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An ecological resilience perspective on cancer: Insights from a toy model

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ABSTRACT

In this paper we propose an ecological resilience point of view on cancer. This view is based on the analysis of a simple ODE model for the interactions between cancer and normal cells. The model presents two regimes for tumor growth. In the first, cancer arises due to three reasons: a partial corruption of the functions that avoid the growth of mutated cells, an aggressive phenotype of tumor cells and exposure to external carcinogenic factors. In this case, treatments may be effective if they drive the system to the basin of attraction of the cancer cure state. In the second regime, cancer arises because the repair system is intrinsically corrupted. In this case, the complete cure is not possible since the cancer cure state is no more stable, but tumor recurrence may be delayed if treatment is prolongued. We review three indicators of the resilience of a stable equilibrium, related with size and shape of its basin of attraction: latitude, precariousness and resistance. A novel method to calculate these indicators is proposed. This method is simpler and more efficient than those currently used, and may be easily applied to other population dynamics models. We apply this method to the model and investigate how these indicators behave with parameters changes. Finally, we present some simulations to illustrate how the resilience analysis can be applied to validated models in order to obtain indicators for personalized cancer treatments.

1. Introduction

The ecological resilience perspective is an emerging approach for understanding the dynamics of social-ecological systems (Holling, 1973; May, 1977; Scheffer et al., 2001; Folke, 2006; Menck et al., 2013; Meyer, 2016). While the stability point of view emphasizes the equilibrium and the maintenance of present state, the resilience point of view focus on shifts between alternative basins of attraction, thresholds, uncertainty and unexpected disturbances. External forces or random events may cause state variable perturbations that drive a nonlinear system, which is initially near a stable state, to enter an undesirable basin of attraction. In this case, the resilience of the original steady state is related with the size and shape of its basin of attraction, and the capacity of the system to persist in this basin of attraction when subject to state variable perturbations. Three different indicators are established in the literature as measures of the resilience of a stable state with respect to state variable perturbations (Walker et al., 2004; Mitra et al., 2015): *latitude*, which is a measure of the volume of its basin of attraction; *precariousness*, which is related with the minimal state space disturbance needed to drive the system outside its basin of attraction; and *resistance*, which is a measure of the deepness of its basin of attraction.

On the other hand, changes in system parameters occur in a slow time scale, due to evolutionary forces or by modifying the intensities of interactions and forces governing such system. In this case, parameters modify the resilience of the system with respect to state variable perturbations. Further, when parameters do change enough, the system may undergo several bifurcations and the phase portrait may change substantially. In this case, one can measure the resilience of the system with respect to parameters changes as the distance to the threshold values for which bifurcations occur. As a consequence of such bifurcations, an undesirable alternative stable state may be created, and its basin of attraction can be achieved by state variable perturbations, as commented above. A more dramatic outcome happens when parameters changes lead to loss of stability of the original steady state or even its disappearance. In this case, a regime shift occurs and the system moves to another state. Now, the question of

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reversibility takes place. Of first importance is the question whether it is possible or not to return the parameters to their original values. When parameters change due to evolutionary factors, it is more likely that this change cannot be undone. Changes due to external forces can be undone more easily through the correct manipulation of those forces (if possible). However, even if the original values can by restored, the reversal to the original stable state may not be completely achieved if the system exhibits hysteresis.

In this paper we illustrate how these concepts of ecological resilience can be applied to cancer, a complex disease whose causes are far from being well understood and whose cure is far from being achieved. Indeed, despite the intense efforts that led the elucidation of many biochemical mechanisms developed by cancer cells to survive (Hanahan and Weinberg, 2011), there is a current debate on which are the major factors that allow the onset of cancer cells. While some argue that alterations in intrinsic cellular processes are the main reasons that some tissues become cancerous (Tomasetti and Vogelstein, 2015), others defend the view that most cases of cancer result from extrinsic factors such as environmental exposure to toxic chemicals and radiation (Wu et al., 2016). With respect to cancer treatment, although the development of new drugs and strategies to treat cancer in the last fifty years achieved good results in many cases, another large portion of cancer patients did not respond well to treatments, or presented tumor recurrence, indicating that there is still a long road in the fight against cancer (Kerbel and Kamen, 2004; Benzekry et al., 2015).

We propose a simple model for tumor growth and apply the above concepts to suggest a framework for viewing the arising of cancer and its effective treatment as critical transitions between two alternative stable states. In this framework, tumor growth and tumor treatment depend ultimately on ecological resilience questions. Further, we briefly review the three resilience indicators commented above, propose a method to calculate these indicators and apply this method to the model. As far as we know, this novel method we propose is simpler and more efficient than those currently used, and can be applied to other population dynamics models to improve their analysis through this resilience perspective.

The paper is organized as follows. In Section 2 the model is presented. In Section 3 the analysis of the model is performed. In Section 4, the results are discussed in the ecological resilience perspective. In Section 5, the method to calculate resilience indicators is presented and applied to the model. Finally, conclusions are presented in Section 6.

2. A toy model for tumor growth

We present a simple model consisting of a system of ODEs describing tumor growth and its effect on normal tissue, together with the tissue response to tumor. Our goal is not to consider the several aspects of tumor growth and to reproduce quantitative behavior with high accuracy, but to use the model to give some insights through a resilience point of view. The model equations are given by

$$\frac{dN}{dt} = r_N - \mu_N N - \beta_1 NA, \tag{1a}$$

$$\frac{dA}{dt} = r_A A\left(1-\frac{A}{K_A}\right) - \beta_3 NA - (\mu_A + \epsilon_A)A, \tag{1b}$$

where N and A stand for normal and tumor cells, respectively. This system is a limit case of a three-dimensional model for oncogenesis encompassing mutations and genetic instability (Fassoni, 2016).

Parameter r_N represents the total constant reproduction of normal cells, and μ_N is their natural mortality. A constant flux for normal cells is considered in the vital dynamics, and not a density-dependent one, like the logistic growth generally assumed (Gatenby, 1995; Gatenby and Gawlinski, 1996; de Pillis and Radunskaya, 2001; McGillen et al., 2014). The reason for this choice is that at a normal and already formed tissue the imperative dynamics is not the cells intraspecific competition by nutrients, but the maintenance of a homeostatic state, through the natural replenishment of old and dead cells (Simons and Clevers, 2011).

On the contrary, cancer cells have a certain independence on growth signals released by the tissue and keep their own growth program, like an embrionary tissue in growth phase (Fedi et al., 1997). Thus a density dependent growth is considered. Several growth laws could be used, such as the Gompertz, generalized logistic, Von Bertanlanfy and others (Sarapata and de Pillis, 2014). We choose the logistic growth due to its simplicity, and a natural mortality μ_A. An extra mortality rate ϵ_A due to apoptosis (Danial and Korsmeyer, 2004) is also included.

Several models for tumor growth consider the phenomena of tumor angiogenesis, i.e., the formation of new blood vessels to feed the tumor, in response to signals released by tumor cells (Kerbel, 2008; Yang, 2012). In order to keep the model as simple as possible, we do not consider angiogenesis here.

Parameter β_3 encompasses, in the simplest way, all negative effects imposed to cancer cells by the many cell types in the normal tissue. These interactions include the release of anti-growth and death signals by host cells (Hanahan and Weinberg, 2011), the natural response of normal cells to the presence of cancer cells, the competition by nutrients with tumor cells and so on. Similarly, parameter β_1 covers all mechanisms developed by tumor cells which damage the normal tissue, like increasing local acidity (Gatenby et al., 2006), supression of immune cells (Facciabene et al., 2012), release of death signals (Hanahan and Weinberg, 2011), and competition with normal cells.

System (1) is similar to the classical Lotka–Volterra model of competition (Fassoni et al., 2014), commonly used in models for tumor growth (Gatenby, 1995; Gatenby and Gawlinski, 1996; de Pillis and Radunskaya, 2001; McGillen et al., 2014) and biological invasions (Fassoni and Martins, 2014), but has a fundamental difference. The use of a constant flux instead a logistic growth to normal cells breaks the symmetry observed in the classical Lotka–Volterra model, so that no equilibrium with $N = 0$ will exist. Thus, normal cells will never be extinct, on the contrary to those models. We believe that this is not a problem, but, on the contrary, is a realistic outcome. Indeed, roughly speaking, cancer 'wins' not by the fact that it kills all cells in the tissue, but by the fact that it reaches a dangerous size that disrupts the well functioning of the tissue and threatens the health of the individual. A constant flux term was already taken in other well-known models for cancer, specifically, to describe the growth of immune cells (Kuznetsov et al., 1994; de Pillis et al., 2005; Eftimie et al., 2011).

Let us comment on some resemblance of system (1) with the well-known system of Kuznetsov et al. (1994), which describes the interaction between immune cells and cancer cells. In that system, equation for immune cells has two production terms: a constant production term (analog to r_N here) and a Michaelis–Menten term representing the recruitment of immune cells due to the presence of cancer cells. If we remove this second term (letting $p = 0$ in their notation), that system becomes equivalent to system (1). Thus, the immune cells of that model have basically the same behavior of normal cells in this model, and the unique difference is the recruitment term. In our model, as the population N is considered as a pool of many different cell types, from which the immune cells are a small fraction, it is natural to include in its dynamics only the