www.simiode.org
SIMIODE A SYSTEMIC INITIATIVE FOR MODELING INVESTIGATIONS & OPPORTUNITIES WITH DIFFERENTIAL EQUATIONS

STUDENT VERSION

Should Cancer Therapy Start Before or After Surgery?

Maila Brucal-Hallare
Department of Mathematics
Norfolk State University
Norfolk VA USA

Iordanka Panayotova
Department of Mathematics
Christopher Newport University
Newport News VA USA

SCENARIO DESCRIPTION

Heart disease, according to the Center for Disease Control and Prevention, is the leading cause of mortality in the USA. Next in the list is cancer. There are many types of cancer but all of them have the same definition, according to the National Cancer Institute [3]:

> *Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.*

This activity is inspired by some current research on having surgery before therapy [6] and having surgery after therapy [5].

As a student of differential equations, there are two verbs in this definition that should engage you: grow (uncontrollably) and spread (to other parts of the body). These two dynamic verbs provide rationale for why many mathematical oncologists use differential equations to investigate cancer growth, spread, and treatments.

Currently, cancer treatments include surgery and various kinds of therapy: radiotherapy, chemotherapy, immunotherapy, hormonal therapy, and even viro-therapy [2]. Refer to another SIMIODE Modeling Activity by the authors on viro-therapy [1]. In this activity, you will explore a basic question: does the order of treatment matter? In particular, suppose that the oncologist has recommended surgery and chemotherapy to treat a cancer. Should the surgery happen before chemotherapy, or after chemotherapy? We shall use a highly simplified differential equation to explore this question. Please remember that this activity is for classroom exploration only and the results of the exploration should not be used in making medical decisions.

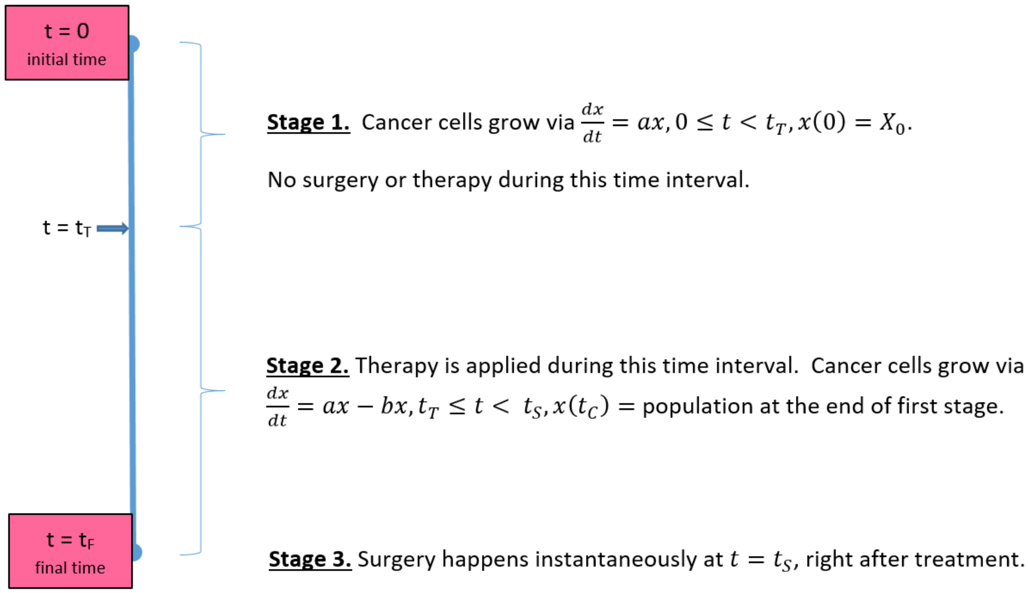

Figure 1. Observation timeline for treatment model 1.

Let $x = x(t)$ represent the cancer cell population at any time t. Suppose $G(x)$ describes the growth rate of cancer cells and $D(x)$ describes the death rate of x due to a certain kind therapy. Let us assume that both growth and death rates are modeled by the linear functions

$$G(x) = ax, \quad D(x) = bx,$$

for some growth parameter $0 < a < 1$ and some treatment parameter $0 < b < 1$ that depend on the specific cancer under investigation.

To analyze the exploration question, we shall assume the following:

1. the initial population of cancer cells is $x(0) = X_0$;
2. surgery happens instantaneously;
3. therapy happens once and over an interval of time of positive length; and
4. after surgery, 99% of the cancer cells have been removed.

We shall explore two treatment models with stages as described below. Both treatment models will have three stages, where $t = 0$ is the initial time, $t = t_S$ is the surgery time, $t = t_T$ is the start of therapy time, and $t = t_F$ is the final time:

- Treatment model 1 considers the treatment scenario when surgery is applied after therapy. The time intervals are $0 < t_T < t_S = t_F$. See Figure 1.
- Treatment model 2 considers the treatment scenario when surgery is applied before therapy. The time intervals are $0 < t_S = t_T < t_F$. See Figure 2.

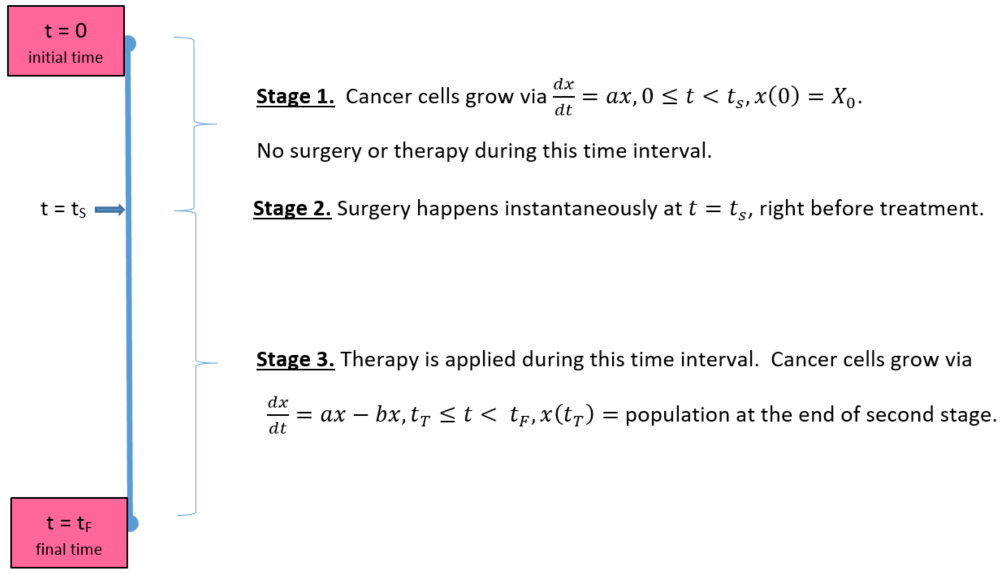

Figure 2. Observation timeline for treatment model 2.

In which of these two treatment scenarios do we end up with less cancer cells? The exercises below will guide you towards a concrete result.

ACTIVITY

Treatment model 1: surgery after therapy.

1. The initial-value problem for stage 1 is

$$\begin{cases} \dfrac{dx}{dt} &= ax, \quad 0 \le t < t_T, \\ x(0) &= X_0. \end{cases}$$

   Using separation of variables and then plugging-in the initial value $x(0) = X_0$ yields

$$\frac{dx}{x} = a\,dt \implies x(t) = \underline{\hspace{6cm}}.$$

2. What is the initial-value problem for stage 2?

$$\begin{cases} \dfrac{dx}{dt} &= ax - bx, \quad t_T \le t < t_S, \\ x(t_T) &= \underline{\hspace{6cm}}, \end{cases}$$

   Using separation of variables and then plugging-in the initial value yields $x(t_T) = X_0 e^{at_T}$,

$$\frac{dx}{x} = (a-b)\,dt \implies x(t) = \underline{\hspace{6cm}}.$$

3. In stage 3, surgery happens instantaneously. Using your answers in the previous item, what is the number of cancer cells at the end of treatment model 1, assuming that surgery removes 99% of the cancer cells from the previous stage?

$$x(t_S) = x(t_F) = \underline{\hspace{6cm}}. \tag{1}$$

Treatment model 2: surgery before therapy.

1. The initial-value problem for stage 1 is

$$\begin{cases} \dfrac{dx}{dt} &= ax, \quad 0 \le t < t_S, \\ x(0) &= X_0. \end{cases}$$

Using separation of variables and then plugging-in the initial value we find

$$\frac{dx}{x} = a\,dt \implies x(t) = \underline{\hspace{6cm}}.$$

2. In stage 2, surgery happens instantaneously at time $t = t_S$. Using your answers in the previous item, what is the number of cancer cells at the end of stage 2, assuming that surgery removes 99% of the cancer cells from the previous stage?

$$x(t_S) = \underline{\hspace{6cm}}.$$

3. What is the initial-value problem for stage 3?

$$\begin{cases} \dfrac{dx}{dt} &= ax - bx, \quad t_T \le t < t_F, \\ x(t_T) &= \underline{\hspace{6cm}}. \end{cases}$$

Using separation of variables and then plugging-in the initial value, we find

$$\frac{dx}{x} = (a-b)\,dt \implies x(t) = \underline{\hspace{6cm}}.$$

4. How many cancer cells are there at the end of treatment model 2?

$$x(t_F) = \underline{\hspace{6cm}}. \tag{2}$$

5. Having completed your computations in the previous exercise, the next step is to compare the numbers in (1) and (2). Did you get equal quantities? Explain why.

Treatment Model 3: Modified Treatment Model 2

1. Treatment models 1 and 2 show us that commuting surgery with therapy, with the assumptions above, did not give any difference in the final counts of the cancer cells. Let us look at a modified version of Treatment model 2. In Treatment model 3, we assume that after surgery, the growth of cancer cells is now modeled by $f(x) = a^2x$, where $0 < a < 1$. See Figure 3.

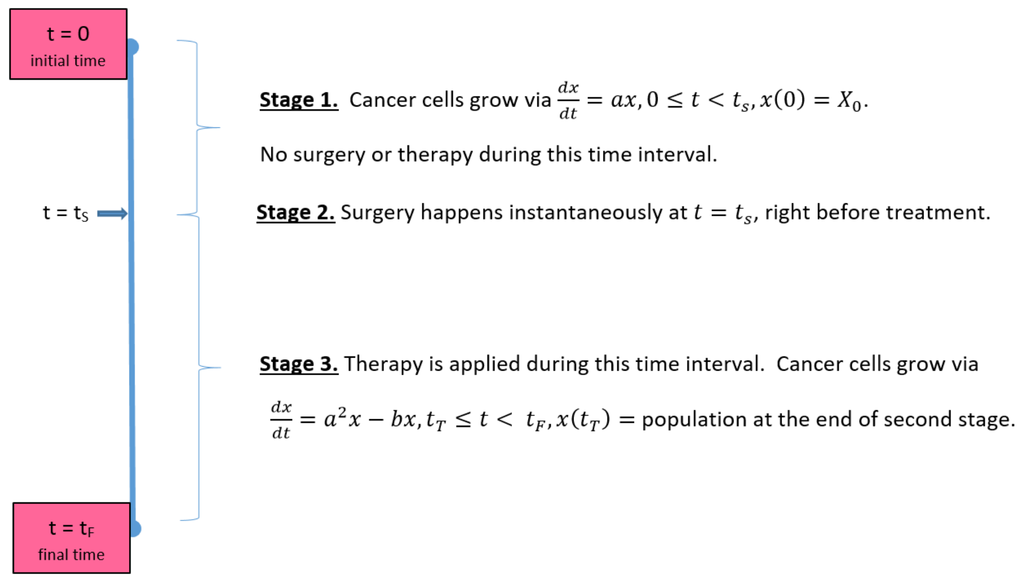

Figure 3. Observation timeline for treatment model 2.

2. The initial-value problem for stage 1 is

$$\begin{cases} \dfrac{dx}{dt} &= ax, \quad 0 \le t < t_S, \\ x(0) &= X_0. \end{cases}$$

Using separation of variables and then plugging-in the initial value we have,

$$\frac{dx}{x} = a\,dt \implies x(t) = \underline{\hspace{4cm}}.$$

3. In stage 2, surgery happens instantaneously at time $t = t_S$. Using your answers in the previous item, what is the number of cancer cells at the end of stage 2, assuming that surgery removes 99% of the cancer cells from the previous stage?

$$x(t_S) = \underline{\hspace{4cm}}.$$

4. What is the initial-value problem for stage 3?

$$\begin{cases} \dfrac{dx}{dt} &= a^2x - bx, \quad t_T \le t < t_F, \\ x(t_T) &= \underline{\hspace{4cm}}. \end{cases}$$

Using separation of variables and then plugging-in the initial value we find

$$\frac{dx}{x} = (a^2 - b)\,dt \implies x(t) = \underline{\hspace{4cm}}.$$

5. How many cancer cells are there at the end of treatment model 3?

$$x(t_F) = \underline{\hspace{4cm}}. \tag{3}$$

6. Having completed your computations in the previous exercise, the next step is to compare the numbers in (2) and (3), for example, by computing the magnitude of their ratios. Observe that many factors will cancel out.
7. Since $0 < a < 1$, conclude your investigation by writing a mathematical prescription on whether surgery should be applied before therapy, given the above assumptions. Make sure that you capture all the assumptions and the main result.

Investigating the assumptions of the models

1. The models that you see above assume that the growth and death rates are both proportional to their population. These assumptions are highly idealized. Depending on the kind of cancer, these rates may vary considerably. Use the internet to find information on the growth rates that mathematical oncologists have been using in their models. A good starting point is [4].
2. The models assume that the surgery is successful and that the population is reduced by a constant factor (in the treatment models above, we assumed 99%). A variant of this is a constant factor K where $|K| \leq e^{-L}$ for some $L > 0$. However, some cancer cells cannot be removed by surgery. In the models, we assumed that the surgery happens instantaneously. How would you modify the model if two non-instantaneous therapies are applied, for example, radiotherapy and chemotherapy?
3. How would you modify the equations in case the oncologist recommends three treatments, one after the other?
4. Out of mathematical curiosity and not out of realistic assumptions, mathematical oncologists analyze equations like $\dfrac{dx}{dt} = ax - bx$ for $a = b, a < b, a > b$. Reflect on the implications of each of these three cases on the two models. Make an intelligent guess on how the magnitudes of a and b affect the efficacy of either treatment models.

REFERENCES

[1] Panayotova, I. N. and M. Brucal-Hallare. 2021. The Good Kind of Virus: Oncolytic Viruses vs Cancer Cells. 6-017-S-OncolyticViruses. https://www.simiode.org/resources/8471.

[2] Breast Cancer: Types of Treatment. 2020. Cancer.net. https://www.cancer.net/cancer-types/breast-cancer/types-treatment.

[3] National Cancer Institute. 2021. What is cancer? https://www.cancer.gov/about-cancer/understanding/what-is-cancer.

[4] Gerlee, P. 2013. The model muddle: in search of tumor growth laws. *Cancer Res*. 73(8): 2407-2411. doi: 10.1158/0008-5472.CAN-12-4355. Epub 2013 Feb 7. PMID: 23393201.

[5] Hennon, Mark, and Sai Yendamuri. 2019. For radiation therapy before surgery in esophageal cancer, dose matters, and with each answer comes more questions. *Journal of Thoracic Disease*. 11,12 (2019): 5662-5663. doi:10.21037/jtd.2019.12.62

[6] Sekiguchi, Atsushi *et al.* 2016. Postoperative hormonal therapy prevents recovery of neurological damage after surgery in patients with breast cancer. *Scientific reports*. Vol. 6 34671. 6 Oct. 2016. doi:10.1038/srep34671.