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Modeling Complex System

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Modeling Cancer Growth and Treatment with Agent-Based Models

Introduction

Cancer remains one of the leading causes of death worldwide, responsible for millions of deaths annually. [1] Recent advancements in computational modeling have allowed researchers to simulate the complex processes underlying cancer development and progression, providing valuable tools for studying tumor dynamics and testing treatment strategies. This project aims to develop a multilayered computational model to simulate cancer growth and evaluate the impact of varying chemotherapy doses and treatment intervals on tumor inhibition and eradication. The model represents a 2-dimensional section of tissue, implemented using Python.

To balance computational efficiency with biological realism, several simplifications are made. These include approximations in gene regulation, cell cycle progression, and cell death, focusing on essential factors such as mutation rates and invasion potential. The mutation mechanism models changes in cell division rate, cell cycle duration, the ability to invade neighboring spaces, and the probability of accumulating further mutations. These are all key aspects of cancer but have incredibly complex mechanisms behind them.[2] While the coarse-graining of these approximations lowers the model's ability to capture the complexity of cellular regulatory pathways fully, they significantly lower computational costs while still allowing for the emphasis on key factors that influence cancer progression.

Chemotherapy is applied at adjustable intervals, with its concentration in the bloodstream modeled to decrease over time as it is metabolized. The treatment increases the probability of cell death by inducing cellular damage, allowing for the simulation of various therapeutic regimens. Together, these simplifications create a computationally efficient yet detailed model of cancer growth dynamics. The model aims to provide insights into the effectiveness of different treatment regimens, contributing to a deeper understanding of cancer progression and therapeutic strategies. Specifically, we aim to examine the impact of high or low-dose chemotherapy at 14 and 28-day treatment schedules on the treatment and eradication of cancer cells.

Methods

The model comprises three interconnected classes: Cell, ExtracellularMatrix (ECM), and Tissue. Each class is designed with specific attributes and methods to simulate its role within the system. The Cell class encodes information for each individual cell. The Tissue class acts as a container for the other classes and includes methods to simulate system dynamics over each timestep.

The Cell class represents the fundamental unit of the model. Each cell tracks its internal concentrations of oxygen and nutrients as well as its progression through the cell cycle, which includes the stages G0, G1, S, G2, and M. Access to nutrients and oxygen directly affects a cell's

ability to progress through these stages. A certain amount of nutrients and oxygen is required to progress from G1 to S and G2 to M, which is biologically correlated with the G1 and G2 checkpoints in the cell cycle. Below are flow diagrams outlining the key logic of the cell's functionality.

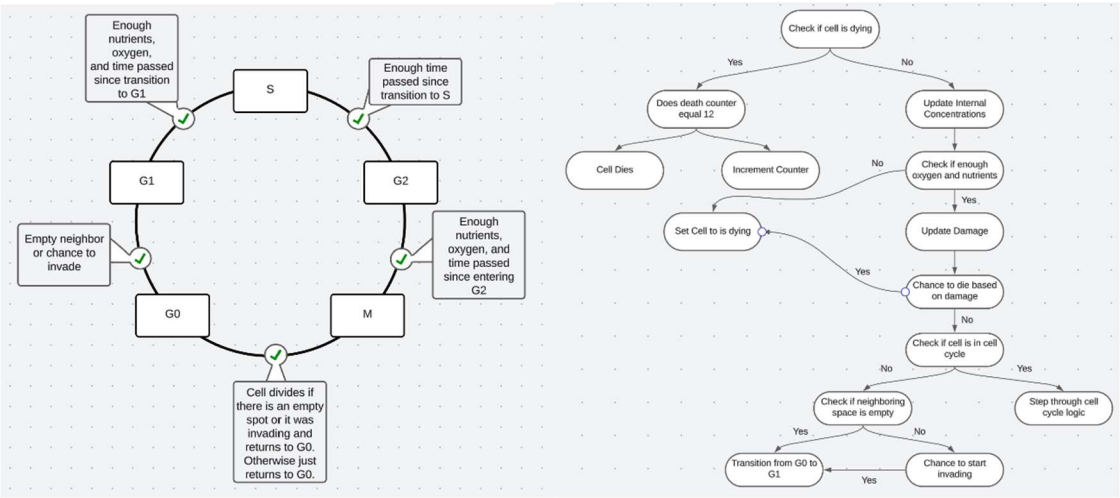

Figure 1: Flow chart describing the decision path used to update each cell during each timestep. Logic for cells was influenced by other papers modeling cancer dynamics using agent-based models.[3,4,5]

Cells can accumulate mutations that influence several properties, including resistance to apoptosis, healing/correction ability, the rate at which a cell can progress through the cell cycle, and the ability to invade neighboring spaces. Cells have a Boolean flag indicating whether or not they are cancer cells. When cancer cells are initialized, the attributes impacted by mutations default to higher values than those of healthy cells. Cancer cells can invade neighboring positions, even if those positions are already occupied. Cells with significant mutations are more likely to undergo cell death as mutations increment cell damage, though this likelihood decreases if their resistance metric is high.

Cells die probabilistically based on their damage value. Damage is limited between zero and one, and the probability of death results from the damage value minus the recovery rate. Damage is induced by the presence of chemotherapy or the occurrence of a mutation. The amount of damage due to chemotherapy is determined by the concentration of chemotherapy and the cell cycle stage. Chemotherapy is also limited to values between zero and one. The chemotherapy concentration is multiplied by either 0.5 if the cell is in G0, 1 for G1 and G2, and 1.5 for S or M. This reflects the true mechanisms by which chemotherapy works as it targets processes that occur during the cell cycle, particularly during the S and M phases.

Cells are assigned lifespans upon initialization, sampled from a normal distribution based on their cell type. Cells die when the age attribute, incremented at each timestep, reaches the cell's lifespan, reflecting natural cellular turnover.

The ECM class is a three-dimensional array where each layer encodes the concentration of oxygen, nutrients, or chemotherapy agents. The diffusion process is simplified to a linearly decreasing concentration gradient with values bounded between zero and one. During each timestep, the ECM updates the concentration of its compartments, and cells uptake each

component at rates dependent on their internal concentrations. A method to deliver chemotherapy exists that sets the concentration in the vasculature to a specified value and then computes the linearly decreasing gradient. In all experiments performed, the concentration was set to 1 in the vasculature for nutrients and oxygen with a step size of 0.02 and 0.01, respectively. Chemotherapy was set to the specified maximum concentration in the vasculature and a step size of 0.04 for the linear decrease with distance. A second method exists to decrease the concentration of chemotherapy using the standard half-life equation. Vasculature is encoded as a simple vessel that runs from the top of the tissue to the bottom in the center column of the array.

The Tissue class integrates the other classes, initializing an array of cells and creating an instance of the ECM class. While these arrays encode different aspects of the tissue, they conceptually occupy the same physical space. The Tissue class manages the simulation over timesteps. During each timestep, the ECM updates its concentrations, after which cells are processed in a randomized order using a method called “update_cell” from the cell class to update internal values and stages of the cell cycle. The method to update a cell returns a Boolean indicating if the cell is ready to divide. Once a cell has progressed through the M phase and either has an empty neighbor or is invading a neighboring cell, the Boolean returned is set to True. At that point, the Tissue class calls another method that returns relevant cell attributes to the dividing cell. It then initializes a new cell with the same attributes as the one that divided.

A one-hour timestep was chosen to provide sufficient granularity for long-term disease progression while maintaining computational efficiency. Smaller timesteps would significantly increase computational costs without substantial improvements in accuracy. The vasculature in the model is simplified, assuming constant nutrient and oxygen concentrations as a continuous, non-depleting source. This assumption aligns with the chosen timestep and reflects reasonable approximations over longer intervals.

For the chemotherapy simulation, different settings for chemotherapy frequency and concentration were tested to evaluate their effects on cancer progression and tissue health. As previously stated, chemotherapy inflicts damage to all cells. Still, it has a more significant impact on cancer cells due to the increased damage to cells in the cell cycle, and cancer cells tend to replicate more rapidly. Four different conditions were tested: high concentrations of chemotherapy with 14 and 28-day treatment intervals and low concentrations with 14 and 28-day intervals. High concentration was a chemotherapy value in the vasculature of 0.6, and low concentrations were 0.3. Each simulation was run for 180 days with timesteps of one hour. For the first 60 days, no chemotherapy was introduced to the system to allow the individual cancer cell placed in the tissue to propagate to a “detectable” size. At the 60-day mark, chemotherapy was delivered and then repeated at either 14 or 28-day intervals. Cancer cell counts were tracked as time passed at 12-hour intervals. Three separate simulations were conducted for each condition to get the average behavior over the stochastic process.

Results

As previously discussed, the goal was to observe the impact of different chemotherapy regimens on the effectiveness of treating cancer. Each cancer growth was initialized with a single cell with the same initial attributes in the same location and allowed to propagate for 60 days before treatment was administered. There is some variation in the results of the same initial

conditions and treatment regimens due to the stochastic nature of the cell mutation and growth logic. Yet overall, it was observed that out of the four settings, the best treatment plan would be low doses at 14-day intervals as this achieved the same results as the high-dose treatments with less chemotherapy administered to the tissue, minimizing the impact on healthy tissue. Anecdotally, when watching simulations of high-concentration chemotherapy, there is a massive die-off immediately after (with respect to time) chemotherapy is administered for both healthy and cancerous cells. This is not present in low-dose applications, and fewer cancer cells die immediately, but the long-term effects are similar. Figures 1 and 2 show samples of simulations and how massive death is observed in high-dose treatments and not in low-dose.

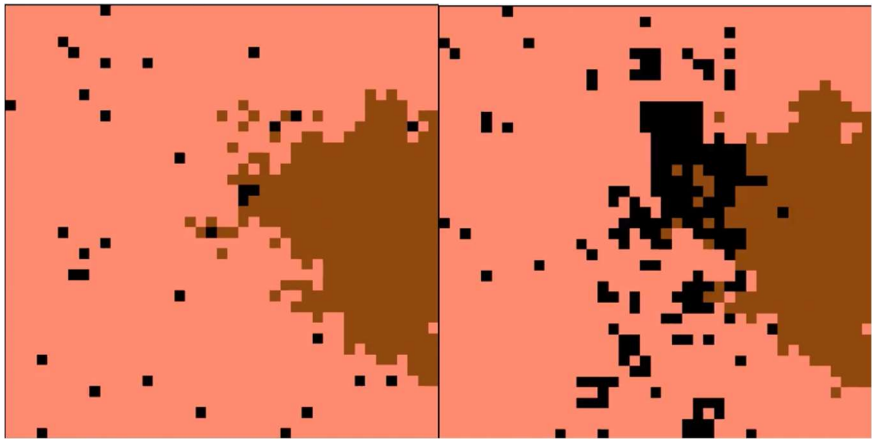

Figure 2: Visualization from a sample high-dose trial. The image on the left shows the cell array immediately before chemotherapy application, and the picture on the right shows the cells right after chemotherapy. Black indicates a vacant spot, so essentially where a cell has died. The pink color is healthy cells, and the brown color is cancer cells.

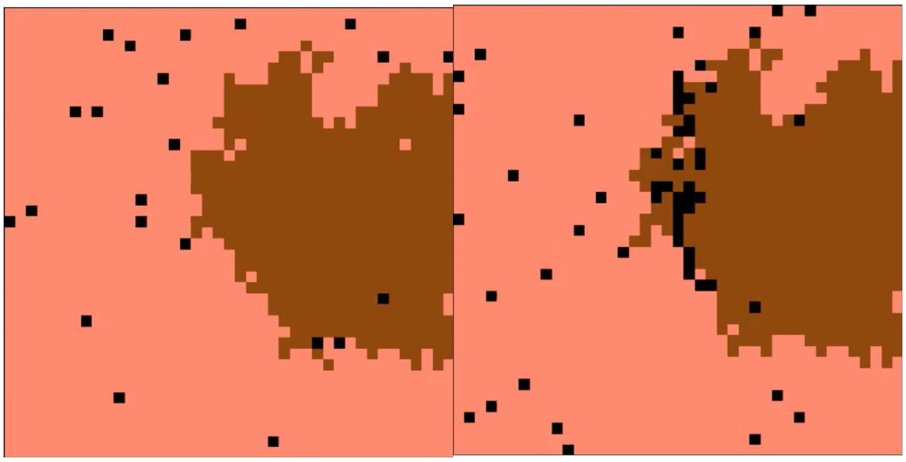

Figure 3: Visualization from a sample low-dose trial. The image on the left shows the cell array immediately before chemotherapy application, and the picture on the right shows the cells right after chemotherapy. Black indicates a vacant spot, so essentially where a cell has died. The pink color is healthy cells, and the brown color is cancer cells.

These findings are supported by the figures below, which show the cancer cell count throughout the simulation. In each trial, the value peaks around the 60-day mark, which is the time cancer is allowed to grow without treatment interference. Despite the lower dose when administered every 14 days, all trials resulted in the eradication of cancer at approximately the 125-day mark, which is the same range as both of the high-dose trials. Logically, it follows that achieving

the same result with less drug administered is a preferable option. Figure 3 depicts the High treatments, and it is seen that there is an intense drop-off after the first dose administered, some recovery, and then a consistent decline. The low-dose trials with a 14-day interval result in a smoother decline in cancer cells, which further supports the evidence shown above, indicating a less widespread impact.

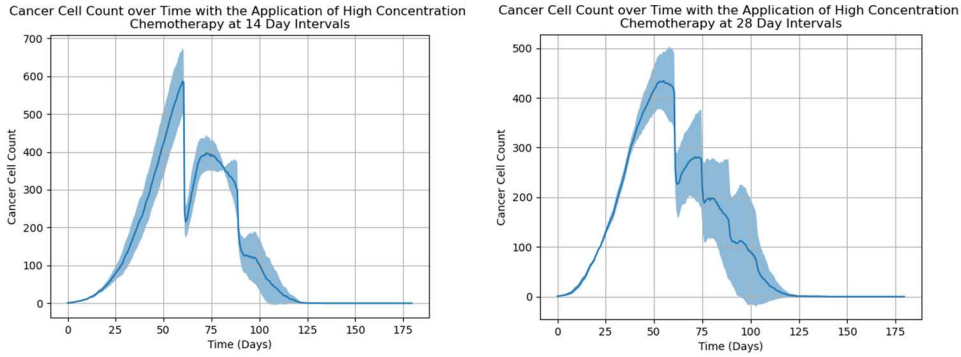

Figure 4: Plots of the number of cancer cells over the course of simulation for high concentrations of chemotherapy with 14- and 28-day treatment intervals. The blue line is the average cancer cell count across the three trials done with the same initial conditions. The shaded blue region is plus or minus one standard deviation.

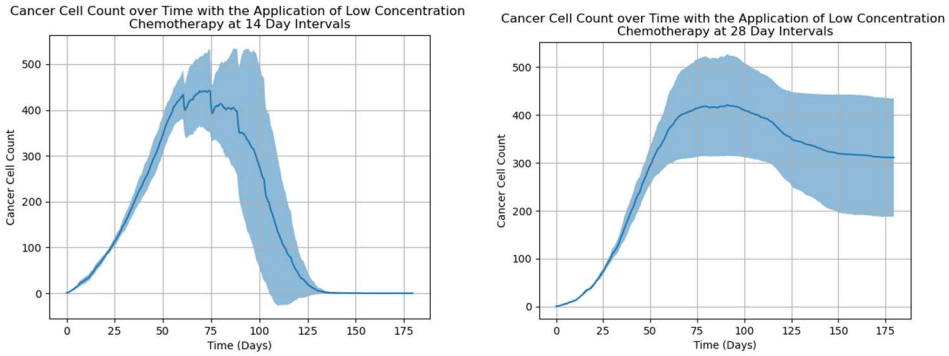

Figure 5: Plots of the number of cancer cells over the course of simulation for low concentrations of chemotherapy with 14- and 28-day treatment intervals. The blue line is the average cancer cell count across the three trials done with the same initial conditions. The shaded blue region is plus or minus one standard deviation.

Both high dose treatment plans were effective at eliminating cancerous tissue. Only the low dose with a 14-day treatment interval eradicated cancer, while the low dose with a 28-day interval seemed to reach a stable point in all its simulations where the cancer was limited to a fixed size but not completely killed off.

Discussion

Computational modeling, as used in this project, offers a valuable tool for identifying areas of interest for further investigation. While modeling cannot replace laboratory research, it can

significantly narrow the domain of possibilities, helping to prioritize experiments and optimize research efforts.

In this model, cancer control is primarily governed by cell death, which represents both immune system-mediated apoptosis and intrinsic cellular mechanisms. This simplification, while necessary to reduce computational complexity, limits the model's interpretability and generalizability. For example, critical interactions such as immune system dynamics or alternative forms of cell death, like necrosis or autophagy, are not represented. Despite these limitations, the model can still provide insights into which cell attributes, such as apoptosis resistance, invasion probability, or mutation rates, contribute to the most aggressive or chemotherapy-resistant phenotypes.

These findings could guide future research toward genetic pathways or alternative therapeutic targets that influence these parameters. For example, identifying specific pathways involved in apoptosis resistance could support the development of drugs that sensitize cancer cells to programmed cell death. Additionally, understanding how invasive behaviors correlate with other traits might lead to novel interventions that limit metastatic potential.

The model also allows for the testing of different chemotherapy regimens to optimize outcomes. By simulating the effects of varying drug concentrations, timing, and frequency, researchers can better understand how to balance the elimination of cancerous tissue with minimizing collateral damage to surrounding healthy cells. This has implications for personalized medicine, where treatment regimens can be tailored to the unique properties of an individual's tumor. Existing literature supports the current study's findings that the lower dose treatment at a higher frequency resulted in almost identical patient outcomes while inducing significantly less toxicity than traditional treatment regimens. [6]

Despite the strengths of this model, there are many drawbacks due to the broad assumptions and generalizations that were made. Major assumptions include the simplification of cell death, homogeneity of cell types, lack of immune response and cells, and simplification of diffusion. Future iterations of this model could incorporate and address these shortcomings, especially with regard to the immune system, by incorporating additional layers of complexity, such as immune system interactions and angiogenesis, which could significantly enhance its predictive power. Moreover, the inclusion of a wider range of treatment modalities, such as immunotherapy or targeted therapy, would allow for more comprehensive testing of combination therapies. The model also has the potential to be customized to specific cell types in the human body. Life span, reproduction rate, nutrient requirements, and more can be specified for different tissue types.

Conclusion

In conclusion, while the model has its limitations, it demonstrates the utility of computational approaches in cancer research. Focusing on the most sensitive parameters and making said parameters easily tunable, our model can suggest promising experimental directions and treatment strategies, ultimately contributing to the broader effort of understanding and combating cancer. By simulating cancer cell progression and testing different treatment regimens, the model demonstrates that a lower dose of the chemotherapy drug administered at 14-day intervals can be as effective as a higher dose of the chemotherapy drug administered at 28-day

intervals in eradicating cancer cells, all while reducing unnecessary cell death. The agent-based modeling approach helps narrow down potential research pathways and experimental designs making lab research and physical experiments more efficient and productive. Future iterations of this model could incorporate more nuanced cellular interactions, immune system dynamics, and diverse treatment modalities which could improve the overall performance of the model. These future iterations could enable the model to be more tailored to specific types of cancers, leading to an improved understanding of optimal treatment plans, which would both save lives and improve the chemotherapy experience for patients.

Citations

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