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Modeling the chemotherapy-induced selection of drug-resistant traits during tumor growth

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ABSTRACT

The emergence of drug-resistance is a major challenge in chemotherapy. In this paper we develop a mathematical model to study the dynamics of drug-resistance in solid tumors. Our model follows the dynamics of the tumor, assuming that the cancer cell population depends on a phenotype variable that corresponds to the resistance level to a cytotoxic drug. The equation for the tumor density is written as a reaction-diffusion equation with a pressure term that depends on the local cell density. The model incorporates the dynamics of nutrients and two different types of drugs: a cytotoxic drug, which directly impacts the death rate of the cancer cells, and a cytostatic drug that reduces the proliferation rate. This model successfully integrates the phenotype structured drug-resistance approach with an asymmetric tumor growth model in space. Through analysis and simulations we study the impact of spatial and phenotypic heterogeneity on the tumor growth under chemotherapy. We demonstrate that heterogeneous cancer cells may emerge due to the selection dynamics of the environment. Our model predicts that under certain conditions, multiple resistant traits emerge at different locations within the tumor. We show that a higher dosage of the cytotoxic drug may delay a relapse, yet, when this happens, a more resistant trait emerges. Moreover, we estimate the expansion rate of the tumor boundary as well as the time of relapse, in terms of the resistance trait, the level of the nutrient, and the drug concentration. Finally, we propose an efficient drug schedule aiming at minimizing the growth rate of the most resistant trait. By combining the cytotoxic and cytostatic drugs, we demonstrate that the resistant cells can be eliminated.

1. Introduction

Drug-resistance to chemotherapy is a key obstacle to successful cancer treatments. The biological mechanisms responsible for the emergence of drug resistance and its propagation have been extensively studied (Gillet and Gottesman, 2010; Teicher, 2006). Those mechanisms involve genetic and/or epigenetic alternations that allow cancer cells to evade one or more drugs (Fodal et al., 2011; Gottesman, 2002; Gottesman et al., 2002). In addition, the local tumor environment, including the availability of nutrients and reduced absorption or metabolism of drugs, provides opportunities for resistant cells to evolve (Gerlinger et al., 2012; Panetta, 1998; Rainey and Travisano, 1998). The complex dynamics of the underlying mechanisms has encouraged the development of mathematical models for describing the emergence and evolution of drug resistance. Such models were used for improving early detection, quantifying intrinsic and acquired resistance cells, and designing therapeutic protocols (Foo and Michor, 2014; Lavi et al., 2012; Michor et al., 2006; Roose et al., 2007; Swierniak et al., 2009). These approaches pave a way towards a better understanding of clinical studies and experimental observations by assisting to decipher the complex mechanisms that control the dynamics of cancer under therapy.

A variety of modeling strategies have been developed to characterize tumor growth and the dynamics of drug resistance. The models range from deterministic to stochastic and from discrete to continuum models. Discrete models include cellular automata (Anderson, 2005; Mallett and De Pillis, 2006) and agent-based modeling (e.g., Mansury et al., 2002). Such models simulate individual cells, whose states are updated based on a given set of rules. Generally, it is straightforward to formulate the biological processes corresponding to tumor invasion and resistance dynamics as a discrete model. Unfortunately, such models suffer from the lack of analytical tools that can be used to analyze their properties, and the computational costs rapidly increase with an increased

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number of agents (cells). In larger-scale systems, continuum methods are good modeling alternatives. Such models include, e.g., ordinary differential equations (Birkhead et al., 1987; Tomasetti and Levy, 2010), partial differential equations (Anderson and Chaplain, 1998; Trédan et al., 2007; Wu et al., 2013), and integro-differential equations (Greene et al., 2014; Lorz et al., 2013).

Models based on partial differential equations have been extensively used to model cancer growth in space and time (see, e.g., Bellomo et al., 2003; Byrne et al., 2006; Cristini et al., 2008; Lowengrub et al., 2010 and the references therein). Initial modeling approaches were mostly based on reaction diffusion systems to describe the interaction between malignant and healthy cells (Gatenby and Gawlinski, 1996; Greenspan, 1976). Many extensions were proposed to include the contribution of proteolytic enzymes, stress-induced limitations, cell adhesion, microenvironment, and vascularization (Anderson, 2005; Byrne et al., 2006; Cristini et al., 2003; Deakin and Chaplain, 2013; Macklin and Lowengrub, 2007; Zheng et al., 2005).

The simplest spatial models of tumor growth assume radial symmetry. Linear and weakly nonlinear analyses have been performed to assess the stability of spherical tumors to asymmetric perturbations (Byrne et al., 2006). An extension to a fully asymmetric growth has been done by regarding the local tissue invasion of a tumor as a free moving boundary problem. To trace the boundary, various numerical techniques have been developed, e.g., boundary integral methods (Cristini et al., 2003) and advanced level-set methods (Macklin and Lowengrub, 2007), in which the nutrients are coupled with a pressure equation and a geometry-dependent jump boundary conditions. This approach was used to successfully study the effects of shape instabilities on both avascular and vascular solid tumor growth (Byrne and Chaplain, 1996; Cristini et al., 2003; Macklin and Lowengrub, 2007; Macklin et al., 2009). However, the cell pressure in these models is governed by the nutrients and the geometry without considering the competition for space that is an important factor in cancer invasion (Brú et al., 2003).

As a consequence, the concept of *homeostatic pressure*, denoting the lower pressure that prevents cell multiplication by contact inhibition, motivated a new generation of models (Byrne and Drasdo, 2009). For example, the porous medium equation was used in Perthame et al. (2014) and Kim et al. (2016). Multiphase mixture models based on the theory of mixtures were proposed in Chaplain et al. (2006), Mcmaster et al. (2012), Byrne and Preziosi (2003) and Preziosi and Tosin (2009). In particular, Perthame et al. (2014) used the porous medium equation to bridge the free boundary models that mostly describe the geometric motion of the tumor with cell population density models.

In parallel to developing models of tumor growth, modeling drug resistance in cancer, took a central role following the seminal works of Goldie and Coldman (1979, 1983a, 1983b). The Goldie and Coldman models that were based on resistance due to point mutations, were extended to multi-drug resistance and optimal control of drug scheduling (Iwasa et al., 2006; Kimmel et al., 1998; Komarova, 2006; Michor et al., 2006). Recent studies emphasize the importance of the tumor microenvironment as a driving force for drug resistance (de Bruin et al., 2013; Gerlinger et al., 2012). Modeling the spatial dependency becomes more significant due to limited perfusion capability of large molecules and the differences in drug exposure based on their distance from the capillary bed (Minchinton and Tannock, 2006; Trédan et al., 2007; Vaupel and Kallinowski, 1989). Once spatially heterogeneous populations appear, they can also modulate the absorption and metabolism of the nutrients and drugs, which further promotes heterogeneity. Thus, various spatiotemporal models have been developed aiming at understanding the tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment (Anderson et al., 2006; Panagiotopoulou et al., 2010; Trédan et al., 2007; Wu et al., 2013).

In this paper, we develop a solid tumor growth model that describes the dynamics of drug resistance. The model considers a continuous trait variable that represents the level of cytotoxic drug resistance (Cho and Levy, 2017; Greene et al., 2014; Lorz et al., 2015; 2013), which agrees with recent cytometry data analysis that reveals continuum phenotypic spaces (Amir et al., 2013; Bendall et al., 2011; Grover et al., 2016). This allows us to study the selection dynamics under microenvironmental constraints, and the response to cytotoxic and cytostatic drugs. The present model extends the framework of Lorz et al. (2013), Lorz et al. (2015) and Cho and Levy (2017) that was restricted to a radially symmetric and fixed boundary by constantly normalizing the radius. We allow the tumor boundary to take a time dependent asymmetric shape. To model such moving boundary, we incorporate a homeostatic pressure driven growth, given by the porous medium equation (Perthame et al., 2014). The growth term is generalized to incorporate the resistance trait.

The paper is organized as follows. In Section 2, the model involving the tumor concentration and the microenvironment variables is introduced with biological assumptions. In Section 3 we use our model to analytically and numerically study the rate of the tumor growth. The time of a relapse with resistant colonies is studied in Section 4. Section 5 presents results obtained when studying tumor growth in a heterogenous environment. In Section 6 we discuss strategies to optimize the drug administration using a combination of the cytotoxic and cytostatic drug. In Section 7 we use the experiments of Mumenthaler et al. (2015) to simulate non-small-cell lung cancer and its resistance to erlotinib. Concluding remarks are provided in Section 8.

2. A model of chemotherapy for heterogeneous tumors

In this section we present our model for the dynamics of the tumor cell density $n(t, x, \theta)$. We assume a two-dimensional problem in space. The phenotype variable, $\theta \in [0, 1]$, represents the level of resistance to cytotoxic agents, with $\theta = 0$ corresponding to fully-sensitive cells, and $\theta = 1$ corresponding to fully resistant cells. We define the total cell density at each time and space location as

$$\rho(t,x) \doteq \int_0^1 n(t,x,\theta)d\theta, \tag{1}$$

and the cell pressure $p(t, x)$ in terms of cell density according to

$$p(t,x) \doteq \frac{k}{k-1}\rho^{k-1}(t,x), \tag{2}$$

with a constant $k > 1$.

The tumor growth is modeled as a porous medium-type reaction-diffusion equation

$$\begin{aligned}\partial_t n(t,x,\theta) &= G(t,x,\theta)n(t,x,\theta) \\ &+\nu_n \Delta n(t,x,\theta) + \nu_p \nabla\cdot(n(t,x,\theta)\nabla p(t,x)).\end{aligned} \tag{3}$$

The first term on the RHS of (3) is a growth term. The reaction term governing the growth is modeled as

$$G(t,x,\theta) \doteq g(t,x,\theta)\, h(p,g), \tag{4}$$

where $g(t, x, \theta)$ is the growth rate and $h(p, g)$ is an indicator function that restricts the growth term considering the cell pressure $p(t, x)$ and homeostatic pressure $\bar{p}$. $h(p, g)$ is defined with a Heaviside function $H(\cdot)$ as follows,

$$h(p,g) \doteq 1 - H(p-\bar{p})H(g). \tag{5}$$

This function restricts the tumor growth when $p > \bar{p}$ and $g > 0$. We impose $\bar{p} = k/(k-1)$ to ensure that the normalized cell density is bounded as $\rho(t, x) \leq 1$.