Modeling Tumor Growth

Project Module Associated with
***2nd Edition, Introduction to Computational Science: Modeling and Simulation* by**

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Project 1 Prerequisite: *One of Module 10.3 on "Spreading of Fire," Module 10.4 on "Movement of Ants–Taking the Right Steps," or Module 10.5 on "Biofilms: United They Stand, Divided They Colonize"*
Project 2 Prerequisite: *Module 2.2, "Unconstrained Growth and Decay"*

Introduction

After feeling a mysterious lump on his shoulder, Theo went to see his doctor. The doctor was not overly concerned and told Theo it was likely a ***lipoma****, a benign, slow-growing, fatty tumor. However, Theo insisted that the lump had appeared suddenly and gotten larger rather quickly. The doctor reluctantly referred him to a surgeon.*

By the time Theo saw the surgeon, the lump seemed to him much larger and was painful to the touch. The surgeon did a physical exam and indicated that it was almost certainly a ***sarcoma****, which is a rare type of cancer that may be found in muscle and various connective tissues (bone, fat, cartilage, etc.) She could do a biopsy to determine if it was a sarcoma, but because the tumor was of moderate size and was located just under the skin, she suggested that she remove the entire lump. They would then analyze the tissue to determine the type of tumor Theo had.*

The surgery removed the tumor and some surrounding, marginal tissue. A sample of the excised tissue was examined microscopically and with special, chemically-based testing. Fortunately, the tumor turned out to be ***nodular fasciitis****, which is a non-malignant, but rapidly growing tumor of the covers of the muscles (fascia). It was <u>not</u> cancer. With the tumor removed and diagnosed as benign, Theo returned home greatly relieved.*

Cancer

Despite considerable progress made in detecting and treating many forms of the disease, one of the most frightening diagnoses a patient can receive from a physician is cancer. A recent study revealed that worldwide in 2015 there were an estimated 17.5 million cancer cases and 8.7 million deaths attributable to cancer. These numbers represented a 33% increase in cancer cases over the preceding decade (2005-2015). About half of the increase was due to an aging population, and another 40% was a result of increasing population (JAMA 2016).

Cancer is not a new disease. We have written records of cancer from Egyptian, papyrus manuscripts, but the Greek physician Hippocrates in 460 BC gave the disease its

name. The Greek word "karkinos" means crab, which may refer to the fingerlike projections of a tumor that reminded early anatomists of a crab. Today, we generally use the word cancer to describe a disease that is characterized by "uncontrolled division of abnormal cells." Such cells are considered malignant and may invade surrounding tissues or spread to other parts of the body (ACS 2017).

When compared to normal human cells, cancer cells are considered abnormal in several ways. Each of these differences promotes cancer cells' abilities to grow without constraint and to become invasive (CRUK 2014, NCI 2017). The following are some major differences between normal and cancer cells:

1. **Cancer cells tend to be less specialized than normal cells.** Your body is made up of many types of cells—muscle, bone, nerve, etc. These "normal" cells matured from unspecialized cells to perform specific functions. Cancer cells remain unspecialized and are unable to function normally.

2. **Because cancer cells often have faulty DNA repair mechanisms, they tend to accumulate genetic changes (mutations).** As defective genes and gene products increase, the cell becomes more abnormal. Normal cells, with functional healing mechanisms, can repair damage for proper cellular function. Without these mechanisms, normal cells will self-destruct.

3. **Cancer cells may not recognize signals from other cells that slow down growth. Consequently, they grow rapidly and without control.** Normal cells respond to such signals that slow down their replication or promote their self-destruction (**apoptosis**). Cancer cells continue to increase in numbers and invade adjoining tissues. Because they do not attach to their neighbors as normal cells do, cancer cells may also spread to other parts of the body.

4. **Cancer cells may be able to elude the defensive systems of your body (e.g., immune system). Additionally, cancer cells may influence the immune system to prevent their destruction.** For instance, cancer cells may produce signals that activate specific immune cells (regulatory T white blood cells) that work to suppress the immune response to the cancer. Also, cancer cells may down-regulate the production of surface markers that help T-killer (cytotoxic T-cell) white blood cells recognize and kill cancer cells (Vinay et al. 2015).

According to the National Cancer Institute, cancer is not one disease, but a "collection of related diseases." There are many types of cancers. Some form solid masses of cells, called **tumors**; and others, termed **hematological** (in blood-forming tissue or immune cells), form no solid tumors (NCI2 2017). Tumors can be **benign** or **malignant**. Benign tumors are generally localized, slow growing, and do not spread to other parts of the body. Nevertheless, they should be monitored and treated because they can cause pain or physical damage and in some cases become malignant. Malignant tumors commonly grow rapidly, may spread from the original site, endure therapy, and may reoccur following surgery or treatment (CRUK 2014; JHU 2016).

One of the ways that normal cells may become malignant is to accumulate a series of genetic changes (altered DNA; **mutations**). Also, these cells may acquire altered expression of genes, brought on by epigenetic factors. **Epigenetic factors** include chemical tags (e.g., methyl group—CH_3), which do not change the DNA sequence, but act a markers or signals that result in an increase or decrease in the expression of the marked genes. Thus, tumor development is a multistep process. Either of these types of change (mutations or epigenetic factors) will yield defective activity of genes that normally suppress cellular proliferation (**tumor suppressor genes**), control ordinary cellular proliferation (**proto-oncogenes**), or are necessary for DNA repair. Cells with such deficiencies become genetically unsound and tend to fail to mature and differentiate. Normal cells generally achieve an equilibrium with cell birth matching cell death, but cancer cells tend to divide continuously, resulting in an ever-increasing population of cancer cells that invade adjacent tissue and/or spread to other body regions through the circulatory or lymphatic systems. The conversion to cancer requires numerous steps of genetic/epigenetic change and may require decades for malignancy to occur (NCI 2017).

Progression of Tumor

When cells begin to grow rapidly, out of control, the condition is termed **hyperplasia**. Although they show no visible defects, changes have taken place that promote too much cell division. As the hyperplastic cell numbers continue to increase, other changes occur that lead to the production of cells displaying aberrant structure and disorganized tissue. This condition is referred to as **dysplasia**. If the mass of abnormal cells remains within the founding tissue and does not invade the surrounding tissues, the condition is sometimes termed **carcinoma *in situ***. The cells may appear even more abnormal and less differentiated, losing their ability to function normally. For instance, if such cells were in the liver, they may become incapable of producing enzymes or other liver secretions. Because of not having spread, such a carcinoma *in situ* is usually removed successfully by surgery. These cells are called **anaplastic**. If cells begin to invade surrounding tissues or pass into circulation (**metastasize**), the developing tumor is termed **malignant** (CancerQuest 2016; Annenberg 2013).

As tumors grow, they need to acquire nutrients, including oxygen, and to dispose of wastes. Normal tissues are supported by a blood supply from existing blood vessels. Cancers grow rapidly, and to access nutrients etc., they typically encourage the growth of new blood vessels from existing ones. Otherwise, the cells that are too far away from periphery of the tumor would die. Thus, cells within the tumor produce chemical signals (**angiogenic**) that stimulate the growth of these new blood vessels. Some of the tumor cells can pass through capillary walls for transport to other body tissues and form secondary tumors (**metastasis**) (Annenberg 2013).

Projects

1. Qi et al. (1993) presents a cellular automaton model of early-stage, microscopic, avascular tumor growth that includes the impact of the immune system. Thus, the model does not consider angiogenesis. Consequently, the model places a limit on the size of the tumor and does not consider metastasis.

The model does consider the proliferation of cancer cells, where a cell can divide into two new cells, without concern for the nutrient amount. As a simplification, the model assumes that one of the two daughter cells occupies the parent cell's site. The challenge of making room for the other daughter cell by pushing out cells in a fixed, rectangular lattice leads to another simplification that violates the realistic biology and physics of cell movement: The other daughter cell occupies a randomly selected normal neighbor, converting the normal cell to an abnormal cell; if no such normal neighbor exists, the cell does not divide.

Let k_1 be the rate of proliferation of cancer cells in a controlled laboratory situation, or ***in vitro***, where the abnormal cells always have enough nutrients. Thus, k_1 is constant. However, in the body, or ***in vitro***, as the tumor enlarges, the nutrient supply, and consequently, proliferation diminishes. Thus, the probability of abnormal cell division *in vitro*, k_1', should get smaller as the number of cancer cells increases. Moreover, with no angiogenesis, division should stop completely when the number of abnormal cells reaches a designated maximum, ϕ. For the sake of the simulation, we assume ϕ is related to the number of cells in the lattice. To reiterate, when the number of cancer cells is close to zero, k_1' should be close to k_1; but as the number of such abnormal cells approaches ϕ, k_1' should approach zero.

Mechanical pressure is also a significant factor in proliferation. Only if the tumor's internal pressure is high enough does a tumor expand properly. Qi et al. assume that the density of the malignant mass models mechanical pressure. Let N be the number of tumor cells (abnormal cells, complex cells formed from the immune system's response to the cancer, and dead cancer cells) in the lattice. Consider the center of a square lattice to be the origin and the center of the tumor. The radius of a tumor cell in row i and column j is its distance from the origin. Let R be the average radius of the malignant cell distribution; that is, R is the sum of the radii of the tumor cells divided by the number of tumor cells. Because we are working in two dimensions, we define the density of the cancer cells, d, to be the number of abnormal cells divided by R^2. The model considers a threshold value of d, d_c. Should the density of cancer cells be larger than d_c, proliferation can proceed to any of the four nearest neighbors (von Neumann neighborhood) that have a normal cell. However, if d is less than or equal to d_c, the second daughter cell can only invade a neighboring normal site in the direction of the center of the mass, the origin (Figure 1). Thus, with fewer options for expansion, tumor expansion is inhibited.

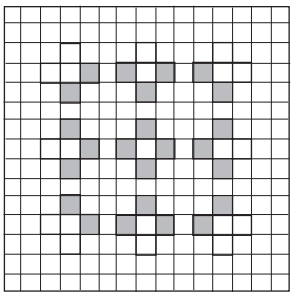

Figure 1 Directions of possible proliferation, shaded, for sites in various locations when $d \le d_c$

Besides proliferation, Qi et al. considers the impact of immune system on the developing tumor. The immune system produces various **effector**, or **cytotoxic**, cells that can attack abnormal cells. The authors model this process by allowing an effector cell to bind with an abnormal cell to form a complex. Should an abnormal cell not attempt to divide, the cancerous cell will bind with an effector with probability k_2. Subsequently, with probability k_3, such a complex dissolves, leaving a dead cell. The model allows a normal cell to replace a dead cell with probability k_4. To simplify and speed the simulation, the model assumes, but does not explicitly include, an effector at each location containing a cell that is not a complex. Consequently, each site in the lattice has one of four possible states: normal cell with implicit effector; abnormal, cancerous cell with implicit effector; complex cell formed from the binding of an abnormal cell and an effector cell; and dissolved complex cell with implicit effector.

a. Develop a cellular automaton simulation of early-stage, microscopic, avascular tumor growth that includes the impact of the immune system. For simplification, allow two proliferating abnormal cells to pick the same random normal location in which to launch their daughter cells, changing the state of that one normal location to be abnormal. Have a square grid with an odd number of cells, n, on each side. Initialize the first grid with all normal cells except a cross of five abnormal cells in the center. Develop an animation of the simulation, and plot the number of abnormal cells, the number of tumor cells (abnormal, complex, dead), and R versus time for 300 time steps. Use the following set of parameters: $n = 101$, $k_1 = 0.74$, $k_2 = 0.2$, $k_3 = k_4 = 0.4$, $d_c = 2.85$, and $\phi = 1000$.

b. The **Gompertz function**, which follows, is one of the best models for predicting the growth of cancer tumors:

$$N(t) = \phi e^{\ln(N_0/\phi)e^{-kt}}$$

where $N(t)$ is the number of abnormal cells at time t, N_0 is the initial number of abnormal cells, ϕ is the carrying capacity, and k is an experimentally determined constant. However, the function is an empirical model that does not incorporate the mechanisms of cancer growth. Adjusting k, find a graph of $N(t)$ that roughly matches the plot your results from Part a, particularly for the first 40 or 50 time steps. What is your k?

2. The **Gompertz differential equation** $\frac{dN}{dt} = kN\ln\left(\frac{M}{N}\right)$ is a model for the growth of the number of tumor cells (N) with M being the carrying capacity and k being a rate constant. However, in the body, the carrying capacity usually is not constant. An increase in the number of tumor cells and physical pressure may expand the membranes on which the tumor is growing, promoting growth of blood vessels that

carry oxygen and other nutrients to the tumor. Such stimulation, which serves to increase M, can be modeled as being proportional to N. In opposition, vascular development can stall, limiting nutrient supply and, thus, inhibiting tumor growth. Such inhibition can be modeled as being proportional to the carrying capacity and the surface area of the tumor. We can use the Gompertz equation with dynamic carrying capacity to model the impact of treatments that target the tumor and/or the vascular supply (Enderling and Chaplain 2014).

a. Assuming a tumor is spherical, find an equation for the surface area as a function of the volume of the tumor. Also, assuming the volume is proportional to the number of tumor cells, find an equation for the surface area as a function of N. Develop a system dynamics model of tumor growth employing parameters for lung carcinoma in mice: $k = 0.192$, stimulatory constant = 5.85, inhibitory constant = 0.00873, initial $N = 1$, and initial $M = 1$. Plot N and M versus time on the same graph, and, also, plot the per capita growth rate versus time. Discuss the results.

b. Chemotherapy or immunotherapy can kill tumor cells. Assume that such anti-tumor treatment reduces the rate of change of the number of tumor cells in an unconstrained manner with the constant of proportionality being between 0 and 1. Model the growth of a tumor, where anti-tumor treatment begins after 40 days of abnormal cells. Run the model twice, for 80 days with constant values of 0.1 and 0.2. Compare and discuss the results.

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