Cellular Automaton Model for Glioblastoma Cell Proliferation

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Introduction

Astrocytes are the most abundant glial cells within the Central Nervous System (CNS) and form an integral part of the blood-brain-barrier[1]. Astrocytomas are the most common primary CNS tumor[1,2]. Astrocytomas' incidence is highest in the frontal lobe and this is hypothesized to be due to certain quantifiable parameters primarily oxygen diffusion, vascularity, and natural cell death rate[3]. Astrocytomas are graded from I to IV. Grade IV Astrocytomas are termed Glioblastomas and have an abysmal 5-yr survival rate of <5% and a 10-yr mortality rate of 99.3% all due to a high proliferation and recurrence rate[4]. Modeling Glioblastoma growth allows for more accurate growth predictions and prognoses[4]. Modeling is also imperative as anticancer treatment plans are increasingly individualized to each patient's needs[4].

Methods

The simplest growth model for tumors in the body is an exponential growth function doubling at a constant rate, so from 1 → 2 → 4 and so on. However, this model is only accurate at the start of tumor growth[5] (Fig. 1). A logistic model is more accurate as it depicts initial exponential growth with an eventual tapering off, exhibiting the tumor reaching carrying capacity[6] (Fig. 1). This carrying capacity is not an absolute value but a range within which a tumor's size fluctuates[6]. This fluctuation is termed stochastic behaviour and a model that fits initial exponential growth, carrying capacity and accounts for stochastic behavior is a Cellular Automaton (CA) model[7]. CA models are common in oncology with a growing body of literature supporting their accuracy especially considering the low computing power required to run the 2 dimensional CA models[7].

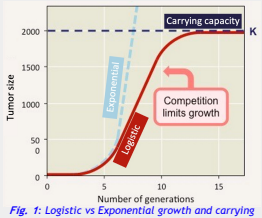

Fig. 1: Logistic vs Exponential growth and carrying capacity

Our model is a 2D CA model that starts with a central tumor/stem cell (red square). That cell can then divide in *up to* 8 directions these possible directions make up that cell's 'neighborhood'. So, a 2D neighborhood CA model can have 2^8=256 possible neighborhood combinations just from one step (yellow arrows in Fig. 2). Each grey cell can then divide outwards. The corner grey cells in 3 directions and other greys in 1 direction (green arrows). So, within 2 steps we yield $2^8*((2^3*4)+(2*4))=10240$ different possible growth combinations. In essence, at each step i.e. from red to grey; grey to white each cell checks how many neighbors it has in each direction. If it's neighborhood it too dense it is deemed quiescent and survives but any cell deemed quiescent >5 times dies. If its neighborhood isn't too dense it is deemed proliferative and can divide in certain direction(s) taking into account its neighborhood density i.e *generally* outwards (but not always due to the complexity of the model and cell death). To model this discrete dynamic system we used NetLogo, as it is the go-to program for biological modeling[7]. Our model was based on an existing model by Uri Wilensky but heavily modified to make it glioblastoma specific (Fig. 3).

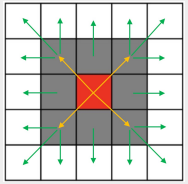

Fig. 2: Depicts the basics of a 2D CA model with red being the central cell

Results

Our NetLogo model yields the three parts of a glioblastoma i.e. a proliferative outer region, a quiescent middle region, and necrotic core in order of increasing cell density (Fig. 3 image). As the cells age, they become darker blue and this is why the center of the tumor is dark, showing the necrotic and quiescent cells while the edges are proliferating depicted by whiter cells. Note that our CA model also exhibits a logistic growth pattern with a fluctuation about the carrying capacity (Fig. 3 plot) . The tumor stabilises about this carrying capacity unless the parameters are changed. The parameters are *Initial_tumor_size* which is number of cells at the start of modelling. *x_coord* and *y_coord* which changes the location of the tumor to visualize the affected structures and *leave_trail* which shows the general direction of tumor growth.

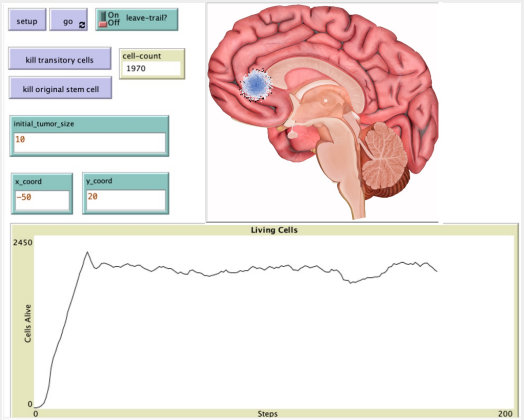

Fig. 3: Depicts the NetLogo 2D CA model with all the adjustable parameters on the left and the tumor model image in the top right with the cells alive (growth) VS steps plot at the bottom

Discussion

Our model depicts initial exponential growth with a fluctuation about the carrying capacity once it is reached, mimicking a tumor's real-life stochastic behavior[6]. The tumor also grows toward nutrient availability/ lowest cell density creating three regions mimicking real life tumor behavior[8]. However, the CA models can be made more accurate by accounting for growth rates based on the anatomical location but this data is highly inconsistent[3]. To make the model more accurate and applicable it also needs to be 3D but this is a huge challenge. Modeling in 2D yields 256 neighborhood states in the first step, but A 3D CA model would have a 26 cell neighborhood and 2^{26} neighborhood states and would likely crash in a few steps. To improve accuracy and give the CA model real predictive power it needs to predict growth in terms of elapsed time and not discrete "steps" but growth rate data is scarce[3]. Although accurate in certain aspects, our CA model requires more computing power and real world data to improve patient outcomes through predictive modeling.

Works Cited available at bit.ly/worksCitedCA