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T MODEL OF GROWTH AND ITS APPLICATION IN SYSTEMS OF TUMOR-IMMUNE DYNAMICS

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Abstract. In this paper we introduce a new growth model called T growth model. This model is capable of representing sigmoidal growth as well as biphasic growth. This dual capability is achieved without introducing additional parameters. The T model is useful in modeling cellular proliferation or regression of cancer cells, stem cells, bacterial growth and drug dose-response relationships. We recommend usage of the T growth model for the growth of tumors as part of any system of differential equations. Use of this model within a system will allow more flexibility in representing the natural rate of tumor growth. For illustration, we examine some systems of tumor-immune interaction in which the T growth rate is applied. We also apply the model to a set of tumor growth data.

1. **Introduction.** In biomedical sciences, the analysis of growth is usually characterized by a rate at which the population size changes. The choice of an appropriate growth model is an integral part of the analysis of the biological systems and will eventually aide the researcher in having a better understanding of the interaction between tumor cells and immune cells as well as the effect of different treatments on cancer growth or inhibition.

Foreign or invader cells found within the body will provoke an automatic immune response from the immune system. Although malignant cancer cells have developed from the cells produced in the body, the immune system is often able to recognize these cells as harmful due to the expression of antigens on the cell surface. Triggering this immune response against the cancer cells enlists the resources of the immune system into the effort to eradicate the tumor. While in certain cases this immune response may be enough to eliminate all of the tumor cells, in many cases the tumor continues to grow, although its progress has been inhibited by the immune response. This potential to trigger an immune response which can either retard the growth of the tumor or eradicate it entirely makes immunotherapy an important area in the treatment of malignant cancers. We are particularly concerned with relations between the tumor cell rate of growth and the response of the effector cells. When representing the overall rate of growth of a tumor, it is important to account for the immune response. And when designing therapies to combat the

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tumor growth, it may be helpful to use the perspective of supplementing the natural immune response.

Among the numerous uses of mathematics in the modeling of cancer, the approach which uses systems of ordinary differential equations to model the interactions among tumor cells and immune cells has been the focus of much work in the previous decades. This approach is particularly well suited to modeling of the tumor immune interactions, and these models have proven successful in representation of important aspects of the underlying biological events and in achieving a deeper level of understanding. We note that use of systems of ODEs to model the interaction of tumors with the immune system and the associated immunotherapy has a basis primarily in two aspects of these models. First the systems use multiple variables to represent the interacting cells, and appropriate terms to represent these interactions. The second point is that the use of differential equations is based upon the understanding that the temporal dynamics of tumor growth are determined by an accurate representation of the rate of growth. This approach using systems of ODEs allows the rates to be determined using all of the variables in the system.

An early model of the dynamics of immune tumor interactions was given in Kuznetsov, et al. (1994), and a nice extension to three variables can be found in Kirschner and Panetta (1998). Beyond the variables in the system, sometimes terms representing particular therapies, such as chemotherapy or immunotherapy, can also be included. This direction of modeling has progressed in numerous directions, modeling important biological issues including issues such as evasion of the immune response, the effects of various therapies, and the role of myeloid cells in specific immune responses. The model of Simeoni et al. (2004) studies tumor growth dynamics in relation to varying regimens, schedules, and dosages of anti-cancer drugs. The newer approach of treating cancer through virotherapy has also been modeled by Bajzer, et al. (2008), and the work of Dingli, et al. (2006) extends to a combined treatment with radiation and virotherapy. The study of Feizabadi and Witten (2010) investigates the effects of chemotherapy on a system incorporating both tumor cell growth and the effects of aging. Immunotherapies also play an important role in improving the cancer immune response, and the paper of Kirschner and Panetta (1998) studies the dynamics between tumor cells, effector cells, and IL-2, explaining both short term oscillations and long term relapse. The more recent paper of Cappuccio, et al. (2006) produces a mathematical model studying the effects of IL-21 on elimination of a tumor through action of NK and $CD8^+$ T cells.

One recent model DeConde, et al. (2005) represents the immune-tumor dynamics after bone marrow transplant in leukemia patients that models the effect of transplanted stem cells and that accounts for the progression of cells through different modes of behavior. The study of tumor-immune interactions in the model of Arciero, et al. (2004) includes the level of antigenicity of the tumor, as well as the dual influence of TGF-â in stimulating tumor growth and inhibiting the immune response. The study of Kareva, et al. (2010) deals with the role of myeloid cells in activating a specific immune response, and this model includes the inhibitory effect of tumor growth on the maturation of myeloid cells, thus diminishing the immune response as the tumor develops.

Another important direction in this field of research is the application of optimal control theory to these systems. The work of Burden, et al. (2004) applies optimal control theory to a system representing immunotherapy with IL-2 to better

understand conditions under which the tumor can be eliminated. The work of Castiglione and Piccoli (2006) applies optimal control to find an optimal schedule for delivery of immunotherapy. The work of Ledzewicz, et al. (2011) applies optimal control to a system representing cancer-immune interactions under chemotherapy and address the problem of moving from initial conditions in the malignant state space into the benign region. The work of d'Onofrio, et al. (2009) applies optimal control to a mathematical model for a combined treatment with chemotherapy and an angiogenic inhibitor, and a similar problem is studied in Ledzewicz, et al. (2011). Another study of Schättler, et al. (2011) demonstrates that the optimal control problem for minimizing tumor volume in a class of models using tumor anti-angiogenesis give optimal controls that are robust with respect to variation in the modeling of vascular support. We mention that for the type of optimal control minimizing tumor volume, as mentioned in the above papers, the assumed rate of growth for the tumor cells plays an important role.

Although the models mentioned above have studied the effects of adjusting individual terms or inclusion of additional terms, there remains the possibility to adjust the assumptions in these models for the rates of growth for individual tumors. It is well known, for instance, that the use of exponential versus logistic growth assumptions can have a considerable effect upon the behavior of a system. Our focus in this paper will be the effects of use of alternative assumptions for tumor growth in a simple system, such as the two by two system in Kuznetsov, et al. (1994). We note that the paper of Ledzewicz, et al. (2011) also considers a model of tumor growth with a wider range of growth rates, including cases of Gompertzian or logistic form, while the model of de Vladar and González (2004) explores the value of Gompertzian growth assumption within a system. Our primary concern will be treatment of one such representative system in which the T model of growth is used. The T model of growth is first introduced in the current article, in Section 2 below, and the ability to represent sigmoidal or biphasic growth, the potential for multiple points of inflection, and flexibility in location of any point of inflection are some important features of this T model of growth. This novel model is directly related to the hyperbolastic growth models H1, H2, and H3 of Tabatabai, et al. (2005), and we also consider briefly the use of these models within a system for immune and tumor dynamics. The motivation for inclusion of the hyperbolastic or the T model for the growth rate in a system of ODEs is the exploration of tumor-immune dynamics for these models which have demonstrated their accuracy in the representation of cellular growth.

The hyperbolastic models H1 to H3 were introduced by Tabatabai, et al. (2005) in the context of developing models with more versatility in representing actual growth rates from experimental data. The models have proven to be highly accurate in the representation of biological growth, with close approximations to experimental results. These models have been particularly accurate in representation of cellular growth, such as growth of tumor cells in Eby, et al. (2010) or growth of stem cells Tabatabai, et al. (2011). Inclusion of these models in the system will allow exploration of the effects for the tumor-immune dynamics.

The new model of growth which we first present in this paper is also designed to be versatile in representing actual growth rates for experimental data, but in this case the primary goal is to represent the biphasic characteristic sometimes observed in growing tumors. Use of appropriate ranges for the parameters in this model makes possible the representation of biphasic growth. Biphasic growth is

not uncommon to observe in tumors and can occur due to a temporary decrease in growth rate. It is observed, for instance in the study of Yuri, et al. (2006) that human breast carcinoma cells have a biphasic response to zeranol. The study of Tao, et al. (2008) on the murine tumor cell line 4T1 which exhibits the capacity to metastasize, observes biphasic growth with regression of growth associated with necrosis and infiltration of leukocytes. In the study of Takeda, et al. (2006) a biphasic effect is noticed in the growth of $CD34^+$ hematopoietic cells treated with NUP98-HOXA9, which is attributed to a rise in the number of self-renewing cells. Clearly biphasic growth is a common occurrence in tumor growth, and introduction of this new model into the systems of ODEs will allow us to study its effects within the tumor-immune dynamics.

2. **T growth model.** The T growth model has an equation of the form

$$S(x) = \frac{M}{1 + \alpha Exp[-\sinh(\beta x)]} \tag{1}$$

where S(x) is the population size, M and β representing carrying capacity and intrinsic growth rate respectively. The parameter α and M are positive. For x=0, α can be interpreted as the number of times initial size S_0 must grow to reach its carrying capacity M. Taking the derivative of the equation (1) with respect to variable x gives the growth rate in the form

$$\frac{dS(x)}{dx} = \beta S(1 - \frac{S}{M})\sqrt{1 + \left[\ln\left(\frac{\alpha S}{M - S}\right)\right]^2} \tag{2}$$

with the initial condition $S(x_0) = S_{0,}$ where the positive parameter α can be written as

$$\alpha = \frac{(M - S_0)Exp\left[\sinh(\beta x_0)\right]}{S_0}$$

where $\sinh(\cdot)$ is the hyperbolic sine function.

For $\beta > 0$, S(x) grows as x increases its value until it reaches its limiting point, and

$$\lim_{x\to\infty} S(x) = M \ and \lim_{x\to-\infty} S(x) = 0$$

For $\beta < 0, S(x)$ decays as x increases its value until it reaches zero, and

$$\lim_{x\to\infty} S(x) = 0 \ and \lim_{x\to-\infty} S(x) = M$$

The inflection point(s) $x=x^*$ of the growth function S(x) can be found by solving the following equation:

$$\frac{\exp\left[\sinh(\beta x)\right] - \alpha}{\exp\left[\sinh(\beta x)\right] + \alpha} = \tanh(\beta x)\sec h(\beta x).$$

The doubling time x_{Double} from size $S=S(x_0)$ to size $S=2S(x_0)$ is given by the equation

$$x_{Double} = \frac{arcsinh\left[\ln\left(\frac{2\alpha S_0}{M-2S_0}\right)\right]}{\beta},$$

where $\text{arcsinh}(\cdot)$ is the inverse hyperbolic sine function.

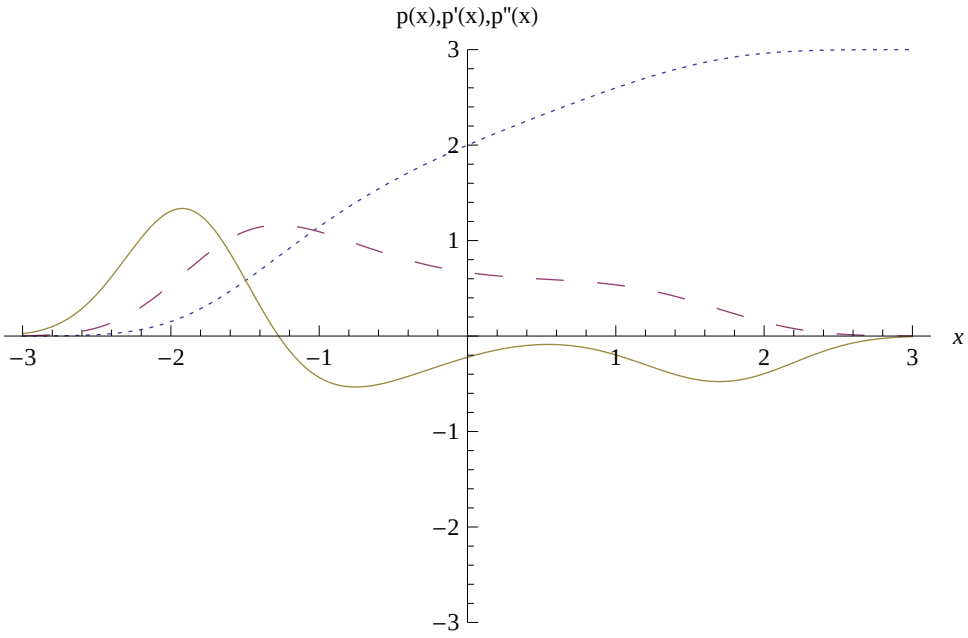

FIGURE 1. Plot of the growth curve, derivative and acceleration using T Model with parameters $(M, \alpha, \beta) = (3, 0.5, 1)$

In general for the positive number k, the time required for the size S=S(x_0) to reach the size S=kS(x_0) is denoted by x_k and is formulated as

$$x_k = \frac{arcsinh\left[\ln\left(\frac{k\alpha S_0}{M-kS_0}\right)\right]}{\beta}.$$

For instance, if S_0represents the volume of multi-cellular tumor sphere at time x=x_0, then x_k gives the time required for the tumor size to reach from S_0size to size kS_0. If k=0.50, then $x_{0.50}$ gives the time required for the current size to reduce to its half size.

The T growth model can be generalized as:

$$S(x) = k + \frac{M-k}{\left(1+\alpha Exp\left[-\theta \sinh\left(\beta\left(x-h\right)\right)\right]\right)^{\frac{1}{\delta}}}$$

Where h and k are shift parameters, (θ, β)jointly represent the intrinsic growth rate and δ is positive. In practice one may start with a T model which may only involve in three parameters M, α, and β. Then if the fit is not good, we suggest adding extra parameter or parameters if necessary.

Figures 1-3 show the graph of the functions S(x), S'(x) and S"(x) for different values of parameters. The dotted curves represent the growth curve. The dashed curve is the graph of the growth rate, or velocity. The solid curve is the acceleration of growth.

3. **Some tumor system models.** Mathematical systems of differential equations for cancers can assist the researchers to investigate the interaction of a growing tumor with the body's immune system. It can also help to discover the effect of

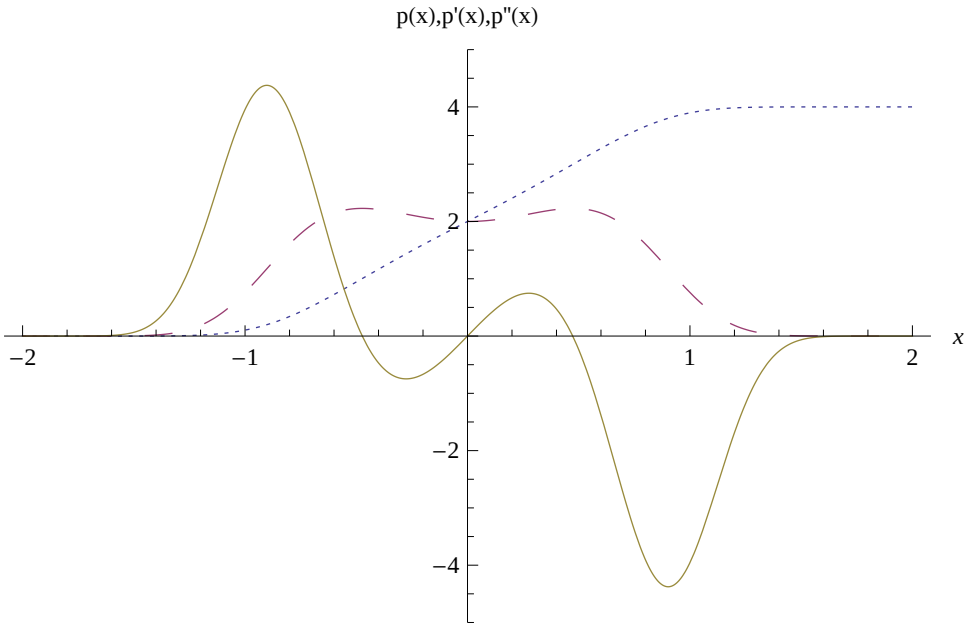

FIGURE 2. Plot of the growth curve, derivative and acceleration using Model with parameters $(\mathrm{M},\alpha,\beta) = (4, 1, 2)$

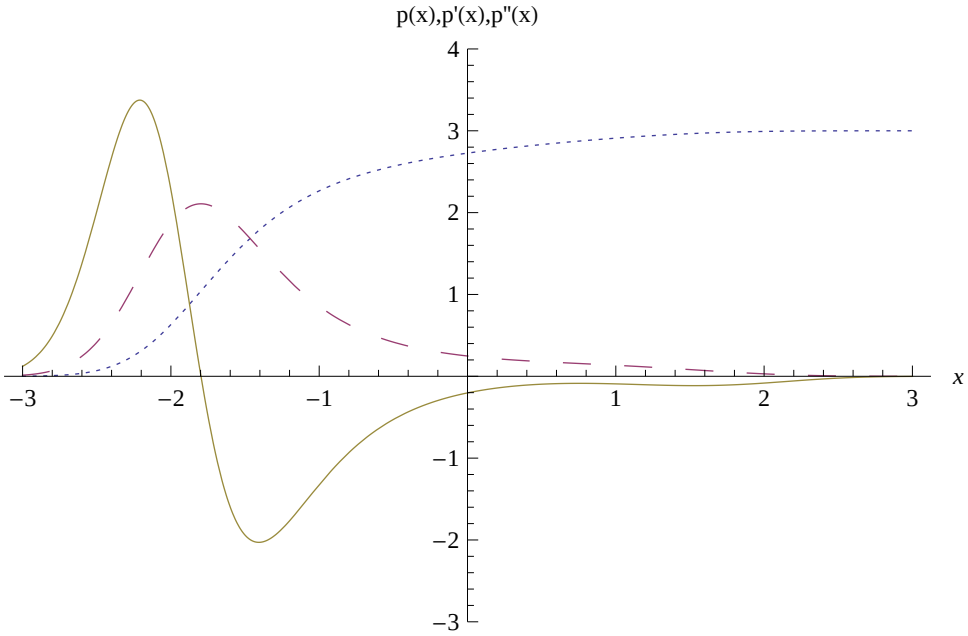

FIGURE 3. Plot of the growth curve, derivative and acceleration using Model with parameters $(\mathrm{M},\alpha,\beta) = (3, 0.1, 1)$

different treatments on tumor growth or inhibition in interaction with the immune system. The T growth model can be used to represent the tumor growth as part of any system of differential equations which investigate tumor growth. Tumor differential systems may involve only the immune system or it may involve in the interaction of treatment(s) with tumor and immune system. The cancer system may include only a single type of treatment such as radiation therapy, chemotherapy, immunotherapy, hyperthermia, photodynamic therapy, or stem cell transplant such as bone marrow, cord blood transplants or peripheral blood. The system may also include a mixed combination of some of the above mentioned treatments.

Consider the nonlinear autonomous system of differential equations describing the interaction between the effector cells and the tumor cells found in Kuznetsov, et al. (1994). The effector cells are the activated immune system cells which are responsible for eliminating the tumor cells. Let T be the population size of tumor cells at time t and E be the size of the effector cells population at time t. Here we assume that the tumor cell population grows according to the model (1). The model is:

$$\frac{dT}{dt} = \beta T\left(1-\frac{T}{M}\right)\sqrt{1+\left[\ln\left(\frac{\alpha T}{M-T}\right)\right]^2} - c_2 ET \tag{3}$$
$$\frac{dE}{dt} = S_1 + \frac{rET}{\sigma+T} - c_1 ET - dE.$$

The initial conditions are: $E(0)=E_0, T(0)=T_0$.Parameter r is the clearance rate of tumor cells as the result of interaction between effector cells and tumor cells. $S_1$is the external effector cells source rate, d is the effector cells death rate, c_1 is the tumor deactivation rate, c_2 is the effector kill rate of tumor cells and $\sigma$is the half-saturation for cancer clearance.

The equilibrium point(s) can be obtained by solving the following system of equations:

$$\beta T\left(1-\frac{T}{M}\right)\sqrt{1+\left[\ln\left(\frac{\alpha T}{M-T}\right)\right]^2} - c_2 ET = 0$$
$$S_1 + \frac{rET}{\sigma+T} - c_1 ET - dE = 0.$$

To get a linear approximation for system (3) about the equilibrium point $\left(E^{\cup}, T^S\right)$ and for the purpose of analyzing the stability of the system (3) near the equilibrium point, we have evaluated the Jacobian matrix which is given by:

$$\begin{bmatrix} \frac{\beta\left(M-2T+M\ln\left(\frac{\alpha T}{M-T}\right)+(M-2T)\left[\ln\frac{\alpha T}{M-T}\right]^2\right)-M\sqrt{1+\left[\ln\left(\frac{\alpha T}{M-T}\right)\right]^2}c_2E}{M\sqrt{1+\left(\ln\left(\frac{\alpha T}{M-T}\right)\right)^2}} & -c_2T \\ \frac{\left(r\sigma-(T+\sigma)^2c_1\right)E}{(T+\sigma)^2} & -d+\frac{rT}{T+\sigma}-c_1T \end{bmatrix}$$

The eigenvalues for model (3) can be obtained by solving the characteristic polynomial equation.

For illustrative purposes we consider model (3) with arbitrarily selected parameter vector of the form: $(M,\alpha,r,\sigma,c_1,c_2,d,s_1,\beta) = (3,1,3,5,0.3,1,0.2,0.3,0.5)$

$$\frac{dT}{dt} = 0.5T\left(1-\frac{T}{3}\right)\sqrt{1+\left[\ln\left(\frac{T}{3-T}\right)\right]^2} - ET \tag{4}$$
$$\frac{dE}{dt} = 0.3 + \frac{3ET}{5+T} - 0.3ET - 0.2E.$$

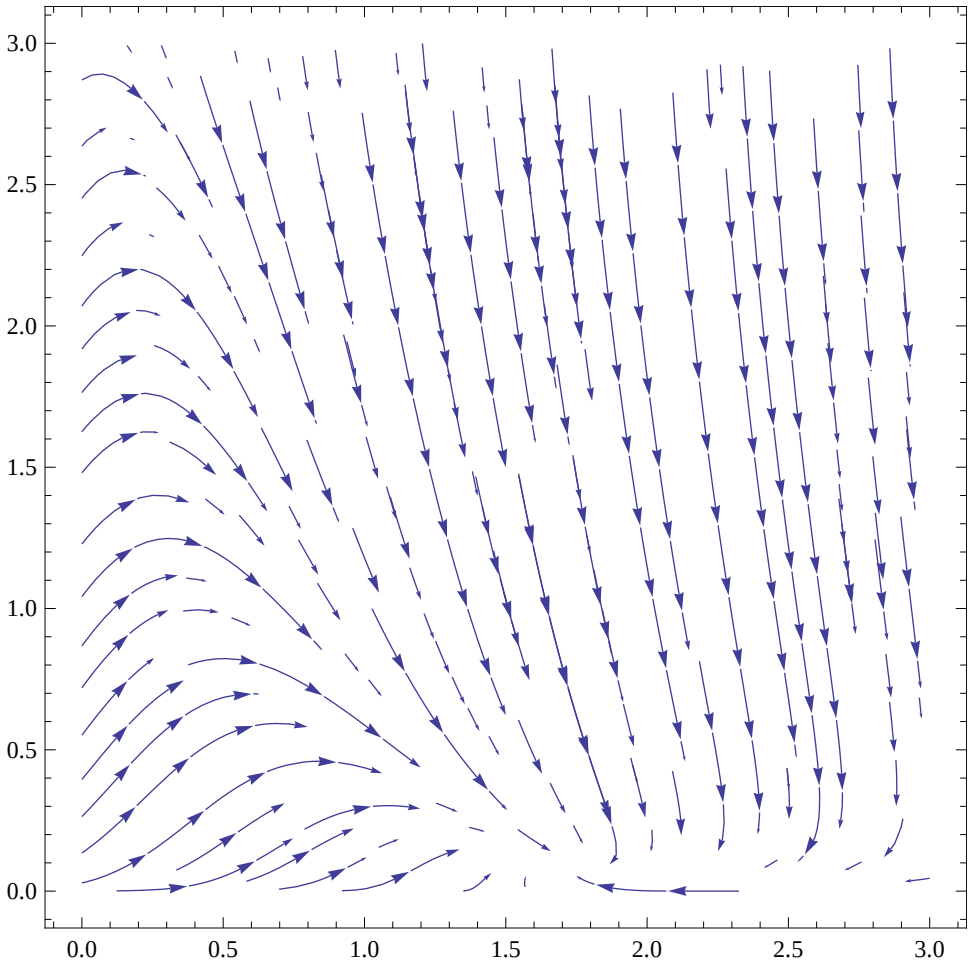

FIGURE 4. Phase diagram of T model

The initial conditions are arbitrary selected as: E(0)=0, T(0)=2.

For system (4) the equilibrium point is $\left(E^{\cup}, T^{S}\right) = (1.73416, 0.0934476)$ and its associated Jacobian has numerical value $\begin{pmatrix} -0.53585 & -0.0934476 \\ 0.482419 & -0.172994 \end{pmatrix}$.

The characteristic polynomial equation is $\mathrm{y}^2 + 0.708845y + 0.13778 = 0$ and the eigenvalues are $(\lambda_1, \lambda_2) = (-0.354422 + 0.110294i, -0.354422 - 0.110294i)$.

The phase portrait for system (4) is given in figure 4. The equilibrium point is a locally stable spiral because eigenvalues are complex conjugates with negative real parts. Figure 5 shows the trajectory of model (4) when starting with the given initial point and ending at the equilibrium point.

If one adds the size of the normal cells population to the model (3) it results in the following three-population model of the form

$$\frac{dT}{dt} = \beta_1 T \left(1 - \frac{T}{M_1}\right) \sqrt{1 + \left[\ln\left(\frac{\alpha_1 T}{M_1 - T}\right)\right]^2} - c_1 ET - c_2 NT$$

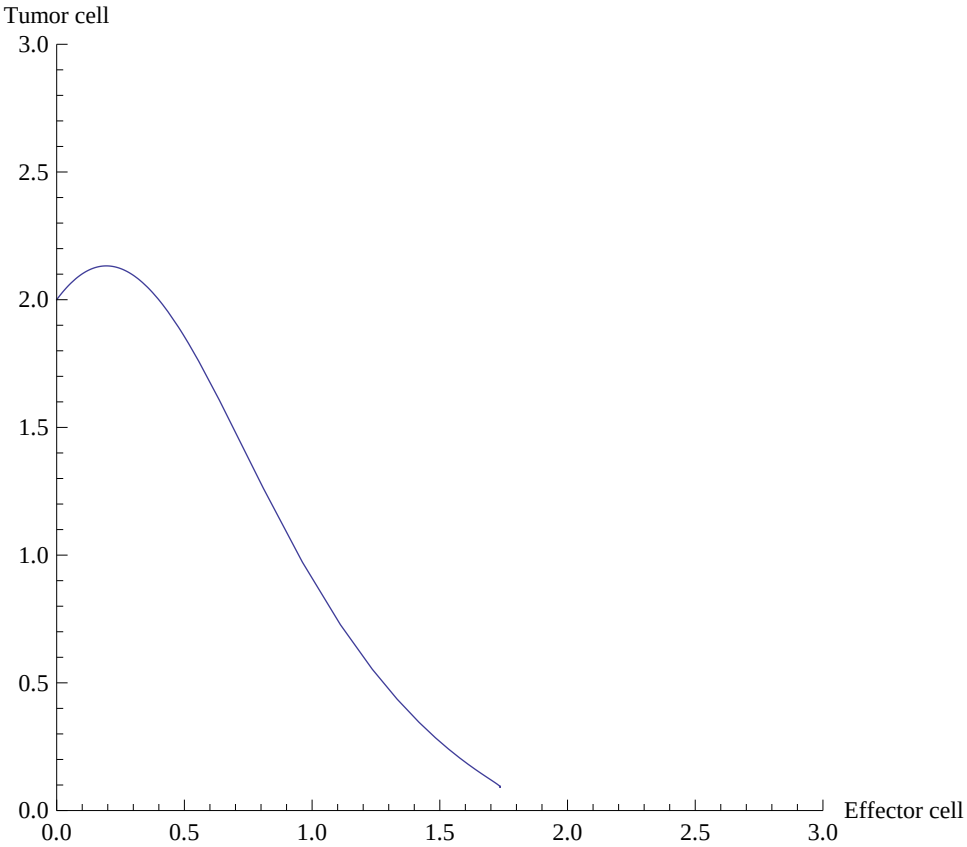

FIGURE 5. Trajectory of T model for (4)

$$\frac{dN}{dt} = \beta_2 N(1 - \frac{N}{M_2})\sqrt{1 + \left[\ln\left(\frac{\alpha_2 N}{M_2 - N}\right)\right]^2} - c_3 NT \tag{5}$$
$$\frac{dE}{dt} = c_4 + \frac{c_5 ET}{c_6 + T} - c_7 ET - c_8 E,$$

with initial conditions E(0)=E_0, T(0)=T_0,$N(0) = N_0$,and the model parameters $M_1, M_2, \alpha_1, \alpha_2, \beta_1, \beta_2, c_1, ...c_8$. Again we assume that both normal cells N and the tumor cells follow the T model (1). We suggest the usage of model (1) in systems involving immunotherapy to boost the immune system to fight tumor cells. Kirschner and Panetta (1998) is one good example of such a system. We recommend the usage of model (1) for tumor growth in immunotherapy system which describes the interaction between the tumor cells, the effecter cells and cytokine interleukin-2 (IL-2). The resulting model would have a form

$$\frac{dT}{dt} = \beta T\left(1 - \frac{T}{M}\right)\sqrt{1 + \left[\ln\left(\frac{\alpha T}{M - T}\right)\right]^2} - \frac{c_1 ET}{c_2 + T} \tag{6}$$
$$\frac{dE}{dt} = c_3 + c_4 T + \frac{c_5 EI}{c_6 + I} - c_7 E$$

$$\frac{dI}{dt} = c_8 + \frac{c_9 ET}{c_{10} + T} - c_{11} I,$$

where the model parameters are M, β,α ,$c_1, ...c_{11}$ and the initial conditions are: E(0)=E_0, T(0)=T_0,$I(0) = I_0$.

4. **Example with tumor growth.** In applying our model, we analyze data from a recent study of Song, et al. (2011) exploring how RNA interference may be used as a treatment to inhibit the growth of nasopharyngeal carcinoma cells. The nasopharyngeal cancers form a common malignant tumor in Southern China for which there are certain limitations or drawbacks to the usual treatments, such as radiotherapy, chemotherapy, immune therapy, surgery, or traditional Chinese medicine. In the search for new therapies, RNA interference technology has been applied to genes involved in the nasopharyngeal caner. The work of Song, et al. illustrates the potential to attain a greater combined effect when applying RNA to silence multiple genes involved in the cancer, as compared to silencing only one. Their results clearly show a significant effect in slowing the tumor growth for each of the four target genes considered in the study: VEGF, C-myc, Survivin, and hTERT. The case where all four of these genes were targeted by RNA interference shows an even larger combined effect on the tumor growth. We mention that a more in depth quantitative analysis of these growth rates of the tumors and the effect of the treatments by RNA inference can be made using either the T-model of this paper or the hyperbolastic model of Tabatabai, et al. (2005). We mention the paper Eby, et al. (2010) in which the hyperbolastic model H3 was applied to give a comparative analysis of tumor growth rates under several treatments, including a combined treatment. See Figure 6, which illustrates the growth curves for the tumor in the cases of no treatment, treatment of RNA interference with VEFG, and the combined treatment in which the RNA interference targets all four genes VEFG, C-myc, Survivin, and hTERT.

Although it is possible to represent the growth curves with any available growth model, the accuracy of the representation will be affected by the model chosen and how well it fits the data. The T-model was developed as a simple two parameter model which is more flexible than the logistic model and thus will yield growth curves better representing the data. One of the special features of the T-model is the capability to represent biphasic data, which is not uncommon in cancer growth. In the following we focus on the group representing treatment by RNA targeting VEGF alone and make a comparison with the logistic growth model and the Gompertz model, two other models commonly used to represent cancer growth.

In each of the cases of the logistic model, the Gompertz model, and the T-model, the two parameters were estimated using nonlinear regression. Using SPSS we found the parameter estimates that best fit the data and also the R^2 values and the MSE of the residuals, representing the accuracy of the model in representing the given experimental data. The T-model had the most accuracy from among the group of models tested, with significantly more accuracy than the other two. The logistic and Gompertz models were on a comparable level, both yielding a reasonably accurate representation of the data. The R^2 for the T-model is 0.999, while the residual MSE is 0.000. This compares to an R^2 of 0.990 and residual MSE of 0.001 for logistic and R^2 of 0.980 and residual MSE of 0.002 for Gompertz. Thus, the T-model does provide an increased level of accuracy with the same number of parameters for data sets such as this one.

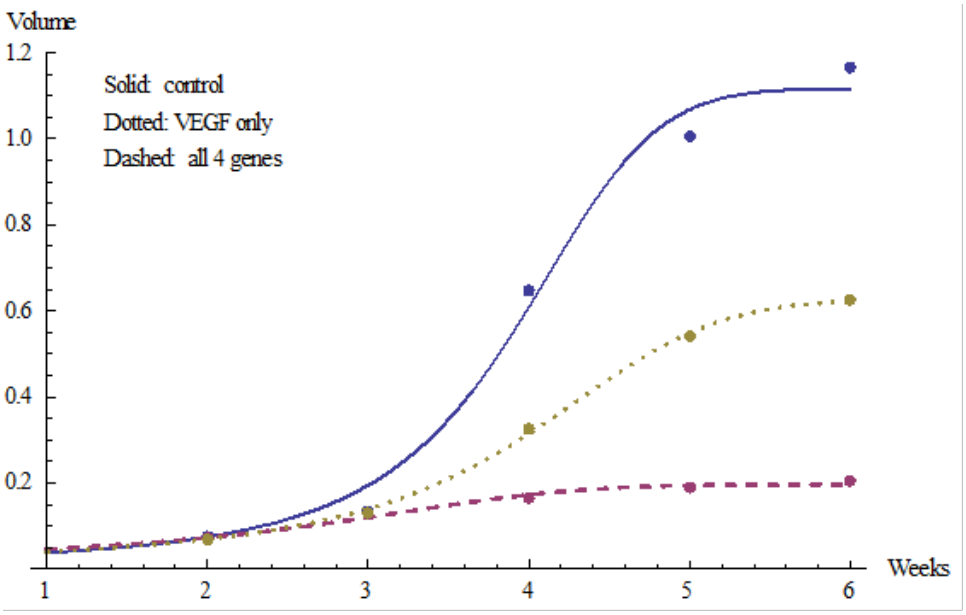

FIGURE 6. Growth curves for Tumors in Cases of Control and RNA Interference

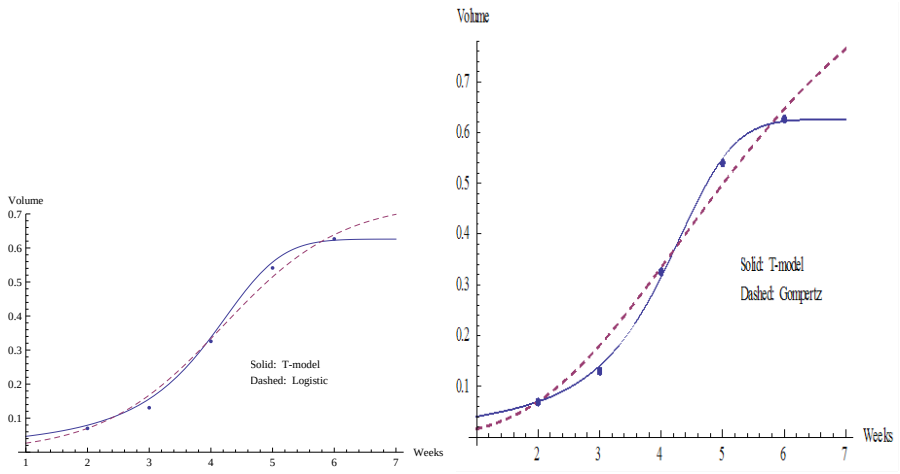

FIGURE 7. Comparison of T-model with Logistic and Gompertz

With these parameter estimates, the growth curves representing the data are given by the following functions. The T-model gives the function

$$P_T(t) = \frac{0.626}{1 + \frac{0.626-0.070}{0.070}\exp\left(-\sinh(0.467t) + \sinh(0.834)\right)},$$

while logistic and Gompertz give

$$P_L(t) = \frac{0.737}{1 + \frac{0.737-0.070}{0.070}\exp(-1.032(t-2))},$$

and

$$P_G(t) = 0.07\exp(-6.411(\exp(-0.432t) - \exp(-0.864))).$$

The comparison among these models is represented in Figures 7 and 8, and we can easily see that both the logistic and Gompertz models have some variance between the data points and the curve, while the curve for the T-model contacts the data points. Clearly the T-model gives a more accurate representation and furthermore gives a better overall representation of the shape of the growth curve.

5. **Conclusion.** The T growth model introduced in this paper follows the tradition of the hyperbolastic growth models in which hyperbolic functions are introduced into the growth model for the purpose of adding to the flexibility of the model and enabling the model to represent certain patterns of growth common to biological settings. This model is introduced with the dual goals of improving the representation of certain patterns of biological growth, particularly biphasic growth and also the goal of providing a flexible but accurate growth model with a small number of parameters that can easily be incorporated as the growth assumptions in a system of differential equations. In this context we are particularly interested in systems representing tumor-immune interactions, but can function equally well in other systems.

This new growth model displays a number of important characteristics that will make it very useful for modeling in mathematical biology. This single model has the ability to represent either sigmoidal or biphasic growth, and it is thus very flexible to represent a variety of growth patterns that are common in tumor growth. This increase in flexibility and in ability to accommodate both sigmoidal and biphasic growth is achieved with the same number of parameters as the logistic and Gompertz models of growth. As a consequence of the flexibility of this model, we find the potential for multiple inflection points within the growth curves represented by the T growth model. Furthermore, in contrast to the case of logistic growth assumptions, there is flexibility in the location of these points of inflection. This flexibility in the location of one or more inflection points provides the opportunity to analyze the time of the maximum or minimum rate of change of number of cells and how it relates to the underlying biological events. Overall we find an increased flexibility in the patterns of growth in the curves represented by the T growth model, allowing the model to accommodate different growth patterns, which is comparable to the value of the hyperbolastic models in representing biological growth.

Our other goal in introducing the T model of growth is for inclusion as assumptions for growth rate for tumor cells within a system of differential equations, particularly those systems of ODEs representing the tumor-immune interactions. Such growth assumptions allow for more flexibility of the model in accommodating the natural rate of growth of the tumor while using the same number of parameters as in logistic growth assumptions. This is in the same tradition as the hyperbolastic growth models, which have been demonstrated to be more accurate than logistic growth models for biological growth, for which the location of the point of inflection requires more flexibility. In substituting the T model of growth into the growth assumptions in a representative system, we were able to demonstrate how easily this model can be applied in the standard analysis of equilibrium points and their stability and phase portrait analysis. Thus we present the T growth model for use in systems as a tool that can assist in analysis of the effectiveness of treatments represented in these systems.

6. A sample SAS program for "T" model.

```
   data growth;
   input t p;
   datalines;
2 0.0700
3 0.1306
4 0.3257
5 0.5413
6 0.6265
;
TITLE 'T Model';
PROC NLIN DATA=growth Method=marquardt;
*M: is the max of p:Population size;Bounds M>=0;
*t: time;
*initializing the parameters;
Parameters M=1 beta=.3;
p0=0.0700; t0=2; *initial volume size of p0=0.0700, initial time of t0=2 in this
example;
MODEL p=M/(1+(M-p0)*exp(sinh(t0*beta)-sinh(t*beta))/p0);
output out=growthb predicted=yp;
run;
   *Scatter plot;
proc sgplot data=growthb noautolegend;
scatter y=p x=t;
series y=yp x=t;
run;

proc gplot data=growthb;
plot p*t yp*t/overlay;
symbol1 v=star c=blue I=none;
symbol2 v=none c=red I=spline;
run;
```

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REFERENCES

[1] J. C. Arciero, T. L. Jackson and D. E. Kirschner, *A mathematical model of tumor-immune evasion and siRNA treatment*, Discrete and Continuous Dynamical Systems—Series B, **4** (2004), 39–58.

[2] Ž. Bajzer, T. Carr, D. Dingli and K. Josić, *Optimization of tumor virotherapy with recombinant measles viruses*, Journal of Theoretical Biology, **252** (2008), 109–122.

[3] J. Burden, J. Ernstberger and K. R. Fister, *Optimal control applied to immunotherapy*, Discrete and Continuous Dynamical Systems—Series B, **4** (2004), 135–146.

[4] A. Cappuccio, M. Elishmereni and Z. Agur, *Cancer immunotherapy by Interleukin-21: Potential treatment strategies evaluated in a mathematical model*, Cancer Research, **66** (2006), 7293–7300.

[5] F. Castiglione and B. Piccoli, *Optimal control in a model of dendritic cell transfection cancer immunotherapy*, Bulletin of Mathematical Biology, **68** (2006), 255–274.

[6] A. d' Onofrio, U. Ledzewicz, H. Maurer and H. Schattler, *On optimal delivery of combination therapy for tumors*, Mathematical Bioscience, **222** (2009), 13–26.

[7] H. P. de Vladar and J. A. González, *Dynamic response of cancer under the influence of immunological activity and therapy*, Journal of Theoretical Biology, **227** (2004), 335–348.
[8] D. Dingli, M. D. Cascino, K. Josić, S. J. Russell and Ž. Bajzer, *Mathematical modeling of cancer radiovirotherapy*, Mathematical Biosciences, **199** (2006), 55–78.
[9] W. Eby, M. Tabatabai and Z. Bursac, *Hyperbolastic modeling of tumor growth with a combined treatment of iodoacetate and dimethylsulfoxide*, BMC Cancer, **10** (2010), 509.
[10] M. S. Feizabadi and T. M. Witten, *Chemotherapy in conjoint aging-tumor systems: some simple models for addressing coupled aging-cancer dynamics*, Theoretical Biology and Medical Modeling, **7** (2010), 21.
[11] I. Kareva, F. Berezovskaya and C. Castillo-Chavez, *Myeloid cells in tumour-immune interactions*, Journal of Biological Dynamics, **4** (2010), 315–327.
[12] D. Kirschner and J. C. Panetta, *Modeling immunotherapy of the tumor-immune interaction*, Journal of Mathematical Biology, **34** (1998), 235–252.
[13] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor and A. S. Perelson, *Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis*, Bulletin of Mathematical Biology, **56** (1994), 295–321.
[14] U. Ledzewicz, H. Maurer and H. Schättler, *Optimal and suboptimal protocols for a mathematical model for tumor anti-angiogenesis in combination with chemotherapy*, Mathematical Biosciences and Engineering, **8** (2011), 303–323.
[15] U. Ledzewicz, M. Naghnaeian and H. Schättler, "Dynamics of Tumor-Immune Interaction Under Treatment as an Optimal Control Problem," Discrete and Continuous Dynamical Systems, 2011, 971–980.
[16] H. Schättler, U. Ledzewicz and B. Caldwell, *Robustness of optimal controls for a class of mathematical models for tumor anti-angiogenesis*, Mathematical Biosciences and Engineering, **8** (2011), 355–369.
[17] M. Simeoni, P. Magni, C. Cammia, G. De Nicolao, V. Croci, E. Pesenti, M. Germani, I. Pogessi and M. Rochetti, *Predictive pharmokinetic-pharmodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents*, Cancer Research, **64** (2004), 1094–1101.
[18] Y. Song, M.-M. Dong and H.-F. Yang, *Effects of RNA interference targeting four different genes on the growth and proliferation of nasopharyngeal carcinoma CNE-2Z cells*, Cancer Gene Ther., **18** (2006), 297–304.
[19] M. Tabatabai, Z. Bursac, W. Eby and K. Singh, *Mathematical modeling of stem cell proliferation*, Medical & Biological Engineering & Computation, **49** (2011), 253–262.
[20] M. Tabatabai, D. K. Williams and Z. Bursac, *Hyperbolastic growth models: Theory and application*, Theoretical Biological and Medical Modeling, **2** (2005), 1–13.
[21] A. Takeda, C. Goolsby and N. R. Yaseen, *NUP98-HOXA9 induces long-term proliferation and blocks differentiation of primary human CD34+ hematopoietic cells*, Cancer Research, **66** (2006), 6628–6637.
[22] K. Tao, M. Fang, J. Alroy and G. G. Sahagian, *Imagable 4T1 model for the study of late stage breast cancer*, BMC Cancer, **8** (2008), 228.
[23] T. Yuri, R. Tsukamoto, K. Miki, N. Uehara, Y. Matsuoka and A. Tsubura, *Biphasic effects of zeranol on the growth of estrogen receptor-positive human breast carcinoma cells*, Oncol. Rep., **16** (2006), 1307–1312.

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