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MATHEMATICAL MODELLING (USING ORDINARY DIFFERENTIAL EQUATIONS) TO STUDY THE GROWTH OF CANCER CELLS AND THEIR OPTIMAL CONTROL

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Abstract- Cancer is considered as the most dangerous disease which is the leading cause of death in all over the world. Exact knowledge of tumor growth is important in cancer treatment. Effective mathematical modelling help researchers to understand the growth pattern of cancer cells and their optimal control strategies.

In this paper, we shall study various Mathematical Models (using ordinary differential equations) to analyze cancer-immune interactions, and in particular, immune-induced tumor dormancy. We shall also evaluate how the prediction of tumor growth changes when chemotherapy or other treatments are induced.

I. INTRODUCTION TO CANCER-IMMUNE INTERACTIONS

Tumor growth within a host is defined by the interactions the cancer cells have with the local environment, including many functionally different immune cells. The intercellular signaling between cancer and stromal cells creates an ever - evolving milieu of cytokines that determine whether the immune cell function will be tumor-promoting or tumor – inhibiting [1] - [6] – and thus the overall tumor growth dynamics. Indeed, growth dynamics vary among lesions within a host [7], across hosts, and following treatments [8], depending on inherent variability in factors such as the sensitivity of cancer cells or the response of host cells to communication signals [9], [10].

Immune-induced tumor dormancy is a transient state of cancer progression during which the abnormal cells and micro environment may evolve over time, but tumor mass remains constant [11]-[13]. Dormancy can occur at any stage and may terminate in either tumor elimination or re-growth [14]. In some instances, the dormancy may persist throughout the patient's lifespan, resulting in an asymptomatic cancer [15]. Immunotherapy aims to boost the cytotoxic immune response to eliminate the disease, but can result in variable and non-intuitive response dynamics, including dormancy or even increased tumor mass prior to regression [8].

An analogy to aid understanding of these complex tumor dynamics lies in the motion of a tumor mass rolling within an immune "potential well", where escape to one side represents tumor elimination,

escape to the other represents tumor progression, and the "trapped" motion within the well represents tumor dormancy [16], see Fig. 1. Understanding the dynamics of tumor growth within a patient is important for treatment planning, especially for secondary or tertiary treatments where environmental regulation is aberrant [9].

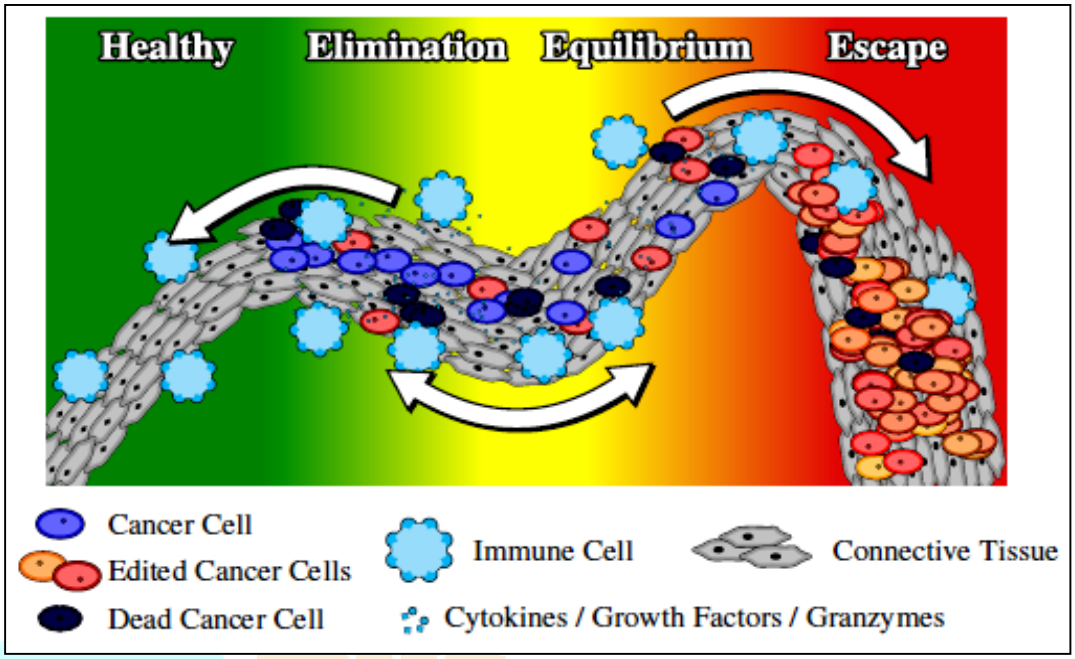

Figure 1. Visualization of cancer-immune dynamics as motion within a potential well (derived from Fig. 10.1 in [16]).

II. RESULTS AND INSIGHTS FROM APPLYING THIS METHOD

With this model we demonstrate how tumor dormancy is a transient state that necessarily ends in either tumor elimination or escape [9], see Fig. 2. This result agrees with real world observations and contrasts the standard (mathematical) view of dormancy as a stable equilibrium [16]-[21] that persists for a long time. This model also captures known non-intuitive tumor dynamics such as accelerated repopulation [22]-[24] and anomalous periods of growth prior to regression that have been observed post tumor treatment [8].

The model also demonstrates the effect of cell-level sensitivity to environmental regulation, showing how inherent variability of response to signals can explain disparate patient outcomes for similar treatment protocols [9], [10]. The method is proposed as a proxy to help analyze patient variability and treatment outcomes to improve understanding of why specific treatments work for some patients but not others.

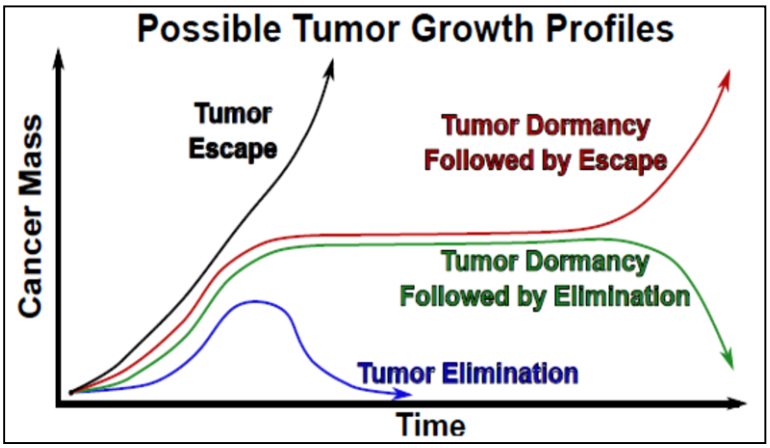

Figure 2. Possible tumor growth profiles including elimination, escape, and transient periods of tumor dormancy.

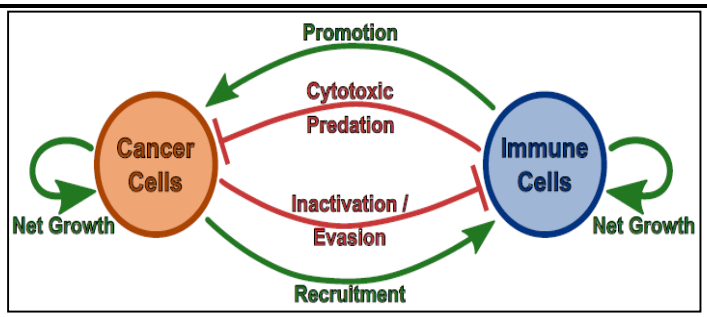

Figure 3. Diagram of cancer-immune interactions that modulate growth dynamics for both cell populations.

III. QUICK GUIDE TO THE METHODS

The method of applying ODEs to study cancer-immune dynamics requires, in the most basic form, prescribing equations for the rate of change over time of the cancer cell and immune cell populations, thus creating a system of two ODEs that are solved simultaneously. Several reviews can be found in the literature [16], [25].

In this approach [9] we do not model specific cytokine concentrations, but rather prescribe functional forms that encompass the net result of many cytokines on the bulk population. This allows for a minimally parameterized model that is easier to validate and more amenable to demonstrating the fundamental dynamics governing the cellular interactions.

Fig. 3 depicts the main mechanisms by which the cancer and immune cells interact. Each population has a net growth rate that is defined as the birth rate less the death rate for that population. Immune cells can promote cancer growth through inflammatory processes that increase blood flow and stimulate angiogenesis, bringing growth factors and nutrients to the tumor site [3]. They can also induce apoptosis through cytotoxic action [4], [26]. Cancer cells, on the other hand, can inactivate immune cells and develop mechanisms to evade immune detection [12], [27], [28]. They also recruit immune cells to the tumor by disrupting tissue architecture and producing chemokines and cytokines [3].

In what follows, we prescribe equations to describe the growth of two cell populations over time, cancer cells $C(t)$ and immune cells $I(t)$. The main assumption of this model is that the cell populations are homogenous, allowing any spatial dependence to be neglected. Each population is assumed to grow in a self-limited logistic manner with carrying capacities (or maximum possible population sizes) K_C for cancer and K_I for immune.

A. *The Governing Equations*

A simple translation of cancer-immune interactions into mathematical form could be along the lines of: the rate of change of the cancer population consists of a net growth term, less an immune-induced predation term, plus an immune-induced stimulation term. Such an additive formulation, however, does not account for the manner in which predation and stimulation occur – which can be tied directly to the ability of cells to sense signals from their environment and proliferate, quiesce, or die accordingly. We thus propose an integrated approach that allows immune actions to modify the net growth term through the following form:

$$\frac{dC}{dt} = \frac{\mu}{\alpha}\left(1+\psi\left(I,C\right)\right)C\left(1-\left(\frac{C}{K_C}\right)^{\alpha}\right) \qquad (1)$$

Here μ and α are parameters that describe the growth and sensitivity of cancer cells to environmental regulatory signals, and Ψ is a function that can describe both immune inhibition and stimulation of cancer growth. An example of a predatory / inhibitory functional form is

$$\psi(I,C) = -\theta\left(\frac{I^{\beta}}{\phi C^{\beta} + I^{\beta}} + \varepsilon log_{10}(1+I)\right) \quad (2)$$

where θ, β, ϕ and ε are immune predation parameters.

The immune population is also described by a modified logistic growth formulation,

$$\frac{dI}{dt}\lambda(I + rC)\left(1 - \frac{I}{K_t}\right) \quad (3)$$

where λ is the growth rate and *r* is a recruitment parameter.

An extension of this model allows the cancer to modify its own carrying capacity via [9], [29]

$$\frac{dK_C}{dt} = pC(t) - qK_C(t)C(t)^{2/3} \quad (3)$$

where *p* and *q* are growth stimulation and inhibition constants, respectively. We may further extend this model to allow carrying capacities to depend on both populations [10], (capturing, for example, immune stimulation through inflammation and angiogenesis) and generally describe them by $\frac{dK_C}{dt} = f(I,C)$ and $\frac{dK_I}{dt} = g(I,C)$.

Parameter values should be determined by fitting the model to experimental or clinical data. Sensitivity analyses can then be used to identify significant determinants of the dynamics in question and 'prune' the formalism of less informative parameters.

B. When this method is useful

We have described how ODEs can be used to track the evolution over time of two populations of cells as they grow within a host. These methods can be used to describe any time evolution, ranging from cellular mass to protein concentration and beyond. Using ODEs to model a biological question requires that there is only one independent variable (such as time) and that all others (such as space) can be neglected. In this case, the structure can simplify over the alternative partial differential equation framework that would be needed if space and time were important, and provide rapid and efficient insights into how the complex immune-cancer dynamic might respond in the clinical context.

Preliminaries: growth laws and tumor growth

In the literature, various growth functions were developed which are used to study widely on the platform of ecology and epidemiology. The growth of a tumor can be modeled through first-order ordinary differential equations by examining the change of tumor volume over time with an initial assumption. The initial condition has been used in most tumor models. Primarily, the tumor growth is designed by considering either the exponential or the logistic growth laws (Wang. 2018; Murray, 2007; Tsoularis and Wallace, 2002). The commonly used exponential growth differential equations are-

- Malthusian model: $\frac{dV}{dt} = rV,\ r > 0.$
- Power law model: $\frac{dV}{dt} = rV^b,\ r > 0, b > 0.$
- Migration model: $\frac{dV}{dt} = rV + K,\ r > 0, K > 0.$

- Gompertz model: $\frac{dV}{dt} = ae^{-\beta t}V, a > 0, \beta > 0.$

Discussion of these models and their graphical solutions are discussed in Appendix A.

The exponential models describe the tumor growth satisfactorily for a certain amount of time. But the volume tends to infinity if growth rate is positive over time which is not realistic. The volume can only increase to a certain level since there are limited resources that are necessary for cell growth and then its gets stable which can be fairly described by the logistic models. The Von Bertalanffy logistic model and the generalized case are discussed in the following subsection while the logistic and Richards' growth functions are presented in Appendix A.

Von Bertalanffy model

Assume that growth is proportional to surface area, since nutrient enters through the surface, and that death is proportional to the tumor size. The model is also known as the surface rule model. It has been successfully applied to describe human tumor growth (Tsoularis and Wallace, 2002).

$$\frac{dV}{dt} = aV^{\frac{2}{3}} - bV \qquad (1)$$

Where a is the growth parameter and b is the growth deceleration parameter. The solution of (1) is given by:

$$V(t) = \left[\frac{a}{b} + \left(V_0^{\frac{1}{3}} - \frac{a}{b}\right)e^{-\frac{1}{3}(t-t_0)}\right]^3.$$

We can show the behavior of the Von Bertalanffy model in the following figure 1.

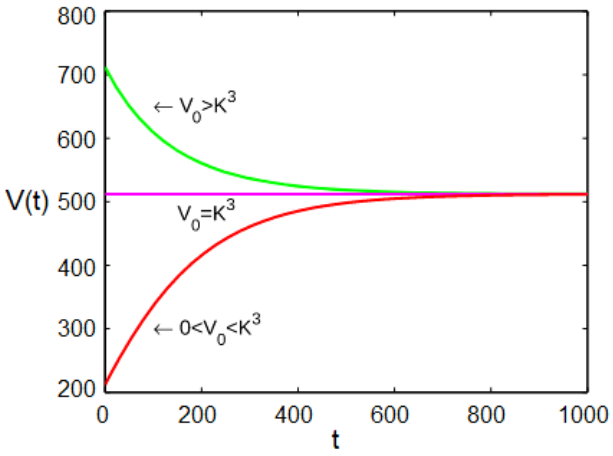

Figure 1: Graph of Von Bertalanffy model (1) with t_0 = 0 days, a = 1.6 × 10^{-7} m^3day^{-1}, b = 0.2 × 10^{-7} m^3day^{-1} and K= a/b.

It may be observed in Figure 1 that by taking the initial cell volume between 0 and the cell volume increases over time the gets stable at $V = \left(\frac{a}{b}\right)^3$. Hence, $V = \left(\frac{a}{b}\right)^3$ is the saturation level of the model.

If we take initial volume $V_0 = \left(\frac{a}{b}\right)^3$ the volume reduces exponentially over time and is stable at $V = \left(\frac{a}{b}\right)^3$. Also if we take $V_0 = \left(\frac{a}{b}\right)^3$ the volume remains constant.

Optimal control

In this section, a model is developed and analyzed with an aim to discuss different strategies to cure cancer. Here we study the optimal control for chemotherapy. This optimal control helps reduce the tumor volume and the side effects of the drugs over a given period of time. Fister and Panetta (Panetta and Fister, 2000) used an optimal technique. There are several models describing chemotherapeutic killing of cancer cells. The analysis presented there is based on the skipper's log-kill hypothesis, which states that killing of cancer cells by injecting chemotherapeutic drugs is proportional to the tumor at time *t*. the results for this hypothesis using the Gompertzian growth model (Lenhart and Workman, 2007) have already be presented in the earlier section. If V(*t*) is the tumor volume at time *t*, the model can be described by:

$$\frac{dV}{dt} = rV(t)\left(1-V(t)\right) - u(t)\delta V(t) \qquad (12)$$

Where r is the natural growth rate of the tumor cell, δ is the magnitude of the dose and *u*(*t*) is the effect and strength of the drug. If *u*(*t*) = 0, there is no drug effect and if *u*(*t*) > 0, the strength of the drug effect is considerable.

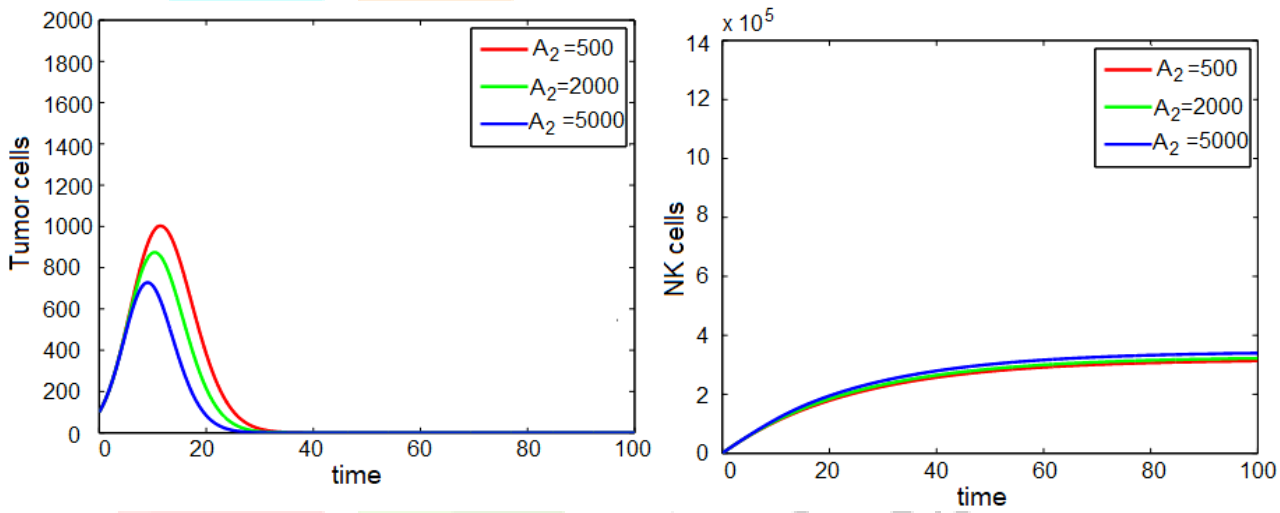

Figure 8: Dynamics of tumor and NK cells with different values of A_2.

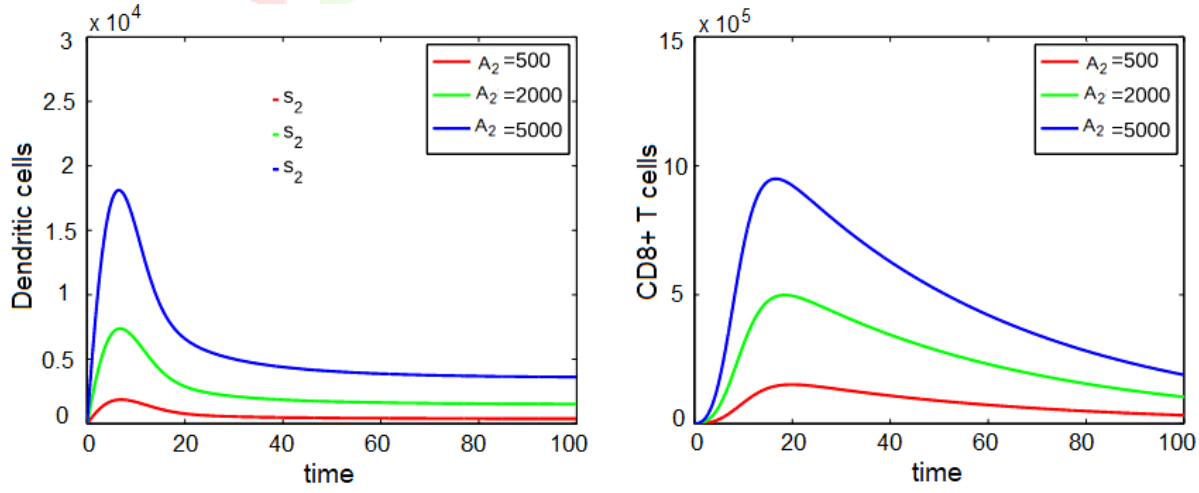

Figure 9: Dynamics of dendritic and CD8+ T cells with different values of A_2.

The objective function can be used minimize the cost of the control, the possible side-effects and the tumor volume V over a time interval. Finally, we require $u(t) \geq 0$ for all t. considering a quadratic objective function, the minimization problem can be defined as follows:

$$\min_u \int_0^T aV(t)^2 + u(t)^2 \, dt$$

Subject to $V'(t) = rV(t)(1 - V(t)) - u(t)\delta(t), V(0) = V_0$

$$u(t) \geq 0$$

Where a is a positive weight parameter. If we solve this problem we can generated different graphs using different values of the parameters. The effects of drugs over time are illustrated in figure.

Using the values of the parameters as r = 0.3, δ = 0.45, V_0 = 0.975 and T = 20, we have compared them by changing the value of a in the same optimization problem. It is observed that volume of the tumor reduces with increase in a.

Also we can observe that results by changing values of the initial density and time periods. We compare the graphs forV_0 = 0.975 and V_0 = 0.6, also taking a longer period of time, T = 40.

One can see that after a short period of time, the result do not change significantly. The reduction rate of the tumor volume is faster for first few days, then it slows down and after sometimes, it becomes uniform. We can also see from the above figure that long time treatment results are similar to those for short time.

If we change the dosage δ of the drug by taking the parameters, r = 0.3, a = 3, V_0 = 0.8, T = 20 and δ = 0.3 and 0.5, we notice that for higher dosage of drugs, reduction of tumor volume is faster. For = 0.5 we notice much more reduction in tumor volume than for = 0.3.

The observations for the study reveal that the time period of the treatment does not effect the reduction process and also the initial volume of tumor. The reduction process is very slow during the first few days.

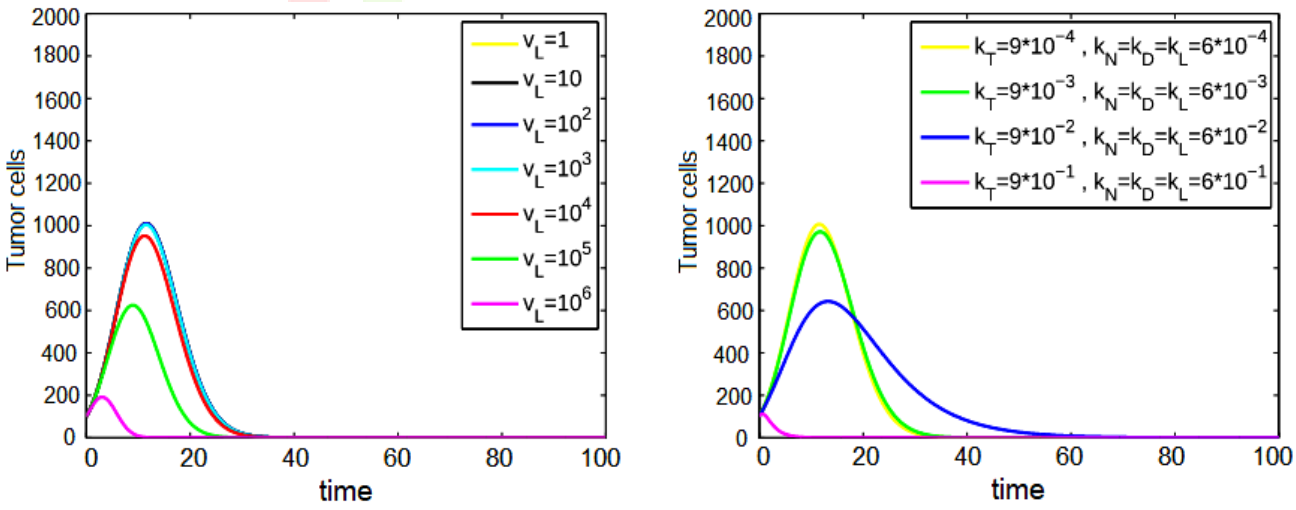

Figure 10: Dynamics of tumor cells with different values of V_L and K_T, K_N, K_D and K_L.

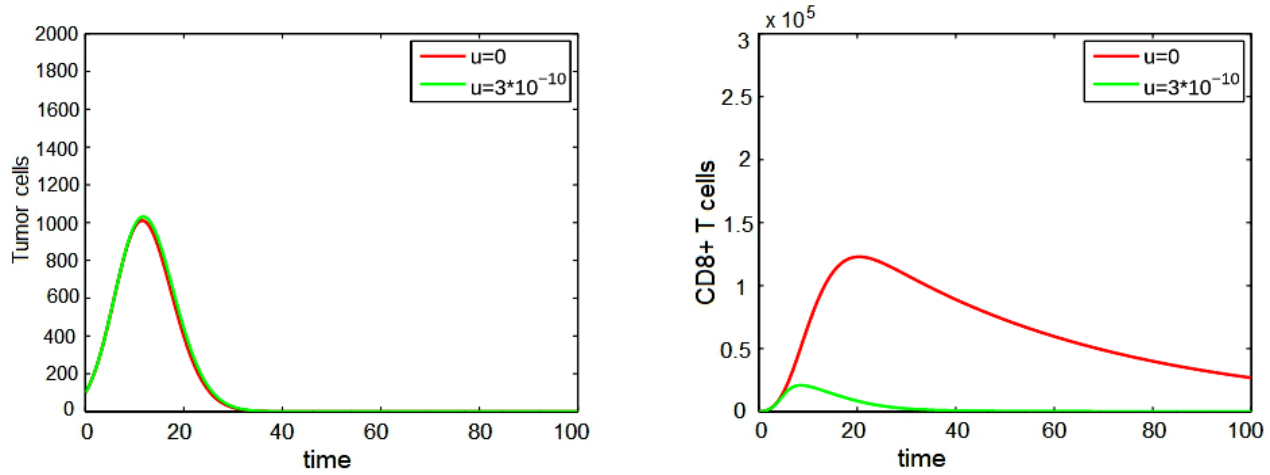

Figure 11: Dynamics of tumor cells and $CD8^+$ T cells with different values of v_3.

But the dosage of medicine plays a vital role in the reduction process. The higher the dose the faster and better is the result. In this case, tumor size is considerably reduced in the first few days and then the process slows down. Therefore we can say that the optimal control is a high drug dosage strategy to reduce cancer, which is common in cancer treatment these days.

A Appendix

Exponential and logistic models

The growth of tumor can be modeled through first-order ordinary differential equations by examining the change of tumor volume V over time t with an initial volume $V(0) = V_0$. This initial condition has been used in most tumor models. Some exponential models that can be conveniently used to describe tumor growth are discussed below. Later in this section, we have presented the discussion of logistic models and their biological feasibility.

Malthusian model

This is the simplest model to describe tumor growth. The growth is proportional to the population of tumor cells. This model is often used to describe a single species population's growth rate. The model has the following form Murray (2007):

$$\frac{dV}{dt} = rV \qquad \text{(A.1)}$$

Where V is the volume of the tumor, r is the growth parameter and t represents time. The solution of equation (A.1) is given by:

$$V(t) = V_{0^{e^{rt}}}$$

The behavior of Malthusian model (A.1) can be seen from the following figure A.1:

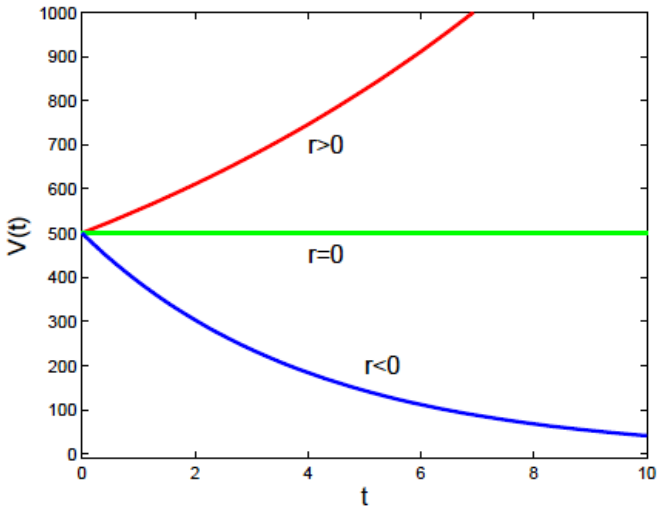

Figure A.1: Graph of Malthusian model (A.1) with initial volume $V_0 = 5\times10^{-4} m^3$.

It is observed in Figure A.1 that the volume of the tumor over time grows exponentially if the growth parameter *r* is positive. If r is negative, it decreases exponentially and if *r* is zero, the cell volume remains constant.

Power law model

The generalization of Malthusian model can be described by the power law model. It was first introduced by Mendelsohn in 1963. This model has the following form Wang (2018):

$$\frac{dV}{dt} = rV^b \qquad \text{(A.2)}$$

Where *r* is the intrinsic growth rate. If b = 1, we get Malthusian model which we have already discussed. This equation has the solution of the following form:

$$V(t) = \left[V_0^{1-b} + r(1-b)(t-t_0)\right]^{1/b-1}$$

Now we can draw the graph from this solution using different value of b. For b = 1, we get the Malthusian model. We consider here two cases for b > 1 and b < 1 and analyze the effect of the exponent in the model.

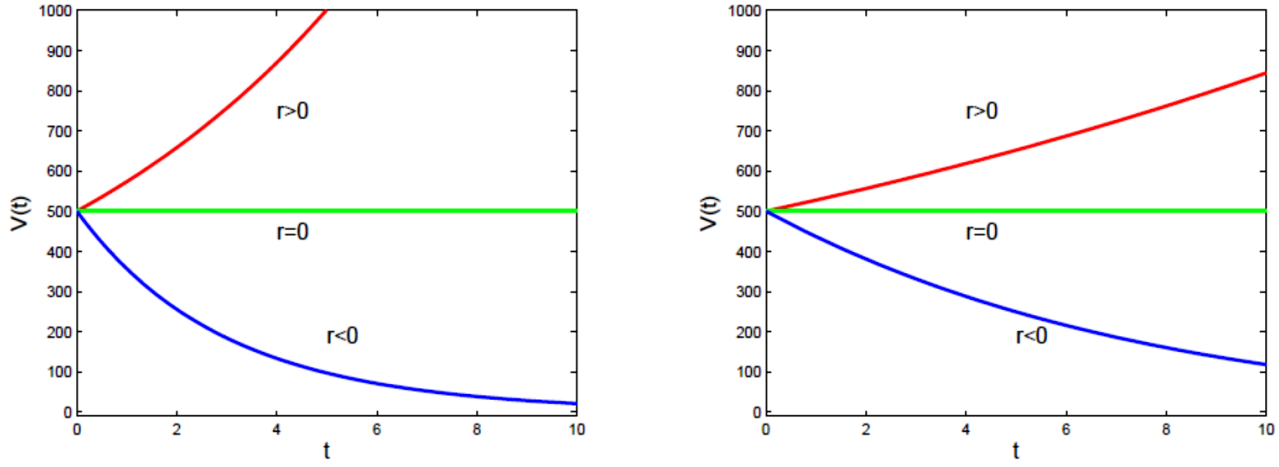

Figure A.2: Power law model (A.2) with initial volume $V_0 = 5 \times 10^{-4}$ m^3 and the exponent, b = 1.05 (left) and b = 0.9 (right).

In Figure A.2, we can see that the graphs are different for b = 1.05 and b = 0.9, therefore the model behaves differently. For b = 1.05 we can observe that the volume increases faster for r > 0, and it decays at faster rate for r < 0. For b = 0.9, we see that the growth rate of tumor volume is slower than the case of the other graph. For r > 0 the volume still increases exponentially but at a slower rate and for r < 0 the volume reduces slowly. So, we can conclude that the growth rate gets faster with increase in the value b.

Migration model

Migration model can be described by a population that obeys an exponential law of growth with migration. Migration can affect the cell volume in two different ways. It can increase the volume by adding newly affected cells or it can reduce the cell volume, which can happen when the tumor cells die. This can be described by following equation Murray (2007) :

$$\frac{dV}{dt} = rV + K \qquad \text{(A.3)}$$

where r is the growth rate and the migration rate is K. When K is positive, more and more normal cells transform into tumor cells and when K is negative the tumor cells die. Now to solve the equation (A.3), let V = u – K/r where $r \neq 0$. Then we have the solution:

$$V(t) = \left(V_0 + \frac{K}{r}\right) e^{r(t-t_0)-\frac{K}{r}}$$

Plots of the solution for different migration rates are shown below:

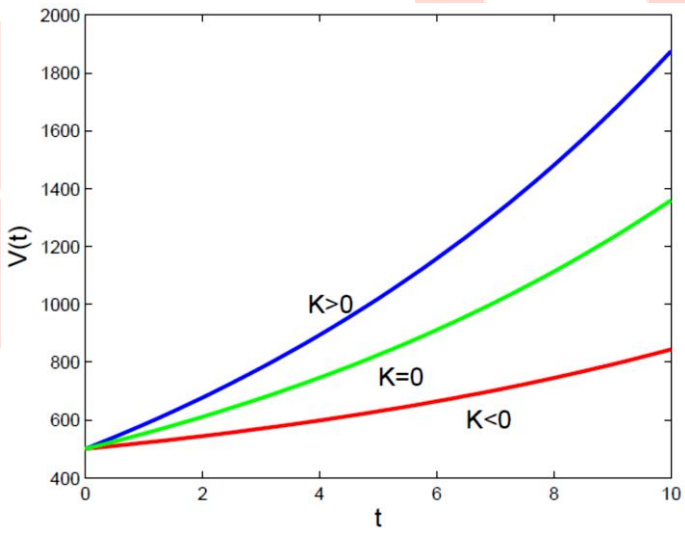

Figure A.3: Graph of migration model (A.3) with various migration rates.

By taking the growth rate r = 10^{-7} m^3 day^{-1} and initial population $V_0 = 5 \times 10^{-4}$ m^3 we can generate the graphs in Figure A.3 over time t = 0 to t = 10 days. Here we can see that if the migration rate is positive, the volume increases at a faster rate than in the case when the migration rate is negative.

For different migration rates, we can explain the behavior of the model (A.3).

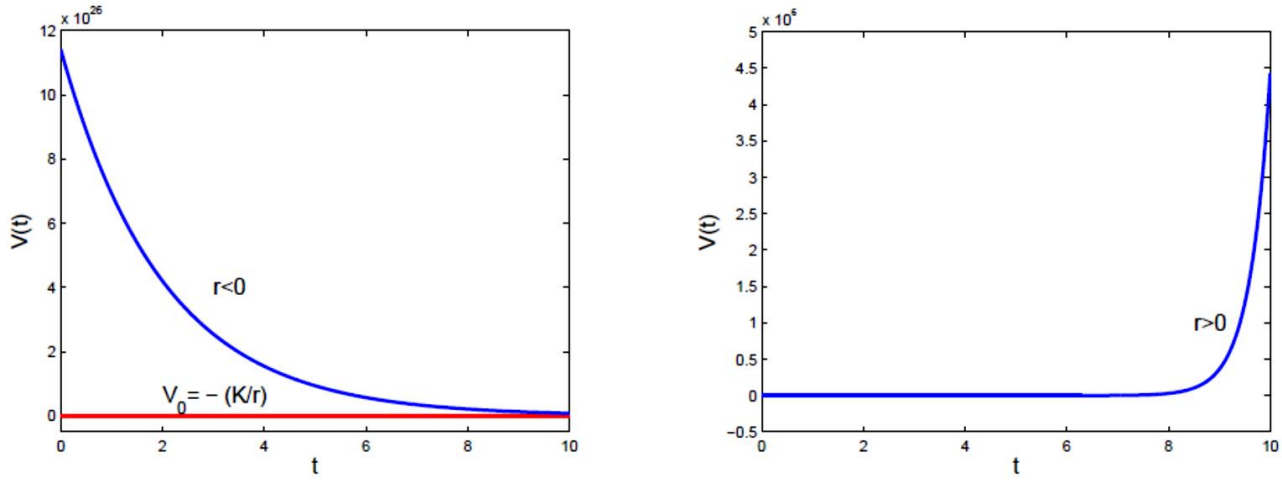

Figure A.4: Graph of migration model (A.3) with K = 3×10^{-5} m^3 day^{-1} and r = - 5×10^{-7}, r = 2.5×10^{-6} m^3 day^{-1}.

From the above graphs A.4 we observe that for growth rate r < 0 the cell volume V is decreasing over time and $V(t) \to \frac{K}{r}$ as $t \to \infty$. Also we see that, if we take the initial volume $V_0 = -\frac{K}{r}$, the system gets stuck. Although the point, $V = -\frac{K}{r}$ is unstable, since the system moves away when we take initial volume near this point. Again for r > 0 we observe that, the cell volume explodes and tends to ∞.

GOMPERTZ MODEL

The Gompertz model exhibits an exponential decay of the growth rate. It has been successfully used to model breast and lung cancer growth. It is a sigmoid function (function that has S shaped curve) which describes growth as being slowest at start and end. It has been modified suitably for use in biology, with regard to detailing populations. The model can be described by the following form Wang (2018); Tsoularis and Wallace (2000):

$$\frac{dV}{dt} = ae^{-\beta t}V \qquad \text{(A.4)}$$

where *a* is the intrinsic growth parameter and β is the parameter of growth deceleration.

Integrating both sides by taking limits from V_0 to V and t_0 to *t*, we get:

$$V(t) = V_0 e^{\frac{\alpha}{\beta}\left(e^{-\beta t_0} - e^{-\beta t}\right)}V$$

For $t_0 = 0$ the graph of this model (A.4) is shown below:

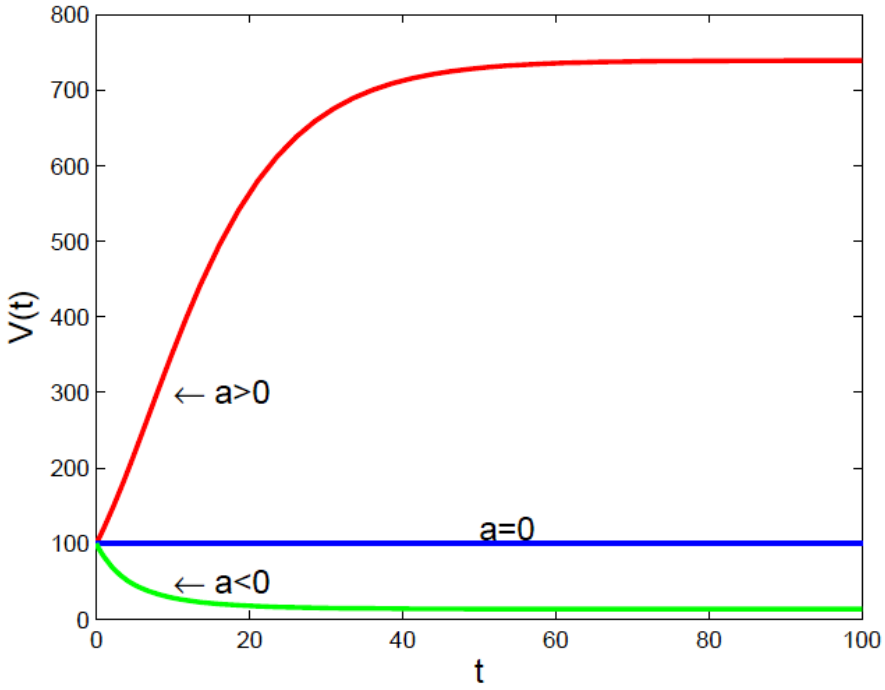

Figure A.5: Graph of Gompertz model (A.4) with $\beta = 1 \times 10^{-7}$ m^3day^{-1} and $V_0 = 10^{-4}$ m^3.

The volume of tumor increases exponentially over time when the growth rate $a > 0$ as seen in Figure A.5. Also we can see that the volume decreases exponentially over time if $a < 0$ and volume is constant if the growth rate is 0.

LOGISTIC MODEL FOR POPULATION GROWTH

The model assumes a linear decrease of the relative growth rate with population size. The maximum size is limited by a carrying capacity K. The model is described by Murray (2007):

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right) \qquad \text{(A.5)}$$

Where a is the coefficient of cell proliferation. We used the carrying capacity, $K = a/b$ where, b is the population deceleration rate. The solution of equation (A.5) is:

$$V(t) = \frac{K}{1 + \left(\frac{K}{V_0} - 1\right)e^{-at}}.$$

The equation is called the logistic law of growth. We can analyze the behavior of the model (A.5) and from the solution is presented in figure A.6.

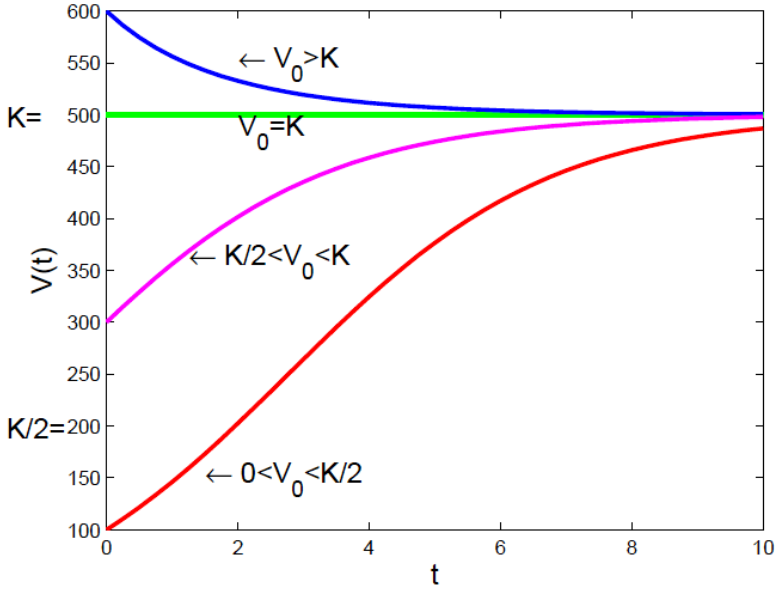

Figure A.6: Graph of logistic model (A.5) with $a = 5 \times 10^{-7}$ $m^3 day^{-1}$ and $K = 5 \times 10^{-4}$.

If we take the initial volume between 0 and K/2, we can see that the volume increases exponentially over time and it gets stable at K. But if we consider the initial volume between K/2 and K the population attains stability faster. If the initial volume is greater than the carrying capacity, then cell volume decreases due to lack of nutrition and therefore the stable position K is attained quickly.

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