Improvement to the Optimal Cancer Strategy in the Presence of TGF-β

Tony Pun, Antony Ibrahim, Cynthia Sanchez, Frederic Y.M. Wan

Saturday, August 17, 2013

Abstract

Transforming growth factor-β, or TGF-β, is a transcription factor that either stimulates or inhibits mitotic events in a cell. We model cancerous growth through genetic instability in the absence and presence of TGF-β. By using three ordinary differential equations, we can map the rates of change of normal cell population, cancerous cell population, and TGF-β concentration computationally. The ultimate goal of the project is to assess the effects of TGF-β on the time available for intervention prior to unacceptable cancerous growth.

1 Introduction

Regulation of the cell cycle involves processes crucial to the survival of a cell including the detection and repair of genetic damage and the prevention of uncontrolled cell division. In the cell cycle, there are various checkpoints that ensure that the dividing cell divides at a steady and healthy pace. Once the body identifies a cell that has failed one of these checkpoints, white blood cells eliminate it. However, if the abnormal cell is not eliminated at the checkpoint, it will continue dividing abnormally and become cancerous. As long as there is one cancer cell, that cell will breed more cancer cells and grow at an exponential rate.

However, cancer is much more intricate than a cell haphazardly dividing at a rapid rate. There are many cellular processes that take place in order for full metastasis to occur and the number depends on the type of tissue. For example, breast cancer requires about nine cellular processes, and colon cancer requires around eleven cellular processes [1].

One parameter that influences how fast cancer grows is genetic instability or the measure of the frequency of DNA mutations that take place in a normal cell. [1] When the immune system detects that cancer is prominent, it will release hormonal cues to tell cells to undergo apoptosis, or self-cell death. However, this method of cancer inhibition is harmful to the body since it kills any cell within range of the hormone; normal or cancerous.

Transforming growth factor-β or TGF-β is one of the most important coenzymes in the body that stops cancer. TGF-β attaches to the plasma membrane via receptors.

These receptors phosphorylate SMAD proteins to cascade down to the nucleus and connect with transcription factors that either stimulate the growth of new cells or stop mitosis completely. Cancer, however, is extremely adaptive and can combat TGF-β in one of two ways. Cancer can remove the core strand of DNA where the transcription factors bind or remove the binding force that allows the SMAD proteins to bind with the transcription factors. In addition, cancer cells can create tumor derived TGF-β which can stimulate cell growth and speedup cancer instead of inhibiting it.

2 Problem & Contributions

This research focused on accessing the effects of TGF-β on tumor growth during the time before the tumor has grown to an unacceptable size. The purpose is to gain insight on the time for medical intervention. In this paper we:

- Accessed the effects of TGF-β on cancer growth and compared the optimal growth times with models ignoring TGF-β.
- Made simulations to determine the optimal switch time T_s more efficient by assuming a bang-bang model
- Formulated an alternative method to solve the model excluding TGF-β by changing the independent variable. This method has computational benefits of precision and speed.

3 The Model Excluding TGF-β

The rate of change of the normal cell population x_1 and cancer cell population x_2 can be modeled using the ordinary differential equations [1]

$$\frac{dx_1}{dt} = -\left(\mu + u_m u\right) x_1 + \left[1 - d\left(u\right)\right]\left(1 - x_1\right) x_1 \equiv g_1 \tag{1}$$

$$\frac{dx_2}{dt} = \frac{1}{\sigma}\left(\mu + u_m u\right) x_1 + + \left[1 - d\left(u\right)\right]\left(a - x_1\right) x_2 \equiv g_2 \tag{2}$$

where u is the scaled mutation rate, $d(u)$ is the death rate of cells, μ is the basic mutation rate per cell, u_m is the range of genetic instability, σ is the ratio of the target cancer cell population and initial normal cell population, and a is the natural growth rate of cancer cells. [1]

x_1 was normalized by the initial cell population size, x_2 was normalized by the target (untreatable) cancer cell population, and $u(t)$ was normalized by the mutation rate such that

$$0 \leq x_1 \leq 1$$

$$0 \leq x_2 \leq 1$$

$$0 \leq u(t) \leq 1$$

Considering the normalization of x_1 and x_2, simulations began with an initial normal cell population and no cancer cell population. This initial conditions can be written as

$$x_1\,(t=0)=1$$

$$x_2\,(t=0)=0$$

To determine the time T when the cancer cell population reaches an unacceptable size, T was defined such that

$$x_2\,(t=T)=1$$

The parameters μ, u_m, and σ were assumed to be constant in each simulation. However, the death rate $d(u)$ was modeled as

$$d(u)=d_m[1-(1-u)^{\alpha}] \tag{3}$$

and the natural growth rate of cancer cells a was modeled as

$$a=a_0 \tag{4}$$

where d_m, α, and a_0 were assumed to be constant in each simulation so that the solution of the system would depend on the scaled genetic instability u. [1]

Although different inhibitory factors and mutation rates were used in each simulation, they each had the same purpose of determining the fastest time that the cancer cell population reaches an untreatable population size or the minimum time T such that $x_2\,(T)=1$

4 Simulation Process

The model in the previous section was simulated in MATLAB to determine which value of u would produce the lowest value of T. For a single simulation, the set of parameters that were used was [2]

$$\mu=.1; u_m=1; \sigma=10; a_0=2; \alpha=1 \tag{5}$$

Once a value of u between 0 and 1 was chosen, the system was solved using the MATLAB subroutine "ode45" using an arbitrary time interval that contained T. This interval was determined using trial and error such that it contained T but minimized computational time. Also, the "odeset" subroutine was used to adjust the error tolerances to improve the accuracy and precision of T and x_2. Solution plots of Cell Population vs. Time is shown in Fig. 1.

Once the system was solved, the "find" subroutine was used to index the two points (t, x_2) closest to when $x_2 = 1$. Using these points, T was found using linear interpolation according to the formula

$$T=\left(\frac{t_f-t_i}{x_{2f}-x_{2i}}\right)(1-x_{2i})+t_i \tag{6}$$

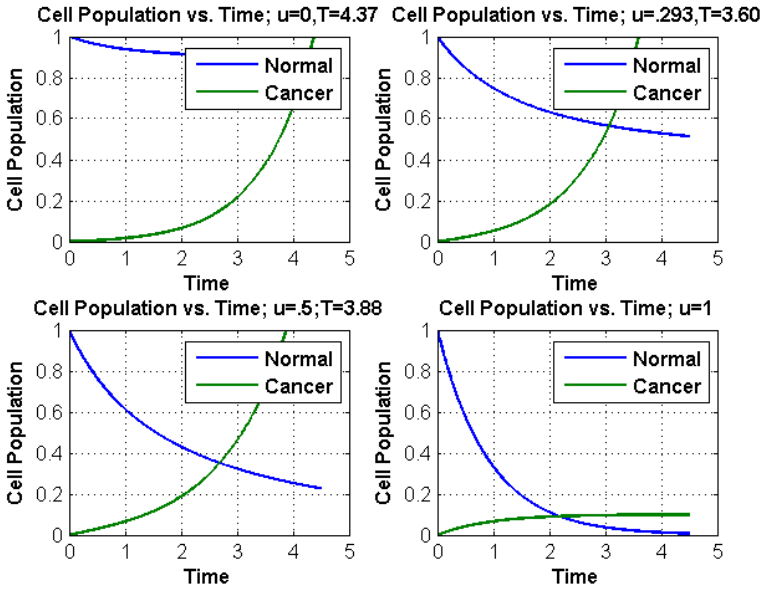

Figure 1: Plots of the model excluding TGF-β for different u values

where (t_i, x_{2i}) is the point found before $x_2 = 1$ and (t_f, x_{2f}) is the point found after $x_2 = 1$.

This method for determining T for a single value of u was made into a MATLAB function and this function was iterated for many values of u between 0 and 1. All values of T were stored in a vector and T_{opt}, the lowest or fastest T value, was determined using the "min" subroutine. A plot of T vs. u is shown in Fig. 2 which illustrates where T_{opt} is.

5 The Model Including TGF-β

The two equation model in section 3 can be modified to simulate the effects of TGF-β on the cancer cell population. The rate of change of TGF-β concentration x_3 can be modeled as [2]

$$\frac{dx_3}{dt} = \beta_3 x_2 (1 - x_3) \equiv g_3 \tag{7}$$

Initially the TGF-β concentration is very low because there are initially no cancer cells. This initial condition can be written as

$$x_3(0) = s_0 \approx 0$$

Equation (7) was developed to model the rate of change of TGF-β but the effects of TGF-β on cancer growth cannot be shown without modifying Eq. (2). The reason for

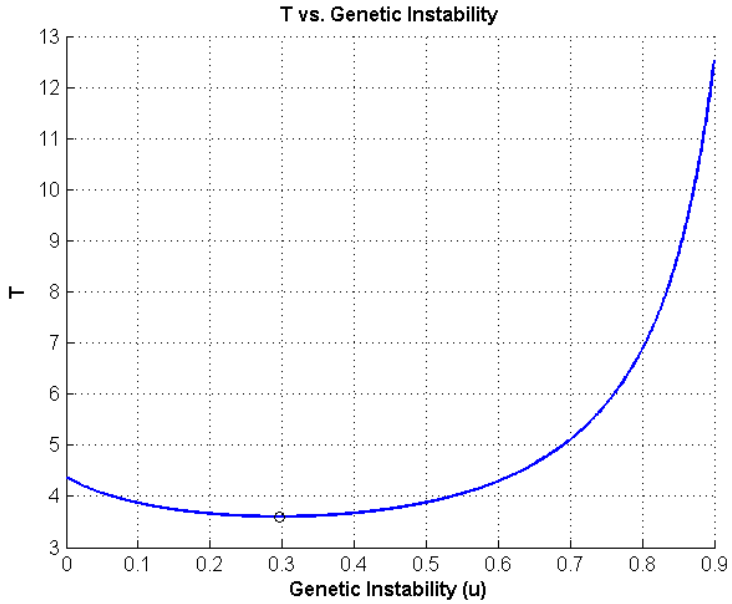

Figure 2: Iterative process to determine T_{opt}

this is that Eq. (2) from the previous model has no dependence on x_3. To fix this, the death rate $d(u)$ and the natural cancer growth rate a were modified by Hill equations [2] such that

$$d(u) = d_m[1-(1-u)^{\alpha}] + \frac{h_m\,(y_c x_3)^m}{1+(y_c x_3)^m} \tag{8}$$

and

$$a = a_0 - \frac{a_m\,(y_c x_3)^n}{1+(y_c x_3)^n} \tag{9}$$

In past research, the coeffcients h_m and a_m were set equal to zero in simulations. Therefore, Eq. (2), the growth equation of the cancer cell population, was not affected by the TGF-β concentration. Our research simulated the effect of TGF-β in MATLAB by setting h_m and a_m to be non-zero constants. The system of ordinary differential equations was solved numerically in MATLAB using a process similar to the one in Section 4. The parameters used were [2]

$$\mu = .1; u_m = 1; \sigma = 10; a_0 = 2; \alpha = 1; \beta_3 = 1; y_c = 1; h_m = a_m = 1; m = n = 2 \tag{10}$$

When TGF-β inhibitory effects was considered, T_{opt} was 4.16 and u_{opt}, the corresponding scaled genetic instability, was 0.226. When the inhibitory effects of TGF-β were ignored ($h_m = a_m = 0$), T_{opt} was 3.60 and u_{opt} was 0.294. The plots of the different cancer growth curves can be shown in Figure 4.

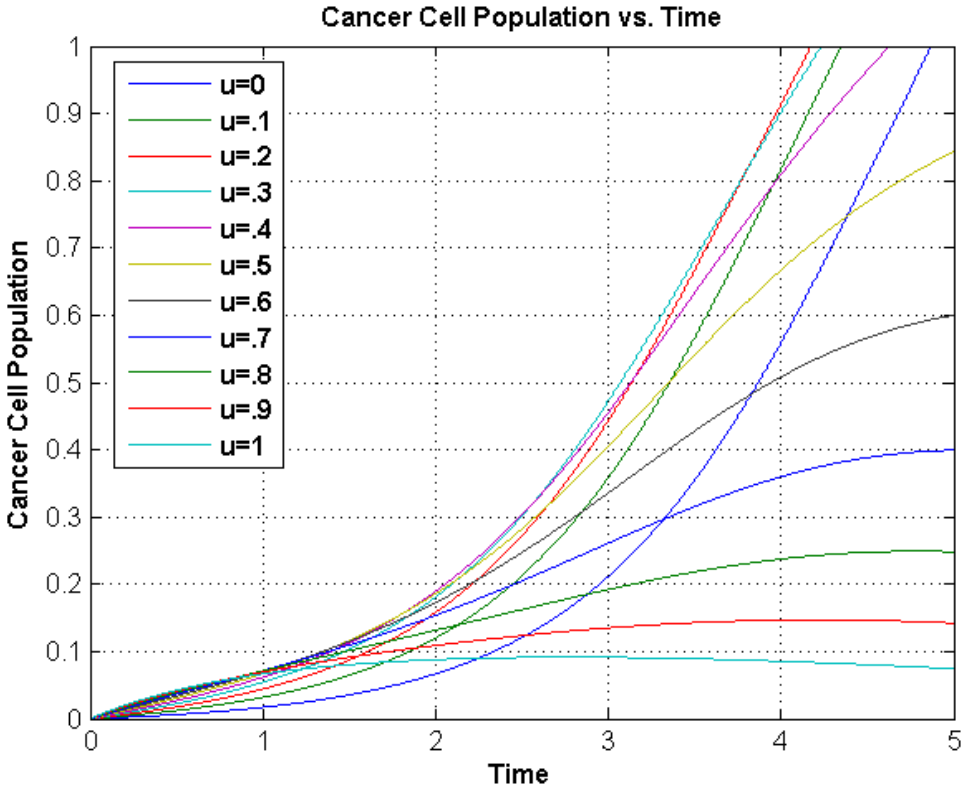

Figure 3: Growth of cancer including TGF-β for different values of genetic instability

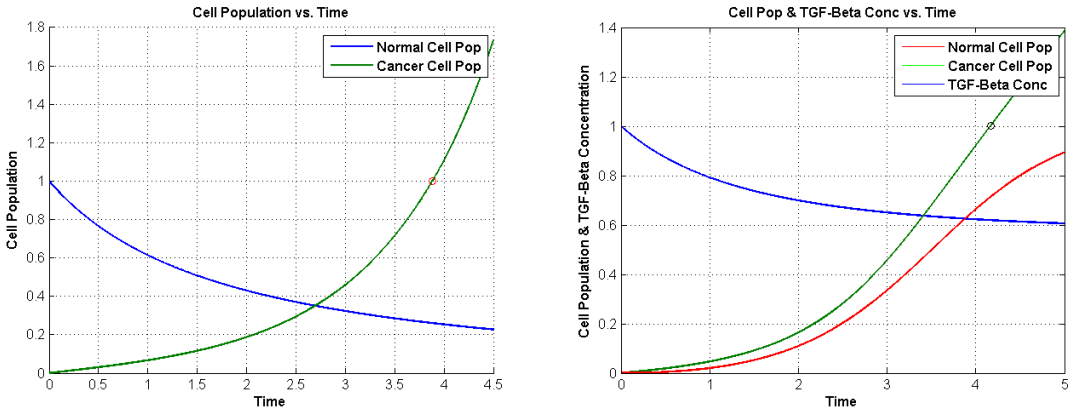

Figure 4: Optimal growth of cancer excluding (left) and including (right) TGF-β

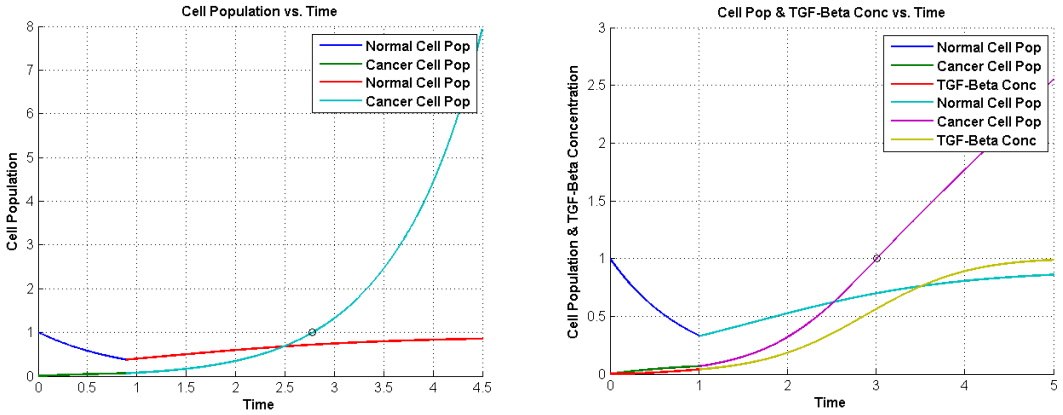

Figure 5: Optimal growth of cancer excluding (left) and including (right) TGF-β assuming bang-bang

6 Switch Point

Past research has shown that for concave ($\alpha > 1$) or linear ($\alpha = 1$) death rates $d(u)$ the optimal strategy for cancer is to initially have high genetic instability which drops sharply in later stages. This is called the bang-bang model [1]. This result was found by simulating many $u(t)$ and determining that there is a switch time T_s that optimizes cancer growth (or T). However, these simulations were inefficient since they tested many different $u(t)$ to determine this result.

Calculations for the switch time can were made more efficient by assuming that the optimal strategy is bang-bang (only applies for $\alpha \geq 1$). These simulations began by choosing a switch time, setting $u = 1$, and solving the system of ODE's for t on $[0, T_s]$ using ode45. The following points were found from the ode45 solution.

$$x_1(t = T_s); x_2(t = T_s); x_3(t = T_s)$$

These points were used as initial conditions for the system from T_s to an arbitrary time contain T and when $u = 0$. T was determined using linear interpolation and the process was iterated for many values of T_s to determine T_{opt}. This process was able to produce the same result as past research [1] using less than half the number of operations. Plots of the optimal cancer growth using the bang-bang model is shown in Fig. 5. The plots are color coded to show where $u = 1$ and $u = 0$.

When the bang-bang model was applied, the results were that $T_{opt} = 2.78$ and $T_s = 0.89$ excluding TGF-β. When TGF-β was included, $T_{opt} = 3.01$ and $T_s = 1.01$. As expected, bang-bang made the values of T_{opt} faster.

7 Alternative Approach: Change of Variables

The system of ordinary differential equations defined by Equations (1) and (2) can be simulated by changing the independent variable from time t to cancer cell population

Table 1: Sample Output Using t (left) and x_2 (right) as the Independent Variable

t	x_2		t	x_2
0.0000	0.0000		0.0000	0.0000
1.5350	0.1206		1.4679	0.1127
2.5475	0.3081		2.5642	0.3127
3.5600	0.7526		3.5751	0.7627
3.7850	**0.9181**		3.7784	0.2664
3.8975	**1.0142**		**3.8816**	**1.0000**
4.2169	1.3467			
4.5000	1.7338			

x_2. Using the chain rule

$$\frac{dx_1}{dx_2} = \frac{dx_1}{dt}\frac{dt}{dx_2} = \frac{g_1}{g_2} \tag{11}$$

$$\frac{dt}{dx_2} = \frac{1}{dx_2/dt} = \frac{1}{g_2} \tag{12}$$

The modified boundary conditions are

$$x_1(x_2 = 0) = 1$$

$$t(x_2 = 0) = 0$$

$$t(x_2 = 1) = T$$

The advantage of this new system is that the range of the independent variable is known (x_2 must be found on $[0, 1]$) which makes it possible to determine the value of T without interpolation methods. It also improves the accuracy and precision of the calculated value of T.

The ode45 subroutine in MATLAB requires that the user inputs the range of the independent variable on which the equations are solved. It will return solution vectors/matrices containing points between the interval and at the endpoints. Some of the points for simulations using t or x_2 as the independent variable are shown in Table 1. These simulations do not consider the effects of TGF-β.

As shown in the data using t as the independent variable, the points closest to having $x_2 = 1$ are somewhere between the endpoints. These points are bolded and must be linearly interpolated to determine T. However, when x_2 is the independent variable, the point where $x_2 = 1$ is an endpoint (bolded) and T can be found immediately. Moreover, the accuracy of T is very high using this method because MATLAB calculates T for $x_2 = 1.0000...$ and there are many zeros after the decimal point. This amount of accuracy is difficult to obtain when t is the independent variable even when the error tolerances are decreased to their limits.

Although T can be determined more precisely by changing variables, this method has a few weaknesses. Eq. (11) and (12) show that the new system of equations require

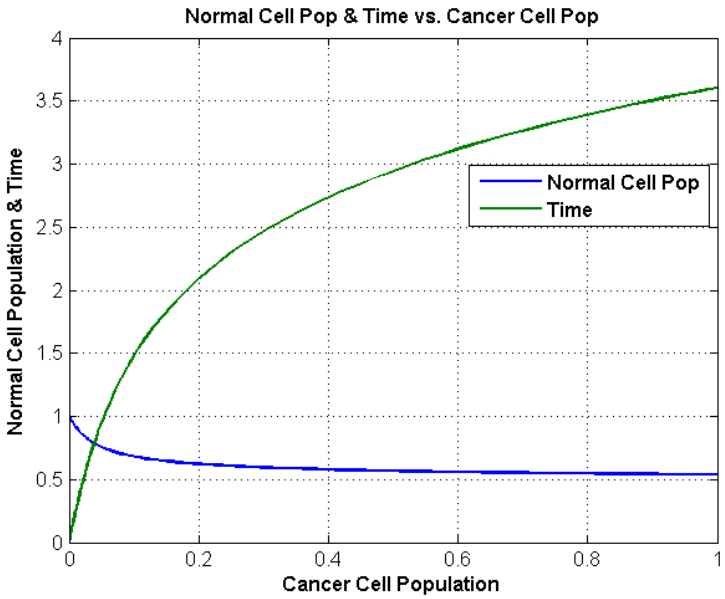

Figure 6: Optimal cancer growth with bang-bang model

divisions by g_2. This slows down computational time and means that calculations may contain errors from attempting to divide by zero. However, when these weakness are negligible, changing variables can be a very powerful method. Results for the switch time when TGF-β effects are considered are shown in Figure 6.

8 Conclusions

The basic model for cancer growth can be simulated in MATLAB for T_{opt} using an ODE solver, linear interpolation, and an iterative process. TGF-β effects can be added to the model by adding a new ODE and modifying the death rate $d(u)$ and the natural growth rate of cancer a so that the cancer cell population depends on TGF-β. When TGF-β inhibitory effects was considered, T_{opt} was 4.16 and u_{opt}, the corresponding scaled genetic instability, was 0.226. When the inhibitory effects of TGF-β were ignored ($h_m = a_m = 0$), T_{opt} was 3.60 and u_{opt} was 0.294.

The optimal switch time for T_s can be found more efficiently by solving the system of ODE's twice for different values of genetic instability and iterating the switch time. When the bang-bang model was applied, the results were that $T_{opt} = 2.78$ and $T_s = 0.89$ excluding TGF-β. When TGF-β was included, $T_{opt} = 3.01$ and $T_s = 1.01$. As expected, bang-bang made the values of T_{opt} faster because of the linear death rate.

The change of variables method uses the chain rule to change the independent variable of the system from time to cancer cell population in order to produce more

precise values of T effectively. It has computational weaknesses since the chain rule adds division terms in the system of equations.

9 Future Work

Some possible projects to extend this research are to

- Formulate a non-iterative method for determining T and T_s and implement it numerically
- Implement other (more efficient) iterative methods for determining T and T_s
- Modify the extended model to consider the role of TGF-β as a cancer promoter
- Modify original model to consider other cancer inhibitors or promoters
- Incorporate the change of variables method for the model with TGF-β
- Create a spatial-temporal model for cancer growth by developing a system of PDE's

References

[1] Komarova, Natalia L., Alexander V. Sadovsky, and Frederic Y.M. Wan. "Selective Pressures For and Against Genetic Instability in Cancer: A Time-dependent Problem."Journal of the Royal Society (2007)

[2] Klinzmann, Alissa, Alice Kwan, Cynthia Sanchez, and Frederic Wan. "Mathematical Model of TGF-β on Cancer Cell Activities." (2012)