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Modeling subspecies and the tumor-immune system interaction: Steps toward understanding therapy

S.A. Menchón[a], R.A. Ramos[b], C.A. Condat[a,*]

[a]CONICET and FaMAF, Universidad Nacional de Córdoba, 5000-Córdoba, Argentina
[b]Department of Physics, University of Puerto Rico, Mayagüez, PR 00681, USA

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Abstract

A mesoscopic nutrient competition model for cancer growth is generalized to describe the growth of a heterogeneous tumor and the interactions between the tumor and the immune system. Our simulations show that the success of a mutation depends not only on its intrinsic competitive advantages, but also on its location in the tumor mass. It is also shown that the simple killing of tumor cells by immune cells, even when their activity is increased by therapy, is not sufficient to stem tumor growth, but another mechanism (such as pinning) is needed for a successful therapy.

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1. Introduction

Although an enormous effort has been made in the pursuit of successful cancer therapies, the results are still not satisfactory. Cancer is the outcome of a long and complex process that involves the accumulation of mutations in the genes that control cell birth and cell death. As a consequence, cancer cell growth is limited by the environmental supply of nutrients and not by the regulation of cell growth and differentiation that characterize normal cells. Moreover, since tumors are not composed of genetically identical cells, these cells can respond in different forms to the presence of the same chemical agent. This may undermine otherwise sound therapeutic strategies [1]. To help in the formulation of effective therapies it is therefore convenient to develop a spatio-temporal model to describe the competitive evolution of two or more cancer cell subspecies and to apply this model to investigate the interaction between the tumor and the therapeutic agent. This is a complex task, but in this paper we have adapted Scalerandi's model of competition for nutrients [2] to describe (A) the simultaneous evolution of two cancer species, and (B) the effect of an immunotherapeutic course on a single-species tumor. This should open the way to an integrated analysis of the interaction between therapeutic procedure and heterogeneous tumor.

*Corresponding author.
E-mail address: condat@famaf.unc.edu.ar (C.A. Condat).

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The study of multiple cellular populations in the cancer context has led to interesting mathematical models. Coldman and Goldie [3] assumed that a mutation generates total resistance to a cytotoxic drug. Then Michelson and coworkers [5] extended the model of Jansson and Revesz [4], which allows one population to emerge from another. In 1998 Panetta [6] used two ordinary differential equations to describe heterogeneous tumor growth, taking into account induced drug resistance. More recently, Kansal and coworkers [7] presented a model that uses a cellular automaton to describe the growth of glioblastoma multiforme. In their model, one subpopulation, with altered cell-doubling time, emerges from another at a randomly chosen site in the proliferative tumor rim.

Although immunotherapy holds promise, its potential has been limited by the baffling complexity of the tumor-immune system interaction [8]. Mathematical modeling has helped us to understand the immunogenic response to a tumor [9–13], but the descriptions are usually zero-dimensional and only the total amounts of the various populations, but not their anatomical distribution, are considered. In this paper, we introduce the spatial aspect in the description of cancer-immune system modeling. We will assume that the cancer cells are attacked by lymphocytes that enter the affected tissue through the circulatory system. Since experimental research indicates that activated lymphocytes effectively surround tumoral regions [14], we also assume that they are chemotactically guided toward the tumor. The guidance is provided by a molecular messenger that is generated by the cancer cells themselves.

In the mesoscopic nutrient competition model of Scalerandi et al. [2], rules formulated at the cell level are implemented as difference equations on a lattice. The equations are then solved using numerical simulations. Among other results, this procedure has led to the reproduction of MRI data for real tumors [15] and to a suitable description of tumoral cord growth [16]. To apply this model to immunotherapy, we need to establish new rules for the additional populations, i.e., the lymphocytes and the molecular messengers. We do this by extending the tumor–lymphocyte interaction model studied by Sotolongo Costa and coworkers [17]. In Section 2 we review the model, which is used in Section 3 to describe two-species tumor growth, and extended in Section 4 to describe the tumor-immune system interaction.

2. The model

We represent the tissue of interest by a square grid, whose node points $\vec{i} = (i,j)$ represent volume elements of tissue that contain many cells and nutrient molecules. Healthy, cancerous, and dead cells coexist there, their concentrations being, respectively, $h(\vec{i})$, $c(\vec{i})$, and $d(\vec{i})$. The total concentration is uniform and normalized. The rules that govern the behavior of the cancer cells are:

(1) *Feeding*. Cancer cells absorb free nutrients at the rate

$$\gamma(\vec{i}) = \gamma_{as}(1 - \mathrm{e}^{-p(\vec{i})}). \tag{1}$$

The absorption rate is proportional to the local free nutrient concentration $p(\vec{i})$ at low concentrations, but it saturates (to γ_{as}) at high concentrations. Absorbed nutrients are transformed into bound nutrients.

(2) *Consumption.* The bound nutrient, whose concentration is $q(\vec{i})$, is consumed by cancer cells at the rate

$$\beta(\vec{i}) = \beta_{as}(1 - \mathrm{e}^{-q(\vec{i})/c(\vec{i})}), \tag{2}$$

where the denominator $c(\vec{i})$ has been included in the exponent because each cell can consume only its own bound nutrient.

(3) *Death.* A fraction χ_1 of cancer cells die when the average amount of bound nutrient per cell, $q(\vec{i})/c(\vec{i})$, falls below a given threshold Q_D.

(4) *Mitosis.* A high concentration of bound nutrient triggers cell replication. A fraction χ_2 of cancer cells replicate if $q(\vec{i})/c(\vec{i})$ exceeds a mitosis threshold Q_M ($Q_M > Q_D$).

(5) *Migration.* A cell that senses a low nutrient level in its neighborhood tends to migrate. We assume that it moves with a migration rate α if $p(\vec{i})/c(\vec{i}) < P_D$, where P_D is the migration threshold.

In Scalerandi's *local interaction simulation approach*, the cellular and nutrient concentrations are modified by the local conditions at each step. The resulting equations must be complemented by suitable initial and