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The Norton–Simon hypothesis and the onset of non-genetic resistance to chemotherapy induced by stochastic fluctuations

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ABSTRACT

By studying a simple but realistic biophysical model of tumor growth in the presence of a constant continuous chemotherapy, we show that if an extended Norton–Simon hypothesis holds, the system may have multiple equilibria. Thus, the stochastic bounded fluctuations that affect both the tumor carrying capacity and/or the drug pharmacodynamics (and/or the drug pharmacokinetics) may cause the transition from a small equilibrium to a far larger one, not compatible with the life of the host. In particular, we mainly investigated the effects of fluctuations that involve parameters nonlinearly affecting the deterministic model. We propose to frame the above phenomena as a new and non-genetic kind of resistance to chemotherapy.

1. Introduction

The large rate of relapses during the chemotherapeutic treatment of solid and non-solid tumors was up to the recent past, and to some extent also currently, mainly explained by the paradigm of Clonal Resistance (CR) [1], i.e. the "Darwinian" emergence, through fast random mutations, of drug-insensitive cells in a tumor under chemotherapy. Biophysics has given an important contribute to the understanding of those phenomena [2,3], and more in general of tumor growth (see Ref. [4–6], and references therein).

However, in the last decade, a number of investigations [7] revealed that a significant fraction of cases of resistance to therapy are not "clonal", i.e. not of genetic nature. In other words, in those cases the resistance is not due to the onset of mutations that are advantageous to the tumor cells. Instead it is actually linked to phenomena that may, broadly speaking, be defined as physical resistance (PR) to the drug. Perhaps the most important among these phenomena are the limited ability of the drug to penetrate into the tumor tissue because of poor or nonlinear diffusivity [8], and anomalous binding of drug molecules to the surface of tumor cells or to the extracellular matrix [9]. This means that resistance cannot only be imputed to a sort of Darwinian evolution of the cancerous population through the birth of new clones, but also to the impaired transport of the drug molecules in the tumor.

Virtually all bioprocesses are subject to fluctuations in their rates of changes, either random or periodic [10,11]. Such fluctuations may interact nontrivially with the intrinsic nonlinear dynamics of the perturbed phenomena [12]. In Ref. [13], we stressed that, for solid vascularized tumors, there is a possible different way for the onset of resistance due to the interplay between a nonlinear population dynamics and noise. This pathway of resistance is induced by the unavoidable stochastic fluctuations in drug pharmacokinetics.

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Here we set the study in a more general framework, including nonsolid tumors, and we show that multistability of tumor size under chemotherapy with cytotoxic agents arises as a natural consequence of the well known Norton–Simon hypothesis [14] if its formulation is suitably extended. Given the multistability of such a system, the addition of stochastic perturbations to the pharmacokinetics of the administered drug leads to the onset of noise-induced transitions. Although we shall consider this phenomenon, this is not the main focus of the present work. Indeed, here we shall be mainly involved in analyzing the consequences of the presence of bounded stochastic fluctuations in the nonlinear interplay between the neoplasm and its microenvironment, which is summarized in an important parameter: the tumor carrying capacity. Moreover, we shall also investigate the possibility of fluctuations in the drug pharmacodynamics, which is also nonlinear. Concerning the representation of noise, we shall only move within the theory of bounded stochastic processes [15], since we shall consider the perturbations of parameters that must remain strictly positive and that nonlinearly affect the growth of the tumor.

2. A Norton–Simon-like model of chemotherapy

Let us consider a tumor – solid or nonsolid – whose size (biomass, number of viable cells, etc.) at time t is denoted as X, and which is growing according to a saturable growth law [3].

$$X' = f\left(\frac{X}{K}\right)X,$$

where $K > 0$, and $f(u)$ is a decreasing function of u such that $f(1) = 0$. The constant K is usually called carrying capacity, and it depends on the available nutrients and/or space for which the tumor cells compete. Another important parameter is the value $\alpha = f(0)$, which we shall call the "baseline growth rate" (BGR). α can be read as a measure of the intrinsic growth rate of the tumor, in the absence of any competition. Of course, since $f(u)$ is decreasing, the BGR is also the maximal growth rate. Although very simple, the above class of models is very effective in capturing the main qualitative [3,4,6] and quantitative [3,5] aspects of tumor growth. Two well known growth laws are the Gompertz law, where $f(X/K) = \beta \log(K/X)$, and the generalized logistic $f(X/K) = \alpha(1 - (X/K)^a)$ with $a > 0$. Note, however, that in the Gompertz case the BGR is infinite, which is not realistic, as pointed out in Refs. [3,6] (and references therein).

Let the tumor be under the delivering of a cytotoxic therapy with a drug whose blood concentration, denoted by $c(t)$, may be periodic or constant. Which is the effect of $c(t)$ on the tumor growth? The log-kill hypothesis [16] prescribes that the rate of tumor cells killing is proportional to the product $c(t)X(t)$:

$$X' = f\left(\frac{X}{K}\right)X - \gamma c(t)X(t). \tag{1}$$

In the case of a bounded intrinsic growth rate, i.e. $f(0) < \infty$, the condition $\langle c(t)\rangle > f(0)/\gamma$ implies that $X(t) \to 0$, independently of $X(0) > 0$.

However, since the seventies Norton and Simon [14] stressed as a potential pitfall of the log-kill hypothesis the fact that the relative killing rate is simply taken proportional to $c(t)$. According to the log-kill hypothesis, the same drug concentration is indeed able to kill the same relative number of cells per unit time independently of the tumor burden. Moreover, the absolute velocity of regression caused by $c(t)$ would be greater in the larger tumors. This is often unrealistic. On the contrary, in clinics it is often observed that the effort to make a large tumor regress is considerably greater, whereas histologically similar tumors of small volumes are curable using the same delivered quantity of the chemotherapeutic agent. A possible cause of this fact is the development of clones of cells that are resistant to the delivered agent. However, since the reduced drug effectiveness may also be present in the very first phases of a therapy, Norton and Simon [14] summarized these observations, by assuming that the parameter γ is not constant but a decreasing function of X, $\gamma(X)$. In particular, Norton and Simon proposed that $\gamma(X)$ were proportional to $f(X/K)$ [14]. We shall not assume this strict hypothesis, we shall consider here a generic γ positive and decreasing in X, depending also on some internal parameters p, which leads to the following non-logkill model:

$$X' = f\left(\frac{X}{K}\right)X - \gamma(X; p)c(t)X, \qquad X(0) = X_0. \tag{2}$$

It is trivial to verify that if $\langle c(t)\rangle > \alpha/\gamma(0; p)$ then the tumor free equilibrium $X_e = 0$ is locally stable, whereas in case of constant continuous infusion, $c(t) = C$, if $\gamma(X; p)C > f(X/K)$ then the tumor free equilibrium $X_e = 0$ is globally stable. In the general case, since $\gamma(K; p) > f(1) = 0$, if $\alpha > \gamma(0; p)C$ there will be an odd number $N \geq 1$ of positive equilibria: $X_1(C, K, p), \ldots, X_N(C, K, p)$, with $X_i < X_j$ if $i < j$, and $X_N < K$. It is easy matter to verify that the odd-numbered equilibria are locally stable, whereas the even-numbered points are unstable. By varying C or K or p one may get one or more hysteresis bifurcations.

3. Including stochastic fluctuations

Let us suppose, for the sake of simplicity, that $\gamma(X; p)C$ be such that three equilibria are present. Then $X_1(C, K, p)$ and $X_3(C, K, p)$ will be locally stable and $X_2(C, K, p)$ will be unstable, and it follows that $X(t) \to X_1(C, K, p)$ for all