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A stochastic multiscale model for acid mediated cancer invasion

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ABSTRACT

Cancer research is not only a fast growing field involving many branches of science, but also an intricate and diversified field rife with anomalies. One such anomaly is the consistent reliance of cancer cells on glucose metabolism for energy production even in a normoxic environment. Glycolysis is an inefficient pathway for energy production and normally is used during hypoxic conditions. Since cancer cells have a high demand for energy (e.g. for proliferation) it is somehow paradoxical for them to rely on such a mechanism. An emerging conjecture aiming to explain this behavior is that cancer cells preserve this aerobic glycolytic phenotype for its use in invasion and metastasis (see, e.g., Gatenby and Gillies (2004) [1], Racker (1976) [2]). We follow this hypothesis and propose a new model for cancer invasion, depending on the dynamics of extra- and intracellular protons, by building upon the existing ones. We incorporate random perturbations in the intracellular proton dynamics to account for uncertainties affecting the cellular machinery. Finally, we address the well-posedness of our setting and use numerical simulations to illustrate the model predictions.

1. Introduction

A recent approach in cancer therapy is to consider the role of tumor microenvironment in the onset of malignancy in tumors. Gatenby and Gillies [3] suggested that environmental conditions may drive the selection of the cancerous phenotype. Hypoxia and acidity, for instance, are factors that can trigger the progression from benign to malignant growth [4,5]. To survive in their environment, tumor cells upregulate certain proton extrusion mechanisms. This boosts apoptosis in normal cells, thereby allowing the neoplastic tissue to extend into the available space. *Tumor acidification* was recognized as an intrinsic property of both poor vasculature and altered cancer cell metabolism. Moreover, the pH directly influences the metastatic potential of tumor cells [6,7].

Starting from these facts, Gatenby and Gawlinski [8] proposed a model for the acid-mediated tumor invasion which uses reaction–diffusion partial differential equations (RD-PDEs) to describe the interaction between the density of normal cells, tumor cells, and the concentration of H^+ ions produced by the latter. Traveling waves were used in this framework to explain the aggressive action of cancer cells on their surroundings [9]. Further developments of Gatenby and Gawlinski's model involve both vascular and avascular growth of multicellular tumor spheroids, assuming rotational symmetry, for which existence and qualitative properties of the solutions were investigated [10]. In [11] the model in [8] for acid-mediated tumor invasion was reconsidered, wherein crowding effects (due to competition with cancer cells) in the growth of normal cells were taken into account. The global existence of a unique solution was proved via an iteration argument.

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All the models mentioned above consider macroscopic dynamics of cancer and normal cell populations which are coupled – still on the macrolevel – with the evolution of extracellular H^+ concentration and possibly also with the concentration of MDEs [12]. It is clear, however, that subcellular, microlevel proton dynamics are actually regulating and are influenced significantly by the events on the higher (i.e., macroscopic and mesoscopic) levels [13,14,5]. Mathematical models studying the interdependence between the activity of several membrane ion transport systems and the changes in the peritumoral space were proposed by Webb et al. [15,16]. They also involve intracellular proton buffering, effects on the expression/activation of MMPs and proton removal by vasculature. [16] also accounts for the influence of alkaline intracellular pH on the growth of tumor cells. Such a model can thus be seen as a first step towards a multiscale setting. The actual invasive behavior, however, can only be assessed when spatial dependence is taken into account. This requires a higher dimensional and more complex modeling framework that couples the subcellular dynamics at microscopic scale with the population dynamics at the macroscopic scale. Micro–macro models of this type (in a different, but related context) were proposed and analyzed e.g., in [17–19].

Stochasticity is a relevant feature inherent to many biological processes occurring on all modeling levels. In particular, it seems to greatly influence subcellular dynamics and individual cell behavior. Models taking this into account were proposed and analyzed in various contexts (cell dispersal, intracellular signaling, radio-oncological treatment, pattern formation) in [20–23]. In the framework of acid-mediated tumor invasion, too, experiments suggest stochasticity in pH dynamics; this refers to variations and uncertainties (essentially due to a random environment) in the behavior of each cell even though they all follow the same biochemical mechanisms. The distribution of intracellular pH (pH_i) at any value of extracellular pH (pH_e) was found to be broader than what was predicted by theoretical models based on machine noise and stochastic variation in the activity of membrane-based mechanisms regulating pH_i [13]. Moreover, excess current fluctuations have been observed in the gating of the ion channels [24].

Motivated by these facts we propose here a stochastic multiscale model for cancer invasion, to be developed in Section 2 and analyzed w.r.t. well posedness in Section 3. Further, in Section 4 we perform some simulation results to illustrate its performance and eventually discuss in Section 5 the results and comment on the potential of this new model class.

2. Model setup

In this section we set up a phenomenological model for the acid mediated tumor invasion. To this aim we identify four main quantities and account for their dynamics: H denotes the proton concentration and refers only to cancer cells, as we are interested in the effect of tumor-induced acidity. Thereby, we take into account both the intracellular protons (whose concentration we denote with H_i) and the extracellular ones, having concentration H_e. The other two quantities are the tumor cell density C and the normal cell density N.

2.1. Microscopic dynamics: the intracellular proton concentration

The dynamics of intracellular protons is described by the following random differential equation:

$$\partial_t H_i = -T_1(H_i, H_e) - T_2(H_i, H_e) + T_3(H_i) + S_1(v) - Q(H_i) + F(\chi_t, H_i) \tag{1}$$

T_1, T_2, and T_3 are real valued functions representing NDCBE, NHE, and AE transporters, respectively.[1] To acquire a concrete form for these transporter terms – in the absence of numerical data – we followed e.g., [15] and tried to mimic for T_1 and T_2 functions the qualitative curves obtained experimentally in [25] for the efflux of protons by NDCBE and NHE in MGU-1 cell lines. For the T_3 function we adopted the approach in [15] and made it a monotone decreasing function of H_i, since the AE acts as a counter-mechanism for the alkalinization of cytoplasm. Furthermore, Q denotes the function representing the loss of free protons due to intracellular buffering (e.g., by organelles). The function S_1 in (1) represents the observed constant acid production rate in cancer cells due to aerobic glycolysis. It is parameterized by tissue vasculature (v). The qualitative features of all these functions are depicted in Figs. 1 and 2.

As a cell is a complex machinery influenced by a plethora of biochemical and background processes, a phenomenological deterministic model is prone to be highly idealized and fails to account for the complex behavior of the intracellular environment and its interactions with the cell's surroundings. One approach to remove this drawback would be to use random terms serving as an ensemble of uncertainties influencing the proton dynamics. Here we consider a state dependent noise of the following form[2]:

$$F(\chi_t, H_i) := F_1(H_i)F_2(B_t^{a,b}) := \vartheta H_i B_t^{a,b}, \tag{2}$$

where $B_t^{a,b}$ is a Brownian bridge process starting at a and ending at b. Thereby, $a, b \in \mathbb{R}$ and ϑ are some independent parameters.

[1] NDCBE (Na^+ dependent Cl^-–HCO_3^- exchanger), NHE (Na^+ and H^+ exchanger) and AE (Cl^-–HCO_3^- or *a*nion *e*xchanger) are specific transporters present on the cell membrane.

[2] Other choices involving e.g., an Ornstein–Uhlenbeck process or a bounded function of a Brownian motion are conceivable as well, see [26] for the use of a Brownian bridge in a problem dealing with a different kind of biological movement.