A mathematical model of diffusion-driven tumor growth with viral therapy

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Abstract

A model for tumor growth with viral therapy is developed and tested. First, a model of tumor growth driven by oxygen diffusion in the absence of therapy is considered. Second, the model is extended to include the effect of viral therapy on the system. Analysis of the model reveals necessary conditions on the virus for successful treatment of the tumor.

1 Introduction

Cancer is a leading cause of death worldwide, killing 7.4 million people in 2004. It is projected to account for an increasing percentage of deaths over the next two decades. However, some of the more common types of cancer, like breast cancer and cervical cancer, have high cure rates when treated early and effectively [1].

We want to solve the problem of how cancerous tumors grow in humans, so that we can determine what the most effective treatments are. In order to develop a qualitative understanding of this process, as a first step, a mathematical model of a tumor is developed, based on growth driven by diffusion of oxygen into the tumor.

There has been great progress in the last ten years in the field of viral therapy as a treatment for malignant tumors [2]. In contrast to chemotherapy, where drugs are used to kill cells, viral therapy is based on the use of oncolytic viruses, which preferentially destroy tumor cells. The virus is injected into the tumor, infecting an initial population of tumor cells. The infected cells spread the virus to uninfected cells, and then die.

Understanding what makes successful viral therapy is crucial for the development of effective viruses and subsequent treatments. The model shows what effects different parameters have on the system, as well as what properties a successful oncolytic virus should have.

2 Developing the growth model

In order to model the behavior of the tumor with viral therapy, we must first understand the model of tumor growth in the absence of therapy. As tumor growth is a process of vast biological complexity, the model has to make some significant simplifying assumptions. The model first assumes that the tumor is spherical in shape, and that growth is isotropic (that is, the tumor expands in all directions). Since there are many mechanisms involved, the model also makes the simplifying assumption that the tumor grows only by diffusion of nutrients into the tumor. This assumption relies on the fact that without therapies or immune response, nutrient diffusion is the main mechanism regulating tumor growth. The model further makes the assumption that oxygen is the main nutrient affecting the system, and the only one considered here. This is justified because oxygen is the nutrient that contributes most to the growth of the tumor.

2.1 Solving the diffusion equation

First, the diffusion equation is solved to determine how the oxygen surrounding the tumor diffuses into the tumor, allowing it to grow. Since the tumor is assumed to be spherical, consider the radially symmetric diffusion equation in three dimensions:

$$\frac{\partial u}{\partial t} = \frac{K}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right) - Q, \tag{1}$$

where u is the concentration of oxygen at a particular point inside the tumor, r is the radius of the tumor, and t is time, so that $u = u(r)$. Since diffusion takes place faster than growth (the time scale for doubling in volume of the tumor is around a day or two, whereas diffusion takes place in a fraction of a second), we consider the steady-state (or equilibrium) diffusion equation. In our case, a constant rate of oxygen consumption Q by the tumor is assumed, so equation (1) simplifies to

$$\frac{Qr^2}{K} = \frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right). \tag{2}$$

We can integrate with respect to r, giving

$$\frac{Qr^3}{3K} + C = r^2\frac{\partial u}{\partial r}, \tag{3}$$

where C is a constant of integration to be determined by the boundary conditions of the problem. Equation (3) can again be rewritten as

$$\frac{Qr}{3K} + \frac{C}{r^2} = \frac{\partial u}{\partial r}, \tag{4}$$

and integrated with respect to r, giving

$$u(r) = \frac{Qr^2}{6K} - \frac{C}{r} + D, \tag{5}$$

where again D is a constant of integration to be determined by the boundary conditions of the problem.

Let $r = b$ be the radius of the tumor. Then $u(b) = u_b$ for some $u_b > 0$, giving our first boundary condition. This value, u_b, is fixed, so that for small enough tumors, the concentration of oxygen inside the tumor is nonzero everywhere. Therefore we expect exponential growth because all the cells in the tumor have sufficient oxygen to divide, and these new cells in turn have sufficient oxygen to divide, and so on. However, since u_b is fixed, eventually the tumor will grow large enough that oxygen will not diffuse all the way to the center of the tumor. That is, the tumor will develop an inner core where the concentration of oxygen vanishes, giving our second boundary condition. The creation of a shell where growth takes place causes linear growth, as cells outside the core divide rapidly, but since the core grows with the tumor, these cells eventually become part of the core and stop dividing. Thus, the spherical tumor becomes separated into an inner necrotic core where cells are not dividing due to the oxygen concentration being zero, and an outer shell where cells are dividing rapidly with nonzero oxygen concentration.

2.1.1 Two distinct cases

The first case is where the oxygen nutrient does not diffuse all the way to the center of the tumor; that is, $u(a) = 0$ for some $0 < a < b$. This gives

$$u_b = \frac{Qb^2}{6K} - \frac{C}{b} + D \tag{6}$$

$$0 = \frac{Qa^2}{6K} - \frac{C}{a} + D. \tag{7}$$

Combining these, and solving for C and D, gives

$$u(r) = \frac{Qr^2}{6K} + \frac{ab(a^2Q - b^2Q + 6u_bK)}{6(a-b)Kr} - \frac{bu_b}{a-b} - \frac{a^2Q}{6K} - \frac{abQ}{6K} - \frac{b^2Q}{6K}. \tag{8}$$

The second case is where the nutrient diffuses all the way to the center of the tumor; that is, $u(0) = u_0 > 0$:

$$u_b = \frac{Qb^2}{6K} - \frac{C}{b} + D \tag{9}$$

$$u_0 = \frac{Q0^2}{6K} - \frac{C}{0} + D. \tag{10}$$

Notice that equation (10) only works if $C = 0$. Then

$$u_b = \frac{Qb^2}{6K} + D. \tag{11}$$

Solving for D gives

$$u(r) = \frac{Qr^2}{6K} + u_b - \frac{Qb^2}{6K}. \tag{12}$$

2.1.2 Calculating the size of the necrotic core

We want to combine these cases, and determine the critical value of the radius b_c at which a necrotic core of radius a develops at the center of the tumor. This is done by finding when the concentration of oxygen at the center of the tumor ($r = 0$) first reaches zero. This can be done by setting $u(0) = 0$ in equation (12), and solving for the boundary term b:

$$0 = u_b - \frac{Qb_c^2}{6K} \tag{13}$$

which implies

$$b_c = \sqrt{\frac{6Ku_b}{Q}}. \tag{14}$$

So when $b < b_c$, oxygen diffuses all the way to the center of the tumor ($u(0) > 0$), and when $b > b_c$, oxygen diffuses only to a region of radius a from the center; that is, $u(r) = 0$ for $0 \leq r \leq a$.

We now quantify the size of the inner core as a function of the parameters. For a fixed $b > b_c$ and fixed $u(b) = u_b > 0$, we consider the diffusion profiles of oxygen concentration from the center of the tumor to b for various values of the inner core radius a. Since the diffusion profiles are differentiable, and $u(r) = 0$ for $r \leq a$ and $u(r) > 0$ for $r > a$, the diffusion profile must satisfy $\frac{\partial u}{\partial r}|_{r=a} = 0$ also. Since equation (8) has an r^2 and a $\frac{1}{r}$ term, this last condition leads to a cubic equation for a. The actual value of the radius of the necrotic core a is the first positive root of the cubic

$$P_3(a) = \frac{Qa^3}{K} - \frac{3Qba^2}{2K} + \frac{Qb^3}{2K} - 3bu_b. \tag{15}$$

Since $P_3(0) = \frac{Qb^3}{2K} - 3bu_b$ and $P_3(b) = -3bu_b$ (and $b > b_c$), such a root always exists between $a = 0$ and $a = b$ [3].

2.2 Growing the tumor

After determining how oxygen diffuses into the tumor, the next step is to evolve our system in time. We do this by first fixing an initial boundary $b_0 > 0$. The rate of growth is assumed to be proportional to the level of oxygen, so that integrating the oxygen concentration over the radius of the tumor gives us the amount by which the tumor radius has grown; that is,

$$\frac{\partial b}{\partial t} = \eta \int_0^b u(r,b)\,dr. \tag{16}$$

The time step Δt and the growth rate η are set so that $\Delta t \cdot \eta = 1$, giving us the following system for increasing the tumor radius:

$$b_{i+1} = \begin{cases} b_i + \Delta t \int_0^{b_i} \eta\, u(r,b_i)\,dr, & \text{for } b_i < b_c; \\ b_i + \Delta t \int_a^{b_i} \eta\, u(r,b_i,a)\,dr, & \text{for } b_i > b_c. \end{cases} \tag{17}$$

In the numerical simulations, we use the O_2 consumption rate $Q = 3.09 \cdot 10^{-4}\,\mathrm{ml}_{O_2}\,\mathrm{cm}^{-3} \cdot \mathrm{sec}^{-1}$ and Krogh's diffusion constant $K = 1.87 \cdot 10^{-5}\,\mathrm{ml}_{O_2} \cdot \mathrm{cm}^{-1} \cdot \mathrm{min}^{-1} \cdot \mathrm{atm}^{-1}$, as given in [4]. This gives the important ratio related to the critical radius b_c:

$$\frac{Q}{6K} = 165.24\,\frac{\mathrm{atm}}{\mathrm{cm}^2}. \tag{18}$$

We first plot the concentration of oxygen versus the radius of the tumor for a tumor with boundary $b > b_c$, and see that the concentration of oxygen for r between 0 and a is indeed zero:

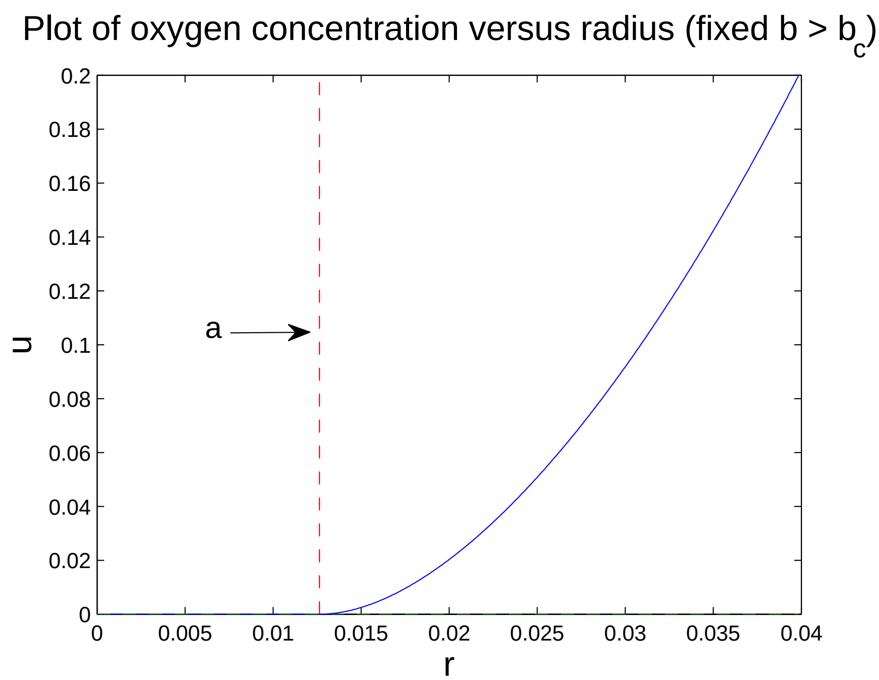


Figure 1: Oxygen concentration versus radius.

In Figure 2, we plot the radius of the tumor versus time, first when $b < b_c$ and the oxygen diffuses to the center of the tumor, and second when $b > b_c$ and the tumor has an inner core where the concentration of oxygen is zero. As expected, we see initial exponential growth followed by linear growth:

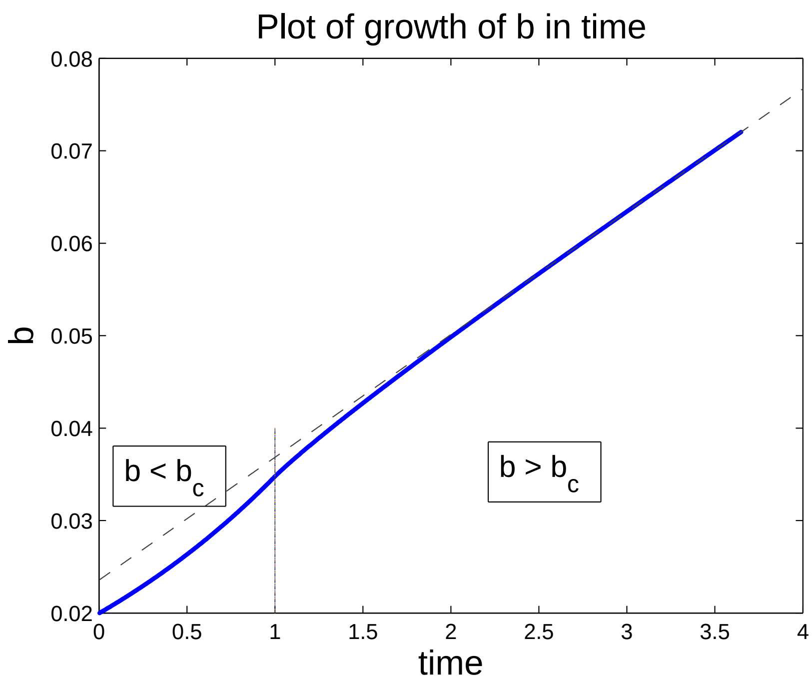


Figure 2: Growth of b in time. Time is scaled so that $t = 1$ corresponds to the time it takes for the tumor to develop a necrotic core. The vertical line represents $b = b_c$. The dotted line indicates that the asymptotic growth is linear.

3 Viral therapy with our growth law

Our model so far describes how a tumor grows in time by diffusion of oxygen. Clearly, in this system, the tumor grows without bound. Thus, we would like to reduce this growth somehow, and ultimately force the tumor to decrease in size.

Of recent interest in the tumor modeling community is viral therapy, where the tumor is targeted with viruses that attack tumor cells. This leads to having two types of cells to model: those which are infected by the virus, and those which are not; in addition, the system should depend on parameters for the growth rate of the tumor, the death rate of the infected cells, and the infection rate of the virus, as described in [5].

We wish to combine the ideas from modeling viral therapy and apply them to our growth model. The effects of the new parameters in our system can then be examined.

The new system is based on our growth model. In addition, it takes into account tumor cell death caused by infection. So the number of cells that die at each time step is a function of the fraction of the tumor cells that are infected with the virus, as well as the death rate of the infected tumor cells. The fraction of infected cells is itself a function of the fraction of cells remaining after cells are killed off in the previous time step, as well as the infection rate of the virus. Thus, at each time step, there are two discrete equations – one for the new tumor radius and one for the new fraction of infected cells.

The revised system is given by first calculating the oxygen concentration for a particular fixed boundary b_i at time step i: $u_i(r) = u(r, b_i)$. Then the tumor radius is updated as follows:

$$b_{i+1} = b_i + \Delta t \left[\int_0^{b_i} \eta \, u_i(r) \, dr \right] - b_i \, \delta \, F_i \, \Delta t, \tag{19}$$

where η is the growth rate of the tumor, δ is the death rate of the infected tumor cells caused by the virus, and F_i is the fraction of infected cells at step i. In this model, only those tumor cells infected with the virus can die. The fraction of infected cells is then updated as follows. Let F_{temp} represent the fraction of infected cells after this round of cell death; that is,

$$F_{temp} = \frac{F_i(1 - \delta\Delta t)}{(1 - F_i) + F_i(1 - \delta\Delta t)} = \frac{F_i(1 - \delta\Delta t)}{1 - F_i\delta\Delta t}. \tag{20}$$

This gives

$$F_{i+1} = F_{temp} + \beta \, F_{temp} \, (1 - F_{temp}) \, \Delta t, \tag{21}$$

where β is the infection rate of the virus.

Since there is no growth or infection when $\eta = 0$ and $\beta = 0$, only infected cells are dying and the radius of the tumor levels off. The radius of the tumor asymptotes to the fraction of uninfected cells (here $F_0 = 0.3$):

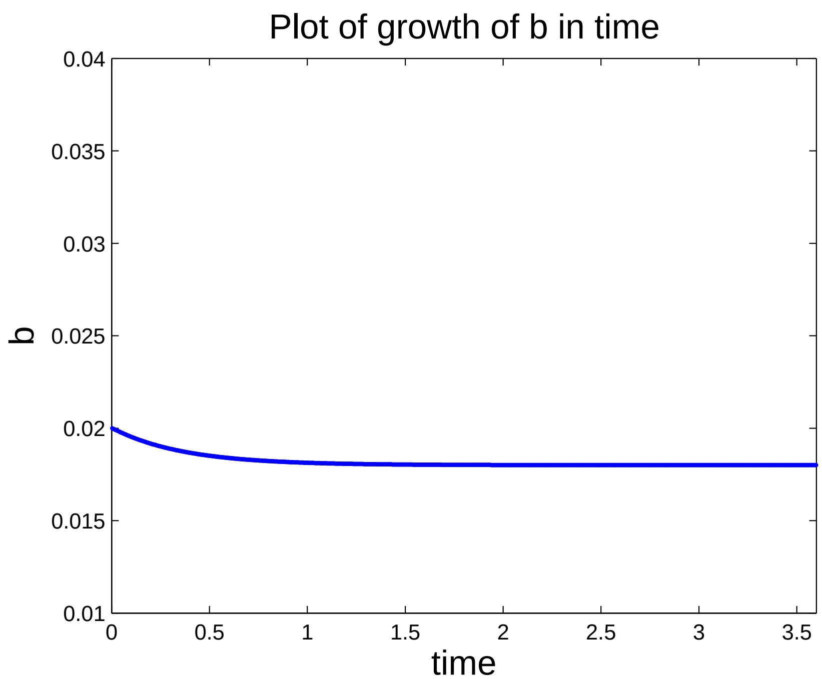


Figure 3: Plot of growth in b versus time, when growth term (η) and infection term (β) are both zero. The radius tends to a constant value, where an equilibrium state with no infected cells is reached.

The following is a table of the behavior of the tumor with various parameters:

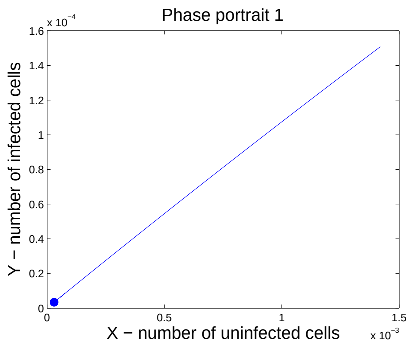
growth	η	1	1	1	1	1	1	1	1	1	1	1	1	1
death	δ	1	1	1	0.5	0.5	0.5	0.5	0.5	2	2	2	2	2
infection	β	0.5	1	2	0.25	0.5	0.75	1	2	0.5	1	1.5	2	2.5
Results	$F_0 = 0.03$	↑	↑	↓	↑	↑	↓	↓	↓	↑	↑	↑	↑	↓
	$F_0 = 0.1$	↑	↑	↓	↑	↑	↓	↓	↓	↑	↑	↑	↑	↓
	$F_0 = 0.3$	↑	↓	↓	↑	↑	↓	↓	↓	↑	↑	↑	↓	↓
growth	η	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
death	δ	0.5	0.5	0.5	0.25	0.25	0.25	0.25	0.25	1	1	1	1	1
infection	β	0.25	0.5	1	0.125	0.25	0.375	0.5	1	0.25	0.5	0.75	1	2
Results	$F_0 = 0.1$	↑	↑	↓	↑	↑	↑	↓	↓	↑	↑	↑	↑	↓

Table 1: Behavior of infected and uninfected cells with various growth (η), death (δ), and infection (β) rates, with the initial fraction of infected cells $F_0 = 0.03$, $F_0 = 0.1$ and $F_0 = 0.3$. An up arrow ↑ indicates that the radius b grows in time and a down arrow ↓ indicates that the radius decays in time.

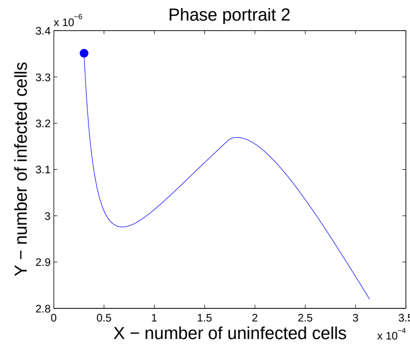
The next table is the same as above, except the arrows have been replaced by numbers corresponding to the different distinct phase portraits we get when we vary the parameters. These portraits are shown in Figure 4.

growth	η	1	1	1	1	1	1	1	1	1	1	1	1	1
death	δ	1	1	1	0.5	0.5	0.5	0.5	0.5	2	2	2	2	2
infection	β	0.5	1	2	0.25	0.5	0.75	1	2	0.5	1	1.5	2	2.5
Results	$F_0 = 0.03$	2	1	5	3	1	5	5	5	3	3	2	**1**	5
	$F_0 = 0.1$	2	**1**	5	3	1	5	5	5	3	3	**2**	**4**	**5**
	$F_0 = 0.3$	2	**6**	5	3	1	5	5	5	3	3	**3**	**6**	**6**
growth	η	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
death	δ	0.5	0.5	0.5	0.25	0.25	0.25	0.25	0.25	1	1	1	1	1
infection	β	0.25	0.5	1	0.125	0.25	0.375	0.5	1	0.25	0.5	0.75	1	2
Results	$F_0 = 0.1$	2	1	5	**1**	1	**4**	5	5	3	3	**3**	4	5

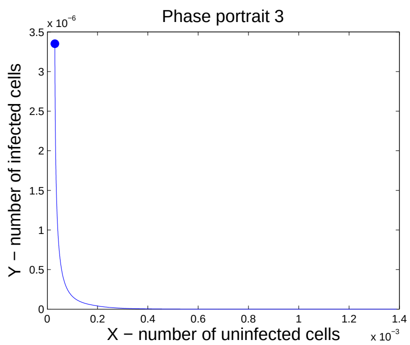
Table 2: Behavior of infected and uninfected cells with various growth (η), death (δ), and infection (β) rates, with the initial fraction of infected cells $F_0 = 0.03$, $F_0 = 0.1$ and $F_0 = 0.3$. The number corresponds to the type of phase portrait, as shown below.



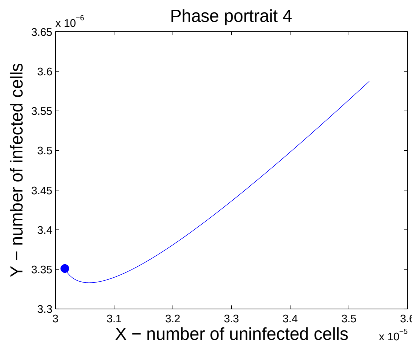
(a) Type 1



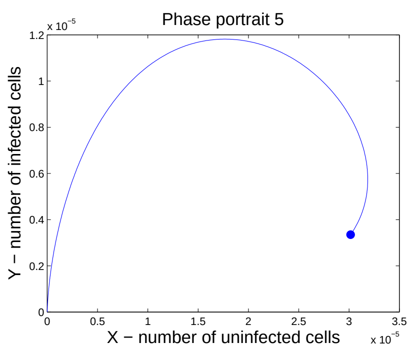
(b) Type 2



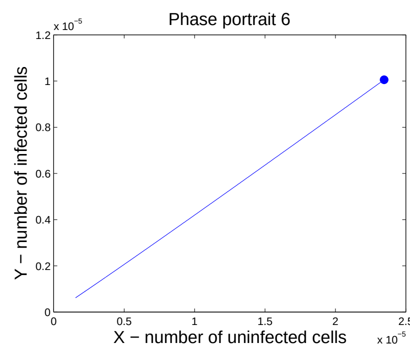
(c) Type 3



(d) Type 4



(e) Type 5



(f) Type 6

Figure 4: Distinct phase portraits from different combinations of parameter values. The blue dots represent the initial populations.

The long-term behavior of the system depends on the choice of parameters. Therefore, we want to identify combinations of parameters leading to different behaviors. We separate the behaviors into 3 cases: unbounded growth of both kinds of cells (types 1 and 4); unbounded growth of uninfected cells, with the infected cell population going to zero (types 2 and 3); decrease of both kinds of cells toward zero (types 5 and 6). This last case corresponds to the therapy working on its own.

For fixed growth rate ($\eta = 1$), Figure 5 shows the behavior of the system for different values of δ and β. The green region indicates that the therapy is working, the red region indicates that both types of cells are growing, and the blue region indicates that only the uninfected cell population is growing:

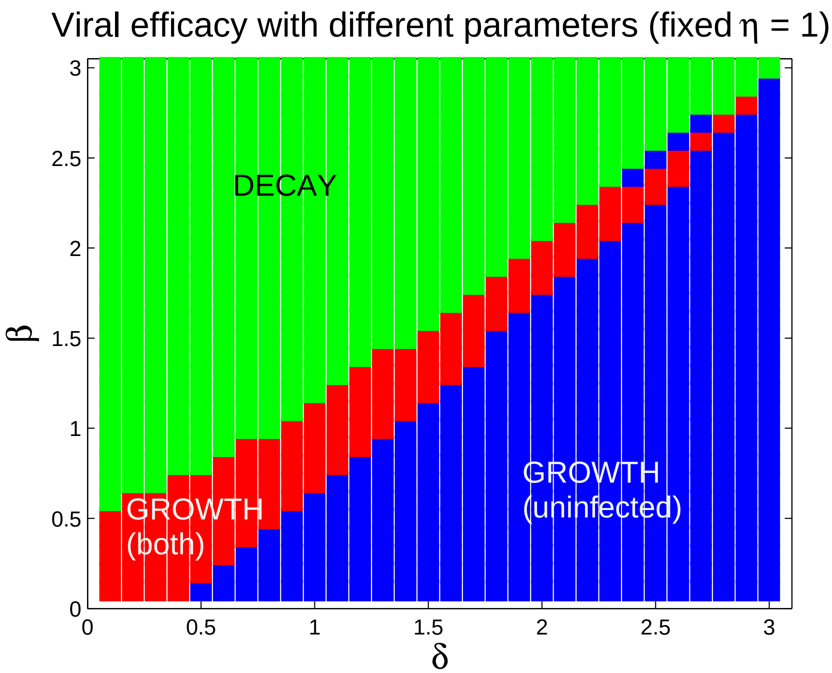


Figure 5: Efficacy of viral therapy for fixed η (growth rate).

In the following plot, the death rate $\delta = 1$ is fixed, and η and β are varied:

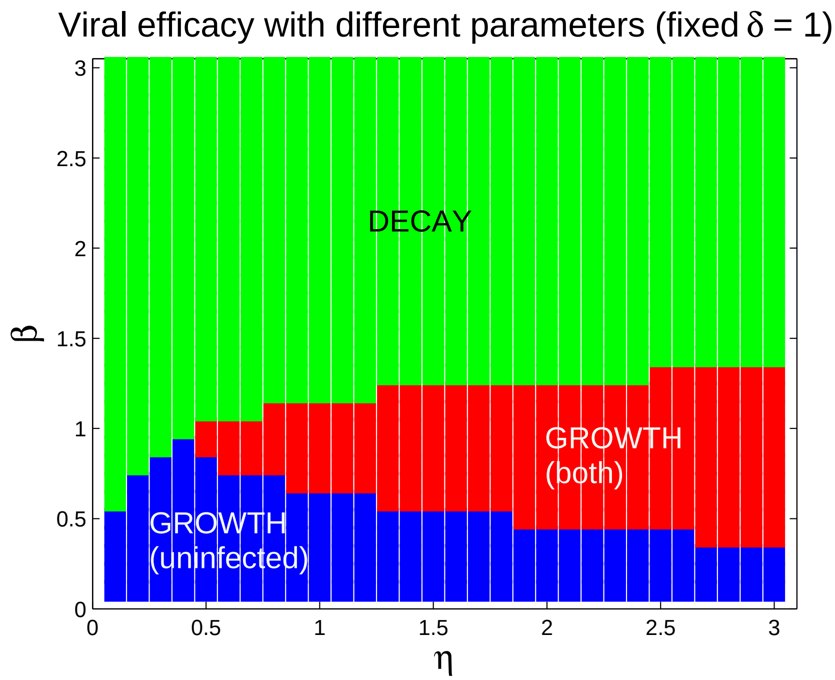


Figure 6: Efficacy of viral therapy for fixed δ (death rate).

Finally, the infection rate $\beta = 1$ is fixed, and η and δ are varied:

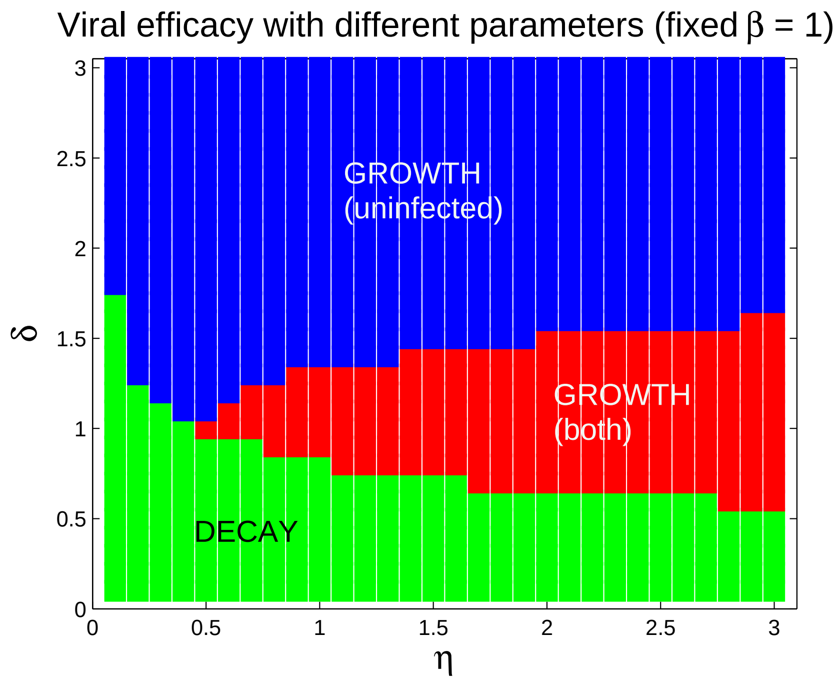


Figure 7: Efficacy of viral therapy for fixed β (infection rate).

4 Discussion

In Figure 5, where the growth rate η was fixed, increasing the death rate δ of the infected tumor cells does not by itself imply that the treatment will be more effective. In fact, the infection rate β needs to be at least as high as the death rate. The reason for this behavior is that if the death rate is too high compared to the infection rate, then the infected cells die off too quickly, and are not able to spread and attack uninfected tumor cells. This result is a major point to consider in developing a virus for therapy – that the ratio between infection rate and death rate is more important than either rate individually.

In the last two plots, we also see – as expected – that increasing the growth rate η of the tumor makes a given treatment less effective. So one must keep in mind when designing a virus that the ratio between infection rate and death rate needs to be high not only so that infected cells do not die off too quickly, but also so that the tumor growth does not outpace the viral infection rate and infected cell death rate.

5 Future work

We have considered a simple model for tumor growth and how it is affected by viral therapy. Future work could include a number of significant improvements. First, we would like to use parameters for growth, death, and infection rates that coincide with actual measured quantities in tumors, rather than looking qualitatively at different ratios between them. Second, tumors do not have a constant rate of consumption. Consumption rate changes in time and thus so does the concentration of oxygen inside the tumor. Various stresses can be put on the boundary of a tumor as it grows, and thus a more rigorous model should take mechanical feedbacks into account. Third, assumptions about the shape of the tumor, the role of diffusion in the growth of the tumor, and the nutrients being limited to oxygen were made to simplify the mathematical calculations. Actual tumors do not follow these simplifying assumptions, so we must begin to incorporate more complicated interactions between the tumor and its outside environment. Finally, we need to include responses to the virus. The reason that viral therapy on its own is not widely used today is that the body's immune system responds to the oncolytic virus the way it responds to any virus – by trying to destroy it.

If we are able to include some of these with the model described here, it seems that we could have a robust model for tumor growth with viral therapy.

References

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