

Lab 6: Cellular automata simulations of tumor growth

For this lab, you will again work in groups of 2–3. All members of each group are expected to contribute equally to all aspects of the lab. Upon completion of the project, each *group* will collaboratively write a report to summarize and analyze its findings.

Introduction

Cancer is a disease in which cells divide in an uncontrolled manner. This abnormal behavior is the result of a number of mutations in the genomes of healthy cells. In this lab, we will not examine these mutations specifically, but rather focus on the cellular behaviors that they cause. In 2000, Hanahan and Weinberg [1] identified six essential “hallmarks” that are characteristic of cancerous cells:

- 1. Sustaining proliferative signaling (i.e., self-growth)** Normal cells divide only when they receive growth “signals” from neighboring cells. Cancerous cells create their own such signals, thereby growing uncontrollably.
- 2. Evading growth suppressors (i.e., ignore growth inhibit)** Normal cells are receptive to “anti-growth signals” sent by neighboring cells when they detect crowding. Cancerous cells can ignore these signals.
- 3. Resisting cell death (i.e., evasion of apoptosis)** Normal cells possess the potential to undergo programmed cell death in response to certain stimuli, such as DNA damage. Cancerous cells can evade this mechanism, thereby continuing to live (and divide) despite inappropriate, and possibly dangerous, cellular behavior.
- 4. Enabling replicative immortality (i.e., effective immortality)** The ends of chromosomes are capped by repetitive sequences called *telomeres*. (In vertebrates, the repeated sequence is TTAGGG.) Every time a linear chromosome is replicated, the new copy has slightly shorter telomeres because the replication machinery cannot reach the very ends of the chromosome. After some number of replications, the telomeres no longer exist, and replication begins to degrade functional regions of DNA, leading to cell *senescence*, in which cells permanently cease to divide. Cancerous cells can produce the enzyme *telomerase*, which lengthens the telomeres. In this way, cancerous cells can avoid senescence and retain the ability to proliferate.
- 5. Inducing angiogenesis (i.e., ability to stimulate blood vessel construction)** Cells acquire oxygen and nutrients necessary for their survival from nearby blood vessels. Limited availability of oxygen and nutrients normally prevents tumors from growing beyond a certain size. However, some cancerous cells can stimulate the growth of new blood vessels from pre-existing ones, a process called *angiogenesis*. Angiogenesis allows a tumor to continue to grow, become malignant, and perhaps invade neighboring tissues.

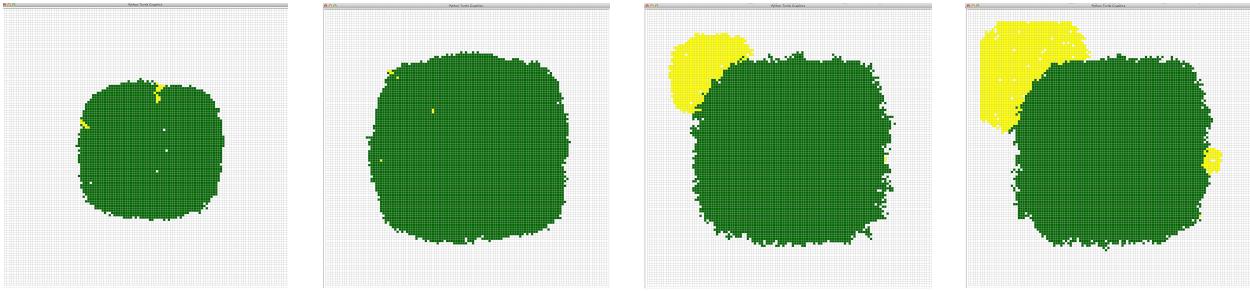


Figure 1: The two-dimensional cellular automata, simulating the growth of two tumors (yellow) over time (left to right).

6. Activating invasion and metastasis (i.e., power to invade other tissues and spread to other organs) *Metastasis* is the ability of tumor cells to migrate and invade other tissues. When the invaded tissues are vital to the body's normal functioning, tumors become life-threatening.

In 2011, Hanahan and Weinberg [2] added four new hallmarks to the original six. We will consider one in particular:

7. Genome instability and mutation (i.e., genetic instability) As tumor cells become damaged, the normal cellular machinery that detects and repairs mutated DNA make break down. This results in an effective increase in the rate of mutations.

In this lab, you will experiment with *cellular automata* that simulate the initial stages of tumor growth, before angiogenesis or metastasis. A cellular automaton consists of a grid of cells that can change their states based on the states of their neighbors. These very simple models have been used to simulate a wide variety of natural *emergent* phenomena, i.e., phenomena that acquire global, large-scale behaviors through only local interactions.

Experimental objectives

We provide two cellular automata simulations with this lab, both of which are implementations of the cellular automaton described in papers by Santos and Monteagudo [3]. The first, `tumor2d.py`, is a two-dimensional cellular automata, illustrated in Figure 1. 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. The second, `tumor3d.py`, is a three-dimensional version, illustrated in Figure 2.

1. Read the following two papers: *Hallmarks of cancer: the next generation* by Hanahan and Weinberg [2], and *Study of cancer hallmarks relevance using a cellular automaton tumor growth model* by Santos and Monteagudo [3]. The first paper describes the cancer hallmarks and the second paper describes the cellular automata that we will be using in this lab.
2. Run the program `tumor2d.py` to simulate cellular growth in two dimensions. Most of the parameters that govern the behavior of the cellular automaton are listed at the top of the program. These may be changed as you experiment with the model.

Describe and explain your observations. For example, why don't the healthy (green) cells grow beyond a certain distance from the center? How are the cancerous (yellow) cells able to

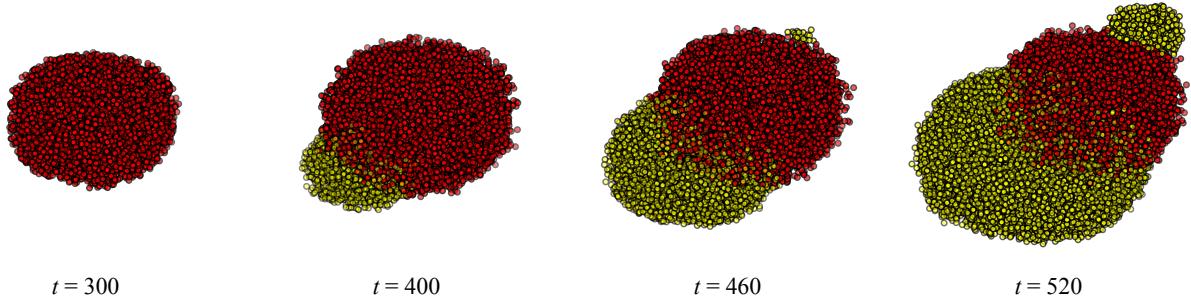


Figure 2: The three-dimensional cellular automata, simulating the growth of two tumors (yellow) over time (left to right).

grow further? Why do some cancerous cells not reach the simulation boundaries?

As the simulation is probabilistic, you will want to rerun it several times to produce different behaviors. Once the cells have stopped growing, click on the window to dismiss it. Another window will then appear with plots of healthy and cancerous cell counts over time.

3. Change some of the parameters in the two-dimensional model, as follows. Describe and explain your observations.

- (a) Decrease `TELOMERE_LENGTH` (`tl` in [3]) to 35.
- (b) Increase `EVADE_APOPTOSIS` (`e` in [3]) to 20.
- (c) Decrease `IGNORE_GROWTH_INHIBIT` (`g` in [3]) to 4.
- (d) Decrease `RANDOM_APOPTOSIS` (`a` in [3]) to 400.

4. Run the program `tumor3d.py` to simulate cellular growth in three dimensions. This simulation will periodically display the three-dimensional growth, at the time intervals defined by the variable `DISPLAY_TIMES`. The initial parameters in this simulation are set to the final parameters in the previous exercise. This program is doing a lot more work to simulate cancer growth in three dimensions, so it may take a while to run.

Again, describe and explain your observations over several runs.

5. Santos and Monteagudo [3] examined the relevance of the various cancer hallmarks through a series of simulations in which they measured the effect of each hallmark by either eliminating it from, or making it the only hallmark allowed in, a simulation. They found that different hallmarks were more important with different sets of parameter values.

We will perform a similar experiment in which, after 100 time units growing healthy cells, we replace 1% of the cells with cells that exhibit some hallmark. After that point, no more mutations will take place.

- (a) Modify `tumor3d.py` so that the function `mutate` does nothing. Then, have the program replace 1% of the cells with cells exhibiting some hallmark after 100 time units.
- (b) Perform the experiment described above using the default parameters, and each of hallmarks 2, 3, and 4. Run 3 trials of 500 time units for each hallmark. Save each final 3-D image and plot for your lab report.
- (c) Now repeat the above experiment with the set of parameters that facilitate tumor growth.

Describe and explain your observations.

Lab report

Each group will write a lab report on this project. Be sure to consult the Lab Report Guidelines handout for general requirements. The total report should not notably exceed 4 pages in length (not including the title page or figures/tables).

You do not need to hand in any programs for this lab.

References

- [1] D. Hanahan and R. A. Weinberg. The hallmarks of cancer. *Cell* 100, pp. 57–70, 2000.
- [2] D. Hanahan and R. A. Weinberg. Hallmarks of cancer: the next generation. *Cell* 144, pp. 646–674, 2011.
- [3] J. Santos and A. Monteagudo. Study of cancer hallmarks relevance using a cellular automaton tumor growth model. *Parallel Problem Solving from Nature*, Part I, LNCS 7491, pp. 489–499, 2012.