Tumor Gompertzian growth by cellular energetic balance

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A macroscopic model of the tumor Gompertzian growth is proposed. The new 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.

A microscopic model of tumor growth in vivo is still an open problem. It requires a detailed description of cellular interactions and a control on the large variety of in situ conditions related to the distributions of nutrient, of oxygen, of growth inhibitors, of blood vessels and capillarity and to the mechanical effects due to tissue elasticity and heterogeneity. On the other hand, in spite of the previous large set of potential parameters, tumors have a peculiar growth pattern that is generally described by a Gompertzian curve, often considered as a pure phenomenological fit to the data. More precisely there is an initial exponential growth (until 1-3 mm in diameter) followed by the vascular Gompertzian phase. Then it seems reasonable to think that cancer growth follows a general pattern that one can hope to describe by macroscopic variables, constrained by a set of environmental conditions crucial to understand the fundamental features of the growth as, for example, the shape and the maximum possible size of the tumor and the onset of the tissue invasion and metastasis. Following this line of research, for example, the universal model proposed in has been recently applied to cancer.

In this paper we consider a macroscopic model of tumor growth that: i) gives an energetic basis to the Gompertzian law; ii) clearly distinguishes among the general evolution patterns, which include feedback effects and 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, but it is a complementary instrument for the description of the tumor growth. The Gompertzian curve is solution of the equation

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

(1)

where \(N(t)\) is the cell number at time \(t\), \(\gamma\) is a constant and \(N_{\infty}\) 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 \(f_p(N) = \gamma \ln \left( \frac{N_{\infty}}{N} \right)\) as the fraction of proliferating cells and \(1 - f_p(N) = f_{np}\) the fraction of non proliferating cells. Here, we observe the difference with respect to an exponential growth that corresponds to a \(N\) independent specific proliferation rate, typical of a system of independent cells. Instead, the logarithmic dependence observed in the Gompertzian law, can be regarded as a sort of feedback mechanism, such that the system, at any time, rearranges the growth rate and the fraction of proliferating cells according to the logarithm of the total number of cells \(N(t)\).

Living tumor cells consume an amount of energy, under the form of nutrient and oxygen, which is recovered from the environment (which will be addressed in the following as \(B\)), represented by a living body (in vivo) or an external solution (in vitro). \(B\), as already mentioned, has also a mechanical action that can be responsible of compression, increase of pressure and density and change of shape of the tumor (addressed in the following as \(A\)). Starting from these observations, we intend to describe the tumor growth on an energetic basis.

Let us first consider the problem at fixed time and recall the first law of thermodynamics. A change of the energy content of a system has three possible origins, namely mechanical work performed on or by the system, variation of the number of elementary constituents (particles), heat exchange with the environment. Accordingly, the internal energy of the system is expressed as the sum of three terms, respectively \(-PV\) (minus the product of pressure times volume), \(\mu N\) (where \(\mu\), the chemical potential, is the change in energy when the number of particles \(N\) is increased by one unit), \(S/\beta\) (heat content).

The basic ingredient in our model is an energy balance law for the tumor in the same spirit of the first law of thermodynamics. However, it should be clear that the variables that we use to describe our system are not properly those introduced in thermodynamics but rather the rules and the relations among these variables are the same as those of thermodynamics. In fact at some fixed time \(t\) one can regard the available energy for the tumor, \(U\), as the sum of three pieces, \(U = \Omega + \mu N + E_M\), where \(\Omega = -PV\) is associated to the mechanical work necessary to contrast the external pressure and to cause a change of shape, \(\mu N\) is proportional to the number of cells \(N\) of \(A\) and \(\mu\) represents the variation in energy related to a change in \(N\) (note, for the sake of clarity, that the mechanical work related to the change in volume of \(A\) due to the increasing number of cells is taken into account in \(\Omega\)) and finally \(E_M\), which represents the energy spent for...
metabolic activities. Since the change in the number of cells in the tumor is due to biological proliferation and by recalling the above definition of \( \mu N \), it is natural to associate \( \mu N \) to the energy that \( A \) needs to generate one new cell, i.e., the energy necessary for reproduction, that has to be distinguished from the energy associated to all the other metabolic processes which is addressed as \( E_M \).

A set of macroscopic variables suitable to describe \( A \) is: the volume of the whole tumor, \( V \), the variable \( \mu \) introduced above that we address as chemical potential, in analogy with the thermodynamical quantity, and \( \beta \), analogous to the thermodynamical inverse temperature, which is introduced, together with its conjugate variable \( S \) (that corresponds to the thermodynamical entropy), by the relation \( E_M = S/\beta \). The variables \( V \), \( \mu \) and \( \beta \) define the macroscopic state of \( A \) at time \( t \).

Statistical mechanics provides a framework that explains the basic laws of thermodynamics starting from a microscopic description of the thermodynamical system. Therefore, having in mind the energetic aspect of the problem, we shall introduce a minimal microscopic model of the cell, where the biological aspects are reduced to the indispensable, which however catches the essential ingredients that provide a sound macroscopic description and a good comparison with the quantitative data. In an extremely simplified picture, we assume that the microscopic states of each cell can be labelled by an integer index \( l \) starting from a ground state level with energy \( \epsilon_l = \epsilon + l \delta \), where \( \delta \) is the minimum positive energy gap between two states. It should be clear that here the energy of a cell indicates the energy that the cell is consuming per unit time, so that it is obvious that the minimum energy in the spectrum must be positive \( \epsilon > 0 \).

According to the basic rules of statistical mechanics, once we have the energy spectrum of a single cell we can determine the grand partition function, \( Z(\beta, V, \mu) = \Pi_{l=0}^{\infty} \exp\left(e^{-\beta(\epsilon_l - \mu)}\right) \) and the grand potential, corresponding to the quantity \( \Omega \) introduced above:

\[
\Omega(\beta, V, \mu) = -\frac{1}{\beta} \ln \mathcal{Z} = -\frac{W}{\beta} e^{-\beta(\epsilon - \mu)} \tag{2}
\]

where \( W = 1/(1 - e^{-\beta \delta}) \). From the derivatives of \( \Omega(\beta, V, \mu) \) we respectively get \( N \), constant \( V \) and \( \beta \), and \( E_M \), for constant \( V \) and \( \mu \):

\[
N = -\left(\frac{\partial \Omega}{\partial \mu}\right)_{V,\beta} = -\beta \Omega \tag{3}
\]

\[
E_M = \left(\frac{\beta \partial \Omega}{\partial \beta}\right)_{V,\mu} = \frac{N}{\beta} \left(1 + C + \ln \left(\frac{W}{N}\right)\right) \tag{4}
\]

where \( C = W/\beta \delta \exp(-\beta \delta) \). From Eqs. 2 and 3 it is straightforward to express \( \mu \) in terms of \( N \): \( \mu = \epsilon + (1/\beta) \ln(N/W) \) and also to derive the average energy per cell: \( U/N = (E_M + \mu N + \Omega)/N = \epsilon + C/\beta \), which shows that \( U/N \) depends on one macroscopic variable only, the inverse temperature \( \beta \), as it is the case for an ideal gas in thermodynamics.

At this point we observe that there are two natural constraints in our model: in fact it is clear that an increase in the number of cells \( N \) requires a positive energy supply which has a direct consequence on the sign of the chemical potential: \( \mu > 0 \). Moreover \( E_M > 0 \) because the cells also require a positive energy supply for their metabolic activity. In addition, in order to compensate any mechanical stress on the tumor we need to require a stronger constraint: \( E_M + \Omega > 0 \). According to the relations derived above, the constraint \( \mu > 0 \) implies a minimum number of cells \( N < N_m = W \exp(-\beta \epsilon) \) and \( (E_M + \Omega)/N = (1/\beta) C + \ln(W/N) \) provides a maximum: \( N < N_\infty = N_m \exp(C + \beta \epsilon) \). Then, by replacing \( N_m \) and \( N_\infty \) in the previous relations we get \( \mu = (1/\beta) \ln(N/N_m) \) and \( (E_M + \Omega)/N = (1/\beta) \ln(N_\infty/N) \). Provided one identifies the maximum number of cells here obtained with the asymptotic value of \( N \) appearing in Eq. 1, the latter equation for \( (E_M + \Omega)/N \) is remarkably similar to the the fraction of proliferating cells at time \( t \), \( f_p(t) \), introduced after Eq. 1 and this will be our starting point to derive the Gompertzian law.

Now we assume that \( A \), due to cellular biological duplication and possible changes induced by \( B \), can modify its macroscopic state and therefore also the macroscopic variables which define the state itself and determine the grand partition function \( Z \). We assume that these changes occur on a time scale that is much larger than the typical time during which the macroscopic variables reach the equilibrium and become constant, so that we can think of the evolution of \( A \) as a slow change from one macroscopic state, where the statistical framework is well defined, to another one, where the same framework, but with different values of the macroscopic variables, holds.

Recalling that at any time fixed \( t \) one can write the identity \( 1 = (f_p + f_{np}) \) and the energy sum rule is \( U = (C/\beta + \epsilon)(f_p + f_{np})N = E_M + \Omega + \mu N \) and, according to the observed similarity between the expressions of \( f_p \) and \( (E_M + \Omega)/N \), it looks natural to identify \( E_M + \Omega = (C/\beta + \epsilon)f_p N \) and, correspondingly \( \mu = (C/\beta + \epsilon)f_p \). This basic assumption is supported by a biological counterpart. In fact in 7 the feedback effect of Eq. 1 is described by introducing some biochemical effects due to growth inhibitor factors, released by the dead cells, which inhibit the proliferation and eventually are responsible of the saturation of the tumor size, so that the concentration of these inhibitor factors should be proportional to \( f_{np} \). In our energetic picture the concentration of inhibitor factors should act enhancing the energy necessary for increasing, through cellular duplication, the number of cells in the tumor and therefore enhancing \( \mu \). Then, the presence of growth inhibitor factors leads to a qualitative proportionality between \( f_{np} \)
and $\mu$ that supports our assumption.

With the statement $E_M + \Omega = (C/\beta + \epsilon)f_\mu N$ it is straightforward to derive the Gompertz equation. In fact, by definition, $\Delta N$ in an interval $\Delta t$ proportional to the number of proliferating cells and then $\Delta N = c_1 \Delta t f_\mu(t) N = c_2 \Delta t (E_M + \Omega)$ with $c_1$, $c_2$ constants. When $\Delta t \to 0$ one recovers Eq. 1 with $\gamma = c_2/\beta$. Remarkably, this model explains the linear correlation between the two standard parameters used to fit the data on tumor growth by the Gompertzian curve [2,3].

A comment is in order. $N_m$ is related to $\mu = 0$. In our set of relations $N < N_m$ corresponds to $\mu < 0$ which is not physically allowed. This indicates that our model and the feedback mechanism embedded in it, start being valid and hold only when $N \geq N_m$. This again fits with the experimental observations that the onset of the Gompertzian growth does not occur at the beginning of the tumor development but only after an exponential phase growth [2]. It is reasonable to think that when $N < N_m$, due to the abundance of energy provided by $B$, the cells of $A$ duplicate as a system of independent cells with no further energetic effort for the duplication due to the presence of the other cells, i.e. with $\mu = 0$ (and not $\mu < 0$), which indicates that the feedback effect should not take place and, as noticed after Eq. 1, this implies an exponential growth. Therefore, even if our model does not work for $N < N_m$, one reasonably expects a continuous crossover between exponential and Gompertzian growth at $N = N_m$.

To analyze some phenomenological implications of our model we shall consider in the following the simple case of the multicellular tumor spheroids (MTS), which follow the Gompertzian growth law as tumors in vivo, despite they have an avascular growth. We shall first consider experiments without external stress and, later, the effects due to a change of the external pressure.

i) ENERGETIC GROWTH

Here we shall refer to experiments where the variation of the external supply of nutrient and/or oxygen is studied [4,5] and we shall rely on a minimal description of the MTS where [2]: a) the thickness, $k$, of the layer where the nutrient and oxygen is delivered (the crust) is independent on the spheroid radius $R$ (as a function of $R$ is constant within 10%); b) the cellular density is constant; and essentially independent of the nutrient concentration; c) the difference in nutrient and oxygen supply for the cells in the inner and outer layers of the crust is negligible in first approximation, d) the cells at distances $d < R - k$ if $R > k$ from the center of the spheroid are dead and only the cells of the crust are alive.

The data, for various concentrations of glucose and oxygen show that [1, 4]: 1) after an initial exponential growth (3-4 days) where the doubling time is independent of the oxygen and glucose concentration, the radius $R$ of MTS grows according to a Gompertzian law as the one in Eq. 1, where $N$ is replaced by $R$ and $N_\infty$ by $R_\infty$ ($R_\infty$ is the maximum radius that the MTS reaches at saturation at very large $t$); 2) there is an approximate linear correlation between $k$ and the logarithm of the glucose concentration, $G_c$, at fixed oxygen quantity; 3) there is a correlation between the radius at the onset of necrosis, $R = k$ and at the growth saturation, $R = R_\infty$.

It is reasonable to think that at the early stages of the growth, when $R < k$, all cells receive the nutrient and oxygen supply while, when $R > k$, due to a more difficult diffusion of the nutrient, there is a fraction of non-proliferating cells and the feedback effect starts. According to our model, we observe the Gompertzian phase for $t \geq t^*$, with $t^*$ defined by the condition $R(t^*) = k$, when the feedback begins. Since there is a simple geometrical relation between $N$ and $R$ due to point b), it is easy to check that, for $R >> k$, our model predicts a Gompertzian growth for the MTS radius up to an asymptotic value $R_\infty$, which is determined by $N_\infty$. In our model, the number of cells at time $t^*$ is fixed by the condition $\mu = 0$, i.e. $N(t^*) = N_m$ and, as seen before, $N_m = N_\infty \exp(-\epsilon \beta - C)$. Putting all together these informations, we find $k = R(t^*) \approx N_\infty^{1/3}$.

Since the experimental data at fixed oxygen quantity, are almost consistent with a linear relation $N_\infty = a(G_c - G_c^0) + N_0^0$ where $a$, $G_c$ and $N_0^0$ are ad hoc constants (see Figure captions for details), [2, 7], we are able to relate the MTS radius at the onset of necrosis, $k$, to $G_c$:

$$k(G_c) = \alpha \left( N_\infty^{1/3}(G_c) - N_0^{0.1/3} \right) + k_0$$

where $\alpha$ and $k_0$ are constants depending on the supplied oxygen. From Eq. 4 one obtains the correlation among $N_\infty$, $G_c$ and $k$. In Fig.1 and Fig. 2 the previous behaviors are compared with data without optimization of the parameters. Despite the oversimplified approach, there is a good agreement with the data. Moreover the proposed model predicts the Gompertzian behavior on the basis of a feedback effect and a constant supply of nutri-
ent for cell and this explains why, under these conditions, the MTS and the in situ tumors follow the same general growth law.

ii) BIOMECHANICAL EFFECTS
The heterogeneous elastic characteristics of the environment give the strongest external constraints\(^1\). Again, the MTS are useful to study how the mechanical features of the environment can modify the growth pattern. When the MTS are under a solid stress, obtained for example by a gel, the experimental data indicate that\(^2\): 1) an increase of the external gel concentration \(C_g\) inhibits the growth of MTS reducing the size of \(R_\infty\) with respect to the case with \(C_g = 0\) (as before \(R_\infty\) is the maximum radius that the MTS reaches at saturation); 2) the cellular density at saturation \(\rho_\infty\) increases with \(C_g\).

In our model the mechanical energy is included in the energetic balance by the term \(\Omega\), and therefore in this problem \(\Omega\) depends on \(C_g\). In particular, for growths in absence of gel, \(C_g = 0\), we neglect its value, \(\Omega \approx 0\), because of the very low pressure \(P \approx 0\), if compared to the case where \(C_g \neq 0\). Also \(N_\infty\) depends on \(\Omega\) and, by recalling that \(N_\infty(\Omega)\) is obtained from the constraint \(E_M + \Omega > 0\) and therefore when \(\Omega = 0\) one can get \(N_\infty(0)\) directly from \(E_M > 0\), it is straightforward to derive \(N_\infty(\Omega) = N_\infty(0)/e\). For a growth with constant density this reduction should also imply a decrease of the maximum size of the spheroids, i.e. \(R_\infty(\Omega) < R_\infty(0)\).

For a quantitative approach one has to take into account the correlation between the density \(\rho\) and the dynamical growth and, since \(\Omega = -N/\beta = -PV\), the pressure is \(P(t) = \rho(t)/\beta\). So, for \(\rho_\infty\), one has \([\rho_\infty(\Omega) - \rho_\infty(0)] = \beta P_e\) where \(P_e\) is the external pressure due to the gel \(C_g\), and \(\rho_\infty(0)\) is the density for \(P_e = 0\), i.e. for \(C_g = 0\). Then \(\rho_\infty\) increases with \(C_g\) according to point 2. A linear fit to the data gives \(\rho_\infty(\Omega) - \rho_\infty(0) = 0.71C_g\)\(^3\), and since \(\rho \sim N/R^2\), one still needs \(N_\infty(\Omega)/N_\infty(0)\) to obtain the dependence of the MTS radius at saturation \(R_\infty(\Omega)\) on \(C_g\). The relation \(N_\infty(\Omega) = N_\infty(0)/e\), derived above is discontinuous in the limit \(\Omega \rightarrow 0\), which is an artifact of our oversimplified microscopic model. However, for intermediate values of the gel concentration we do not expect large deviations from this result and we use it, in first approximation, to determine \(R_\infty(\Omega)\) in terms of \(C_g\). According to this procedure we have no adjustable parameters left and the comparison with the data is reported in Table I for \(C_g\) in the range 0.3 – 0.8 %.

| \(C_g\) (percent) | \(2R_\infty(\Omega)\) [\(\mu m\)] exper. | \(2R_\infty(\Omega)\) [\(\mu m\)] fit |
|-----------------|---------------------|---------------------|
| 0.3             | 450                 | 452                 |
| 0.5             | 414                 | 429                 |
| 0.7             | 370                 | 404                 |
| 0.8             | 363                 | 394                 |

In conclusion, in the presented model the Gompertzian growth is essentially due to an average energetic balance which represents a macroscopic description of a complex underlying dynamics. The comparison with the MTS data suggests that it is a good starting point for a macroscopic analysis of tumors in vivo and indeed the Gompertz equation has interesting properties that can explain why this approximation works in realistic conditions\(^4\).

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