \right)$$

(2)

where $C$ is given by $C = R\beta\delta \exp(-\beta\delta)$. From the previous equations it is straightforward
to express $\mu$ in terms of $N$ : $\mu = \epsilon + (1/\beta)\ln(N/R)$.

To find the evolution of the system $A$ which takes into account the internal feedback mechanism we recall some results obtained in [5] :

1. the energetic balance requires that the growth with cellular feedback starts at a minimum number of cells $N_m$ and saturates at a maximum value, $N_{\text{max}}$ related by $N_{\text{max}} = N_m\exp(1 + \beta\epsilon)$.

2. For $N_m \gg 1$, $M_e = E_M/N + \Omega/N = (1/\beta)\ln(N_{\text{max}}/N)$ is a decreasing function of $N > N_m$ and there is a simultaneous reduction of the total metabolic energy per cell and an increase of specific energy required for the growth: there is an energetic balance between $M_e$ and $\mu = (1/\beta)(1 + \beta\epsilon + \ln(N/N_{\text{max}}))$. Moreover $M_e$ is proportional to $f_p(t)$.

Then it is possible to derive the Gompertz equation for the growth, $\Delta N$ in an interval $\Delta t$. $\Delta N$ is proportional to the number of proliferating cells and then one can write $\Delta N = c_1 \Delta t f_p(t)N = c_2 \Delta t M_e N$ where $c_1$ and $c_2$ are constants. This gives in the continuum limit Eq. (1) with $\gamma = c_2/\beta$.

III. APPLICATION TO MULTICELLULAR TUMOR SPHEROIDS

The first step to analyze the phenomenological implications of the model and to describe the dependence of the growth on the external conditions is to consider the multicellular tumor spheroids (MTS). A minimal MTS description consists of a spherical growth where a) the thickness, $k$, of the layer where the nutrient and oxygen is delivered (the crust) is independent on the spheroid radius $R$; b) the cell density is constant; c) the cells in the crust, receive a constant supply of nutrient for cell; d) at time $t$ the cells are non proliferating if they are at distances $d < R - k$ if $R > k$ from the center of the spheroid. For $R < k$ all cells are proliferating.

To separate the effects of the external constraints due to energy supply from those related to biomechanical conditions, it is better to consider first the MTS growth without external and internal stress and to introduce later these effects.
A. Energetic MTS growth

In this case the external conditions are experimentally modified by changing the oxygen and nutrient concentration in the environment. At fixed value of these concentrations, the maximum allowed number of cells in the MTS is $N_{\text{max}}$. For $R < k$ all cells receive the nutrient and oxygen supply while for $R > k$ there is a fraction of non proliferating cells and the feedback effect starts. The growth of the MTS is due to the proliferating cells in the crust and one obtains that the MTS radius $R$, for $R >> k$, follows a Gompertzian law as the one in Eq. (1), with $N$ replaced by $R$ and $N_{\text{max}}$ by $R_{\text{max}}$, where $R_{\text{max}}$ is the maximum radius of the spheroid corresponding to the maximum number of tumor cells $N_{\text{max}}$. The experimental results show that after 3-4 days of initial exponential growth the spheroids essentially follow the Gompertzian pattern \[7\].

According to our model, at time $t > t^*$, such that $R(t^*) = k$, a fraction of the total cells becomes non proliferating, the feedback effect starts and the growth rate decreases according to the Gompertz law. The number of cells at time $t^*$ is fixed by the condition $N(t^*) = N_m \[5\]$. On the other hand, the variation of the concentration of nutrient and/or of oxygen modifies the total energy supply, that is the value of $N_{\text{max}}$ and, since $N_m = N_{\text{max}} \exp(-\epsilon\beta - 2)$, there is a clear correlation among the external energetic "boundary conditions", the value $N_{\text{max}}$ and the thickness of the viable cell rim which corresponds to the radius of the onset of necrosis. It can be shown \[5\] that ($G_c$ is the glucose concentration):

$$k(G_c) = \alpha \left( N_{\text{max}}^{1/3} - N_{\text{max}}^0 \right)^{1/3} + k_0$$

(3)

where $\alpha$ and $k_0$ are constants depending on the supplied oxygen. From Eq. (3) one obtains the correlation among $N_{\text{max}}$, $G_c$ and $k$. In Fig.1 and Fig. 2 the previous behaviors are compared with data without optimization of the parameters.

B. Biomechanical effects

The experimental data indicate that when MTS are under a solid stress, obtained for example by a gel, the cellular density $\rho$ is not constant and depends on the external gel concentration $C_g$. In particular the results in \[9\] show that: 1) an increase of the gel concentration inhibits the growth of MTS; 2) the cellular density at saturation increases with the gel concentration. In the model the mechanical energy is included in the energetic balance.
of the system by the term $\Omega = -N/\beta = -PV$ where the pressure is $P(t) = \rho(t)/\beta$. The introduction of this term decreases the value of $N_{\text{max}}$ with respect to the case in Sect. III A and this reduction should also imply a decrease of the maximum size of the spheroids, i.e. $R_{\text{max}}(P)$ by increasing the pressure. The comparison with the data is reported in Table I for $C_g$ in the range 0.3 − 0.8 % (see [5] for details).

| $C_g$ (percent) | $2R_{\text{max}}(\Omega)$ [µm] exper. | $2R_{\text{max}}(\Omega)$ [µm] fit |
|----------------|----------------------------------------|----------------------------------|
| 0.3            | 450                                    | 452                              |
| 0.5            | 414                                    | 429                              |
| 0.7            | 370                                    | 404                              |
| 0.8            | 363                                    | 394                              |

TABLE I: Comparison with the experimental data as discussed in the text. The experimental error is about ±10%.

[1] B. Gompertz, *Phyl. Trans. R. Soc.*, 115, 513 (1825).
[2] G.G. Steel, “Growth Kinetic of tumors”, Oxford Clarendon Press, 1977; *Cell tissue Kinet.*, 13, 451 (1980); T.E. Weldon, “Mathematical models in cancer research”, Adam Hilger Publisher, 1988 and refs. therein.
[3] G.B. West *et al.*, *Nature* 413, 628 (2001).
[4] C. Guiot *et al.*, *J. Theor. Biol.* 25, 147 (2003).
[5] P. Castorina and D. Zappalà, “Tumor Gompertzian growth by cellular energetic balance”, q-bio.CB/0407018.
[6] M. Marusic *et al.*, *Cell Prolif.* 27, 73 (1994); Z. Bajzer *et al.* in: “Survey of model for tumor-immune system dynamics”, J.A. Adams and N. Bellomo eds., Birkhauser 1997; A. Bru *et al.*, *Phys. Rev. Lett.* 81, 4008 (1998); Z. Bajzer, *Growth Dev. Aging*, 63, 3 (1999); N. Bellomo *et al.*, “Mathematical topics on the modelling complex multicellular systems and tumor immune cells competition”, Preprint: Politecnico di Torino, 2004.
[7] J. P. Freyer, R.M. Sutherland, Cancer Research, 46, 3504 (1986).

[8] L. Norton et al., Nature 264, 542 (1976); L. Norton Cancer Research, 48, 7067 (1988).

[9] G. Helmlinger et al., Nature Biotechnology, 15, 778 (1997).
FIG. 1: Thickness (µm) vs. glucose concentration (mM). Figure (a) is for an oxygen concentration of 0.28 mM and Figure (b) is for an oxygen concentration of 0.07 mM.

FIG. 2: Spheroid saturation cells number vs. diameter (µm) at which necrosis first develops. Circles refer to culture in 0.28 mM of oxygen Triangles refer to culture in 0.07 mM of oxygen.