Research Statement
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1 Interests

My research interest is cancer modeling at the micro- and macro-scales using mathematical analysis and computer simulations. My current research focuses on tumor modeling where I study tumor morphology and its invasiveness using models derived from generalized reaction-diffusion models.

2 Motivation

Cancer development begins with genetic mutations that enable uncontrolled growth and proliferation of cells in the body. Clusters of cancerous cells form tumors that subsist on the nutrients in the surrounding tissue and remain mostly benign until the nutrients run low (avascular tumor). Low levels of nutrient may trigger cells to induce a new capillary network from nearby blood vessels (vascularized tumor). A tumor becomes invasive when cancerous cells invade neighboring tissues or move to distant tissues (metastasis) via the circulatory or lymphatic system, leading to malignancy and the formation of tumors in other locations of the body and causing death.

One of the defining characteristics of aggressive tumors is an unstable morphology, including the formation of invasive fingers and protrusions observed both in vitro and in vivo. Growing protrusions (shape instabilities) are associated with local invasiveness, which is often the precursor to tumor metastasis.

3 Tumor invasiveness as a function of adhesion and proliferation

Pioneering work modeled tumor tissue as a growing body of an ideal fluid mediated by surface tension-like forces at the tumor-host interface. Modern models consider resistance through elastic and viscous stress to account for stretch and deformation properties of the tissue, making the representation more realistic. Our goal is to understand tumor invasiveness and investigate the effects of stress on tumor morphology.

Byrne & Chaplain (1996, 1997) [3, 4] revealed that cell-cell adhesion and external nutrient concentration are key parameters controlling the stability of three-dimensional multicellular spheroids. Extending this work, Cristini et al. (2003) [7] proposed that two non-dimensional parameters could help describe the complexity of tumor shapes observed in avascular (e.g. in vitro) and vascular (e.g. in vivo) conditions. Here, we complement and extend the work in Cristini et al. (2003) [7] by employing three macroscale single-phase sharp interface models, and by applying linear stability analyses to further elucidate the
Following Byrne & Chaplain (1995) [2] and our previous work (Cristini et al. (2003) [7]), we first consider nonnecrotic tumours in a vascularized environment, and later simplify the model to the avascular condition to compare its predictions to our in vitro experiments (Frieboes et al. (2006) [10]). We describe cell-cell adhesive forces by a surface tension at the tumour-tissue interface. Tumour growth is governed by the balance between cell mitosis and apoptosis, as well as cell-cell adhesion. The rate of mitosis depends on the concentration of nutrient that obeys a diffusion-reaction equation within the tumour volume.

We have formulated and analyzed three models describing tumor growth, using three different physical relations to describe the stress and deformation of the tumor tissue: Darcy’s law, Stokes flow, and the combined Darcy-Stokes flow. The Darcy’s law, which models flow through a porous medium, was previously considered by Greenspan (1976) [14], Byrne & Chaplain (1995) [2], Friedman & Reitich (1999) [11], Cristini et al. (2003) [7], and others. Stokes flow, which describes the flow of a very viscous fluid, was studied by Friedman & Hu (2007) [12]. Both models were investigated by Franks & King (2003) [9] and King & Franks (2004) [16]. By adding a viscous stress to Darcy’s law, we formulated the Darcy-Stokes law, also known as the Brinkman equation, which was simulated but not analyzed by Zheng et al. (2005) [20].

At the boundary, we assume the Laplace-Young boundary condition (Young 1805 [19]), which is used in fluid mechanics to model force imbalance between two heterogeneous phases. We assume here that tumour and host cells tend to stay with their own kind, causing an imbalance of adhesion forces at the interface. Finally, we assume the normal velocity at the interface to be in the normal direction, and allow the tumour interface to evolve according to the normal velocity.

Two dimensionless parameters $G$ and $A$ were introduced that describe cell adhesion and cell death, respectively, although the definition of $G$ is model-dependent. The linear stability analyses reveal that these parameters are determinants of tumor shape morphology. We considered an avascular spherical tumor, and triggered a small perturbation on the tumor interface, resembling initial tumor invasiveness. We studied tumor shape stability (the ability of the tumor to return to being spherical or exhibit protrusions) described by the three physical relations and evaluated the consistency between theoretical model predictions and experimental data from small tumors grown in the petri dish in the laboratory [10]. Our results show that the Stokes model is most consistent with experimental data. The model also predicts that tumors tend to grow along paths that straddle the region separating stable and unstable evolution. This can have important implications for treatment as some therapies may push the growth into the unstable region leading to invasiveness, while others may result in stable evolution and reduced invasion. Finally, parameter values for mathematical models can be extracted from a limited set of data to create a self-consistent modeling framework that can be extended to the multiscale study of cancer. A paper concerning this work was recently published in the Journal of the Royal Society Interface [17].
The study in [17] focused on tumors that are nearly spherical. As the next step, we plan to investigate the dynamics of tumors that may be far from spherical to examine the effect of nonlinearities on tumor invasiveness. Simulations of the Darcy model has been done by Cristini et al. (2003) [7] using the boundary integral method. We are currently developing a boundary integral method to study the nonlinear dynamics of the Stokes model. We will also consider other models of soft tissue mechanics such as elasto-viscoplastic constitutive laws and develop a corresponding morphological linear stability theory. Additionally, we wish to extend the model to include tumor interactions with the local environment such as that with the extracellular matrix. The models will allow us to formulate strategies to reduce invasiveness through treatment and manipulation of the tumor microenvironment.

4 Tumor invasiveness in the migration/proliferation dichotomy

Tumor invasion of normal tissue is a complex process involving cell migration and proliferation. In another study, we look at the invasiveness of glioblastoma multiforme, an aggressive form of brain tumor where cells invade the tissue in a diffuse manner making them difficult to treat since the low density of tumor cells that travel to other areas of the brain go undetected. Experimental evidence suggests that cell motility and proliferation are inversely correlated in gliomas [13], with proliferating tumor cells moving slowly and rapidly migrating tumor cells proliferating slowly. This observation is commonly referred to as the migration/proliferation dichotomy. Several recent studies have investigated the influence of the migration/proliferation dichotomy on tumor invasion [1, 5, 6, 8, 15].

In order to understand better the invasiveness of malignant gliomas and what controls the change in cell phenotype, we develop a mathematical model of reaction-diffusion type and propose that phenotypic changes are is regulated by the cell density.

We decompose the tumor cells into two sub-populations: a migrating population and a proliferating population. We use a reaction-diffusion framework to model population spread (assuming linear diffusion) and logistic growth to model cell proliferation. The phenotypic switch is modeled by an exchange between the two sub-populations using a density-dependent probability for an immotile cell to become motile in response to the local density, and vice versa. We consider two complementary mechanisms for the phenotypic transitions. Under the first mechanism ($M_1$) the cells become more motile (i.e. switch from immotile (Type 2) to motile (Type 1)) when the local total density is low (sparse environment), and less motile when the density is large (crowded environment). Conversely, under the second mechanism ($M_2$), cells become more motile when the local total density is high.

In the absence of proliferation, motile cells can enter resting phases and become immotile, which characterizes a sub-case of our model (go-or-rest). When proliferation is included, only immotile cells can proliferate, which characterizes a go-or-grow model.
We have found that neither model exhibits Turing instabilities under the switch mechanism \( M_2 \), whereas under the autocatalytic mechanism \( M_1 \), Turing instabilities can occur for certain parameter ranges, leading to cell patterning. Additionally, in the go-or-rest model, immotile cells accumulate to form aggregates due to a crowding effect when \( M_1 \)-regulated, which in turn limits cell motility. In the go-or-grow model, the same mechanism leads to oscillatory dynamics. Another interesting aspect of the go-or-grow model is the presence of traveling wave behavior, where traveling wave solutions exist with either a spatially uniform core, oscillations at the wave front and stationary pattern within the core, or oscillatory dynamics extending to the entire domain due to Turing instability. These dynamic, heterogeneous spatio-temporal solutions demonstrate the ability of the density-dependent go-or-grow mechanism to produce complicated dynamics associated with tumor heterogeneity and invasion. Details of this work can be found [17], which was recently submitted for publication.

As a next step for this line of study, we will investigate the influence of the phenotypic switch on the emergence of front instabilities associated with invasive fingering.

References


