A two-clones tumor model: Spontaneous growth and response to treatment

Ilaria Stura [a,*], Ezio Venturino [b], Caterina Guiot [a]

[a] *Dipartimento Neuroscienze, Università di Torino, Corso Raffaello 30, 10125 Torino, Italy*
[b] *Dipartimento di Matematica "Giuseppe Peano", Università di Torino, via Carlo Alberto 10, 10123 Torino, Italy*

ARTICLE INFO

ABSTRACT

The paper aims at providing a general theoretical frame bridging the macroscopic growth law with the complex heterogeneous structure of real tumors. We apply the "Phenomenological Universality" approach to model the growth of cancer cells accounting for "populations", which are defined not as biologically predefined cellular ensemble but as groups of cells behaving homogeneously with respect to their position (e.g. primary or metastatic tumor), growth characteristics, response to treatment, etc. Populations may mutually interact, limit each other their growth or even mutate into another population. To keep the description as simple and manageable as possible only two populations are considered, but the extension to a multiplicity of cell populations is straightforward.

Our findings indicate that the eradication of the metastatic population is much more critical in the presence of mutations, either spontaneous or therapy-induced. Furthermore, a treatment that eradicates only the primary tumor, having a low kill rate on the metastases, is ultimately not successful but promotes a "growth spurt" in the latter.

1. Introduction

Tumor is a very inhomogeneous system of cells [1] dynamically interacting and adapting to their environment. Normally two or more cell populations coexist, e.g. the primary tumor and one or more secondary ones, generated by cells of the primary tumor which moved to lymph nodes or distant organs. Adaptation to different environments normally modifies the cells characteristics, originating a different cell population. To account for any heterogeneity among cells, due to whatever cause or nature, different cell populations are considered. The transformation of a given population into another one is termed mutation whenever the phenotypic modifications reflect genetic alterations. Sometimes such mutations may be induced or modulated in response to therapies (see [2] in case of the prostate cancer). As a matter of fact, primary tumors are normally treated by surgical eradication or radical radio therapy. When unsuccessful, tumor seeds may survive generating a local recurrence (whose cells may be somewhat different from their progenitor, adding a new cell population into the picture). At the same time, in order to prevent

or, more often, to control distant tumor spread, systemic therapies are delivered, generally called chemo-therapies. Nowadays, also hormone therapies are very common to contrast the growth of hormone-sensitive tumors, like breast and prostate cancer. In this last case it is well known that, after an initial reduction of the tumor volume, the growth of hormone-resistant cells will finally induce an almost uncontrollable tumor saturation [2]. Any realistic model should therefore take into account the appearance of therapy-induced cell mutations.

The key question in the modeling strategy is how strong the interplay among different cell populations must be. Since they are part of the same organism, a "minimal" hypothesis states that they share the same overall energetic and physical resources. Since the total tumor carrying capacity is limited, it is therefore reasonable to assume that the growth of both cell populations is constrained [3,4]. However, several authors (see for instance [5,6]) have speculated about the possibility that the whole tumor (i.e primary, nodes and metastases) behaves as a "coherent body". Experimental evidences of enhanced proliferation of the dormant secondary tumors following the surgical excision of the primary one have been shown in both animal [7,8] and human [9,10] models. A recent model of [3] shows that the effect of primary tumor resection on the growth of bone metastases is not always favorable: since large tumors limit the resources available

* Corresponding author. Tel.: +39 0116708198.
E-mail addresses: ilaria.stura@unito.it (I. Stura), ezio.venturino@unito.it (E. Venturino), caterina.guiot@unito.it (C. Guiot).

for the growth of smaller ones, the resection of the primary tumor may trigger the proliferation of dormant tumors by promoting their vascularization and growth.

The biological mechanisms underlying the above macroscopic findings are still debated. The simultaneous production of growth hormones and angiogenic factors as well as of their inhibitors by the primary tumor, and their different stability (normally the inhibitors have a longer lifetime) may explain the successful control of the metastatic progression until the primary tumor is present. Also the post-surgery wound healing processes and the resulting local and systemic inflammation may be responsible for secondary tumor growth [11,12].

We investigate here the equilibrium conditions of two asymmetrical cell populations, paying close attention to their stability or instability, which are assumed to predict the successful cure or the fatal evolution of the tumor. The parameter conditions ensuring the stable configuration, i.e. the stop of the tumor growth, are outlined in detail.

The paper is organized as follows. In Section 2 the governing equations for the cell populations growth, with or without therapeutic interventions, are presented. In Section 3 two non-mutating populations are investigated, assuming as mutual interplay the constraint on the total carrying capacity, accounting for the geometrical restrictions and the overall environmental conditions, such as growth factor release and energetic resources. The response to therapies is investigated in Section 4. Section 5 considers the spontaneous or therapy-induced emergence of a mutated population. In Section 6 the results are collected in a phase-space diagram encompassing real clinical situations occurring in a large population of patients at different stages of tumor evolution. We focus on possible practical applications as the case of recurrent prostate cancer, where previously prostectomized patients are treated with Androgen Deprivation Therapy (ADT). Such therapy is very effective on the initially predominant hormone-sensitive cancer cells, but promotes a mutation into non-hormone sensitive cells and finally fails in controlling tumor proliferation. A final discussion concludes the paper.

2. The model

The recently proposed Phenomenological Universalities (PUN) approach [13–16] actually includes most of the growth models proposed in the past within a single mathematical frame: they range from simple exponential to logistics and Gompertzian growth, to the ontogenetic model of [17]. PUN was successfully applied to describe the tumor multi-passage transplant in mice [6], external stresses limiting tumor invasiveness [18], multi-cellular tumor spheroids [19] as well as to simulate the response to selected therapies [20]. Applications to other growth phenomena, such as human height from birth to maturity [21] show that the model may easily include "growth spurts" provided a "piece-wise" formulation is used. In this setting, each time interval is characterized by its own specific parameter values. Extensions of PUN to multiple cells populations have been proposed as well, e.g. proposing a "vector" PUN model [22].

The PUN approach describes tumor growth in a very general way, see [15,16] for details:

$$
\begin{cases}
\dfrac{dN(t)}{dt} = c(t)N(t) \\
\dfrac{dc(t)}{dt} = \displaystyle\sum_{i=0}^{n} \beta_i c^i
\end{cases}
\tag{1}
$$

where N is the cancer cells population, $c(t)$ is the growth rate function and n is the degree of the Taylor expansion. This approach generalizes the most used equations in population growth, in fact: in the case $n = 0$, $c(t)$ constant, N grows following an exponential law; for $n = 1$, it follows a Gompertzian law and for $n = 2$ a West/logistic growth law, [23].

2.1. U_0 – Malthus growth law

The first approximation of tumor growth is the exponential law; in fact, at an initial stage, tumor cells duplicate very fast with a fixed doubling time (i.e. the time in which the cancer mass doubles) which estimates the rate of the exponential growth.

Using PUN notation, we see that, for $n = 0$, from (1) the derivative of c is a constant; assuming it vanishes, $\beta_0 = 0$, it follows that $c(t) = c_0$ which in turn implies $N(t) = e^{c_0 t}$, upon integration of the first (1). For $c_0 > 0$, the model exhibits an unbounded population growth. However, real tumors cannot expand indefinitely because of physical constraints. Thus, in the subsequent sections we will not consider this unrealistic case anymore.

2.2. U_1 – Gompertzian growth law

This function describes the tumor development more realistically. Indeed, following an initial exponential unrestricted phase, due to lack of nutrients and space the tumor population growth progressively slows down until finally the tumor population attains its carrying capacity. The mathematics reflects the biological processes, i.e. the cancer core becomes hypoxic and necrotic while the proliferating tumor border may reach some physical barrier such as tissue or bones and it stops growing. The dynamic system, in the $U1$ case, is:

$$
\begin{cases}
\dfrac{dN(t)}{dt} = c(t)N(t) \\
\dfrac{dc(t)}{dt} = \beta_1 c + \beta_0
\end{cases}
$$

Integrating the second equation by separation of variables, setting $\beta_0 = 0$, $c_0 = e^{-\beta_1 t_0}\beta_1^{-1}$, $\beta = \beta_1 < 0$ and then substituting $c(t)$ into the first one we have:

$$
\frac{dN(t)}{dt} = c_0 e^{\beta t} N(t)
\tag{2}
$$

whose solution is:

$$
N(t) = N_0 e^{\frac{c_0}{\beta}(e^{\beta t}-1)}.
\tag{3}
$$

where β is inversely proportional to the tumor carrying capacity and c_0 denotes the growth rate. Note that in this case the carrying capacity depends on the initial condition N_0.

To emphasize the role of the carrying capacity, Eq. (3) can be rewritten as:

$$
N(t) = N_\infty e^{ze^{-rt}}
\tag{4}
$$

where $N_\infty = \lim_{t \to \infty} N(t) = N_0 e^{-\frac{c_0}{\beta}}$ is the carrying capacity and r the exponential growth rate. We can easily transform (3) into (4) back and forth by setting $r = -\beta$, $N_\infty = N_0 e^{-\frac{c_0}{\beta}}$ and $z = \frac{c_0}{\beta}$.

2.3. U_2 – West growth law

West and collaborators have published their allometric theory to give a robust physical foundation to the empirical relationship between the basal metabolic rate and the 3/4 power of the mass observed in all living beings (Kleiber scaling law, [24]) This formalism has been extended by [15] for tumors. In addition to the carrying capacity, a second independent parameter relating the cellular metabolic energy and the energy required for duplication comes into play. Also this function could be derived by the PUN approach, in fact for $n = 2$ we have:

$$
\frac{dc(t)}{dt} = \beta_0 + \beta_1 c + \beta_2 c^2.
$$

This is a very general equation that defines a class of functions; in particular, choosing $\beta_2 = -\frac{1}{4}$, $t_0 = 0$ and β_1 inversely proportional to