Hybrid multi-scale modeling of brain tumor progression

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Abstract. Cancer is the leading cause of premature death in industrialized countries. According to the World Health Organization, in 2005, almost 11 million new cases of cancer were diagnosed, and 7.6 million people died from the disease. A better understanding of tumor growth is essential for the development of therapeutics for solid cancers. Tumor progression depends on the intricate interplay between biological processes that span the molecular and macroscopic scales. We present a mathematical agent-based model that describes the progression of a solid tumor by capturing the interplay between the temporal-spatial distribution of key biochemical cues (e.g., nutrients, growth factors) and the intracellular signaling pathways (e.g., MAPK pathway) that determine the fate of every tumor cell. The model was used to simulate the early stages of tumor development, before the onset of tumor-induced angiogenesis.

1 Introduction

Cancer is the second leading cause of death in the United States, accounting for 1 out of every 4 deaths (cancer.org, accessed September 25, 2007). Research efforts to try to alleviate this disease have resulted in declining death rates for the 4 most common cancers (i.e., prostate breast, lung, colorectal) (cancer.gov, accessed September 25, 2007). However, for some cancers, such as glioblastoma multiforme, there have been no significant treatment advancements in the past 25 years. Median survival for patients receiving optimal treatment (which includes surgical, radiation, and chemotherapy) is only about 12 months, with a very small chance of long term survival [37]. The dismal prognosis for patients diagnosed with glioblastoma has sparked considerable efforts, clinically and otherwise, to understand the progression
of this disease [17, 39, 31, 35, 19, 15, 9]. Mathematical models and computational tools are increasingly being accepted in cancer research as aids for visualizing and integrating information, testing different mechanism hypotheses and suggesting optimal treatment strategies [4, 23, 29, 42, 14, 16, 34, 38, 41].

The progression of a solid tumor is the ultimate outcome of several time and space dependent interacting processes which entail the combined intracellular and extracellular events that govern cell survival, proliferation, and migration, as well as angiogenic, inflammatory, and immune responses. Modeling and computations have already made significant headway by introducing quantitative abstractions of key signaling cascades (e.g., EGFR, VEGFR) that direct the cell’s response to extracellular stimuli at the micro-scale [32, 28, 20] as well as tumor evolution descriptions [24, 5, 41, 2, 11] at the macro-scale. Brain tumor models are a subset of a broad spectrum of general tumor progression models that vary in their level of detail [3, 7, 25, 26, 30].

Mathematically, one of the most sophisticated frameworks is the so called agent-based modeling. The key idea of this approach is to capture the evolution of a solid tumor as the result of the collective behavior of individual cells. In turn, the behavior of every cell is predicted by a set of rules parameterized by the level of key biochemical cues [5, 41]. However, mathematical and computational requirements have driven these initial attempts to use simplified descriptions of the temporal-spatial distribution of extracellular species, the intracellular events or both. In this work, we present a multi-scale agent-based model of describes the progression of a solid tumor by capturing in detail the interplay between the temporal-spatial distribution of key biochemical and the intracellular signaling pathways that determine the fate of every tumor cell. In the following sections we present a brief description of the model and the main simulation results.

2 Model description

In this section, we establish a model’s framework to describe tumor growth and invasion resulting from the proliferation and migration of individual tumor cells under biologically relevant conditions that consider both internal cell dynamics and the surrounding extracellular matrix. To achieve this goal, a large number of biochemical components of both the intra- and extra-cellular domains were integrated to capture the principal characteristics of tumor progression. Specifically, we consider that the state of every tumor cell (i.e., proliferating, migrating, quiescent or necrotic) will be determined by the level of activation of the Ras-Raf-MEK-ERK cascade and the local glucose and oxygen levels. The Ras-Raf-MEK-ERK cascade is triggered by the activation of the EGF receptor (EGFR) by the transforming growth factor α (TGFα) which diffuses from the blood vessels and also is produced by tumor cells. The computational details of the various different components of the model are discussed below.

We consider a 2D extracellular environment with a blood vessels distribution as shown in Fig. 1. Glucose, oxygen and TGFα concentrations are assumed to be continuous fields (thus allowing us to employ a set of PDEs to describe the
material balances). The cells are treated as discrete entities that may occupy a lattice point on a regular square grid. Healthy cells are assumed to consume glucose and oxygen at a constant rate and are destroyed on contact by invading tumor cells. The parameters of extracellular model were collected from the open literature [41, 24, 21, 10] when available or estimated to fit the reported average glucose, oxygen and TGF\(\alpha\) physiological concentrations [13, 12]. Tumor cells were also assumed to modify the extracellular matrix, resulting in a decrease of the effective diffusion coefficients [40]. Blood vessel provided the necessary nutrients to the tumor cells (i.e., glucose, oxygen and TGF\(\alpha\)). When encircled by proliferating tumor cells, vessels can become compressed and destabilized (vessel co-option) [22]. In this work we assumed that the tumor compresses a vessel when tumor cell proliferates into the space corresponding to the vessel. The vessel is then completely degraded and the tumor occupies the vessel space in its entirety. As stated above, tumor cells can be necrotic, quiescent, proliferating or migrating depending on the local concentration of glucose and oxygen and the activation level of their MAPK pathway. Viable tumor cells (i.e., non-necrotic cells) consume glucose and oxygen at higher rates than normal cells and produce TGF\(\alpha\) at rate determined by intracellular signaling. Necrotic cells were assumed to be completely inert, simply occupying space. The intracellular MAPK pathway is represented by a set of ODEs [32] to calculate the TGF\(\alpha\) dependent activation level of ERK and the amount of autocrine TGF\(\alpha\) produced.

Mathematically, the tumor growth process is mathematically represented by the following hybrid system of partial and ordinary differential equations,

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\begin{align*}
\frac{\partial C_{\text{ext}}}{\partial t} &= \nabla \cdot (D(z)\nabla C_{\text{ext}}) + S(z, C_{\text{ext}}, C_{\text{int}, i}) - R(z, C_{\text{ext}}, C_{\text{int}, i}), \; C_{\text{ext}} \in \Omega \\
\frac{\partial C_{\text{ext}}}{\partial z} &= Q(C_{\text{ext}}), \; C_{\text{ext}} \in \Gamma \\
\frac{dC_{\text{int}, i}}{dt} &= f_i(C_{\text{ext}}, C_{\text{int}}), \; i = 1, ..., N
\end{align*}
\]

where \(C_{\text{ext}}\) denotes the concentrations of extracellular species (i.e., glucose, oxygen and TGF\(\alpha\)), \(C_{\text{int}}\) denotes the concentration of the intracellular species (\(N = 14\) in the current model). \(\Omega\) is defined as the computational domain of the PDEs and \(\Gamma\) is the boundary of \(\Omega\). \(Q(\cdot)\) specifies the Neumann boundary condition. \(S(\cdot)\) and \(R(\cdot)\) refer to production and consumption terms respectively. \(D(z)\) is the diffusion coefficient which depends on the location of the tumor cells. \(f_i(\cdot, \cdot)\) are the right-hand side functions of the ODEs describing the intracellular dynamics, for which the intracellular processes are described either by mass action kinetics or by Michaelis-Menten kinetics [32].

The simulation is started with the system at steady-state with the tissue consisting of only normal cells, at which time, a small core of 16 cancer cells (a \(4 \times 4\) square) is introduced at the center of the domain. At every time step (\(\Delta t\)), the extracellular (PDEs) model is integrated to determine the glucose, oxygen and TGF\(\alpha\) concentration profiles (see Fig. 2). These concentrations are inputs to the intracellular model for every cell, which is integrated to determine the ERK activation and
Figure 1. Spatial domain with irregular distribution of blood vessels. The graph shows the initial oxygen level. The red spots correspond to the location of the blood vessels. Tumor growth takes place within the square at the center of the graph and the surrounding space is a buffer region.

the TGFα production rate, which then becomes an input to the PDE, which is integrated again until both the intracellular and extracellular models report the same value for TGFα. The phenotype of every cell is then determined depending on the level of glucose, oxygen and ERK activation and the position of cells and spatial dependent parameters are updated. The integration proceeds then in time until a cancerous cell reaches the boundary of the simulation domain or a pre-specified time limit is reached. The evolution rules to determine the phenotype of each cell are as follows:

- The probability of a viable tumor cell to remain alive depends on the local glucose and oxygen concentrations; there is a high probability it will become necrotic if their levels drop below a pre-specified threshold.
- If a viable cell “survives”, then its phenotype is decided by a biased random process depending on the strength of the ERK activation. The decision process assigns to the cell a higher probability to become (or remain) quiescent,
migrate or proliferate for low, medium or high ERK levels, respectively; the phenomenological threshold values are based on experimental observations [18].

- A cell that proliferates grows at a rate that depends on the glucose and oxygen concentrations; it will eventually divide if there is a free space in its neighborhood (i.e., not occupied by another cancer cell), otherwise it will become quiescent.

- Similarly, a tumor cell with migrating phenotype can move only to a free space on its neighborhood. In order to select the direction where the cell will move, we are considering that the cell can move to any free space in its neighborhood with a probability parameterized by the glucose and oxygen levels (is similar to the biased random walk of [1]).

3 Simulation results

We used the proposed model to assess the effect of the metabolic unbalance provoked by the tumor cells on the histological characteristics of the tumor. We also investigated the role of the autocrine signaling of TGFα and its effect on the growth rate of the tumor. In the presented simulation a real life source of nutrients topol-
ogy was used, based on medical images. In this section we present the simulation results.

The unbalance between the higher metabolic demand of the growing tumor and the supply capacity of the degenerating vasculature results in a decrease of glucose and oxygen below the level required for cell viability (Fig. 3(f)). The direct consequence of the drop of nutrient levels is the formation of a core of necrotic cells. The first necrotic cell appears at day 29 and by day 35 a incipient necrotic core can be clearly observed (Fig. 3(c)). As can be seen in Fig. 3(b), the death rate of tumor cells increases abruptly at day 33, however the number of proliferating and migrating cells continues to increase almost at a constant rate while the rate at which tumor cells become quiescent seems to decrease slightly. The tumor grows with a regular, compact, circular shape irrespective of the distribution of blood vessels as can be seen in Fig. 3 (a, c, and e). However, the thickness of the shell of alive cells depends on the concentration of nutrients at the edge of the tumor and consequently on the location of the blood vessels (Fig. 3(e)).

The effect of the autocrine signaling of TGF\(\alpha\) on the growth rate of the viable cells can be observed in Fig. 3(b) and (d). At the earliest stage of the tumor development the level of TGF\(\alpha\) is low and the quiescent and migratory phenotypes are favored. However, the level of TGF\(\alpha\) is enough to activate ERK and stimulate the secretion of TGF\(\alpha\) by the tumor cells. Since the population of tumor cells is small, the accumulation of TGF\(\alpha\) is slow. It takes approximately 13 days to reach the level of TGF\(\alpha\) that favors the proliferation of tumor cells. At this point, there is a marked change in the rate of growth of the viable tumor cells and a concomitant increase in the level of TGF\(\alpha\). As the tumor grows, TGF\(\alpha\) surpasses the level required to reach the maximum level of ERK activation to such extent that the subsequent decrease on the TGF\(\alpha\) due to the formation of the necrotic core does not decrease the activation level of ERK (Fig. 3(f)). This abnormally high level of TGF\(\alpha\) (or other growth factors in general) could make blocking its signal using targeted inhibitors difficult and therefore it contributes to the limited therapeutic effect that has been observed in some targeted therapies [33, 36]. This result suggest that targeting disruptions of the autocrine loop for TGF\(\alpha\) could be a complementary strategy to enhance the clinical effect of such targeted strategies.

4 Conclusions

Mathematical modeling and computations can be efficiently used to organize and integrate the ever increasing experimental data in cancer research as well as powerful tools to explore and generate new testable hypothesis. In this work we presented a multi-scale agent-based model to simulate the progression of a solid tumor. The model integrates processes that occur at different levels such as the diffusion of nutrients and signaling molecules (i.e., tissue level) and the signaling cascade that direct the fate of the tumor cells (i.e., cellular level). We used the model to simulate the early stages of tumor development, focusing on the effect of nutrient supply and the autocrine signaling of TGF\(\alpha\) on the growth rate and characteristics of the tumor. This model is the starting point to construct more complete model that include more
Figure 3. Simulation results of tumor growth. Snapshots of the tumor at different times (a, c, e). Time evolution of the number of tumor cells (b), maximum TGFα concentration within the tumor and maximum ERK activation (d), and minimum glucose and oxygen levels (f). The insets in (d) correspond to the concentration profiles of TGFα at the time indicated by the arrows.
and more detailed descriptions of signaling pathways (e.g., PI3K-Akt, PLC), tumor induced angiogenesis, pharmacokinetics/pharmacodynamics. We will furthermore focus on its extension to a 3D space, a computationally difficult extension which requires specific refinement of current simulation methodologies.
Bibliography


