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Research paper

# Destruction of solid tumors by immune cells

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ABSTRACT

The *fractional cell kill* is a mathematical expression describing the rate at which a certain population of cells is reduced to a fraction of itself. In order to investigate the fractional cell kill that governs the rate at which a solid tumor is lysed by a cell population of cytotoxic $CD8^+$ T cells (CTLs), we present several *in silico* simulations and mathematical analyses. When the CTLs eradicate efficiently the tumor cells, the models predict a correlation between the morphology of the tumors and the rate at which they are lysed. However, when the effectiveness of the immune cells is decreased, the mathematical function fails to reproduce the process of lysis. This limit is thoroughly discussed and a new fractional cell kill is proposed.



## 1. Introduction

Immunotherapy has been focusing great attention among cancer therapies in the recent past years. Adoptive cell transfer using chimeric antigen receptors [1,2], the modulation of CTLA-4 activity by means of monoclonal antibodies [3], or the blocking of the PD-1 receptor [4], are a few outstanding examples. The progress of tumor immunotherapy with T lymphocytes mainly relies on our capacity to uncover and understand the molecular and cellular basis of the T-cell-mediated antitumor response. However, due to the highly complex regulatory mechanisms that control both cell growth and the immune system, this task can be hardly achieved without the use of mathematical models. From a theoretical point of view, these models provide an analytical framework in which fundamental questions concerning cancer dynamics can be addressed in a rigorous fashion. The practical reason for their development is to make quantitative predictions that permit the refinement of the existing therapies, or even the design of new ones.

Mathematical models of tumor growth and its interaction with the immune system have demonstrated their potential to explain different properties of tumor-immune interactions [5]. Among these models, a continuous ODE model was engineered in [6] to explore a possible dynamical origin of the dormancy and the sneaking-through of tumors. Such model consists of two cell populations (tumor and immune effector cells), and describes their interaction as an enzymatic process. In particular, these authors consider that the rate at which the tumor is lysed by the cytotoxic cells, *i. e.*, the fractional cell kill, increases linearly with the number of immune cells. In other words, it is possible to increase without bounds the speed at which the tumor is destroyed, by simply adding more immune cells. Following this work, a more specialized model was designed years later [7], which includes the adaptive ($CD8^+$ lymphocytes) and the innate (NK cells) cell-mediated immune responses. This model was validated using experiments in mice [8] and humans [9]. In order to reproduce the experimental

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data, the authors incorporated a new fractional cell kill. More specifically, these authors noticed that the fraction of lysed tumor cells after a few hours, plotted versus different values of the ratio between the initial number of immune and tumor cells, saturates for increasing values of the latter. Consequently, they proposed a sigmoid function [7] depending on the effector-to-target ratio as the mathematical function describing the rate at which a tumor is lysed.

In [10] we have developed a simpler model, validated it, and proposed several hypotheses to explain the nature of the fractional cell kill. In particular, it was suggested that the saturation might arise as a consequence of T cell crowding, which depends on the geometry of the tumor. The main purpose of this work is to characterize more rigorously the nature of the mathematical expression that governs the lysis of tumor cells by cytotoxic cells. Our study supports the previous hypothesis, indicating that this mathematical function emerges from spatial and geometrical restraints. Interestingly, simulations are provided in the limit of immunodeficient environments, where saturation becomes less evident. We demonstrate that the current mathematical function works bad for such environments, and retake the conceptual framework of enzyme kinetics to propose another fractional cell kill. We show that this new function behaves better in the limit in which the immune cell population is small compared to the tumor size, and that the parameters appearing in it have a clear physical and biological interpretation.

## 2. Models

### 2.1. An hybrid cellular automaton model

The simulations are accomplished by means of a cellular automaton (CA) model developed in [11] to study the interactions between tumor and immune effector cells. This model was built on a previously CA model designed to study the effects of competition for nutrients and growth factors in avascular tumors [12]. It is hybrid because the cells are treated discretely, allowing them to occupy several grid points in a particular spatial domain, and evolve according to probabilistic and direct rules. On the other hand, the diffusion of nutrients (such as glucose, oxygen and other types of nutrients) from the vessels into such spatial region is represented through linear reaction-diffusion equations, which are continuous and deterministic. Two types of nutrients are utilized in this model, making a distinction between those which are specific for cell division $N(x, y, t)$, and others $M(x, y, t)$ that are related to the remaining cellular activities. The partial differential equations for the diffusion of nutrients are

$$\frac{\partial N}{\partial t} = D_N \nabla^2 N - k_1 T N - k_2 H N - k_3 E N \tag{1}$$

$$\frac{\partial M}{\partial t} = D_M \nabla^2 M - k_4 T M - k_5 H M - k_6 E M, \tag{2}$$

where $T(x, y, t)$, $H(x, y, t)$ and $E(x, y, t)$ are functions representing the number of tumor, healthy and immune cells at time $t$ and position $(x, y)$. For simplicity, we assume that both type of nutrients have the same diffusion coefficient $D_N = D_M = D$. Following [11], we consider that the competition parameters are equal $k_2 = k_3 = k_5 = k_6 = k$, except for the tumor cells, which compete more aggressively. We set $k_1 = \lambda_N k$ and $k_4 = \lambda_M k$, with $\lambda_M$ and $\lambda_N$ greater than one. An adiabatic limit is considered, assuming that the solutions are stationary. This approximation holds because the time it takes a tumor cell to complete its cell cycle, which is of the order of days [13], is much longer than that of the diffusion of nutrients. A quadrilateral domain $\Omega = [0, L] \times [0, L]$ is considered and Dirichlet boundary conditions are imposed on the vertical sides of the domain, where the vessels are placed, assigning $N(0, y) = N(L, y) = N_0$ and $= M(0, y) = M(L, y) = M_0$. For simplicity, the horizontal upper and lower bounds of the domain obey periodic boundary conditions $N(x, 0) = N(x, L)$ and $M(x, 0) = M(x, L)$, wrapping them together to form a cylinder.

Finally, the diffusion equations are nondimensionalized as explained in [12], and the equations are numerically solved by using finite-difference methods with successive over-relaxation. The resolution of the grid $n$ equals 300 pixels in all our simulations. For a detailed description of the CA algorithm we refere the reader to [12]. The simulations here presented are carried out in two successive steps. The first is devoted to the growth of the tumors, while the second focuses on the lysis of tumor cells by CTLs.

1. We generate distinct solid tumors as monoclonal growths, arising after many iterations of the cellular automaton. At each CA iteration the tumor cells can divide, move or die attending to certain probabilistic rules that depend on the nutrient concentration per tumor cell and some specific parameters. Each of these parameters $\theta_a$ represent the intrinsic capacity of the tumor cells to carry out a particular action $a$. The precise probabilistic laws and the corresponding actions are described in detail in Appendix A. Attending to morphology, diverse types of tumors can be generated, depending on the nutrient competition parameters among tumor cells $\alpha$, $\lambda_N$. We simulate four types of geometries (spherical, papillary, filamentary and disconnected), and inspect four tumors of different sizes for each shape.
2. The lysis of tumor cells is a hand-to-hand struggle comprising several processes. After recognition of these cells through antigen presentation via MHC class I molecules, the $CD8^+$ T cells proceed to induce apoptosis. The principal mechanism involves the injection of proteases through pores on the cell membrane, that have been previously opened by polymerization of perforins. Even though death may take about an hour to become evident, it takes minutes for a T cell to