IMO 1 Exam 2

Ana Milena Forero Pinto

November 6th, 2022

Normal human tissue is homeostatic which means that they maintain a certain approximate form and size through controlled proliferation and apoptosis. Often this is possible using a simple internal counting mechanism measuring the number of divisions a cell has gone through. Loss of feedback regulation can result in uncontrolled growth of the total cell population. Different treatment strategies exist for cancers arising in this tissue.

1 Question 1

Write down a diagram of the described biological system of tissue homeostasis. Denote variables with capital Roman letters and parameters with small Greek letters in the flow diagram.

1.1 Solution

The system that I considered to model tissue homeostasis was based on https://www.pnas.org/doi/full/10.1073/pnas.1107621108#sec-3. This system (see figure 1) is composed of two different cell types, one is a stem cell population denoted by S, and characterized by infinite division capacity with no death; and the second is a differentiated cell population, D, that do not divide but always die with a death rate δ.

Figure 1 shows the negative feedback loop in red, on the probability of division p. This feedback can be modeled as a decreasing function of the number of differentiated cells and can be explained as an effect due to a chemical signal that differentiated cells secrete, which modulates p.

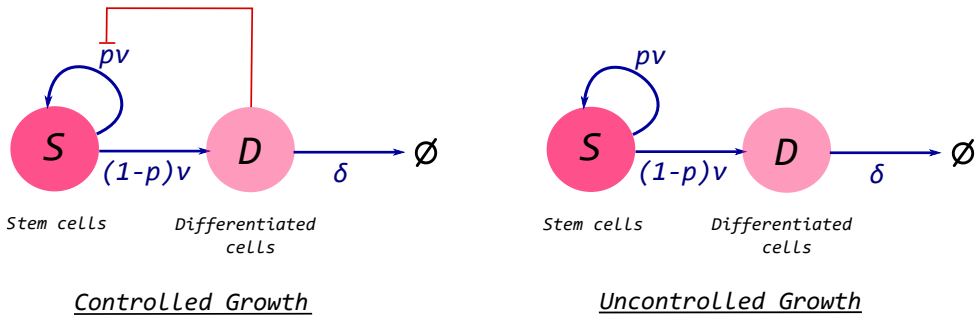

Figure 1: Flow diagram for a symmetric stem cell division. Tissue homeostasis is achieved when there is negative feedback control, red inhibition line, on the parameter p (left panel). Homeostasis is lost and uncontrolled proliferation is achieved when there is no negative feedback loop (right panel). For both figures, S represents the number of stem cells, and D the number of differentiated cells. p is the probability of giving rise to two stem cells after division, and $1-p$ is the probability to give rise to two differentiated cells. ν is the proliferation rate of stem cells and δ is the death rate of differentiated cells.

2 Question 2

Introduce a mechanism of cancer treatment into the system. Discuss the mechanism of action of this treatment and give a (generic or specific) example from clinical oncology.

2.1 Solution

A mechanism to kill cancer cells - characterized by rapid growth and division- would be one that kills only the cells that are highly dividing in all the tissue. An example of this type of treatment is chemotherapy. Some drugs can damage cells where they are about to divide, i.e., at the point of splitting or while they are making copies of their genes before they split. Chemotherapy works by acting on cells that grow and divide rapidly, and it is much less likely to damage cells that are at rest.

In normal tissues, the proliferation of somatic stem cells is regulated by negative feedback (as I tried to model in figure 1), so the action of chemotherapy is not expected to significantly damage stem cells. But in the uncontrolled scenario that would not be the case.

To model the action of chemotherapy in the case of uncontrolled growth, a time-dependent stem cell death rate $\kappa(t)$ can be defined (see figure 2). The specific time dependence is defined by the treatment schedule. In this project, quiescent stem cells and differentiated cells are not affected directly by the treatment, since chemotherapy is much less likely to damage cells that are at rest.

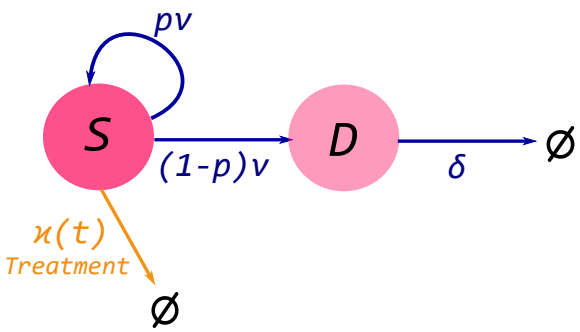

Figure 2: Model for the action of chemotherapy in the uncontrolled growth of tissue. The time-dependent death rate of stem cells, $\kappa(t)$, corresponds to the action of the treatment.

3 Question 3

Formulate a CA model of the above system. Implement the model in a software tool of your choice.

3.1 Solution

The CA model starts with one stem cell at time 0. The rules for tissue homeostasis are the following:

- **Stem cells:**
  - Each time step a stem cell tries to divide. In the division process, the cell can give rise to **two** stem cells with probability p or **two** differentiated cells with probability $1 - p$. **Symmetric division.**
  - No stem cells die.
  - Stem cells can divide only if the number of neighbors is less than 8.

– Before each cell division the probability p is modulated by the number of differentiated cells, following a Hill function:

$$p \to \frac{p}{1+\gamma D} \tag{1}$$

- **Differentiated cells:**
  - No differentiated cells divide.
  - Differentiated cells die each certain -fixed- number of iterations (to model death rate) counted from their birth.

Treatment: is introduced at a certain time and works by killing cells that are dividing each time step; in this case, stem cells that are not surrounded by 8 neighbor cells.

4 Question 4

Identify model parameters that yield tissue homeostasis and identify model parameters that disrupt homeostasis and yield abnormal growth.

4.1 Solution

Parameters of the cell lineage model: p, γ, ν, and δ. The ABM explicit parameters are p and γ. The proliferation rate ν and death rate δ are implicit, this is by defining the proliferation time step (1 day), and counting the days that a differentiated cell has been alive.

The parameters that yield homeostasis are: initial division probability $p > 0.5$, $\gamma << 1$ and $\gamma \neq 0$, and small death rate, δ, which corresponds to a large number of alive days. In my code, I used: $p = 0.85$, $\gamma = 0.009$, and waited 20 days for the death of differentiated cells, counted from the moment a cell emerges.

With these parameters I was able to obtain transient homeostasis from day 12 until day 25 (see figure 3). Since the code involves probabilities, each run is stochastic, it leads to different trajectories. Therefore, the curves shown in figure 3 are obtained by averaging 20 trajectories, made by executing the same code 20 times with the same initial conditions and parameters. If $p < 0.5$, the average behavior would be systematic cell death over time, without achieving homeostasis.

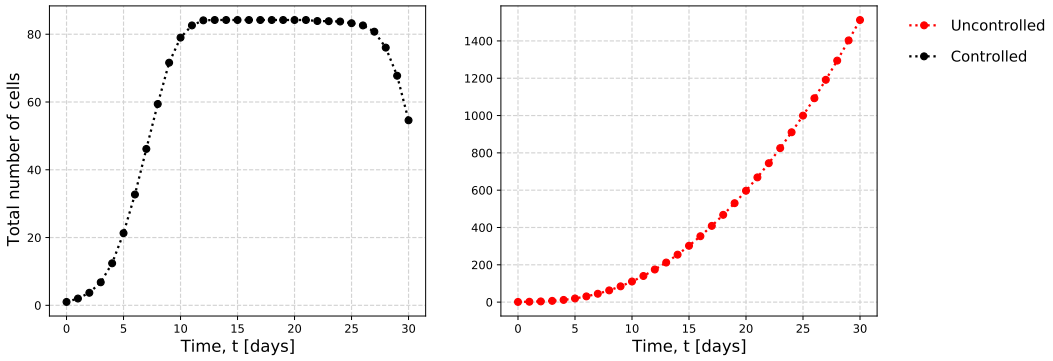

Figure 3: On the left, in black, controlled tumor growth. It was achieved by using a negative feedback loop with parameters: $p = 0.85$, $\gamma = 0.009$, and waiting 20 time steps (days) for the death of differentiated cells, "alive days". On the right, in red, the same system but without control, i.e., $\gamma = 0$.

To disrupt homeostasis and obtain abnormal growth I just set the parameter $\gamma = 0$, to remove the feedback loop. The result can be seen on figure 3, red curve.

5 Question 5

Simulate how tumor dynamics change after treatment.

5.1 Solution

Figure 4 shows the results for the change of dynamics of tumor growth when introducing the treatment defined in sections 2 and 3. Cells grow rapidly until the treatment is administered. When the treatment is on, stem cells die rapidly, and then the total number of cells decreases slowly due to the constant death rate of differentiated cells since the treatment does not affect them. The figure also shows a transient homeostatic behavior.

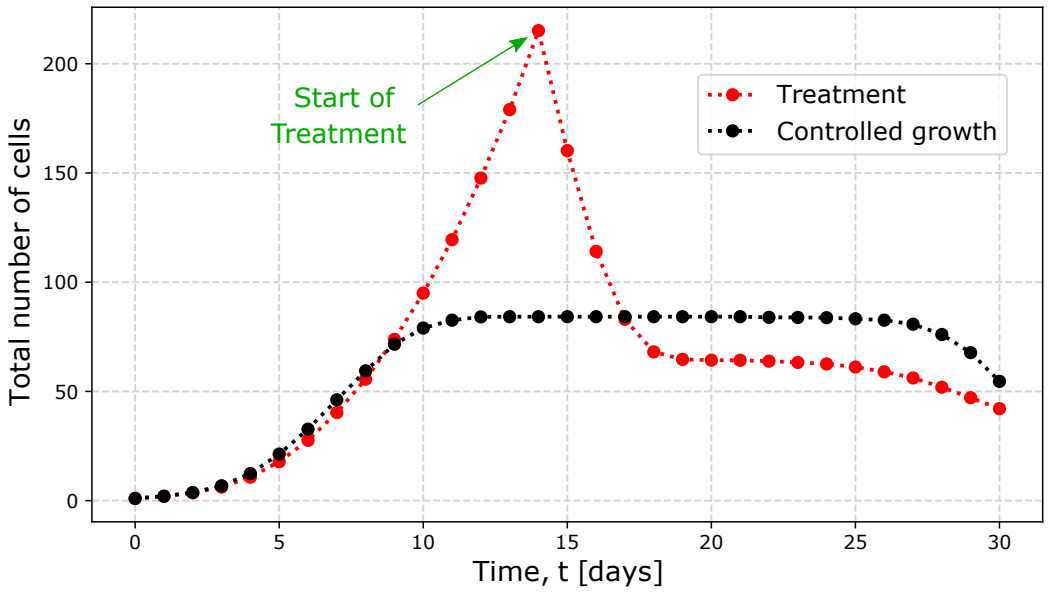

Figure 4: Comparison of Controlled cell's growth (in black) and the action of chemotherapy in the uncontrolled growth case (in red).

6 Code

The code for this project is attached together with this document. Or can be found at: https://colab.research.google.com/drive/1Ec41Y12UC_VFG34d8xxe2mgxI5F8NPm6?usp=sharing