Modeling Brain Tumors with Cellular Automata

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02-712 Computational Methods for Biological Modeling and Simulation

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Introduction

Here, we develop a brain tumor growth model using Cellular Automata. Brain cancer can be fatal, with survival rates of 21% for those over 40 [1]. A comprehensive understanding of tumor growth dynamics and rates guides crucial treatment aspects, including diagnostic protocols, surgical interventions, and optimal screening timelines. Cellular Automaton (CA) is a fitting mathematical framework to model tumor growth. CA models are agent-based, where the simulation environment is divided into a lattice and cells are assigned to the lattice. Each cell is an individual agent with limited information about its local environment and neighbors, which is used to define the cell's state. By defining rules on how cells interact based on their state, emergent properties can arise from a CA model. Since tumors are emergent systems, consisting of many individual cancer cells that make "individual decisions" according to local information - a CA is useful for modeling tumors. Cells within an organism act on information only known to them and differentially use the same genome to respond in various ways to their environment, making a CA an appropriate analog to cellular biology. A CA state can be a biological cell type or subtype, while the lattice is the body's environment. We use these rules to simulate temporal tumor dynamics in a two-dimensional tumor growth region. This approach holds promise in contributing valuable insights beyond theoretical realms, augmenting our understanding of brain cancer dynamics.

Methods

Cellular Automaton Model Specification

A CA model consists of a grid of cells, a set of states for each cell, a neighborhood configuration defining interactions, and transition rules determining how cells change states over discrete time steps. Our particular CA model of tumor growth attempts to reflect the idealized tumor structure depicted in Figure 1, with the growth region consisting of the following types of cells: proliferative tumor cells at the periphery, whose reproduction causes expansion of the tumor; nonproliferative tumor cells interior to the proliferative layer that are no longer able to divide; necrotic cells at the core of the tumor; and an external region of healthy, non-tumor cells. The behavior of the cells in the model depends on their type.

We apply probabilistic rules to the cells in our simulation to account for the heterogeneity of genuine tumors and the inherently stochastic nature of factors driving tumor growth.

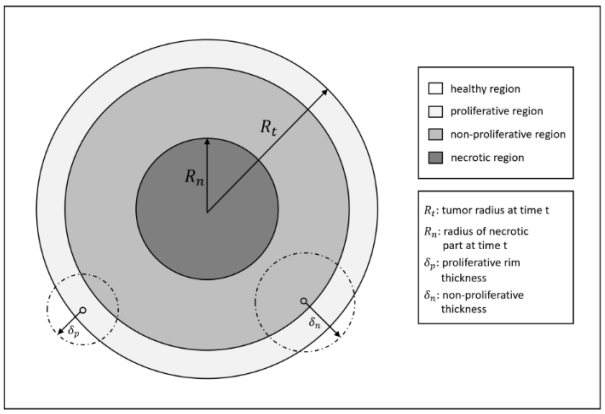

Figure 1: Idealized Model of Tumor Structure [Ref. 3]

The irregular spatial arrangement of cells across the region is attained through a process known as random sequential addition. This involves adopting random lattice vertices within the region, ensuring that all inter-vertex distances surpass thresholds R_s. These thresholds are dependent on the vertices' distances from the center of the region, as indicated in Equation (1).

2D Equations	**3D Equations**	
$R_s = 0.146r^{1/3}$	$\mathrm{R}_s = 0.146r^{2/3}$	(1)
$P_d = P_o(1 - \frac{r}{R_{\max}})$	$\mathrm{P}_d = P_o(1 - \frac{r}{R_{\max}})$	(2)
$\delta_n = aR_t^{1/2}$	$\delta_n = aR_t^{2/3}$	(3)
$\delta_p = bR_t^{1/2}$	$\delta_p = bR_t^{2/3}$	(4)
$R_t = \frac{\sum_{i=1}^{N_p} r_i}{N_p}$	$\mathrm{R}_t = \frac{\sum_{i=1}^{N_p} r_i}{N_p}$	(5)

Equations for 2D and 3D simulations differ in exponents to distance terms used in lattice generation and application of certain rules regarding cell state transitions. Most simulations we have executed, including all those visualized in the results, have been 2D.

The result is a lattice of randomly distributed cellular centers that is generally denser toward the center of the tumor region. The spatial arrangement of cells can be visualized using the Voronoi Tessellation, which partitions the region in such a way that each partition contains all points closer to a lattice vertex than any other. By obtaining the related Delaunay triangulation of the lattice vertices, each cell's immediate neighbors can be deduced, from which we can build an adjacency matrix. Consequently, the model possesses an implicit network structure, enabling the application of rules to cells not only based on their type but also on their local structure.

Simulating Tumor Evolution

Table 1: Constant Input Parameters

Parameter	Description
P_0	Probability of cell division linked to growth rate
a	Necrotic thickness controlled by nutrition
b	Proliferative thickness regulated by nutrition
$R_{\max}$	Maximum tumor extent due to pressure

As the model simulation progresses through discrete time steps from an initial state of one central proliferative cell, the cellular automaton model evolves by successive updates to cells' types through the application of probabilistic rules. First, proliferative cells are chosen for replication based on position *r* with a probability p_d, as defined by Equation (2). When a dividing cell is identified, its immediate neighbors and successive neighbors within a distance of $\boldsymbol{\delta}_p$, calculated using Equations (4) and (5), are examined. If a non-tumor cell is encountered within this range, it is transformed into a proliferative tumor cell, reflecting the displacement of the non-tumor cell by the new proliferative cell. In cases where no suitable cell is found (due to insufficient space), the cell transitions to a non-proliferative state. Then, non-proliferative cells located beyond a distance of $\boldsymbol{\delta}_n$ from the tumor periphery undergo necrosis, simulating a response to inadequate nutrition, as determined by Equations (3) and (5).

Results

The first goal of our project was to define a realistic matrix to represent cells in the tumor growth region. We wished to incorporate irregular shape and size, with smaller cells towards the center of the tumor. We successfully implemented a grid of randomized cells using Voronoi Tessellation and Delaunay Triangulation. Our grid is visualized in Figure 2.

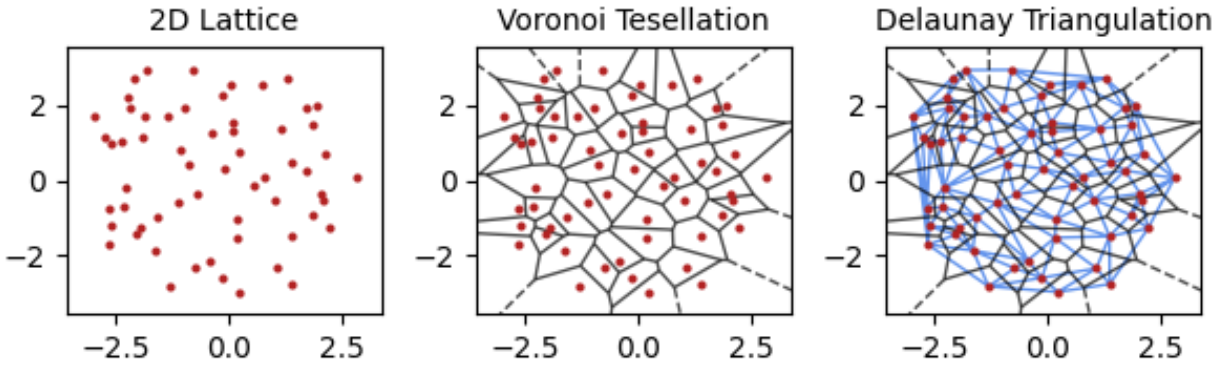

Figure 2: Grid Formation Procedure using random sequential addition in the first plot, followed by Voronoi tessellation and Delaunay triangulation.

We then implemented code to run our simulation in 2 dimensions as described in our methods. Our model includes several parameters, which must be tuned to find the correct values such that the model creates a realistic depiction of tumor growth. We used grid searching

methods to determine optimal parameters to achieve tumor growth resembling the tumor growth model reflected in Figure 1. We tried a range of values for parameters a and b with the set value $p_0 = 0.6$ (Figure 3). We looked for parameters that consistently, defined as in 60% of trials, ran for the entire number of 100 timepoints. This means that the tumor did not consistently die out quickly. We then visualized tumor cell states over time for the ideal parameter combinations to find which parameters showed tumor growth patterns reflecting the expected behavior visualized in Figure 1. A set of ideal parameters to replicate brain tumor growth patterns were determined to be $a = 0.9$, $b = 2$ and $p_0 = 0.6$ (Figure 4a).

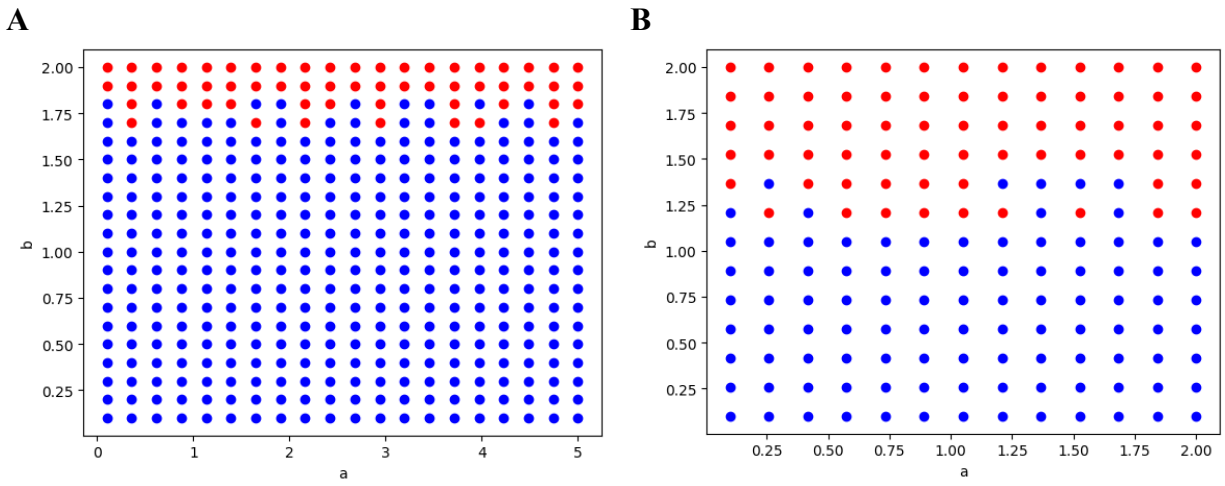

Figure 3: Hyperparameter tuning for *a* and *b*. Red points indicate values of *a* and *b* that provide simulations with an average length of 50 timesteps across attempted simulations. Notice successful proliferation for b ≥ 1.7 for (A), whereas b ≥ 1.25 for (B)
(A) Grid search using 1000 cells initial lattice
(B) Grid search using 2000 cells initial lattice

We also explored the parameter space to understand how variation in the parameters can lead to different tumor growth behavior. When p_0, the baseline probability of cell division, is decreased, the tumor grows at a slower rate (Figure 4c,d). When a, necrotic thickness, is increased, tumor cells remain non-proliferative and do not enter the necrotic state as often (Figure 4b). When b, the proliferative thickness, is decreased, the tumor cells do not replicate as quickly, as cells do not have enough nutrition to expand (not shown).

We additionally wanted to investigate the tumor growth rates over time with different parameter configurations (Figure 4d). With our optimal parameters, visualized in pink, we see exponential growth for about the first 60 timepoints. For the rest of the timepoints, we see leveled growth resulting in a plateau, as the tumor begins to lack resources due to its large size. We see similar growth behavior for the parameters used in figure 3b, where the tumor grew, but did not become necrotic, which is expected. When p_0 is decreased in value, we see slower, non-exponential growth. We expected slower growth, and it is an interesting result to see that the tumor does not grow exponentially and that it does not reach a plateau. This is a result that the

tumor with a slower growth rate does not run out of resources, and therefore continues to grow at the same rate for the entire time the simulation was run. It is expected that the tumor would reach a plateau if the simulation was run for more timepoints for this set of parameters.

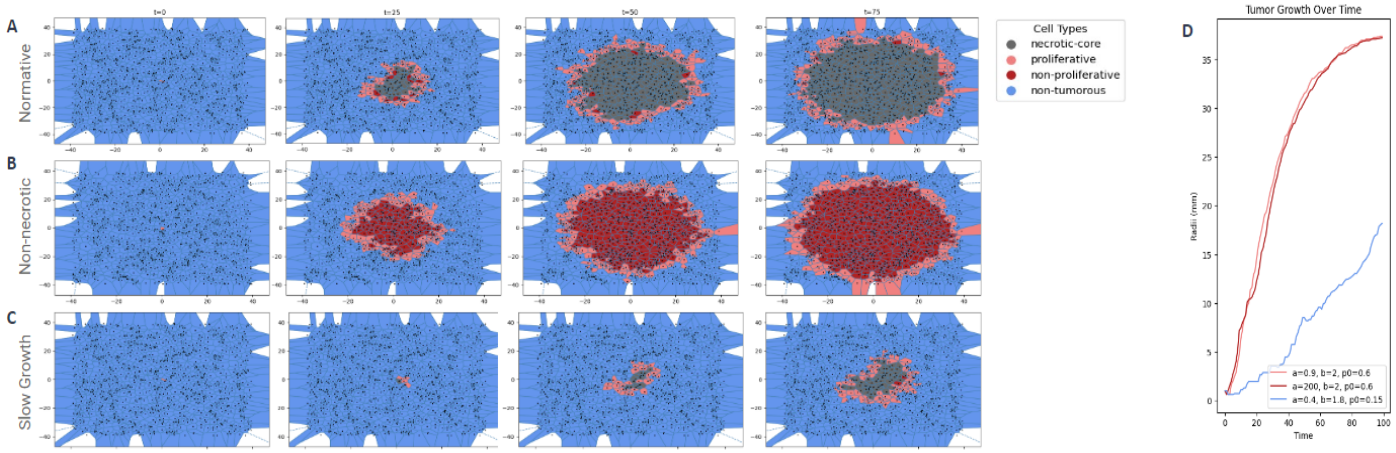

Figure 4: Tumor growth Progression with varied parameters

Finally, we implemented the model for 3-dimensional tumor growth, which required different equations to define tumor growth, as described in the methods section. We also performed grid search for optimal parameters, as the system is constrained differently when surrounded by cells in all directions, affecting the probability of division. We found it more difficult to determine optimal parameter combinations for the more complicated 3-dimensional system. Overall, we determined that parameters of p_0=0.6, $b \geq 3.5$ and values of a in the range [0,2] resulted in the simulation running for 100 timepoints in at least 60% of trials via grid search, meaning that these are the range of parameters we would need to investigate further via visualization for expected tumor growth behavior.

Discussion

CA models are suitable for modeling emergent systems due to their agent-based nature. Our implementation is particularly useful for modeling tumors because it attempts to reflect biology in important ways: First, our model allows tumor cells that are surrounded by other cells to divide based on a probabilistic equation designed to model tumor mechanical confinement pressure coupled with equations designed to model nutritional gradients within the tumor and paracrine signaling between cells. Second, the probabilistic nature of our model allows us to directly mimic the stochasticity of nature. By having probabilistic equations which reflect the underlying probabilities in biology, we can get an idea of how likely a single cancer cell will become a full blown tumor or instead die out, based on parameters selected and a given initial lattice. Some simulations result in tumors evolving and others simply die out in a few steps which mirrors reality as not all cancer cells become tumors. Third, the simulation is relatively computationally efficient: we have an unchanging lattice and a set of states, and the states of all cells within the lattice get updated each time step according to four rules, enforcing model simplicity while retaining the desired biological relevance. Since the amount of communication between cells is limited to neighbors within a small distance, this means the model could be

parallelized with moderate ease by appropriately handling sub-lattice boundaries. Finally, the model generalizes easily to three dimensions. We have run 3D simulations successfully with minimal modification, namely in exponents of terms in the equations used for application of distance-based rules.

While our model can show the expected growth pattern of a brain tumor with appropriate parameters, we have made several assumptions that cause our model to be a simplification of the true tumor growth process in the brain. The cells in our matrix, while non-uniform in shape, are immobile. Cancer cells are mobile, and are capable of metastasis in actuality. To model this behavior, the cell lattice could be made more realistic by allowing cells to change the extracellular matrix as the tumor develops. We also assume the tumor is monoclonal, with only a single tumor genotype. This is unrealistic, as tumors often gain additional mutations and form subpopulations due to the rapid replication rate. We assume that if a tumor cell is selected to divide in a timestep but it cannot find a location to divide, it becomes non-proliferative, which may not always be the case. An additional simplification used in our model is that we set the tumor center to the initial cancerous cell. As the tumor grows, we assume that the initial cancerous cell will remain at the center, and calculate probabilities of cell division based on this assumption. It is possible however, that the cell expands in one direction, and the initial cancerous cell is not close to the center of the tumor, impacting the accuracy of the tumor growth model. Finally, the inherently stochastic nature of the random sequential addition process generating the system's spatial lattice can give rise to inconsistent evolution of the system unless a sufficiently large number of lattice points are generated in the space. In our execution of the model, we tended to favor moderate numbers of lattice points within the defined region out of runtime and visualization considerations, and consequently observed that the resulting density of the lattice toward the tumor center could give rise to different growth behavior over the evolution of the system, as seen in figures 3a and 3b.

Course Relevance

One of the course's main objectives is to teach us how to formally define and reason about mathematical models of biological systems. Our project, which constructed a CA model to mimic solid tumor growth, fits well within this objective. Four course topics essential to the building of our model include: stochastic modeling, implicit network structure, population dynamics, and parameter tuning.

Stochasticity is integral for this model. We used a probabilistic model to capture how likely a cancer cell will divide based on proximity to the tumor center. This accounts for the inherent stochasticity in normal cell division [4] and genomic instability resulting in more irregular, unpredictable cell division for cancer cells [5]. By allowing cancer cells to probabilistically divide, the model can capture how likely a cancer cell will become a full tumor based on the parameters selected. By lowering the base probability, p_0, we can see cases where the tumor ends up growing some but dying out much earlier than other selections of p_0 across many simulation attempts. A classic, deterministic approach to modeling tumor dynamics is the Gompertz equation [2]. This sigmoidal function mimics a perfectly spherical tumor, with slower growth rate at the start and end of the tumor and exponential growth rate during the middle stages of the tumor. This theoretical result provides a good mathematical model of ideal

scenarios but does not account for the stochastic nature of cell division and cancer. The CA model offers a logical framework to incorporate probabilities into sigmoidal growth modeling of tumors.

Delaunay triangulation creates sets of simplices embedding the lattice into a network/graph structure where each node is a cell with edges connected to nodes representing cells directly adjacent to the cell in the lattice. This operation provides a convenient method for building an adjacency matrix between cells in the lattice. Thus, the network structure of our cells based on the biological lattice generated through RSA followed by Voronoi tessellation is highly important for the viability of the model. As mentioned in the discussion, the initial lattice generated has a large impact on simulation results (Figure 3A vs 3B). Learning which types of network structures generated by RSA/Voronoi would be an important next step in future applications of the model.

The cellular automaton model we have defined is also similar to the Moran process. In the Moran process, a population has a constant of N individuals. At time t=0, one of these individuals has genotype-A and N-1 individuals have genotype-B. The Moran process is a simple model for studying fixation probability of mutants in a population. Likewise, we can explore the probability that a tumor dies out early or ends up taking over the entire lattice/tissue representing the space inside the brain. Predicting the likelihood certain mutations cause a cancerous cell to move beyond the tumor initiation stage to tumor progression is an important problem that our model could be applied towards [6].

Finally, we had to perform parameter tuning. We performed a basic grid search over the a and b parameter space. We demonstrated from the grid search that a only affects necrotic regions and therefore, the proliferation is not controlled by a. That is, given a sufficiently b and p_0 we can choose any value of a and get somewhat reasonable results. In the future, fitting the parameters to experimental results would provide a more informed approach, allowing us to perform a true parameter optimization. We could define a loss function across each time point predicted by the model and images from cancer plates (2D) or tumor cross sections (3D), and try to find the parameters which minimize the difference in coloration between the two.

Conclusion

A Cellular Automaton (CA) is a mathematical model of a spatially distributed process consisting of an array of cells that evolve stepwise according to states of neighboring cells and a set of state-dependent rules. These models are advantageous in simulating intricate biological processes in organisms. Kansal et al. developed a 3D CA model that can simulate the growth of proliferative brain tumors. Jaki subsequently adapted the prior work by incorporating angiogenesis, an extracellular matrix and oxygen and nutrient coefficients, presenting a 2D CA model for the simulation of brain tumor growth. Our model uses the same basic framework of the Kansal model and the Jaki thesis, with the same cell types and rules driving system evolution.

We were able to simulate the progression of brain tumor growth within two-dimensional space with our implementation of the CA growth model. Reasonable tumor growth trajectories and anomalous growth trajectories could be observed with a small number of cell types, rules,

and parameters; simulating the evolution of the model is consequently not computationally expensive. In subsequent analyses, researchers should consider conducting a qualitative assessment of the model's performance by comparing it with clinical data. This assessment validates whether the model's predicted tumor sizes at specific intervals align with the actual dimensions observed in patients at the corresponding time points. Simplifying the real tumor's biological processes in our 2D model necessitates advancing the model to 3D, thereby approaching a more real representation of the intricate biological dynamics inherent in real tumor growth. In future development, we can incorporate more parameters and perform simulations in the presence of external factors such as chemotherapy, surgical removal of tumor cells, immune response, angiogenesis, and more.

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