CS 309: Computational Biology

Fall 2021

Lab 6: Cellular automata simulations of tumor growth

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Introduction

Cancer is a disease in which certain cells of the body grow uncontrollably and spread to other parts of the body. While cell division is a commonly smooth process for forming new cells, sometimes the orderly process breaks down, resulting in abnormal or damaged cells growing and multiplying when they shouldn't. Cancer can start almost anywhere in the human body and can spread into, or invade nearby tissues, while also being able to travel to distant places in the body to form new tumors (a process called metastasis).

The phenotypic differences between healthy and cancer cells in the "The Hallmarks of Cancer" article describe the six fundamental alterations in cells that collectively dictate malignant growth: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. A recent update included two additional hallmarks: reprogramming of energy metabolism and evasion of immune destruction, which appeared to be essential abilities of cancer cells.

In 2020, there were a total of 9,958,133 deaths worldwide due to cancer (International Agency for Research on Cancer) which further motivates the goal of this lab. Over time, the mortality rate from cancer has increased sufficiently which is why it is a topmost priority to obtain more knowledge on the matter so that a cure can be developed in the future.

Understanding the factors that contribute to a cancer diagnosis is an important step in the direction of finding ways to prevent and cure it. In light of this, lots of research has been conducted to uncover the characteristics of cancerous cells. Therefore the goal of this lab is to expand the knowledge of cancer cell mutations. This is achieved by carefully interpreting and analyzing the 2D as well as 3D simulations of cancer cells. This simulation provides a visualization of cellular growth according to a number of parameters and then plots counts of healthy and cancerous cells over time. Further, this lab examines what parameters correlate to the size and presence of cancerous cells.

Results

In the random 2D simulation with initial parameters(Figure 1), the healthy cells do not grow beyond a certain distance from the center, while the cancerous cells usually grow from the sides of the healthy cells and out of the boundaries. In the line graphs comparing the number of healthy and cancerous cells over time (Figure 2), the number of healthy cells usually increases rapidly until it reaches a maximum value and plateaus after that on average. Meanwhile, the cancerous cells remain at 0 and then begin to increase rapidly just as the healthy cells flatten out. Figure 2 shows an example from a random simulation.

Figure 1: Random 2D Simulation with Initial Parameters

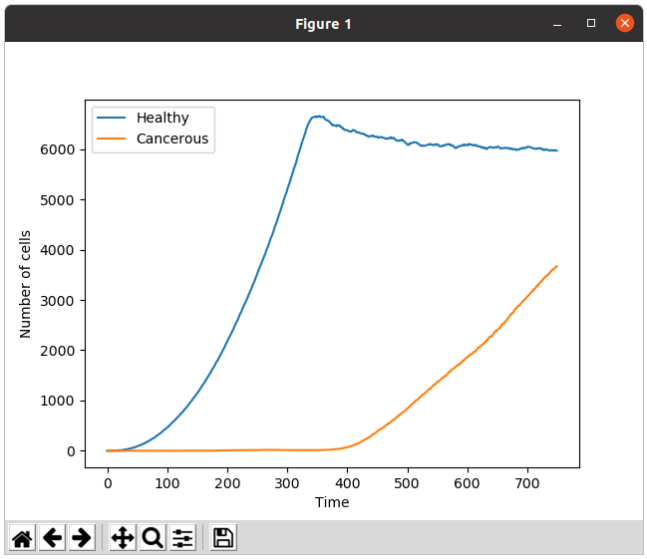


Figure 2: Rate Comparison Graph for Random Simulation with Initial Parameters

In order to experiment with cancer growth, we modified parameters including the telomere length (decreasing from 50 to 35), increasing the ability to evade apoptosis (from 10 to 20), the constant for ignoring growth inhibition (decreased from 10 to 4), and the constant for determining random apoptosis (decreased from 1000 to 400) which helped facilitate cancer growth. Then once again, we observe the 2D simulation. Generally, the healthy cells grow up to a much shorter radius (distance) than with the initial parameters while the cancerous cells grow

to be much larger than those using the initial parameters. This observation is the result of modifying the parameters to facilitate cancer growth. Therefore, in the 2D simulation(Figure 3), we observe a shrink for the size of healthy cells and an expansion for the size of cancerous cells, and in the line graph(Figure 4), we observe a decrease in the number of healthy cells and an increase in the number of cancerous cells.

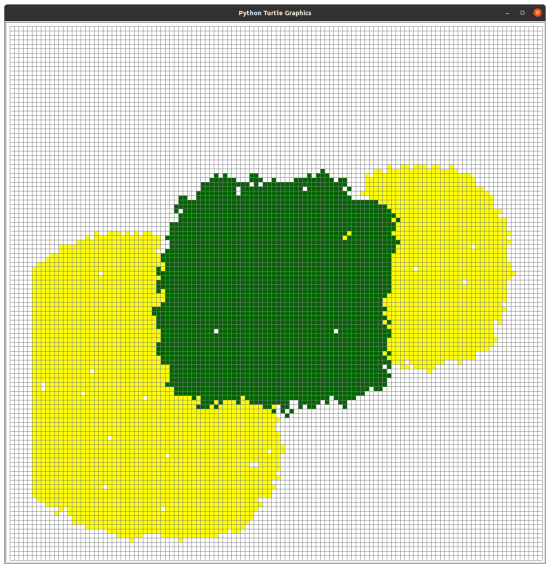


Figure 3: Random 2D Simulation with Modified Parameters

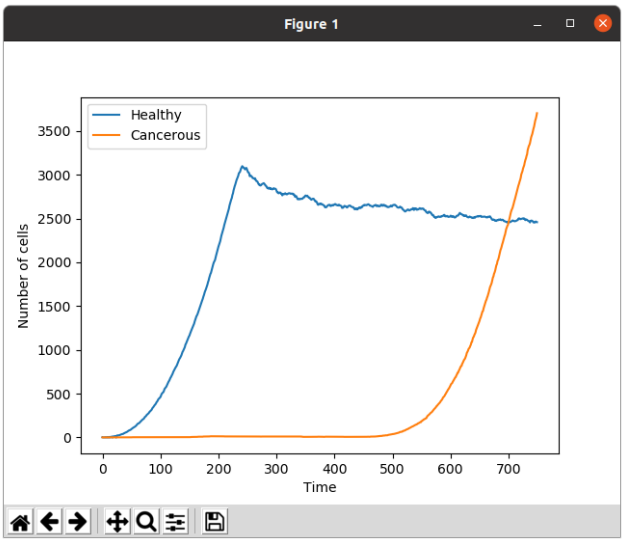


Figure 4: Rate Comparison Graph for Random Simulation with Modified Parameters

Then we run the 3D simulation and observe the development of cells. In the 3D simulation(Figure 5), we got a better view and understanding of how healthy and cancerous

cells grow over time. The healthy cells do not grow beyond a certain distance from the center, while the cancerous cells usually grow from the sides of the healthy cells and out of the boundaries. Additionally, the number of healthy cells decreases at a certain point while the number of cancerous cells increases dramatically and does not cease to stop growing(Figure 6).

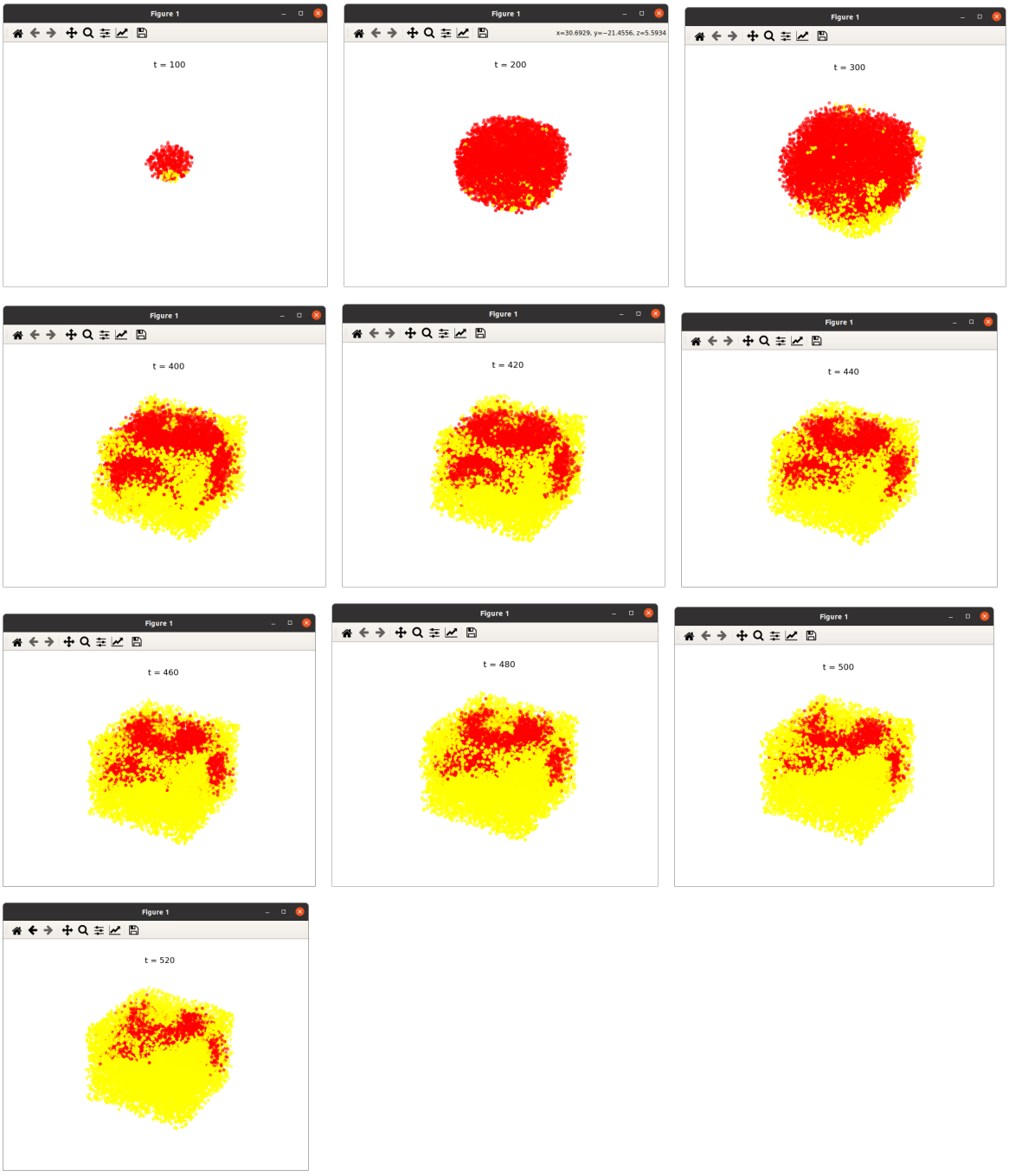


Figure 5: Random 2D Simulation with Parameters Suitable for Cancer Growth

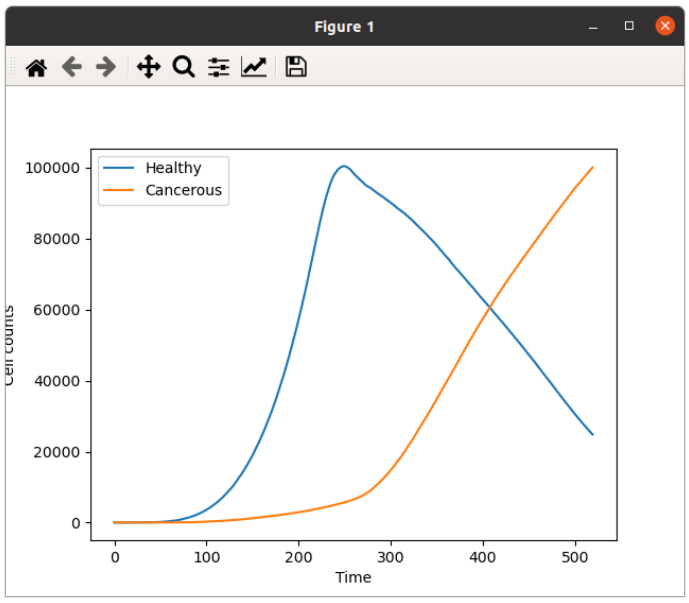


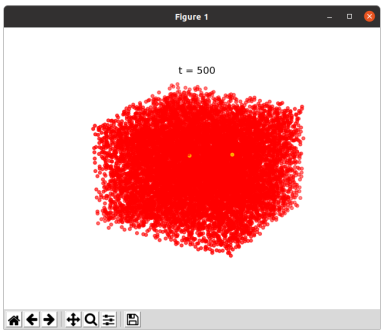
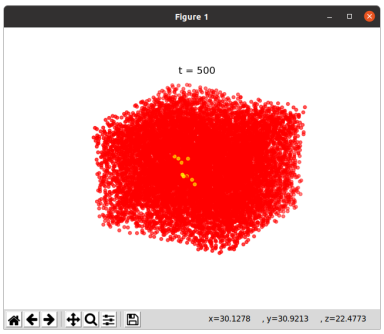
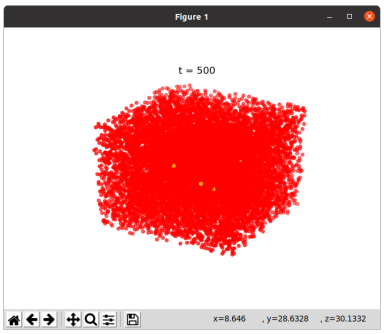
Figure 6: Rate Comparison Graph for Random Simulation with Parameters Suitable for Cancer Growth

Default Values

Afterward, we conducted a series of simulations in which we measured the effect of each hallmark by replacing 1% of the cells with cells exhibiting some hallmarks after 100-time units with default parameters and cancer facilitating parameters.

With the replacement of 1% of cells with the Ignore Growth Inhibit hallmark using default Parameters(Table 1), we found that after three trials of simulations, there was almost no growth of cancerous cells, and the growth of healthy cells increased and stopped at a certain point (around time 300).

Ignore Growth Inhibit: Hallmark 2

		
Trial 1	Trial 2	Trial 3

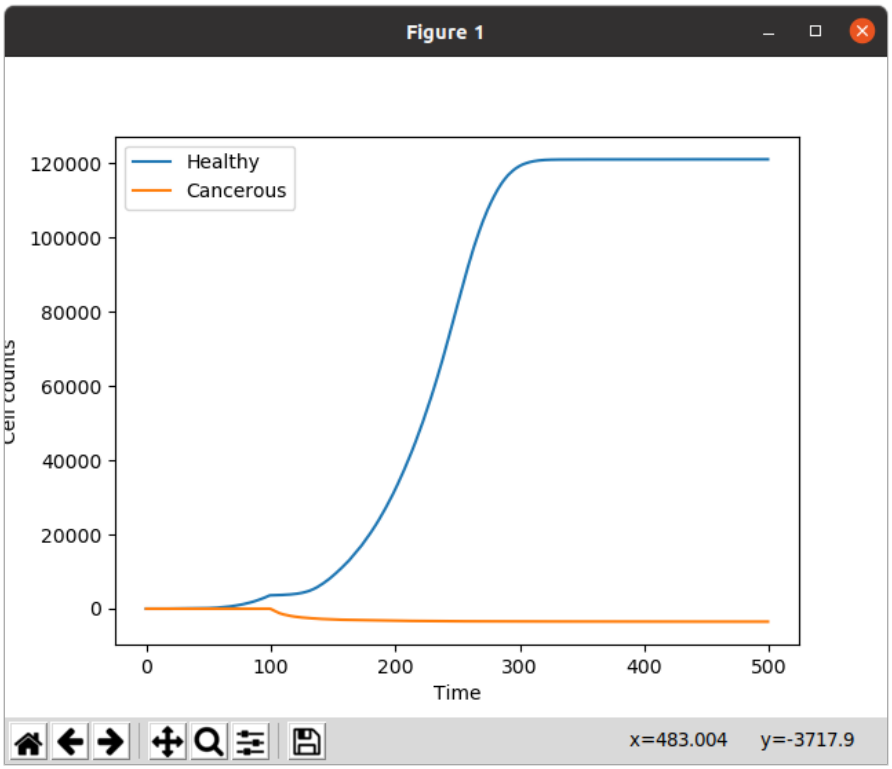
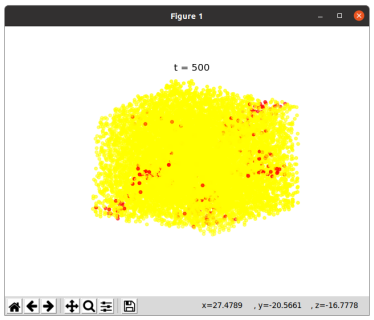
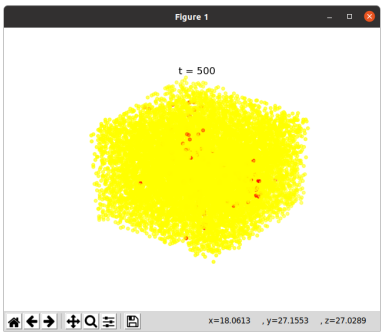
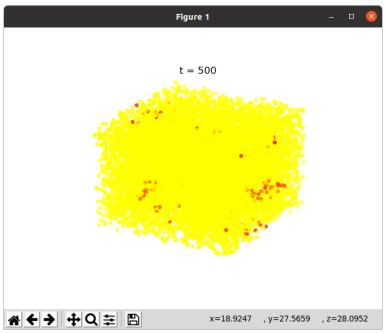


Table 1. Simulation and Rate Comparison of The Replacement of 1% of Cells With Hallmark: Ignore Growth Inhibit Using Default Parameters

With the replacement of 1% of cells with the Evade Apoptosis hallmark using default parameters(Table 2), we found that after three trials of simulations, there was almost no growth of healthy cells, and the growth of cancerous cells increased and stopped at a certain time (around time 250).

Evade Apoptosis: Hallmark 3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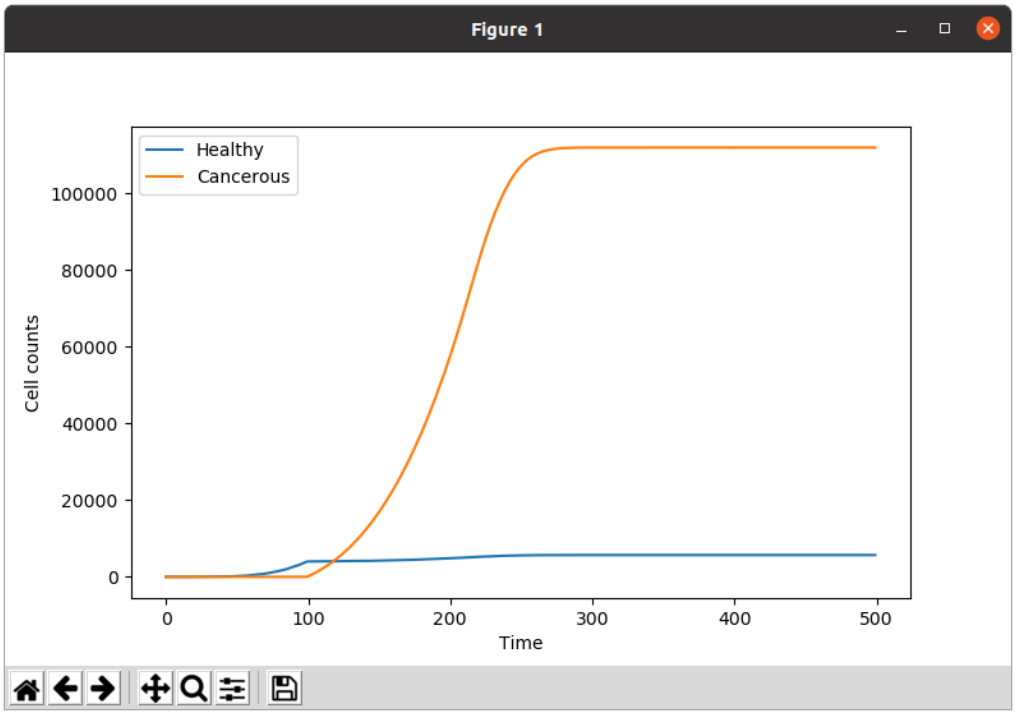
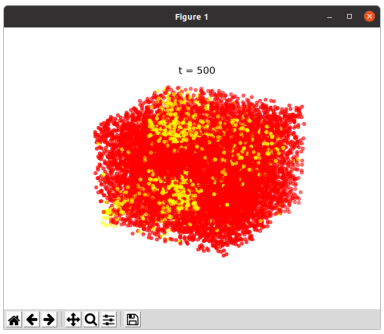
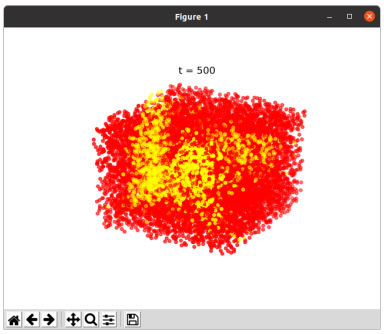
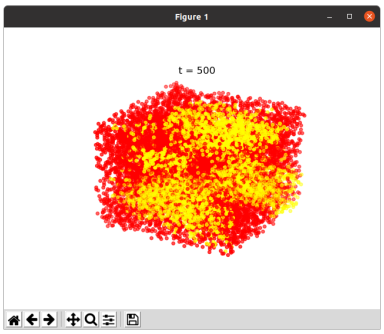


Table 2. Simulation and Rate Comparison of The Replacement of 1% of Cells With Hallmark: Evade Apoptosis Using Default Parameters

With the replacement of 1% of cells with the Effective Immortality hallmark using default parameters (Table 3), we found that after three trials of simulations, there was almost no growth of healthy cells and cancerous cells until around time 100. Then, both cells begin to increase at a quick rate, until around time 250 where the cancer cells begin to decrease. It is also observed that the decrease of cancer cells is linear.

Effective Immortality: Hallmark 4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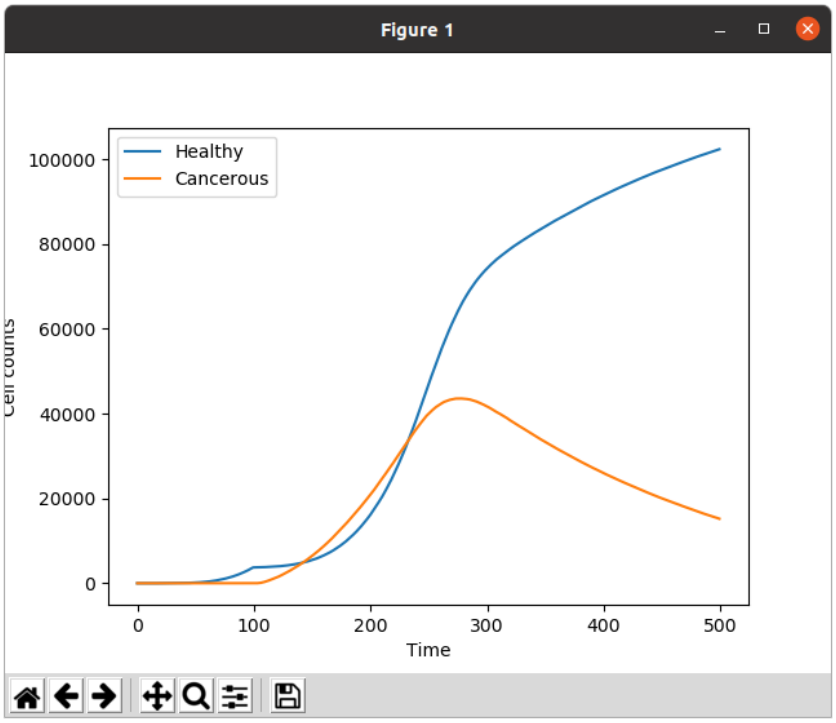
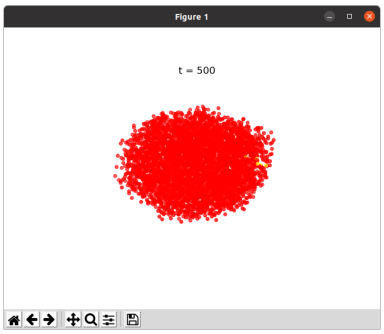
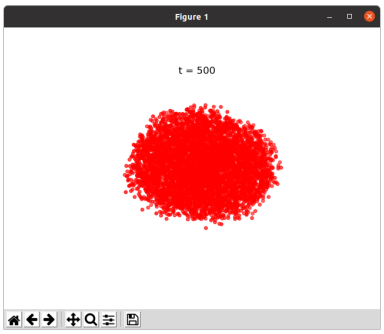
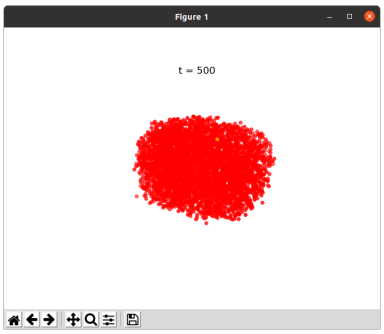


Table3. Simulation and Rate Comparison of The Replacement of 1% of Cells With Hallmark: Effective Immortality Using Default Parameters

Values for Cancer

With the replacement of 1% of cells with the Ignore Growth Inhibit hallmark using Cancer facilitating Parameters(Table 4), we found that after three trials of simulations, there's almost no growth of cancerous cells, and the growth of healthy cells increased and stopped at a certain point. Interestingly, the cancer cells dip below 0 after time 250.

Ignore Growth Inhibit: Hallmark 2

		
Trial 1	Trial 2	Trial 3

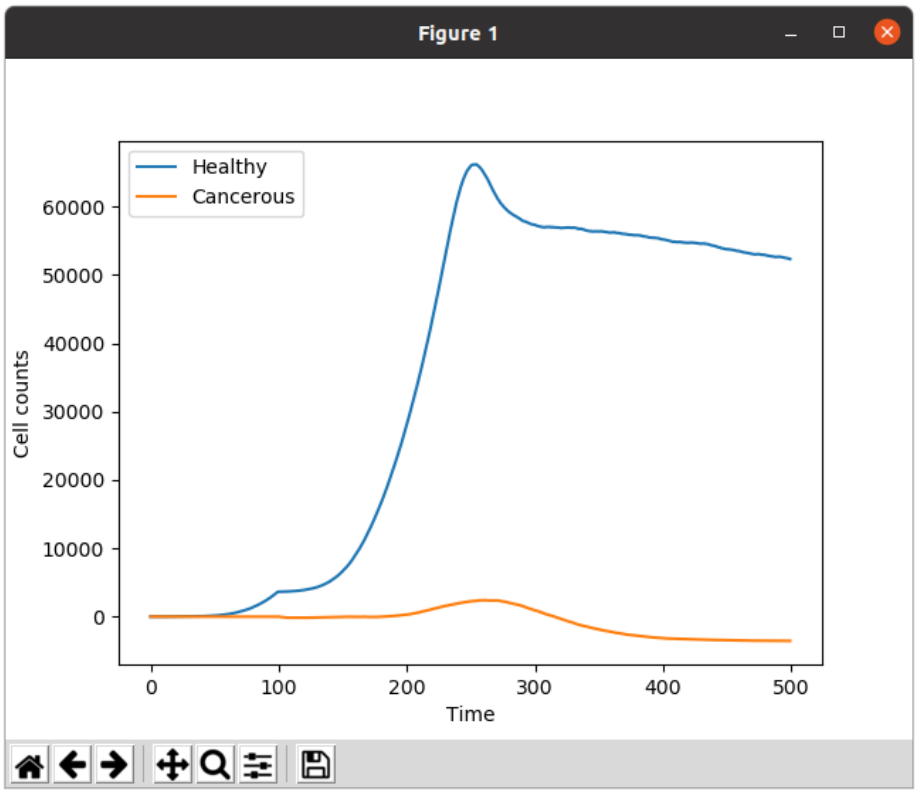


Table 4. Simulation and Rate Comparison of The Replacement of 1% of Cells With Hallmark: Ignore Growth Inhibit Using Cancer Facilitating Parameters

With the replacement of 1% of cells with the Evade Apoptosis hallmark using Cancer facilitating Parameters(Table 5), we found that cancerous cells begin to rapidly increase around time 100 and then rapidly decrease around 150 seconds later. The growth of healthy cells is rather steady throughout.

Evade Apoptosis: Hallmark 3

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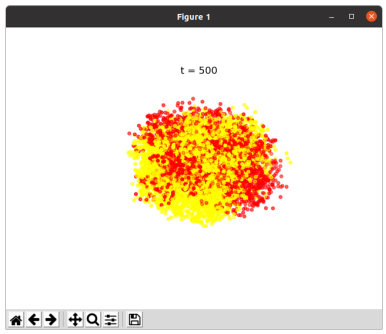
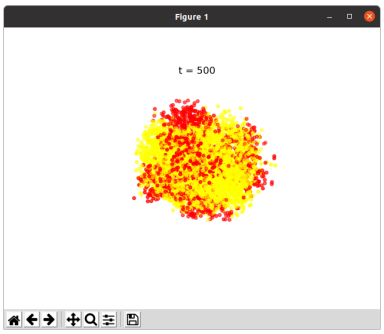
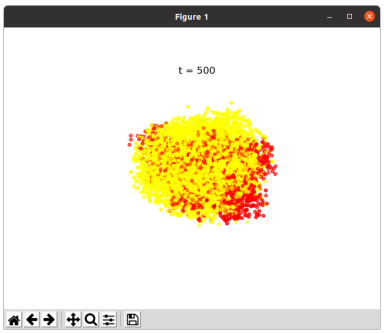
<tr><td> 
</td><td> 
</td><td> 
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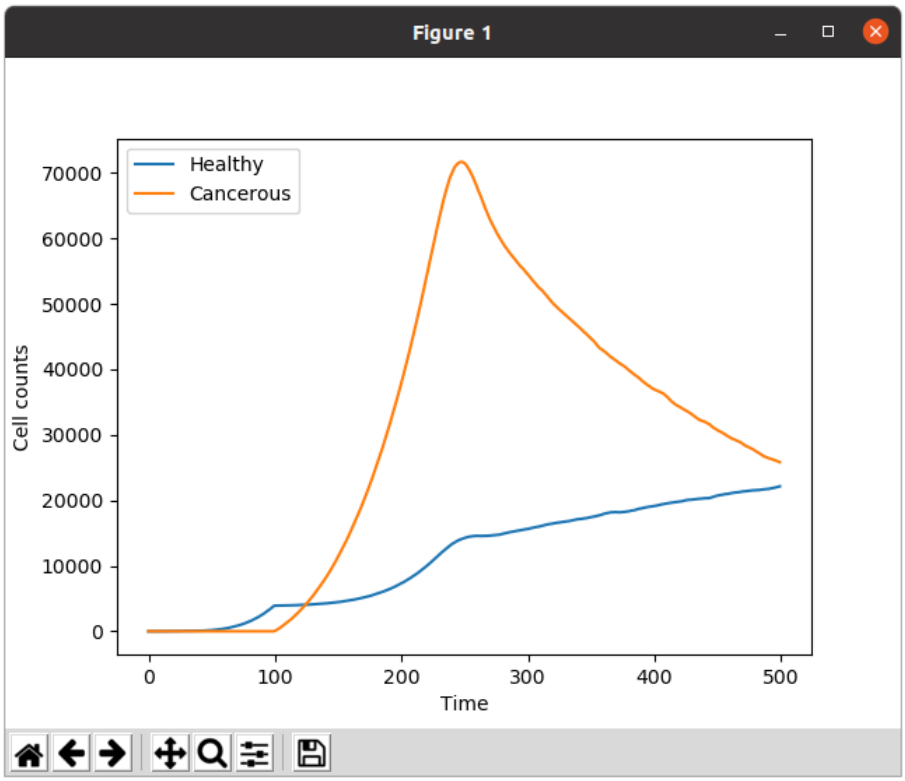
<tr><td colspan="3"> 
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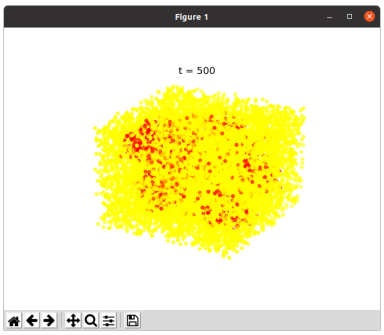
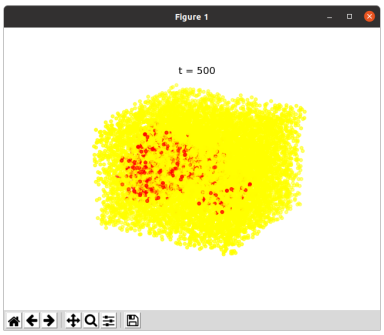
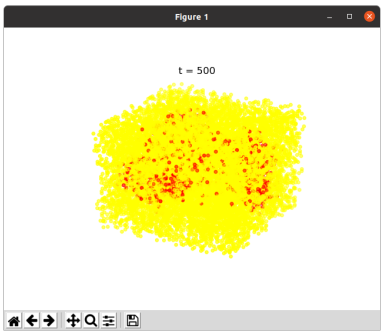
Table 5. Simulation and Rate Comparison of The Replacement of 1% of Cells With Hallmark: Evade Apoptosis Using Cancer Facilitating Parameters

With the replacement of 1% of cells with the Effective Immortality hallmark using Cancer facilitating Parameters(Table 6), we find that there is an exponential increase of cancerous cells in the time period 100 to 200 in the three trials. We notice that after that the cancerous cells start to decrease linearly while the healthy cells increase linearly. We also notice that there is an instant increase (bump on the blue line) when the cancerous cells increase displaying how healthy cells are now damaged.

Effective Immortality: Hallmark 4		
		
Trial 1	Trial 2	Trial 3

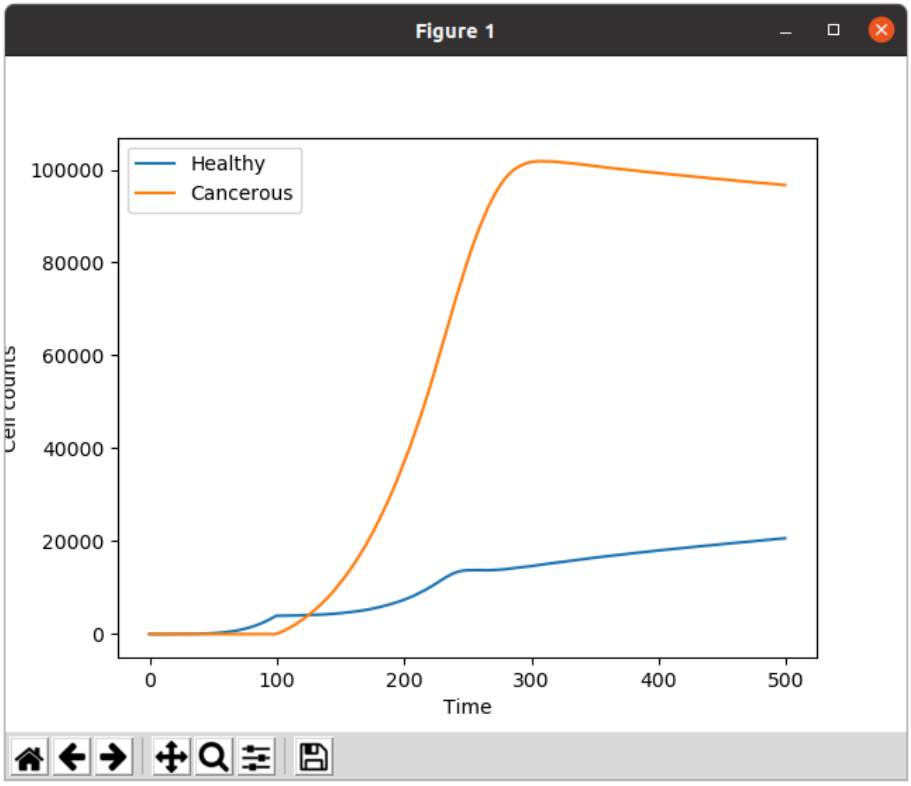


Table 6. Simulation and Rate Comparison of The Replacement of 1% of Cells With Hallmark: Effective Immortality Using Cancer Facilitating Parameters

Discussion

Based on our result from both 2D and 3D plots, we see an unlimited growth of cancerous cells that grow out of the boundary. We also see that the growth of healthy cells is always limited within a certain boundary. The reason for this behavior in healthy cells can be explained by the

characteristics of normal cells. For example, normal cells divide only when they receive growth signals from neighboring cells (Hanahan, 2011). This amongst other factors means that normal cells are bound to stop dividing at a certain point. Cancerous cells, on the other hand, are able to grow further because their mutations cause them to disobey the cell regulation during the cell division process, and they are also able to create their own growth signals and grow uncontrollably. On a number of the simulations, some of the cancerous cells do not reach the simulation boundaries, and is likely the depletion of nutrients and oxygen which help them develop (Santos, 2012).

According to either 2D, 3D plots and the line graphs with initial parameters, we observe a shrink in the number of healthy cells and an expansion of cancerous cells over time. The visualizations of the occurrence could be explained by the hallmarks of cancerous cells. The number of healthy cells flattened out because they are receptive to the anti-growth signals sent by neighboring cells when they detect crowding, and they cease to grow. Meanwhile, the cancerous cells disobey the growth inhibition signals. As a result, the number of healthy cells decreases, and the number of cancerous cells increases (Santos, 2012).

Then we modified parameters including the decreasing telomere length, increasing the ability to evade apoptosis, and decreasing the constant for ignoring growth inhibition. As a result, in both a 2D simulation and a line graph, we got a smaller healthy cell region and an increasing region of cancerous cells. This could be explained by the parameter modification. If the telomere length is shorter, that means the cell will receive the inhibition signal sooner. If the ability to evade apoptosis increases, the cell with cancer hallmarks are less likely to die in each cell cycle. If the constant for ignoring growth inhibition decreases, the cell with cancerous hallmarks would be more likely to kill off the normal cells. If the constant for determining random apoptosis, the chances for cells to die in each cell cycle decreases(Hannah, 2011). Since there are more chances for healthy cells to die and lower chances for cancerous cells to die, the number of cancerous cells increases while the number of healthy cells decreases.

For default parameter-based simulation, we found that Hallmark Evade Apoptosis has the most powerful ability to cause cancerous cells and eliminate the healthy cells. While the Hallmark Ignore Growth Inhibit has the most powerful ability to completely stop the growth of cancerous cells and thrive the healthy cells. Hallmark Effective Immortality grows both healthy and cancer cells. For cancer facilitating parameters, The hallmark Ignore Growth Inhibit still thrives the healthy cells but grows small amounts of cancerous cells. The hallmark Evade Apoptotis grows cancerous and healthy cells in a relatively same amount. Surprisingly, the hallmark Effective Immortality springs from the growth of cancerous cells. Therefore, we hypothesize that under the default parameters, the hallmark Evade Apoptosis is the most effective behavior to manifest cancer. Under the cancer-facilitating parameters, hallmark Effective Immortality is the most effective behavior to manifest cancer.

Future work

To reach the ultimate goal of curing cancer in the future, the next step would be to investigate the impact of future anti-cancer drugs on the hallmarks of cancer. This targeted therapy's goal would be to find the right combination of medication based on how they impacted the hallmarks of cancer. While avoiding damage to other healthy tissue, this would help target the defect in the cell mechanism that causes specific cancer. However, one should also consider the resistance mechanism of cancerous cells and how that plays into the modification of these hallmarks.

Future work may also include further examination of cancerous cells to identify other factors that are also playing a role in the manifestation of cancer. While there are numerous factors identified by the hallmarks of cancer, there is a high probability that there exists another factor impacting how one approaches the development of anti-cancer drugs. It is also equally probable that there exists an interaction between the current factors that affect the growth of cancer in individuals. An examination of other factors and internal interactions in between the factors gives further insight into how cancerous cells operate.

Accordingly, external factors that can increase the chances of cancerous growth should also be considered. In continued research, apparent links between psychological stress and cancer have been shown to arise in several ways. For example, people under stress may develop certain behaviors, such as smoking, overeating, or drinking alcohol, which increase a person's risk for cancer. Or someone who has a relative with cancer may have a higher risk for cancer because of a shared inherited risk factor (NCI). While not directly correlating to stress, there are still layers of factors that in turn can be linked to stress as well as to the manifestation of cancer. Therefore, a thorough examination can lead to new insights about curing an (in many cases) fatal disease.

External Sources

1. "Global Cancer Observatory ." International Agency for Research on Cancer. Accessed December 16, 2021. https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf.

2. Hanahan, Douglas, and Robert A. Weinberg. "Hallmarks of Cancer: The Next Generation." *Cell* 144, no. 5 (2011): 646–74. https://doi.org/10.1016/j.cell.2011.02.013.

3. "Psychological Stress and Cancer." *National Cancer Institute*, https://www.cancer.gov/about-cancer/coping/feelings/stress-fact-sheet.

4. Santos, José, and Ángel Monteagudo. "Study of Cancer Hallmarks Relevance Using a Cellular Automaton Tumor Growth Model." *Lecture Notes in Computer Science*, 2012, 489–99. https://doi.org/10.1007/978-3-642-32937-1_49.