Bull Math Biol (2018) 80:1059–1083
https://doi.org/10.1007/s11538-017-0263-8

SPECIAL ISSUE : MATHEMATICAL ONCOLOGY

Ordinary Differential Equation Models for Adoptive Immunotherapy

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Received: 6 July 2016 / Accepted: 24 February 2017 / Published online: 5 April 2017

Abstract Modified T cells that have been engineered to recognize the CD19 surface marker have recently been shown to be very successful at treating acute lymphocytic leukemias. Here, we explore four previous approaches that have used ordinary differential equations to model this type of therapy, compare their properties, and modify the models to address their deficiencies. Although the four models treat the workings of the immune system in slightly different ways, they all predict that adoptive immunotherapy can be successful to move a patient from the large tumor fixed point to an equilibrium with little or no tumor.

Keywords Chimeric antigen receptor T cells · ODE models · Stability analysis · Saturating response · Acute lymphoblastic leukemia

1 Introduction

With the use of gene transfer technologies, T cells can be genetically modified to stably express antigens on their surface. Chimeric antigen receptors (CARs) are an application of this approach that combines an antigen recognition domain of a specific antibody with the intracellular domain of the CD3-ζ chain into a single chimeric protein (Eshhar et al. 1993; Park et al. 2011). In most cancers, tumor specific targets are not well defined, but in B-cell neoplasms such as lymphoblastic leukemias, the surface

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marker CD19 is an attractive target because its expression is restricted to normal and malignant B cells and B-cell precursors. In a recent study (Maude 2014), a total of 30 children and adults with relapsed or refractory acute lymphoblastic leukemia (ALL) received T cells transduced with a CD19-directed chimeric antigen receptor CTL019. Complete remission using this approach, which is called adoptive immunotherapy, was achieved in 27 out of 30 patients.

As described in an earlier study of two patients conducted by the same group of researchers (Grupp 2013), each patient received a total dose of 10^8 CD3+ cells per kilogram (1.2×10^7 CTL109 cells per kilogram), given over a period of three consecutive days. Both children had an increase in circulating lymphocytes and neutrophils in the 2 weeks after CTL109 infusion. Approximately one month after infusion, morphologic remission of leukemia was achieved in both children. While the therapy was successful, both patients had acute toxic effects, which consisted of a fever and a cytokine-release syndrome, which occurred in 27% of the patients in the larger study. The goal of this paper is to develop a simple ODE model of adoptive immunotherapy. To do this, we will analyze four previously studied models, compare their properties, and modify them to address some of their deficiencies.

Kuznetsov et al. (1994) introduced the following simple model of the interaction of a tumor with effector cells (cytotoxic T lymphocytes) produced by the immune system. Here, we use the notation of the original papers to make it easier to compare results. The model takes the form

$$\begin{aligned} \frac{\mathrm{d}T}{\mathrm{d}t} &= aT(1-bT) - nET \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= s - dE + pE\frac{T}{g+T} - mET, \end{aligned} \tag{1}$$

where T = tumor cells, E = effector cells.

In words, in the absence of a tumor, effector cells are produced at rate s and die at rate d and thus reach an equilibrium of s/d cells. In the absence of an immune response, the tumor shows logistic growth. Effector cells kill tumor cells according to mass-action dynamics nET, dying as a result of this interaction at rate mET. Finally, the production of effector cells is stimulated by the presence of the tumor, but due to the Michaelis–Menten-type term $p_0ET/(g+T)$, there is a maximum rate at which effector cells are produced. Based on tumor data from a mouse model, they assigned values to the parameters. Their mathematical analysis found equilibria and investigated their stability. We will describe their results in Sect. 2. For the moment, we want to concentrate on comparing the modeling approaches.

Kirschner and Panetta (1998) added interleukin-2 (denoted by I) to the model, which is produced by CD4+ cells and stimulates the production of effector cells.

$$\begin{aligned} \frac{\mathrm{d}T}{\mathrm{d}t} &= r_2T(1-bT) - aE\frac{T}{g_2+T} \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= s_1 + cT - \mu_2E + p_1E\frac{I}{g_1+I} \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= s_2 - \mu_3I + p_2E\frac{T}{g_3+T}. \end{aligned} \tag{2}$$

As in the previous model, the tumor shows logistic growth, but now effector cell production is stimulated in proportion to the tumor mass and by the presence of interleukin but with a response that saturates for large I. Finally, interleukin is produced due to the interaction of effector cells and tumor cells.

Kirschner and Paneta set $s_1 = s_2 = 0$ in their initial analysis. They viewed $s_1 > 0$, $s_2 = 0$ as adoptive cellular immunotherapy, $s_1 = 0$, $s_2 > 0$ as interleukin therapy, and $s_1 > 0$, $s_2 > 0$ as combination therapy. In contrast, we will take $s_1 > 0$, $s_2 > 0$ to reflect the fact that CD4+ and CD8+ are always present, see e.g., Mohri (2001). Motivated by the treatment described above, we will view adoptive immunotherapy as a perturbation that adds effector cells to the tumor equilibrium, rather than a constant influx of new cells.

Dong et al. (2014) modified the previous approach to use H (the number of CD4+ helper cells) as a variable instead of the interleukin levels:

$$\begin{aligned}\frac{\mathrm{d}T}{\mathrm{d}t} &= aT(1-bT) - nET\\ \frac{\mathrm{d}E}{\mathrm{d}t} &= s_1 - d_1E + pEH\\ \frac{\mathrm{d}H}{\mathrm{d}t} &= s_2 - d_2H + k_2TH.\end{aligned} \tag{3}$$

Tumor growth is again logistic, but in contrast to (2), all the interactions are mass action. As we will see in Sect. 4, this change drastically alters the qualitative properties of the model.

In 2004, Moore and Li introduced a model with naive T cells and effector cells in order to study chronic myelogenous leukemia. They used T_n and T_e for the two types of T cells and C for cancer so we have changed their variables to N, E, and T. After changing notation and replacing their Gompertzian growth by logistic, the system becomes

$$\begin{aligned}\frac{\mathrm{d}T}{\mathrm{d}t} &= aT(1-bT) - \gamma_cET\\ \frac{dE}{dt} &= s_e - d_eE + \alpha_cET/(T+g) + \alpha_nk_nN\frac{T}{T+g} - \gamma_eET\\ \frac{\mathrm{d}N}{\mathrm{d}t} &= s_n - d_nN - k_nN\frac{T}{T+g}.\end{aligned} \tag{4}$$

As in (1), the interaction between tumor cells and effector cells causes the death of each following mass-action dynamics. The stimulation of the production of effector cells due to the presence of tumor follows a saturating response. A new feature here is the terms with $k_nT/(T+g)$ which model activation and proliferation of naive T cells in the lymph nodes to produce an average of α_c effector cells per naive cell.

There are other more complex models, such as the ones of Pillis and Radunskaya (2006) and Pillis et al. (2005). Here, we will concentrate on the four models described above in order to understand the implications of the different modeling choices, e.g., the choice of the third variable used in the immune system model and mass-action

kinetics versus a saturating response. To reduce the differences between the models, we eliminate the direct stimulation of effector cells by the tumor in the last three models. Since the tumor stimulates the third variable that, in turn, stimulates effector cell production, direct stimulation is not necessary and may not be biologically realistic. In any case, comparing our results with conclusions in the original papers shows that removing these terms does not change the qualitative behavior of the system.

In Sects. 2–5, we will analyze (1)–(4). In Sect. 6, we state our conclusions.

2 Kuznetsov et al. (1994) (KMTP)

The model is

$$\frac{\mathrm{d}E}{\mathrm{d}t} = s - dE + pE\frac{T}{g+T} - mET$$
$$\frac{\mathrm{d}T}{\mathrm{d}t} = aT(1-bT) - nET.$$

Based on mouse data, they propose the following concrete values:

$$s = 13,000 \text{ cells day}^{-1} \quad d = 0.0412 \text{ day}^{-1} \quad p = 0.1245 \text{ day}^{-1}$$
$$a = 0.18 \text{ day}^{-1} \quad b = 2 \times 10^{-9} \text{ cells}^{-1} \quad g = 2.019 \times 10^{7} \text{ cells}$$
$$m = 3.422 \times 10^{-10} \text{ day}^{-1}\text{cells}^{-1} \quad \gamma_c = n = 1.101 \times 10^{-7} \text{ day}^{-1}\text{cells}^{-1}.$$

The death rate $d = 0.0412$ day^{-1} corresponds or an exponential life time with mean $1/d = 24.27$ days. Setting $T = 0$, we see that in the absence of tumor there are $s/d = 315,534$ effector cells in equilibrium.

The first step in Kuznetsov et al. (1994) is to nondimensionalize the system. Let $x = E/E_0$, $y = T/T_0$ where $E_0 = T_0 = 10^6$ and let $\tau = nT_0t$ where $n = 1.101 \times 10^{-7}$. This choice will turn $-nET$ into $-xy$. Note that $\tau = 0.1101t$, or $t = 9.80$ days, corresponds to $\tau = 1$. If we let

$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = \sigma - \delta x + \rho x\frac{y}{y+\eta} - \mu xy$$
$$\frac{\mathrm{d}y}{\mathrm{d}\tau} = \alpha y(1-\beta y) - xy \tag{5}$$

then since

$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = \frac{1}{E_0}\cdot\frac{\mathrm{d}E}{\mathrm{d}t}\cdot\frac{\mathrm{d}t}{\mathrm{d}\tau} \quad \text{and} \quad \frac{\mathrm{d}y}{\mathrm{d}\tau} = \frac{1}{T_0}\cdot\frac{\mathrm{d}T}{\mathrm{d}t}\cdot\frac{\mathrm{d}t}{\mathrm{d}\tau}$$

the new constants are

$$\sigma = \frac{s}{nT_0E_0} = 0.1181 \quad \delta = \frac{d}{nT_0} = 0.3743 \quad \rho = \frac{p}{nT_0} = 1.131 \quad \alpha = \frac{a}{nT_0} = 1.636$$
$$\eta = g/T_0 = 20.19 \qquad \beta = bT_0 = 2.0 \times 10^{-3} \qquad \mu = m/n = 3.11 \times 10^{-3}.$$

Steady states. There is a tumor-free equilibrium with

$$y_0^* = 0 \qquad x_0^* = \sigma/\delta = 0.3155.$$

This root will be unstable if $\alpha > \sigma/\delta$ since for y small

$$\frac{\mathrm{d}y}{\mathrm{d}t} \approx \alpha y - x^* y$$

and the tumor will grow. To check stability for $\alpha < \sigma/\delta$, we linearize to get

$$L = \begin{pmatrix} -\delta - \mu y + \rho \frac{y}{y+\eta} & \rho x \frac{\eta}{(\eta+y)^2} - \mu x \\ -y & \alpha(1-\beta y) - \alpha\beta y - x \end{pmatrix}. \tag{6}$$

When $y = 0$, $x = x_0^*$, this is

$$\begin{pmatrix} -\delta & \rho x_0^*/\eta - \mu x_0^* \\ 0 & \alpha - x_0^* \end{pmatrix}.$$

If $x_0^* = \sigma/\rho > \alpha$, then the trace will be negative and the determinant positive so the tumor-free equilibrium is stable.
Interior equilibria. If $y > 0$, then for $\mathrm{d}y/\mathrm{d}\tau = 0$, we need $x = \alpha(1-\beta y) \equiv g(y)$. $\mathrm{d}x/\mathrm{d}\tau = 0$ when

$$x = \frac{\sigma}{\delta + \mu y - \rho y/(\eta + y)} \equiv f(y).$$

Multiplying top and bottom by $\eta + y$, we have $\mu y^2 + (\mu\eta + \delta - \rho)y + \delta\eta$. For the particular values we are considering

$$b \equiv \mu\eta + \delta - \rho = (3.011 \times 10^{-3})(20.59) + 0.3743 - 1.131 = -0.69592,$$

so $b^2 - 4\mu\delta\eta = 0.39327$ and the denominator can vanish. It has roots at

$$y = \frac{-b \pm \sqrt{b^2 - 4\mu\delta\eta}}{2\mu} = 11.42 \text{ and } 219.70$$

The null clines are graphed in Fig. 1. There are three interior equilibria.

To check the stability of B, C and D, we use the equilibrium equations to simplify the diagonal elements

$$\begin{pmatrix} -\sigma/x & x\left(-\mu + \rho\frac{\eta}{(\eta+y)^2}\right) \\ -y & -\alpha\beta y \end{pmatrix}.$$

The trace is always negative. A little computation shows that the determinant is positive for fixed points B and D, but negative for fixed point C, so we have the stabilities indicated in Fig. 1.

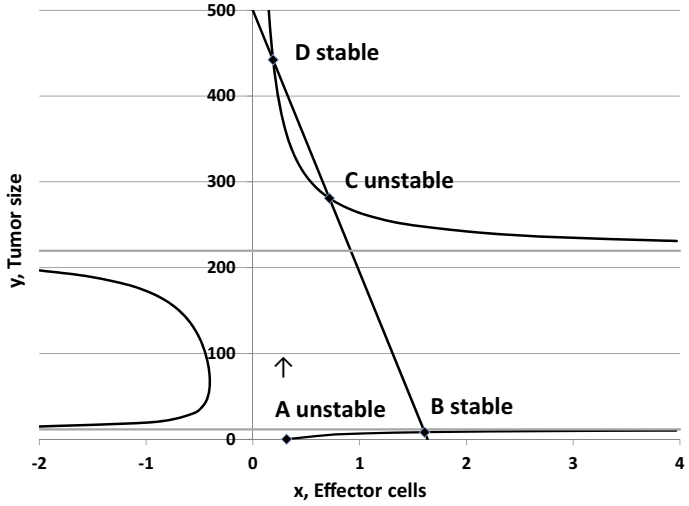

Fig. 1 Graph of null clines in the model of Kuznetsov et al. (1994) The units are millions of cells. $g(y)$ is a straight line. $f(y)$ has three pieces because the denominator has two positive roots. There is the tumor-free equilibrium $A = (0.3155, 0)$. In addition, the null clines intersect in three points $B = (1.6093, 8.158)$, $C = (0.7172, 280.8)$, and $D = (0.1825, 442.2)$

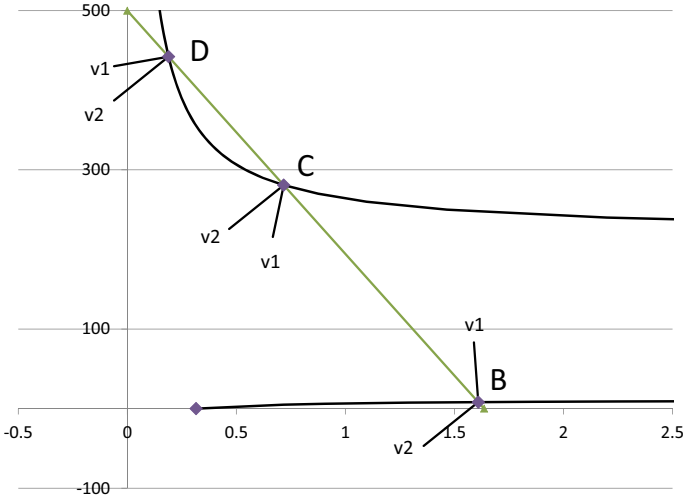

Fig. 2 A geometric way of determining the stability of fixed points in the plane shows that as long as the intersections exist, B and D are stable and C is unstable. If we have a matrix with *top row* v_1 and *bottom row* v_2, then the absolute value of the determinant is the area of the trapezoid with vertices 0, v_1, $v_1 + v_2$, and v_2. The sign is positive if the vectors v_1 and v_2 are a left-handed coordinate system. That is, they have the same relative position as the unit vectors $e_1 = (1, 0)$ and $e_2 = (0, 1)$, or if e_1 is your thumb and e_2 your first finger, they look like your left hand

These stability results can also be found by using geometry rather than algebra. See Fig. 2.

Adoptive immunotherapy See Fig. 3.

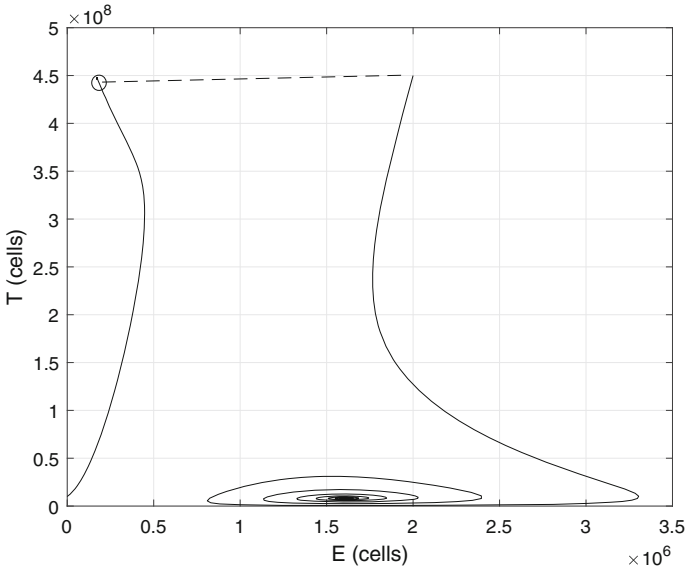

Fig. 3 This numerical solution of the ODE shows that if the patient is in the large tumor equilibrium and we add 2×10^8 effector cells (indicated by the *dotted line*), then we end up in the small tumor equilibrium with $E = 1.61 \times 10^6$ and $T = 8.158 \times 10^6$. The other trajectory starts near 0 and goes to the large tumor state

3 Kirschner and Panetta (KP) (1998)

This model takes the form

$$\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= r_2 T(1 - bT) - aE\frac{T}{g_2 + T} \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= s_1 - \mu_2 E + p_1 E\frac{I}{g_1 + I} \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= s_2 - \mu_3 I + p_2 E\frac{T}{g_3 + T}.
\end{aligned} \tag{7}$$

As explained in the Introduction, we have removed the $+cT$ term from $\mathrm{d}E/\mathrm{d}t$. KP vary the parameters s_1 and s_2 with the others set to the following values:

$$\begin{aligned}
&r_2 = 0.18\ \text{day}^{-1} \quad a = 1\ \text{day}^{-1} \quad b = 1 \times 10^{-9}\ \text{cells}^{-1} \quad g_2 = 10^5\ \text{cells} \\
&\mu_2 = 0.03\ \text{day}^{-1} \quad p_1 = 0.1245\ \text{day}^{-1} \quad g_1 = 2 \times 10^7\ \text{cells} \\
&\mu_3 = 10\ \text{day}^{-1} \quad p_2 = 5\ \text{day}^{-1} \quad g_3 = 10^3\ \text{cells}
\end{aligned} \tag{8}$$

Eventually, we will set $s_1 = 10{,}000$ and $s_2 = 38{,}000$.

Theorem 1 *The tumor-free equilibrium exists if* $s_2 < s_{2,c} = \mu_2\mu_3 g_1/(p_1 - \mu_2)$. *It has*

$$T_0^* = 0 \quad I_0^* = \frac{s_2}{\mu_3} \quad E_0^* = \frac{s_1}{\mu_2}\left[1 + \frac{s_2 p_1}{\mu_2\mu_3 g_1 - s_2(p_1 - \mu_2)}\right]$$

The tumor-free equilibrium is stable when $aE_0^*/g_2 > r_2$.

Remark 1 For our concrete values, $I_0^* = 3,800$ and $E_0^* \approx s_1/\mu_2 = 333,333$.

Proof Suppose $T_0^* = 0$. In this case, $I_0^* = s_2/\mu_3$. Substituting this in the first equation becomes

$$s_1 = \left(\mu_2 - p_1\frac{I_0^*}{g_1 + I_0^*}\right)E_0^*$$

so to have an equilibrium, we must have $\mu_2(g_1 + I_0^*) - p_1 I_0^* > 0$ which holds if

$$I_0^* < \frac{\mu_2 g_1}{p_1 - \mu_2} \quad \text{or} \quad s_2 < s_{2,c} \equiv \frac{\mu_2\mu_3 g_1}{p_1 - \mu_2}. \tag{9}$$

For our concrete parameters $s_{2,c} = 63{,}492{,}063$. When $s_2 < s_{2,c}$, we have

$$E_0^* = \frac{s_1(g_1 + I_0^*)}{\mu_2(g_1 + I_0^*) - p_1 I_0^*}. \tag{10}$$

Filling in the value of I_0^* and doing some algebra gives the formula for E_0^* in the theorem. The tumor-free equilibrium will be unstable if $r_2 > aE_0^*/g_2$ since a small tumor will grow. For our concrete parameters that is $E_0^* < 18{,}000$. Using (10) and $I_0^* = s_2/\mu_3$, this means

$$s_1 = E_0^*\left(\mu_2 - \frac{s_2 p_1}{\mu_3 g_1 + s_2}\right) < 18{,}000\left(0.03 - \frac{0.1245 s_2}{10^6 + s_2}\right). \tag{11}$$

When $s_2 = 0$, this is $s_1 < 540$. When $s_2 = s_{2,c}$, this is $s_1 = 0$.

To check stability when $aE_0^*/g_2 > r_2$, we look at the linearization

$$L = \begin{pmatrix} r_2(1 - bT) - r_2 bT - aEg_2/(g_2 + T)^2 & -aT/(g_2 + T) & 0 \\ 0 & -\mu_2 + p_1 I/(g_1 + I) & g_1/(g_1 + I)^2 \\ p_2 Eg_3/(g_3 + T)^2 & p_2 T/(g_3 + T) & -\mu_3 \end{pmatrix}. \tag{12}$$

Using the second equation in (7) to simplify $L_{2,2}$ and setting $T = 0$ gives

$$\theta I - L = \begin{pmatrix} \theta - r_2 + aE/g_2 & 0 & 0 \\ 0 & \theta + s_1/E & g_1/(g_1 + I)^2 \\ -p_2 E/g_3 & 0 & \theta + \mu_3 \end{pmatrix}. \tag{13}$$

The determinant is $(\theta - r_2 + aE/g_2)(\theta + s_1/E)(\theta + \mu_3)$ so the eigenvalues are $-s_1/E$, $r_2 - aE/g_2$, and $-\mu_3$. If $aE/g_2 > r_2$, then all three eigenvalues are negative. □

Interior equilibria. To look for other fixed points we begin by noting that $dT/dt = 0$ when

$$E = \frac{r_2}{a}(g_2 + T)(1 - bT).$$

Rearranging gives $bT^2 - (1 - g_2 b)T - g_2 + aE/r_2 = 0$, which has roots

$$\frac{(1 - g_2 b) \pm \sqrt{(1 - g_2 b)^2 - 4b(aE/r_2 - g_2)}}{2b}. \tag{14}$$

There will be no roots if $1 - 2g_2 b + g_2 b^2 - 4baE/r_2 + 4bg_2 < 0$ which holds if

$$E > \frac{r_2(1 + g_2 b)^2}{4ab}.$$

For our concrete values, this is $E > 4.5 \times 10^7$.

$dE/dt = 0$ when

$$0 = s_1 - \mu_2 E + p_1 E\left(1 - \frac{g_1}{g_1 + I}\right).$$

Rearranging we have $p_1 E g_1/(g_1 + I) = s_1 + (p_1 - \mu_2)E$ or

$$I = g_1\left(\frac{\mu_2 E - s_1}{(p_1 - \mu_2)E + s_1}\right). \tag{15}$$

$dI/dt = 0$ when

$$I = \frac{s_2}{\mu_3} + \frac{p_2 E}{\mu_3} \cdot \frac{T}{g_3 + T}.$$

Our concrete values have $g_3 = 10^3$. To begin our analysis, we will look at the behavior of the system in the part of the space where T is large enough so that $T/(T + 10^3) \approx 1$. In this case, the last equation becomes

$$I = \frac{s_2}{\mu_3} + \frac{p_2 E}{\mu_3}. \tag{16}$$

Note that the equations in (16) and (15) do not depend on T, and they will be a good approximation to the true null clines when $T \gg 10^3$. See Fig. 4.

Combining (16) and (15) shows that if (E, I) is a fixed point, then

$$\frac{s_2}{\mu_3} + \frac{p_2 E}{\mu_3} = g_1\left(\frac{\mu_2 E - s_1}{(p_1 - \mu_2)E + s_1}\right). \tag{17}$$

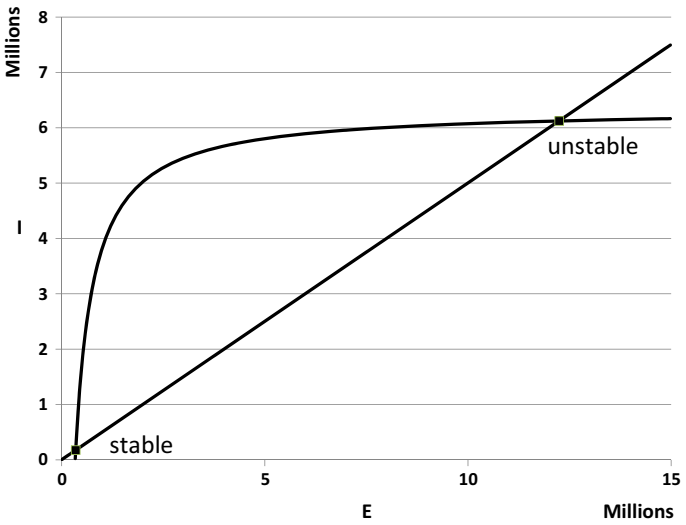

Fig. 4 Null clines (16) and (15)

Cross-multiplying we have

$$((p_1 - \mu_2)E + s_1)\left(\frac{s_2}{\mu_3} + \frac{p_2 E}{\mu_3}\right) = g_1(\mu_2 E - s_1)$$

which is a quadratic equation $\alpha E^2 + \beta E + \gamma = 0$ with

$$\begin{aligned}\alpha &= (p_1 - \mu_2)\frac{p_2}{\mu_3}\\ \beta &= -g_1\mu_2 + \frac{s_2(p_1 - \mu_2)}{\mu_3} + s_1\frac{p_2}{\mu_3}\\ \gamma &= g_1 s_1 + s_1 s_2/\mu_3.\end{aligned} \tag{18}$$

When $s_1 = 10{,}000$ and $s_2 = 38{,}000$, the two roots of the quadratic equation are

$$E_1 = 345{,}909 \qquad E_2 = 1.224 \times 10^7. \tag{19}$$

Using $I = (s_2 + p_2 E)/\mu_2$ we find that the corresponding values of I are

$$I_1 = 176{,}754 \qquad I_2 = 6.123 \times 10^6. \tag{20}$$

Using (14), we see that corresponding to E_i there are two roots $T_{i,1} < T_{i,2}$ where

$$\begin{aligned}T_{1,1} &= 1.825 \times 10^6 \qquad T_{2,1} = 7.324 \times 10^8\\ T_{1,2} &= 1 \times 10^9 \qquad T_{2,2} = 9.266 \times 10^8.\end{aligned}$$

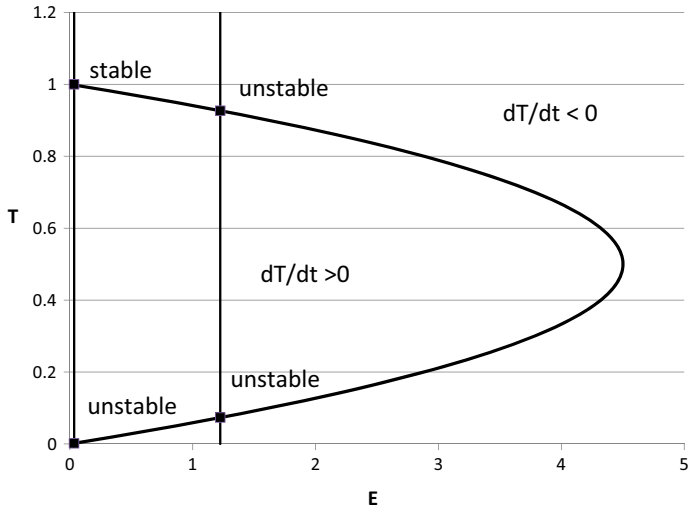

Fig. 5 Values of E are $\times 10^7$, T are $\times 10^9$ cells. *Solid curve* is the null cline $\mathrm{d}T = 0$. *Vertical lines* are the roots $E_1 = 0.0346$ and $E_2 = 1.224$. With each value of E, the quadratic equation gives us two values of T, so there are four interior roots in addition to the stable tumor-free equilibrium at $(0.3333, 0)$. Values of $\mathrm{d}T/\mathrm{d}t$ indicate that it will take a substantial influx of effector cells to get around the region where $\mathrm{d}T/\mathrm{d}t > 0$

See Fig. 5 for a summary.

Stability analysis. The (E, I) subsystem in (7) is (for large T) independent of T so we begin by studying this limit. Linearizing around a fixed point gives

$$\begin{pmatrix} \mathrm{d}E/\mathrm{d}t \\ \mathrm{d}I/\mathrm{d}t \end{pmatrix} = \begin{pmatrix} -\mu_2 + p_1 I/(g_1 + I) & p_1 E g_1/(g_1 + I)^2 \\ p_2 & -\mu_3 \end{pmatrix} \begin{pmatrix} E \\ I \end{pmatrix}. \tag{21}$$

The equation $\mathrm{d}E/\mathrm{d}t = 0$ implies that in equilibrium $-\mu_2 + p_1 I/(g_1 + I) = -s_1/E < 0$ so the trace is negative. The determinant is

$$\frac{s_1 \mu_3}{E} - p_1 p_2 E \frac{g_1}{(g_1 + I)^2}.$$

Using the values given in (19) and (20), we see that for our concrete values the determinant of the matrix in (21) at (E_1, I_1) is positive, while the determinant at (E_2, I_2) is negative. Thus, (E_1, I_1) is stable, while (E_2, I_2) is a saddle point. This conclusion can also be found using the geometric reasoning in Fig. 2, so the result holds as long as the intersections exist.

Combining this analysis with Fig. 5, we see that $(E_2, I_2, T_{2,1})$, $(E_2, I_2, T_{2,2})$, $(E_1, I_1, T_{1,1})$ are unstable. To show that the remaining equilibrium $(E_1, I_1, T_{1,2})$ is stable we note that if we take $T = 10^9$ in (12), then (13) becomes

$$\theta I - L = \begin{pmatrix} \theta + r_2 & a & 0 \\ 0 & \theta + s_1/E & g_1/(g_1 + I)^2 \\ 0 & -p_2 & \theta + \mu_3 \end{pmatrix},$$

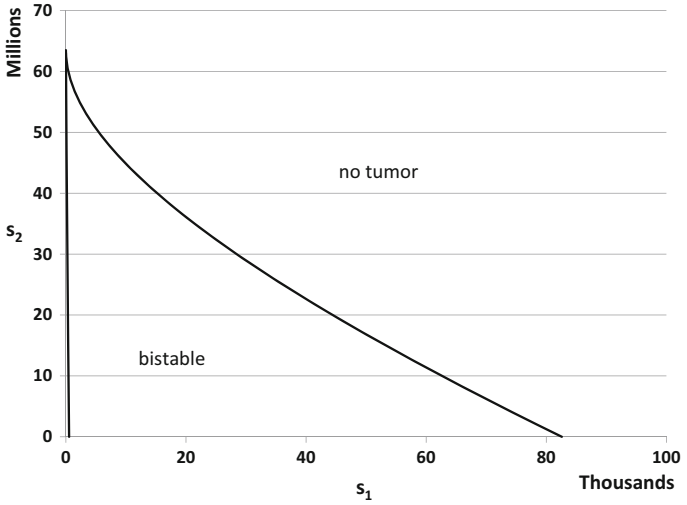

Fig. 6 Phase diagram. The curve very close to the y-axis that ends at $s_1 = 540$ is defined by (11). Between it and the y-axis, the tumor-free equilibrium is unstable. The other curve is the smaller root of (22). Note that this figure looks much different than the hand-drawn panel A of Figure 6 in Kirschner and Panetta (1998)

and the characteristic polynomial $\det(\theta I - L)$ has the form $\theta^3 + b_1\theta^2 + b_2\theta + b_3$ where

$$
\begin{aligned}
b_1 &= r_2 + s_1/E + \mu_3 > 0 \\
b_2 &= r_2\left(\frac{s_1}{E} + \mu_3\right) + \left[\frac{s_1\mu_3}{E} + \frac{p_2q_1}{(g_1+I)^2}\right] > 0 \\
b_3 &= r_2\left(\frac{s_1\mu_3}{E} + \frac{p_2q_1}{(g_1+I)^2}\right) > 0.
\end{aligned}
$$

To check the computation, recall that b_1 is the trace of $-L$, b_2 the sum of its 2×2 principal minors, and $b_3 = \det(-L)$. As the formulas show all three $b_i > 0$. By the Routh–Hurwitz condition, the equilibrium is locally stable if $b_4 \equiv b_1b_2 - b_3 > 0$. This is easy to see since r_2 times the term in square brackets in b_2 is b_3 and the other terms in b_1b_2 are positive. The reader should note that this argument shows that the large tumor equilibrium is stable (when it exists).

This picture will hold as long as the four roots exist, however using (18) we see that to have a solution we must have

$$(600{,}000 - 0.00945s_2 - s_1/2)^2 \geq 0.189\left(2 \times 10^7 + \frac{s_2}{10}\right)s_1$$

or s_1 is less than the smaller root of

$$\frac{s_1^2}{4} - (4.38 \times 10^6 - 0.02385s_2)s_1 + (600{,}000 - 0.00945s_2)^2 = 0. \qquad (22)$$

When $s_2 = 0$, this says $s_1 \leq 82,251$, while if $s_2 = s_{2,c}$ this says $s_1 \leq 0$. See Fig. 6.

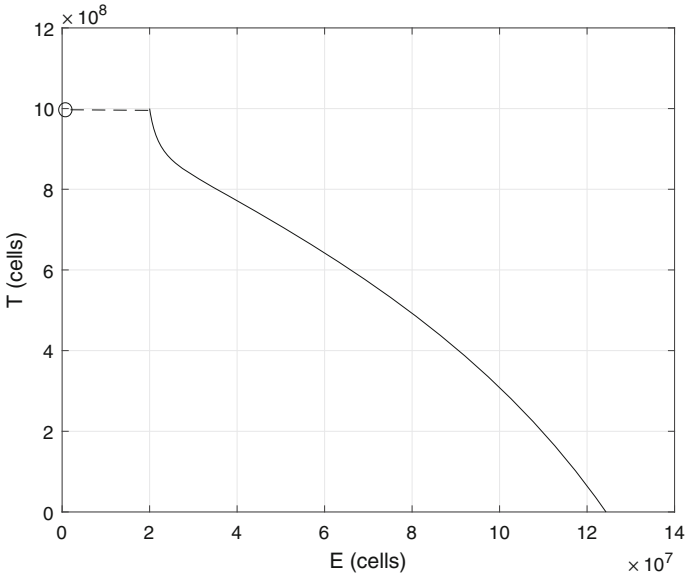

Fig. 7 In this numerical solution of the ODE, the patient was in the large tumor equilibrium of 1×10^8 cells and 2×10^7 effector cells were added. It may seem that the number of effector cells E hits the axis a little above 1.2×10^8. However, after reaching this position the solution goes down the E axis to the tumor-free equilibrium

Adoptive immunotherapy. We expect that adoptive immunotherapy will work in the bistable region in the phase diagram in Fig. 6. In Fig. 7, we consider the situation when $s_1 = 10{,}000$, $s_2 = 38{,}000$ and the other parameters are given in (8).

4 Dong, Miyazaki, Takeuchi (DMT) (2014)

Again to make it easier to compare with Dong et al. (2014), we return to using their notation. As before, we have removed the term $k_1 T E$ from $\mathrm{d}E/\mathrm{d}t$ which models direct stimulation of effector cell production by the tumor:

$$\begin{aligned} \frac{\mathrm{d}T}{\mathrm{d}t} &= aT(1 - bT) - nET \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= s_1 - d_1 E + pEH \\ \frac{\mathrm{d}H}{\mathrm{d}t} &= s_2 - d_2 H + k_2 T H. \end{aligned} \tag{23}$$

DMT vary the parameters k_1 and k_2. The others are assigned values

$$\begin{aligned} &a = 0.168 \text{ day}^{-1}, \quad b = 2 \times 10^{-9} \text{ cells}^{-1}, \quad n = 10^{-7} \text{ cells}^{-1} \text{ day}^{-1}, \\ &s_1 = 11,810 \text{ cells day}^{-1} \quad d_1 = 0.03473 \text{ day}^{-1}, \\ &s_2 = 38,000 \text{ cells day}^{-1} \quad d_2 = 0.0055 \text{ day}^{-1}. \end{aligned} \tag{24}$$

Their first step is to nondimensionalize the system. Let

$$x = \frac{T}{T_0} \qquad y = \frac{E}{T_0} \qquad z = \frac{H}{T_0} \qquad \tau = nT_0 t$$

where $T_0 = 10^6$ cells and $n = 10^{-7}$ cells^{-1} day^{-1}. Thus, $nT_0 = 10^{-1}$, i.e., $\tau = 0.1t$, or time $t = 10$ corresponds to time $\tau = 1$. Changing variables the system becomes

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}\tau} &= \alpha x(1 - \beta x) - xy \\ \frac{\mathrm{d}y}{\mathrm{d}\tau} &= \sigma_1 - \delta_1 y + \rho yz \\ \frac{\mathrm{d}z}{\mathrm{d}\tau} &= \sigma_2 - \delta_2 z + \omega_2 xz. \end{aligned} \tag{25}$$

The growth rate is now $\alpha = a/nT_0$ with $\beta = bT_0$. The production rates are now $\rho = p/n$ and $\omega_2 = k_2/n$. Death rates $\delta_i = d_i/nT_0$, while the input rates are $\sigma_i = s_i/(nT_0^2)$. Thus, the concrete example has

$$\begin{aligned} \alpha = 1.636, \quad \beta = 0.002, \quad \sigma_1 = 0.1181, \\ \delta_1 = 0.3473, \quad \sigma_2 = 0.38, \quad \delta_2 = 0.055, \end{aligned}$$

and they vary ρ and ω_2. Later, we will take $\rho = 0.03$ and $\omega_2 = 0.01$.
Equilibria. The first step in the analysis is to find fixed points of the dynamics, which satisfy

$$\begin{aligned} 0 &= x(\alpha(1 - \beta x) - y) \\ \sigma_1 &= y(\delta_1 - \rho z) \\ \sigma_2 &= z(\delta_2 - \omega_2 x). \end{aligned} \tag{26}$$

Theorem 2 *The tumor-free equilibrium has* $x_0^* = 0$, $z_0^* = \sigma_2/\delta_2$, *and*

$$y_0^* = \frac{\sigma_1}{\delta_1 - \rho\sigma_2/\delta_2}.$$

It exists if $\rho < \rho_0$, *and is stable if* $\rho > \rho_1$ *where*

$$\rho_0 = \frac{\delta_2}{\sigma_2} \cdot \delta_1 \quad \textit{and} \quad \rho_1 = \frac{\delta_2}{\sigma_2}\left(\delta_1 - \frac{\sigma_1}{\alpha}\right).$$

Remark 2 In our concrete example, $\rho_1 = 0.039819$, $\rho_0 = 0.050267$, $z_0^* = 6.9091$, and $y_0^* = 0.8433$, where the units for the last two numbers are millions of cells.

Proof For $y_0^* > 0$, we must have $\rho < \delta_1\delta_2/\sigma_2 = \rho_0$. The fixed point is unstable if

$$\alpha > y_0^* = \frac{\sigma_1\delta_2}{\delta_1\delta_2 - \rho\sigma_2} \tag{27}$$

because in this case a small tumor will grow. Rearranging this becomes

$$\frac{\rho\sigma_2}{\sigma_1\delta_2} < \frac{\delta_1}{\sigma_1} - \frac{1}{\alpha} \quad \text{or} \quad \rho < \frac{\delta_2}{\sigma_2}\left(\delta_1 - \frac{\sigma_1}{\alpha}\right) = \rho_1.$$

To check stability for $\rho > \rho_1$, we linearize around the fixed point

$$L = \begin{pmatrix} \alpha(1-\beta x) - \alpha\beta x - y & -x & 0 \\ 0 & -\delta_1 + \rho z & \rho y \\ \omega_2 z & 0 & -\delta_2 + \omega_2 x \end{pmatrix}. \tag{28}$$

To find the eigenvalues for the tumor-free equilibrium, we set $x = 0$ and look at

$$\theta I - L = \begin{pmatrix} \theta - \alpha + y & 0 & 0 \\ 0 & \theta + \delta_1 - \rho z & -\rho y \\ -\omega_2 z & 0 & \theta + \delta_2 \end{pmatrix}. \tag{29}$$

Recalling that $z_0^* = \sigma_2/\delta_2$, the determinant of $\theta I - L$ is

$$(\theta - \alpha + y_0^*)(\theta + \delta_1 - \rho\sigma_2/\delta_2)(\theta + \delta_2).$$

The eigenvalues are $-\delta_2$, $\rho\sigma_2/\delta_2 - \delta_1$ and $\alpha - y_0^*$. The second one is negative if $\rho < \rho_0$. The third is negative if $\alpha < y_0^*$, i.e., $\rho > \rho_1$. □

When the source terms $\sigma_1, \sigma_2 > 0$ any equilibrium will have $y^*, z^* > 0$. Thus, by (26) any equilibrium with $x^* > 0$ must satisfy

$$y^* = \alpha(1 - \beta x^*) \qquad z^* = \frac{\sigma_2}{\delta_2 - \omega_2 x^*}$$

which requires

$$0 < x^* < 1/\beta \quad \text{and} \quad x^* < \delta_2/\omega_2. \tag{30}$$

To look for other interior equilibria, we note that the first equation in (23) implies that in equilibrium

$$y_1(x) = \alpha(1 - \beta x). \tag{31}$$

This a straight line that always goes through the point $(1/\beta, 0)$. See Fig. 8. The third equation in (26) implies $z = \sigma_2/(\delta_2 - \omega_2 x)$. Using this in the second equation in (26), we have

$$y_2(x) = \frac{\sigma_1}{\delta_1 - \rho\sigma_2/(\delta_2 - \omega_2 x)}. \tag{32}$$

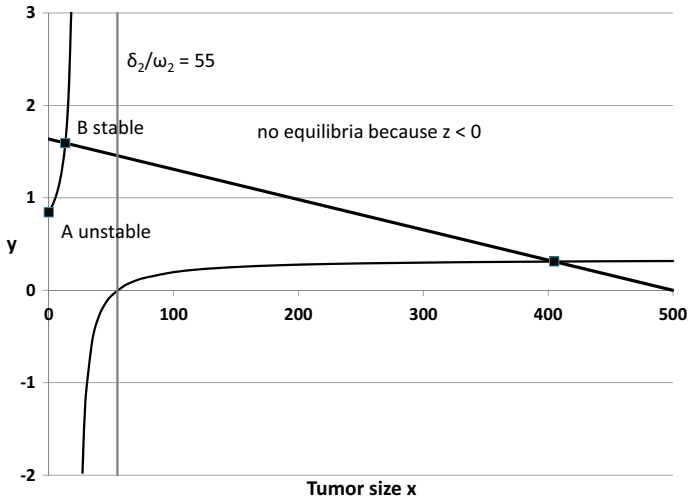

Fig. 8 Null clines of DMT with values given in (24), $\rho = 0.03 < \rho_0$, and $\omega_2 = 0.001$

When $x = 0$, this is $\sigma_1\delta_2/(\delta_1\delta_2 - \rho\sigma_2) = y_0^*$. The denominator is 0 when $\delta_1(\delta_2 - \omega_2 x) = \rho\sigma_2$. That is, when

$$x = \frac{\delta_1\delta_2 - \rho\sigma_2}{\delta_1\omega_2} \equiv x_0. \tag{33}$$

As $x \uparrow x_0$, $y(x) \to \infty$. As $x \downarrow x_0$, $y(x) \to -\infty$. Note that (32) implies $y(\delta_2/\omega_2) = 0$. As $x \to \infty$, $y(x) \to \sigma_1/\delta_1 > 0$ so the null clines $\{y_1(x) = 0\}$ and $\{y_2(x) = 0\}$ intersect at a point with $\hat{x} \in (\omega_2/\delta_2, 1/\beta)$ but at that point $\hat{z} = \sigma_2/(\delta_2 - \omega_2 x) < 0$ so this is not an equilibrium.

There is an intersection of the null clines at $\bar{x} < \delta_2/\omega_2$ if $y_1(0) > y_2(0)$, that is, if $\alpha > y_0^*$. By the reasoning just after (27) this is equivalent to $\rho < \rho_1$. We will call this equilibrium B. If $\rho_1 < \rho < \rho_0$ then equilibrium B disappears and the tumor-free equilibrium is stable. If $\rho > \rho_0 = \delta_1\delta_2/\sigma_2$, then x_0 defined in (33) is negative, i.e., the first branch of $y_2(z)$ lies to the left of the y axis, so there is no equilibrium. The third equation in (25) implies $\liminf_{\tau\to\infty} z(\tau) \geq \sigma_2/\delta_2$, so using the definition of ρ_0 we see that eventually $\rho z(\tau) - \delta_1 > 0$ and it follows that $y(\tau) \to \infty$.

Stability analysis Our next goal is to complete the proof of the following Table (x means the equilibrium does not exist) by showing the result in the upper right corner:

	A	B
$\rho < \rho_1$	Unstable	Stable
$\rho_1 < \rho < \rho_0$	Stable	x
$\rho_0 < \rho$	x	x

We begin by noting that (26) implies

$$0 = \alpha(1 - \beta x) - y$$

$$\sigma_1/y = \delta_1 - \rho z$$
$$\sigma_2/z = \delta_2 - \omega_2 x.$$

Using these equalities, we can simplify the matrix in (28) to

$$L = \begin{pmatrix} -\alpha\beta x & -x & 0 \\ 0 & -\sigma_1/y & \rho y \\ \omega_2 z & 0 & -\sigma_2/z \end{pmatrix}$$

and we look at

$$\theta I - L = \begin{pmatrix} \theta + \alpha\beta x & x & 0 \\ 0 & \theta + \sigma_1/y & -\rho y \\ -\omega_2 z & 0 & \theta + \sigma_2/z \end{pmatrix}.$$

The characteristic polynomial takes the form $\theta^3 + b_1\theta^2 + b_2\theta + b_3$ where

$$b_1 = \alpha\beta x + \sigma_1/y + \sigma_2/z > 0$$
$$b_2 = \alpha\beta x\left(\frac{\sigma_1}{y} + \frac{\sigma_2}{z}\right) + \frac{\sigma_1\sigma_2}{yz} > 0$$
$$b_3 = \alpha\beta x\frac{\sigma_1\sigma_2}{yz} + \rho\omega_2 xyz > 0.$$

As the formulas show all three $b_i > 0$. By the Routh–Hurwitz condition, the equilibrium is locally stable if $b_4 \equiv b_1 b_2 - b_3 > 0$. In the example drawn in Fig. 8,

$$x_B^* = 13.26 \qquad y_B^* = 1.5923 \qquad z_B^* = 9.104.$$

Using the formula above, we find $b_1 = 0.3562$, $b_2 = 0.3127$, $b_3 = 0.008422$, so $b_4 > 0$ and the fixed point is stable. Dong et al. (2014) show that when ω_2 is increased a Hopf bifurcation can lead to a stable periodic orbit. We will ignore that here because the analysis predicts that adoptive immunotherapy, as we have formulated it, does not work. We never have a situation where the tumor-free and tumor states are both stable.

4.1 Modified DMT Model

To address the lack of bistability, we will introduce saturation into interactions with the tumor:

$$\frac{dx}{d\tau} = \alpha x(1 - \beta x) - y\frac{x}{x + \eta_1}$$
$$\frac{dy}{d\tau} = \sigma_1 - \delta_1 y + \rho yz$$
$$\frac{dz}{d\tau} = \sigma_2 - \delta_2 z + \omega_2 z\frac{x}{x + \eta_3}. \tag{34}$$

The tumor-free equilibrium is the same as for the original equation: $z_0^* = 6.9091$, $y_0^* = 0.8433$. To look for interior fixed points, we note that the last equation implies

$$z = \frac{\sigma_2}{\delta_2 - \omega_2 x/(x + \eta_3)}.$$

If $\delta_2 > \omega_2$, which holds for our concrete parameters, then $z > 0$ for all $x \geq 0$. The second equation implies

$$y = \frac{\sigma_1}{\delta_1 - \rho z} = \frac{\sigma_1}{\delta_1 - \rho\sigma_2/[\delta_2 - \omega_2 x/(x + \eta_2)]} \equiv y_2(x).$$

The last equation is messy, but it is easy to see that $y_2(x)$ is increasing in x

$$y_2(0) = \frac{\sigma_1}{\delta_1 - \rho\sigma_2/\delta_2} = y_0^* \qquad y_2(1/\beta) \approx \frac{\sigma_1}{\delta_1 - \rho\sigma_2/(\delta_2 - \omega_2)}.$$

As before for the tumor-free equilibrium to exist, we need $\delta_1 - \rho\sigma_2/\delta_2 > 0$ which is $\rho < \delta_1\delta_2/\rho = \rho_0$. If we use the concrete values and set $\rho = 0.03$ and $\omega_2 = 0.01$, then

$$y_2(0) = \frac{0.1181}{0.3473 - 6.909\rho} = 0.8433 \quad \text{and} \quad y_2(1/\beta) = \frac{.1181}{.3473 - 8.444\rho} = 1.255.$$

The first equation in (34) is

$$y_1(x) = \alpha(x + \eta_1)(1 - \beta x)$$

$y_1(1/\beta) = 0$ while $y_1(1/2\beta) > \alpha/4\beta = 204.5$ so there will be an intersection C near $x = 1/\beta$ $y_1(0) = \alpha\eta_1$, and $y_1(-\eta_1) = 0$ so:

- if $y_1(0) < y_2(0)$, then there will be an intersection producing an equilibrium B near $x = 0$. However, the picture is different than it was before. The tumor-free equilibrium A is stable because it sits above the null cline $\mathrm{d}x/\mathrm{d}\tau = 0$. The equilibrium at the intersection of the null clines is unstable, and the large tumor equilibrium will be stable.
- If $y_1(0) > y_2(0)$, then there is no intersection near $x = 0$. The tumor-free equilibrium is unstable because it sits beneath the null cline $\mathrm{d}x/\mathrm{d}\tau = 0$, and the large tumor equilibrium C will be stable with the intermediate equilibrium B unstable. This follows from the geometric reasoning in Fig. 2.

Under our concrete parameters if $\eta_1 = 0.1$, i.e., the original half-saturation level was 10^5, then we are in the case $y_1(0) < y_2(0)$. To complete our choice of parameters, we set $\eta_3 = 0.1$ also. Figure 9 shows a picture of the null clines. Figure 10 shows that if enough effector cells are given then adoptive immunotherapy is effective.

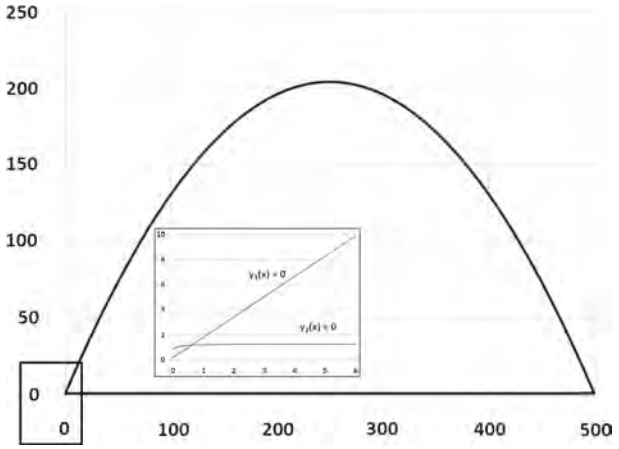

Fig. 9 A look at the null clines $\{y_1(x) = 0\}$ and $\{y_2(x) = 0\}$. The *inset* shows an enlarged picture of the situation near 0

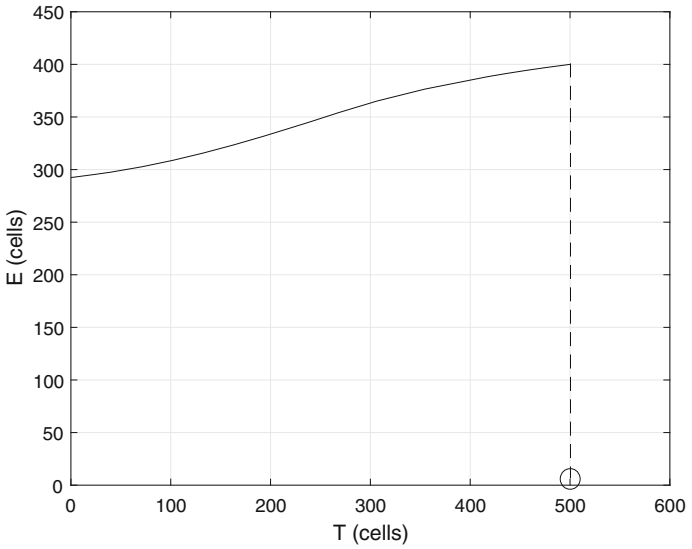

Fig. 10 Numerical solution of (34) shows that if we add 4×10^8 effector cells then we end up in the tumor-free equilibrium. This may not be clear from the picture, but once the trajectory gets near $T = 0$ when $E \approx 300$ it moves along the axis to the tumor-free fixed point at $E = 0.8437$

5 Moore and Li (ML) (2004)

Again, we have eliminated the term $\alpha_c ET/(T + g)$ from dE/dt which proposes that the tumor directly stimulates the production of effector cells:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = aT(1 - bT) - \gamma_c ET$$

$$\frac{dE}{dt} = s_e - d_e E + \alpha_n k_n N \frac{T}{T+g} - \gamma_e E T$$
$$\frac{dN}{dt} = s_n - d_n N - k_n N \frac{T}{T+g}. \tag{35}$$

Here, for consistency with other models, we use T, E, and N for variables instead of C, T_e, and T_n

Moore and Li use Gompertzian growth $r_c T \ln(T_{\max}/T)$ and take $r_c = 0.03$. To stay close to the parameters of the three previous models, we set a = 0.18 day^{-1}. They express α_n is dimensionless, T, E, and N in units of $cells/\mu l$ and use

$b = 1/300{,}000$ (cells/μl)$^{-1}$ $\gamma_c = \gamma_e$=0.005 (cells/μl)$^{-1}$ day^{-1} $g = 100$ (cells/μl)
$k_n = 0.001$ day^{-1} $\alpha_n = 0.41$ $s_e = 0$ (cells/μl) day^{-1}
$d_e = 0.06$ day^{-1} $s_n = 0.073$ (cells/μl)day^{-1} $d_n = 0.04$ day^{-1}

If we change from cells/μl to cells and recall that the human body has about 5 l of blood, then

- The value of b translates into carrying capacity of 1.5×10^{12}, and this is much larger than the others which are about 10^9, but in many human tumor growth models the carrying capacity is taken to be 10^{12}, a lethal tumor burden.
- γ_c becomes 5×10^{-9} which is smaller than the choices of KMTP: 1.107×10^7, and DMT: 10^{-7}. In addition, here $\gamma_e/\gamma_c = 1$, while in the first paper $\gamma_e/\gamma_c = 0.00311$ and in the second $\gamma_e = 0$.
- The half-saturation value g becomes 10^8, similar to the value of $g = 2.019 \times 10^7$ in KMTP and $g_1 = 2 \times 10^7$ in KP.
- The death rates $d_n = 0.04$ and $d_e = 0.06$ translate into expected lifetimes of 25 days for naive T cells and 16.66 days for effector cells, similar to previous estimates.

The value of $s_n = 0.073$ seems too small. If there is no tumor, then the number of naive cells per μl equilibrates to $s_n/d_n = 1.825$. On page 517 of Moore and Li (2004), the authors quote Mohri (2001) to argue that the CD4+ T cells in healthy individuals is approximately 1080 cells/μl. For this to hold, we need $s_n = 43.2$. They also quote a figure of 600 cells/μl for CD8+. For this to hold we need $s_e = 36$. It also seems that the value of $\alpha_n = 0.41$ is too low. On page 517, the authors quote Janeway et al. (2001) as saying that an activated T cell proliferates for approximately 7 days producing 1000 daughter cells. For this reason, we will take $\alpha_n = 100$ cells generated per day.

Based on the discussion above, we will use the following values in our concrete example

$b = 1/30{,}000$ (cells/μl)$^{-1}$ $\gamma_c = 0.005$ (cells/μl)$^{-1}$ day^{-1}
γ_e=0.0001 (cells/μl)$^{-1}$ day^{-1}
$g = 100$ (cells/μl) $k_n = 0.001$ day^{-1} $\alpha_n = 100$ $s_e = 36$ (cells/μl) day^{-1}
$d_e = 0.06$ day^{-1} $s_n = 43.2$ (cells/μl)day^{-1} $d_n = 0.04$ day^{-1} (36)

Theorem 3 *The tumor-free equilibrium has* $T_0^* = 0$, $E_0^* = s_e/d_e$, *and* $N_0^* = s_n/d_n$. *It is stable when*

$$a < \gamma_c E_0^* \tag{37}$$

Remark 3 For our concrete values, $E_0^* = 600$ and $N_0^* = 1080$.

Proof If $a > \gamma_c E_0^*$, then a small tumor will grow. To show that it is stable if (37) holds, we note that linearizing the system gives

$$L = \begin{pmatrix} a(1-bT) - abT - \gamma_c E & -\gamma_c T & 0 \\ -\gamma_e E + g\alpha_n k_n N/(T+g)^2 & -d_e - \gamma_e T & \alpha_n k_n T/(T+g) \\ -g k_n N/(T+g)^2 & 0 & -d_n - k_n T/(T+g) \end{pmatrix}. \tag{38}$$

When $T = 0$, we have

$$\theta I - L = \begin{pmatrix} \theta - a + \gamma_c E & 0 & 0 \\ \gamma_e E - \alpha_n k_n N/g & \theta + d_e & 0 \\ k_n N/g & 0 & \theta + d_n \end{pmatrix} \tag{39}$$

so the characteristic polynomial is

$$(\theta - a + \gamma_c E)(\theta + d_e)(\theta + d_n) = 0.$$

Under our assumption (37), all three eigenvalues are negative, so the tumor-free equilibrium is stable. □

To find other equilibria, we note that $\mathrm{d}N/\mathrm{d}t = 0$ implies

$$N = \frac{s_n}{d_n + k_n T/(T+g)}. \tag{40}$$

Using this in the one term in the second equation that contains N, the system becomes

$$\begin{aligned} \frac{\mathrm{d}T}{\mathrm{d}t} &= aT(1-bT) - \gamma_c ET \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= s_e - d_e E + \frac{\alpha_n k_n s_n}{d_n + k_n T/(T+g)} \cdot \frac{T}{T+g} - \gamma_e ET. \end{aligned}$$

The right-hand sides are 0 when

$$E = f(T) = a(1-bT)/\gamma_c \tag{41}$$

$$E = g(T) = \left(s_e + \frac{\alpha_n k_n s_n T/(T+g)}{d_n + k_n T/(T+g)} \right) \cdot \frac{1}{d_e + \gamma_e T}. \tag{42}$$

To compute solutions, it is useful to first consider our concrete example. When T is large $T/(T+g_i) \approx 1$ so the second null cline is

$$E \approx \left(s_e + \frac{\alpha_n k_n s_n}{d_n + k_n}\right) \frac{1}{d_e + \gamma_e T} = \frac{141.37}{0.06 + 0.001T}. \tag{43}$$

The first null cline is $36(1 - bT)$ where $b = 1/30{,}000$ so we want to solve

$$0.06 + 0.001T - 0.06bT - 0.001bT^2 = \frac{141.37}{36} = 3.93.$$

Multiplying by 1000 and rearranging this becomes $bT^2 - 0.998T + 3870 = 0$. The solutions are

$$\frac{0.998 \pm \sqrt{(0.998)^2 - 4(3870)/30{,}000}}{2b} = \frac{0.152}{b}, \qquad \frac{0.8454}{b}.$$

Using (43) and (40), we find

$$\begin{aligned} T_1^* = 4,560 \qquad E_1^* = 30.6 \qquad N_1^* \approx \frac{s_n}{d_n + k_n} = 1053.65 \\ T_2^* = 25,362 \qquad E_2^* = 5.56 \qquad N_2^* \approx \frac{s_n}{d_n + k_n} = 1053.65. \end{aligned}$$

These are equilibria B and C in Fig. 11.

Stability analysis The geometric approach of Fig. 2 shows that B is unstable in the $T-E$ plane. Using (38) with the equations in (35), we see that in general the linearization is

$$L = \begin{pmatrix} -abT & -\gamma_c T & 0 \\ -\gamma_e E + \alpha_n k_n N \frac{g}{(T+g)^2} + \left(-s_e - \alpha_n k_n N \frac{T}{T+g}\right)/E & \alpha_n k_n \frac{T}{T+g} \\ -k_n N \frac{g}{(T+g)^2} & 0 & -s_n/N \end{pmatrix}.$$

Since $g = 100$, when $T = 25,362$ we have

$$\theta I - L \approx \begin{pmatrix} \theta + abT & \gamma_c T & 0 \\ \gamma_e E & \theta + (s_e + \alpha_n k_n N)/E & \alpha_n k_n \\ 0 & 0 & \theta s_n/N \end{pmatrix}$$

so the characteristic polynomial is $\theta^3 + b_1\theta^2 + b_2\theta + b_3$ with

$$\begin{aligned} b_1 &= abT + (s_e + \alpha_n k_n N)/E + s_n/N > 0 \\ b_2 &= \Delta + (s_e + \alpha_n k_n N)s_n/EN + abT s_n/N \\ b_3 &= \Delta s_n/N \end{aligned}$$

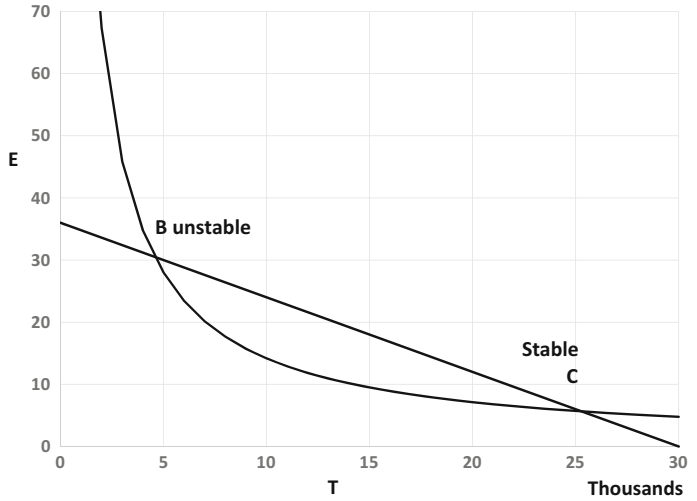

Fig. 11 Null clines for the Moore–Li model with parameters given by (36). The tumor-free equilibrium A with $E_0 = 600$ is off the top of the graph

where $\Delta = abT(s_e + \alpha_n k_n N)/E - \gamma_c T \gamma_e E$. To show that b_2, b_3, and $b_1 b_2 - b_3 > 0$ it is enough to check that $\Delta > 0$.

Lemma 1 $\Delta = 0$ *occurs when the two equilibria* $B = C$.

Proof Geometrically, this is obvious because it is where the determinant b_3 vanishes. Using (40) and (42), we see that

$$(s_e + \alpha_n k_n N)/E = d_e + \gamma_e T.$$

The first equation in (35) implies

$$\gamma_c T \gamma_e E = \gamma_e a T(1 - bT)$$

so we have

$$\Delta = aT[b(d_e + \gamma_e T) - \gamma_e(1 - bT)].$$

Our quadratic equation has the form

$$(d_e + \gamma_e T)(1 - bT) = K$$

for some constant. The derivative of the left-hand side is

$$\gamma_e(1 - bT) - b(d_e + \gamma_e T).$$

We have a double root when the derivative is 0, which is the same as $\Delta = 0$. □

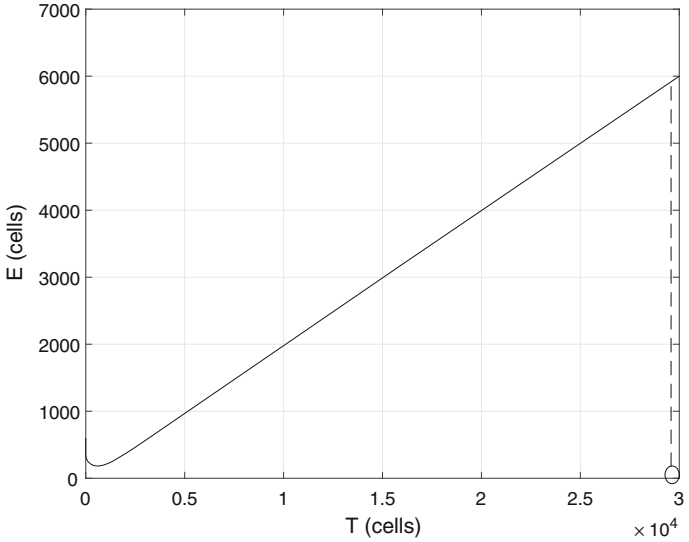

Fig. 12 This numerical solution of the ODE in (35) with parameters given in (36) shows that if the patient is in the large tumor equilibrium and we add 6×10^9 effector cells, then we end up in the tumor-free equilibrium, which is at 600 on the E axis

Adoptive immunotherapy Figure 12 shows that in our concrete example adoptive immunotherapy is successful.

6 Conclusions

Here, we have explored four models of the interaction of tumors with the immune system. In the process, we have established a structure unifying the models in order to compare and contrast their behavior. Kuznetsov et al. (1994) used a simple model with only tumor and effector cells. The other three systems introduced a third variable that stimulates the production of effector cells. Kirschner and Panetta (1998) used interleukin, Dong et al. (2014) helper cells, and Moore and Li (2004) naive T cells. Based on our analysis of the models, we modified the DMT model to introduce saturating interactions between the tumor cells and the two other species, and we made substantial changes to the parameters of ML.

Once this was done, the four models had similar qualitative behavior: there are two stable equilibria, a "tumor-free" state (in which there is no tumor or a very small one) and a large tumor. For each model, we showed that if adoptive immunotherapy was done as described in Grupp (2013), and if enough effector cells were added, then the system could be moved from the large tumor state to the tumor-free condition. While all four models predict success, the details show considerable differences. The number of effector cells needed ranged from 2×10^7 to 6×10^9. In addition, the way the system moved from one equilibrium to the other was different. In DMT and ML, the effector cell concentration never exceeded the initial value. In KMTP, it was never

more than 1.5 times the initial dose. However, in KP there was a cytokine storm after treatment that increased the initial dose of 2×10^7 to six times the initial value before it crashed back to a low level.

We have mathematically shown that in four different approaches to modeling the immune system, adoptive immunotherapy can work as a successful cancer treatment. However, the observations in the last paragraph show that in order to develop an accurate model for assessing treatment, we need to choose the correct way to model the immune system and find the right parameters for modeling tumor immunotherapy in humans.

Acknowledgements Funding was provided by National Science Foundation (Grant No. DMS 1505215).

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