3-1996

# Effects of Vascularization on Lymphocyte/Tumor Cell Dynamics: Qualitative Features

J. A. Adam
*Old Dominion University*, jadam@odu.edu



## Original Publication Citation

Adam, J. A. (1996). Effects of vascularization on lymphocyte/tumor cell dynamics: Qualitative features. *Mathematical and Computer Modelling*, *23*(6), 1-10. doi:10.1016/0895-7177(96)00016-7

Pergamon

*Mathl. Comput. Modelling* Vol. 23, No. 6, pp. 1–10, 1996

0895-7177/96 $15.00 + 0.00

S0895-7177(96)00016-7

# Effects of Vascularization on Lymphocyte/Tumor Cell Dynamics: Qualitative Features

J. A. ADAM
Department of Mathematics and Statistics, Old Dominion University
Norfolk, VA 23529, U.S.A.
adam@math.odu.edu

**Abstract**—By adapting a pre-existing model to include the effects of vascularization within a tumor or multicell spheroid, a predator-prey system describing the cell populations of a solid tumor and reactive lymphocytes is formulated. The paper serves as a review of the minimal deterministic approach to tumor-host immune system interactions while examining, in a qualitative manner, the modifications to the dynamics induced by a simple representation of the vascularized tumor. In addition, the possibility of limit-cycle behavior is studied by regarding each of six parameters present in the model as a bifurcation parameter. Thus, in principle, well-defined and periodic oscillations in both lymphocyte and tumor cell populations may occur under appropriate circumstances; whether or not such oscillations are sustainable by the host, and their stability, amplitude and period depend on aquisition of more quantitative information concerning the relevant parameter ranges.

**Keywords**—Vascularization, Tumor, Lymphocyte, Hopf bifurcation, Limit cycles.

## 1. INTRODUCTION

In [1], a deterministic predator-prey model was presented which described the cell population dynamics of a solid tumor in the presence of a specifically reactive lymphocyte population stimulated by and antagonistic to the tumor. In this relatively simple model of immune response, the lymphocytes produced by the host are regarded as predators and the tumor cells are regarded as prey. Since the growth kinetics of multicell spheroids are similar to *in vivo* tumors, the model here may apply to the early vascular stage of growth of these spheroids when inserted into laboratory mammals. In the present paper the basic model is modified to include, in a primitive manner, the effects of vascularization. The resulting nonlinear system of equations contains six parameters, each of which may be regarded as a bifurcation parameter when the remainder are held constant. Formal expressions are given for conditions under which Hopf bifurcation may occur, and qualitative conclusions are drawn for tumor-host interaction.

A common tool for studying the existence of stable equilibrium points and/or limit cycles in predator-prey systems is Kolmogorov's theorem [2,3]. The theorem is usually stated for populations $x(t)$ and $y(t)$ in the autonomous form

$$\frac{dx}{dt} = x\,f(x,y),$$
$$\frac{dy}{dt} = y\,g(x,y),$$

with $f$ and $g$ continuously differentiable functions of their arguments, and subject to nine further conditions [3]. However, the system arising in this paper (see equations (10) and (11)) fails to

satisfy several of these conditions, rendering the theorem inapplicable. Thus, a more detailed investigation of the present model is necessary, leading, as noted above, to model-specific conditions for Hopf bifurcation.

The paper is arranged as follows. Section 2 describes the general model by setting out explicitly the assumptions inherent in the model and formulating the governing equations. A bifurcation analysis is presented in Section 3, followed by discussion of the qualitative features of the model in Section 4. An Appendix contains a brief discussion of those aspects of Hopf bifurcation germane to the present study.

## 2. THE GENERAL MODEL

In what follows (see [1,4]):

$L$ = number of free lymphocytes on the tumor surface,
$C_f$ = number of cancer cells within the spherical tumor and on its surface that are not bound by a lymphocyte,
$C_0$ = number of cancer cells on the tumor surface that are not bound by lymphocytes,
$C$ = total number of cancer cells comprising the tumor,
$C_s$ = total number of cancer cells (bound and unbound) on the cancer surface,
$L_c$ = maximum number of lymphocytes that can be attained (saturation level).

Since within the tumor no cancer cell is bound by a lymphocyte, the following relationship exists:

$$C = C_f - C_0 + C_s. \tag{1}$$

The assumptions inherent in this model differ from those in [1] only insofar as additional terms representing the effects of vascularization on growth rates of free lymphocytes and cancer cells are concerned; this is, however, a significant difference as it enables our model to account (in a phenomenological manner) for modifications of the population dynamics due to enhanced nutrient supply within the tumor.

### 2.1. Assumptions

(1) Only cells on the tumor surface are vulnerable to attack.
(2) The lymphocyte death rate is a first-order process, with rate constant $\lambda_1$.
(3) The growth rate of surface lymphocytes is given by $aC_0f(L)$, where $a$ is a constant. Specifically,
$$f(L) = L\left(1 - \frac{L}{L_c}\right). \tag{2}$$
(4) In the absence of lymphocytes, the growth rate of cancer cells is a first-order process with rate constant $\lambda_2$.
(5) The elimination rate of cancer cells is proportional (with constant of proportionality $b$) to the product of the number of free lymphocytes and unbound cancer cells on the tumor surface.
(6) The tumor remains spherical at all times.
(7) There are no differences in cell numbers per unit volume within the tumor.
(8) There is an equilibrium relation between the free and bound lymphocytes.
(9) The rate of change of the free lymphocyte population is reduced by an amount proportional to the surface area of the tumor that is penetrated by the vascular network.
(10) The rate of change of the total number of cancer cells is enhanced by an amount proportional to the volume of the tumor that is occupied by the vascular network.

In these last two assumptions we further posit that the specified surface area/volume penetration is proportional to the tumor surface area/volume, respectively. This can be modified somewhat, but is not unreasonable biologically and certainly provides some additional mathematical simplification.

## 2.2. Governing Equations

We first note that assumptions (6) and (7) imply that

$$C_s = gC^{2/3} \tag{3}$$

where $g$ is a positive constant. Assumption (8) implies that

$$C_s = C_0 = KC_0L, \tag{4}$$

in terms of the equilibrium constant $K$ for lymphocyte-cancer cell interaction. Thus, it follows that

$$C_0 = \frac{gC^{2/3}}{1+KL}. \tag{5}$$

From (1), therefore,

$$C_f = C - \frac{gKLC^{2/3}}{1+KL}. \tag{6}$$

We are now in a position to write down the complete pair of predator-prey equations for the system, namely:

$$\frac{dL}{dt} = -\lambda_1 L + aC_0\left(1 - \frac{L}{L_c}\right) - \hat{\beta}_1 C^{2/3}, \tag{7}$$

$$\frac{dC}{dt} = \lambda_2\left(C - \frac{gC^{2/3}KL}{1+KL}\right) - \frac{bgKLC^{2/3}}{1+KL} + \beta_2 C, \tag{8}$$

where $\hat{\beta}_1$ and $\beta_2$ are constants representing the "efficiency" of penetration of the tumor surface area and volume, respectively. In terms of the new variables and parameters

$$\begin{aligned} x &= KL, & y &= KC, \\ x_c &= KL_c, & \alpha_1 &= agK^{-2/3}, \\ \alpha_2 &= gk^{1/3}\left(\lambda_2 + bK^{-1}\right), & \beta_1 &= \hat{\beta}_1 K^{1/3}, \end{aligned} \tag{9}$$

these equations become, respectively,

$$\frac{dx}{dt} = -\lambda_1 x + y^{2/3}\left\{\frac{\alpha_1 x\left(1-(x/x_c)\right)}{1+x} - \beta_1\right\} \equiv F(x,y), \tag{10}$$

$$\frac{dy}{dt} = (\lambda_2 + \beta_2)\, y - \frac{\alpha_2 x y^{2/3}}{1+x} \equiv G(x,y). \tag{11}$$

The domain restrictions are $0 \le x \le x_c$; $y \ge 0$, and $\alpha_1 > 0$, $\alpha_2 > 0$, $\beta_1 \ge 0$, $\beta_2 \ge 0$, $\lambda_1 > 0$, $\lambda_2 > 0$. Critical or equilibrium points occur when

$$F(x,y) = 0 = G(x,y). \tag{12}$$

Obviously $(0,0)$ is such a point, and is unstable (see the discussion below). If $x$ and $y$ are both nonzero, then eliminating $y$ between the equations (12) yields the following expression for the $x$-location of remaining critical points:

$$k_1 = \frac{x^2\left(1-(x/x_c)\right)}{(1+x)^3} - \frac{k_2 x}{(1+x)^2} \equiv \psi\left(x_c, k_2; x\right), \tag{13}$$

where

$$k_1 = \frac{\lambda_1 (\lambda_2 + \beta_2)^2}{\alpha_1 \alpha_2^2}, \tag{14}$$

and

$$k_2 = \frac{\beta_1}{\alpha_1}. \tag{15}$$

Qualitatively, we may understand the solutions of (13) by examining the intersection of the horizontal line $y = k_1$ with the graph of $y = \psi(x)$. In Figure 1, $\psi(x)$ is illustrated for several values of $k_2$, including that corresponding to no vascularization ($k_2 = 0$). The maximum value of $\psi(x)$ occurs at

$$x_m = \alpha^{-1} \left(1 + \sqrt{1 - \alpha k_2}\right), \tag{16}$$

where $\alpha = 1 + (3/x_c) - k_2$.

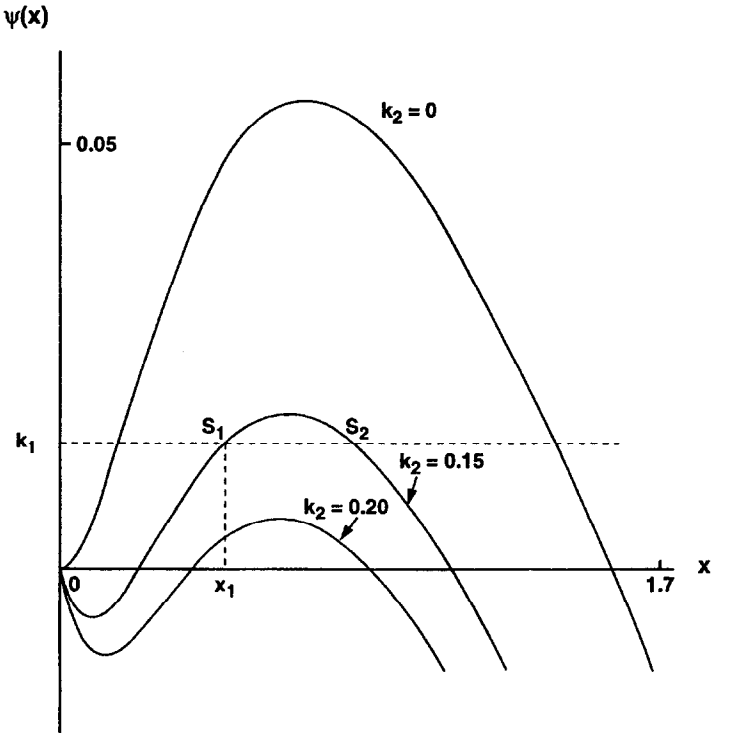


Figure 1. The function $\psi(x_c, k_2; x)$ for various values of $k_2$; the intersections with $\psi = k_1$ define the equilibrium points $S_1(x_1, y_1)$ and $S_2(x_2, y_2)$. In this figure, $x_c = 1.5$.

Clearly a restriction on $k_2$ for $x_m$ to be real is that $\alpha k_2 \leq 1$. The expression for $\psi(x_m)$ is complicated and we do not write it here; it is sufficient for our purposes to make several observations. First, in the absence of vascularization ($k_2 = 0$)

$$x_m = \frac{2x_c}{x_c + 3} \quad \text{and} \quad \psi(x_m) = \frac{4x_c^2}{27\,(1 + x_c)^2}. \tag{17}$$

Second, as $k_2$ increases away from zero, $x_m$ decreases, as of course does $\psi(x_m)$. Eventually there is a critical value of $k_2$ above which $\psi(x) \leq 0$ for all $x \in [0, x_c]$, again placing a constraint on acceptable values of this parameter. Third, it is clear that increasing $\beta_1$ and $\beta_2$ (with other parameters constant) will increasingly separate the two graphs whose intersection we seek.

There are zero, one or two points of intersection depending on whether $k_1$ exceeds, equals or is exceeded by $\psi(x_m)$, respectively. The topological dynamics of these critical points remain the

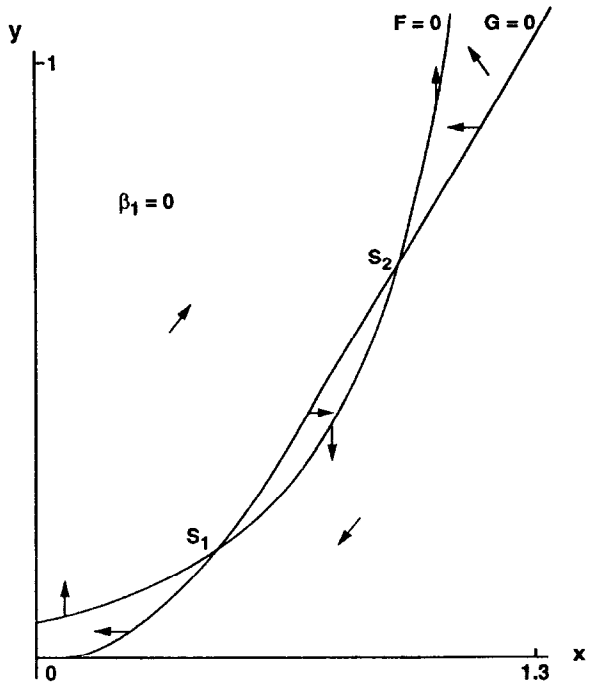


Figure 2. Graphs of $F(x,y) = 0$, $G(x,y) = 0$ for $\beta_1 = 0$ (avascular case), $x_c = 1.5$. Their intersection defines the equilibrium points $S_1$ and $S_2$ of Figure 1. The arrows indicate the direction of flow of local trajectories.

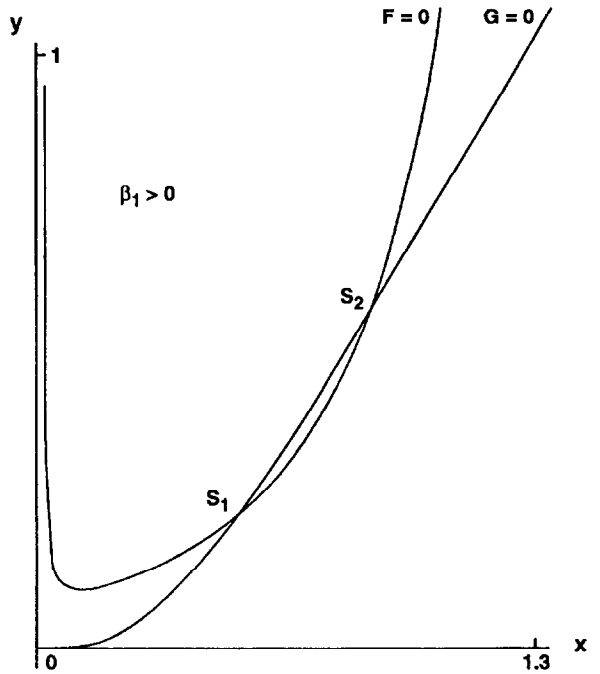


Figure 3. As Figure 2, but with the vascularization parameter $\beta_1 > 0$. In both this figure and Figure 2 there is a horizontal asymptote for $G$ of $(\alpha_2/(\lambda_2 + \beta_2))^3$, not attained here.

same, it is readily seen, in the $k_2 \neq 0$ case as in the $k_2 = 0$ case (though of course the critical points are functions of all the parameters in general). Thus, when $k_1 > \psi(x_m)$ the only critical point is $(0,0)$: it is unstable; for any initial nonzero value of $(x,y)$ the trajectories approach $(x_c, \infty)$, i.e., uncontrollable tumor growth.

If $k_1 = \psi(x_m)$ then the second critical point is $(x_m, \psi(x_m))$. Here again, this is unstable with trajectories approaching $(x_c, \infty)$; for a more detailed discussion of the trajectories, see [1]. Finally, if $k_1 < \psi(x_m)$ there are two points of intersection, $S_1(x_1, y_1)$ and $S_2(x_2, y_2)$; $S_2$ is a saddle point, and therefore, unstable, but $S_1$ may be a center, node or focus and either stable or unstable. It is the point $S_1$ that is the focus of our attention in this paper. Figures 2 and 3 show the intersection of $F(x, y) = 0$ and $G(x, y) = 0$ in this case.

Before proceeding with the analysis of equilibrium point $S_1$, we note that increasing $\lambda_1, \lambda_2, \beta_1$ or $\beta_2$ or decreasing $\alpha_1$ or $\alpha_2$ favors tumor survival (i.e., by tending to render $S_1$ nonexistent). Decreasing $\lambda_1$, $\lambda_2$, $\beta_1$ or $\beta_2$, or increasing $\alpha_1$ or $\alpha_2$ may favor a stationary state of oscillation of the system (i.e., limit cycle). In the expression for $k_1$ we also note that variations in $\alpha_2, \lambda_2$ or $\beta_2$ may have more significant influence on the dynamics of the system than comparable variations in $\lambda_1$ or $\alpha_1$.

## 3. BIFURCATION ANALYSIS

If $(x_1, y_1)$ is the equilibrium point of interest, then a linearization about this equilibrium

$$x = x_1 + u, \qquad y = y_1 + v$$

yields, in particular,

$$\frac{d^2u}{dt^2} - \mathrm{Tr}(J)\frac{du}{dt} + \mathrm{Det}(J)u = 0, \tag{18}$$

where $J$ is the Jacobian matrix

$$J(x_1, y_1) = \begin{pmatrix} \dfrac{\partial F}{\partial x} & \dfrac{\partial F}{\partial y} \\ \dfrac{\partial G}{\partial x} & \dfrac{\partial G}{\partial y} \end{pmatrix}, \tag{19}$$

and the partial derivatives are evaluated at $(x_1, y_1)$. Specifically,

$$\frac{\partial F}{\partial x} = -\lambda_1 + \alpha_1 y_1^{2/3}\left[\frac{1 - (2x_1/x_c) - (x_1^2/x_c)}{(1 + x_1)^2}\right], \tag{20}$$

$$\frac{\partial F}{\partial y} = \frac{2}{3}y_1^{-1/3}\left[\frac{\alpha_1(1 - (x_1/x_c))\,x}{1 + x_1} - \beta_1\right], \tag{21}$$

$$\frac{\partial G}{\partial x} = \frac{-\alpha_2 y_1^{2/3}}{(1 + x_1)^2}, \tag{22}$$

$$\frac{\partial G}{\partial y} = \lambda_2 + \beta_2 - \frac{(2/3)\alpha_2 y_1^{-1/3} x_1}{1 + x_1}. \tag{23}$$

The explicit dependence on $y_1$ may be removed using the equilibrium equations

$$F(x_1, y_1) = 0; \qquad G(x_1, y_1) = 0. \tag{24}$$

After considerable algebra we find,

$$-\mathrm{Tr}(J) = \sigma(x_1)$$

$$= \lambda_1\left\{\frac{x_1^2(1 + (1/x_c)) - k_2(1 + x_1)^2}{x_1(1 + x_1)(1 - (x_1/x_c)) - k_1(1 + x_1)^2}\right\} - \frac{1}{3}(\lambda_2 + \beta_2), \tag{25}$$

$$\mathrm{Det}(J) = \tau(x_1)$$

$$= \frac{\alpha_1(\lambda_2 + \beta_2)y_1^{2/3}}{(1 + x_1)^2}\left[\frac{x_1}{3x_c}\left(\frac{2x_c}{x_1} - x_c - 3\right) + \frac{k_2}{3}\left(1 + \frac{1}{x_1}\right)\left(1 + x_1 - \frac{2x_1}{x_c}\right)\right]. \tag{26}$$

Again, if required, the dependence on $y_1$ may be eliminated using $F(x_1, y_1) = 0$ or $G(x_1, y_1) = 0$. The characteristic equation corresponding to (18) is

$$\lambda^2 + \sigma(x_1)\lambda + \tau(x_1) = 0, \tag{27}$$

where $\lambda$ is an eigenvalue of the matrix $J(x_1, y_1)$.

When $k_2 = 0$, the maximum value of $\psi(x_c; x)$ occurs at $x_m = (2x_c/(x_c + 3))$, from which it follows that $\tau(x_1) > 0$ when $k_2 = 0$. When $k_2 \neq 0$, a useful analytic expression for the location of the maximum value of $\psi$ is not readily available, but it can be shown that $x_m$ moves to the left as $k_2$ increases from zero. Thus, the location of the equilibrium point $(x_1, y_1)$ is still such that $(2x_c/x_1) - x_c - 3 > 0$. It follows that a sufficient condition for $\tau(x_1) > 0$ is that

$$x_c\left(1 + \frac{1}{x_1}\right) > 2\,. \tag{28}$$

When $\tau(x_1) > 0$, then there exist two pure imaginary eigenvalues

$$\lambda = \pm i\omega = \pm i\sqrt{\tau(x_1)}, \tag{29}$$

whenever

$$\sigma(x_1) = 0, \tag{30}$$

which we rewrite as

$$\frac{\lambda_2 + \beta_2}{3\lambda_1} = \frac{x_1^2(1 + (1/x_c)) - k_2(1 + x_1)^2}{x_1(1 + x_1)(1 - (x_1/x_c)) - k_2(1 + x_1)^2}\,. \tag{31}$$

We are at liberty to choose any element of the six element set $\{\lambda_1, (\lambda_2 + \beta_2), \alpha_1, \alpha_2, \beta_1, x_c^{-1}\}$ as the bifurcation parameter. We identify the elements in the order shown as $e_i$, $i = 1, \ldots 6$, respectively. Each $e_i$ can be expressed in terms of the remaining $e_i$ via (30), and that expression defines $e_i(c)$, the critical value for pure imaginary eigenvalues to occur.

It follows from differentiating equation (27) with respect to $e_i$ that

$$2\lambda\frac{\partial\lambda}{\partial e_i} + \sigma\frac{\partial\lambda}{\partial e_i} + \lambda\left\{\frac{\partial\sigma}{\partial e_i} + \frac{\partial\sigma}{\partial x_1}\frac{\partial x_1}{\partial e_i}\right\} + \left\{\frac{\partial\tau}{\partial e_i} + \frac{\partial\tau}{\partial x_1}\frac{\partial x_1}{\partial e_i}\right\} = 0, \tag{32}$$

where we have noted that $x_1$ is in general an implicit function of the $e_i$ (see, e.g., equation (13)). In principle, from expressions (13), (25) and (26) we may determine all the derivatives present in (32): note from (13) that $x_1$ satisfies the cubic equation

$$\left(k_1 + x_c^{-1}\right)x_1^3 + (3k_1 + k_2 - 1)\,x_1^2 + (k_2 + 3k_1)\,x_1 + k_1 = 0\,. \tag{33}$$

From this we may obtain, using Cardan's solution, a specific functional form for $x_1$ (the smallest positive root) in terms of the $e_i$ (expressed through $k_1$ and $k_2$). We may also use (33) to determine $\frac{\partial x_1}{\partial e_i}$ for each $e_i$ in an obvious fashion, through we do not do so here.

At $e_i = e_i(c)$, we find from (32) that

$$\left.\frac{\partial\lambda}{\partial e_i}\right|_{e_i(c)} = -\frac{1}{2}\left\{\frac{\partial\sigma}{\partial e_i} + \frac{\partial\sigma}{\partial x_1}\frac{\partial x_1}{\partial e_i}\right\}\Bigg|_{e_i(c)} \pm \frac{i}{2\omega}\left\{\frac{\partial\tau}{\partial e_i} + \frac{\partial\tau}{\partial x_1}\frac{\partial x_1}{\partial e_i}\right\}\Bigg|_{e_i(c)}. \tag{34}$$

The required transversality condition (see [5–9] and the Appendix) is

$$\mathrm{Re}\left(\frac{\partial\lambda}{\partial e_i}\right)\Bigg|_{e_i(c)} \neq 0\,. \tag{35}$$

As noted above, for each $e_i$, the corresponding $e_i(c)$ is found from the condition (30). Since $x_1$ is a function of the $e_i$, this requires considerable algebra or numerical work, and will be considered elsewhere. Nevertheless, it is clear that in general, condition (35) will be satisfied for each $e_i$, the exceptions occurring for specific combinations of the $e_i$ (a set of measure zero). Since at this time it is not possible to do other than estimate the numerical values for the $e_i$, we are in a position to draw only qualitative conclusions. Nevertheless, even a primitive model such as this can provide insight into some of the more subtle aspects of the effects of vascularization on the immune response to tumor growth, as discussed below.

# 4. DISCUSSION

As noted in Section 2, the ultimate behavior of the system studied here is determined by whether or not in expression (13), $k_1$ is greater than, equal to or less than the maximum value of $\psi(x_c, k_2; x)$, i.e., $\psi(x_m)$, where $x_m$ is given by equation (16). Phase plane analysis indicates that in the first two situations all trajectories move towards $(x_c\,, \infty)$, i.e., unbounded tumor cell proliferation. Reasons why this may occur are most easily seen from the expressions (14) and (15) for $k_1$ and $k_2$, respectively, in conjunction with Figure 1. *Increasing*

(i) the lymphocyte death rate $\lambda_1$,
(ii) the growth rate of cancer cells $\lambda_2$,
(iii) the degree of vascularization of the tumor ($\beta_1$ and $\beta_2$),

or *decreasing*

(iv) the growth rate of surface lymphocytes $a$, (and hence, $\alpha_1$) or
(v) the elimination rate of cancer cells $b$, (and hence, $\alpha_2$)

tend to increase $k_1$ and $k_2$, moving the system towards $(x_c, \infty)$. On the other hand, *decreasing* (i)–(iii) and *increasing* (iv)–(v) reduce $k_1$ and $k_2$, rendering it more likely that the condition $k_1 < \psi(x_m)$ will occur. Indeed, parameter ranges exist for which this will occur, and in these regimes the possibility exists for periodic oscillations of lymphocyte and tumor cell populations to occur in the form of limit cycle behavior.

Clearly $k_2$ is more sensitive to variations in the quantities $(\lambda_2 + \beta_2)$ and $\alpha_2$ than to variations in $\lambda_1$ and $\alpha_1$ (changing the latter only affects the tumor indirectly; changing the former affects the tumor directly). As pointed out in [1], should oscillations occur, their significance will depend on their location in the phase plane and upon their amplitude. If they are such that the host can tolerate the maximum levels of tumor and lymphocyte cells (i.e., the amplitude is small enough), and the limit cycle is stable, then survival of both populations is possible (see references [5–9] for analytic details of limit-cycle stability). The periods of such oscillations will determine how realistic such models might be for studies of tumor remission, for example.

Although not explicitly identified here, the possibility exists for anomalous behavior to occur. This was first noted in [1] and the incorporation of terms corresponding to the vascularization of the tumor will not change the qualitative nature of the phenomenon. Examples of such anomalous behavior are uncontrolled tumor growth (ultimately) arising from a *reduction* in the number of tumor cells or an *increase* in the number of lymphocytes. This can occur according to the model when the limit cycle is such that a perturbation to the trajectory moves it out of one region into another which has $(x_c, \infty)$ as the inexorable limit. Such perturbations of course, being external to the system, may correspond to surgery, with consequent aggressive tumor cell proliferation, or therapy of some kind designed to reduce the tumor cell population. Infusion of lymphocytes in some treatment modalities may also have this highly undesirable consequence. Indeed, as early as 1971, Prehn [10] found that an increase in the number of lymphocytes could enhance the likelihood of tumor survival under certain circumstances.

What has been shown in this paper is that although the presence of vascularization in general enhances the likelihood of tumor survival, as one would expect, the possibility exists that Hopf bifurcation about a steady state can still occur in a variety of different contexts: in principle each of the six parameters $\{\lambda_1, \lambda_2 + \beta_2, \alpha_1, \alpha_2, \beta_1, x_c^{-1}\}$ can be a bifurcation parameter, and variations in any of these may significantly effect the nonlinear dynamics of the populations considered here. A detailed numerical study in the neighborhood of these bifurcations is clearly desirable, but the experimental data does not provide enough information on parameter ranges to justify this at present. However, some related parameter information is available (see references in [11]), and a similar approach with a smaller parameter space would be to consider bifurcation phenomena using the set $\{k_1, k_2, x_c^{-1}\}$.

Further developments are possible along other lines. In [1], a modification of the basic model allowed for lymphocytes to enter the system at a steady rate, by adding a constant source term

$\lambda_1 x_0$ to the right hand side of equation (10). The dynamics, even in the avascular case, are then much more complicated because there may be more equilibrium points. In a sequel to that paper [12], the authors introduced a delay in the formation of killer lymphocytes. The introduction of a second stage allows tumor development from even a single cell (i.e., "de novo" tumor growth). Thus, the lymphocytes are not active as soon as they are produced, but mature at a fixed rate. In addition, the saturation term for lymphocytes was represented by $\exp(-L/L_c)$ rather than $(1-L/L_c)$. Finally, noting that a tumor is frequently vascularized (as assumed here), assumption (1) was modified to include all tumor cells, not merely those on the surface, because lymphocytes may now have access to the entire tumor volume. However, the presence of a vascular network will undoubtedly enhance the proliferation rate of tumor cells also (represented by the term $\beta_2 y$ in (11) in the present model). Furthermore, the present model also contains the above modified assumption insofar as it corresponds to a reduction of the term $\lambda_1$ in equation (10).

More recently, an entirely different approach to the dynamics of tumor-host immune interactions has been formulated, based on the modeling of cellular interactions after the fashion of nonlinear statistical mechanics [13]. The philosophy behind this method of modeling is entirely complementary to the deterministic type of model adopted here, and it would be of interest to pursue the interconnections between the two approaches, particularly in the light of [13, Section 5], and related comments made in [14].

# APPENDIX
# HOPF BIFURCATION

Adapting the approach of [4] to the present problem we define

$$\frac{d\underline{x}}{dt} = \underline{f}\,(\underline{x}; e_i)\,, \qquad i = 1,2,3,4,5,6 \tag{A.1}$$

to be a real two-dimensional system of differential equations where $\underline{x} = (x,y)^t$; $\underline{f}(\underline{x}; e_i) = (F(x,y;e_i)\,,\, G(x,y,e_i))^t$ is a vector-valued function, each component of which is analytic in $\underline{x}$ and each $e_i$ for $\underline{x}$ in some domain $\mathcal{D}$ of the Cartesian plane (first quadrant), and the $e_i$ are six bounded parameters. We identify the point $\underline{x}_i = (x_1, y_1)^t \in \mathcal{D}$ as a critical or equilibrium point of (A.1) for each $e_i(c)$, i.e.,

$$\underline{f}\,(\underline{x}_1; e_i(c)) = \underline{0} \tag{A.2}$$

for each $e_i$ (the remaining four parameters being held fixed). If none of the eigenvalues of the matrix

$$J\,(\underline{x}_i; e_i(c))$$

is zero, there is, by continuity, a unique equilibrium point $\underline{x}(e_i)$ in a suitable $\epsilon$-neighborhood of $\underline{x} = \underline{x}_1(e_i(c))$ for every sufficiently small $|e_i|$, $\underline{x}(e_i)$ being analytic at $e_i = e_i(c)$.

Then we may state that aspect of the Hopf bifurcation theorem required for the purposes of this paper.

THEOREM. *Assume the following conditions hold for the system (A.1).*

(i) *The function $\underline{f}$ is analytic in an $\epsilon$-neighborhood of $(\underline{x}, e_i) = (\underline{x}_1, e_i(c))$.*

(ii) *The matrix $J(\underline{x}_1, e_i(c))$ has exactly two nonzero pure imaginary eigenvalues, $\pm i\omega(e_i(c))$, and no zero eigenvalues.*

(iii) *If $\mu(e_i) + i\omega(e_i)$ is the eigenvalue of $J(\underline{x}, e_i)$ which is the continuous extension of $i\omega(e_i(c))$, then $\frac{\partial \mu}{\partial e_i}\big|_{e_i(c)} \neq 0$. (This is the transversality condition referred to in Section 3 of the paper.)*

*Then there exists a family of real periodic solutions $\underline{x} = \underline{x}(t;\epsilon)$, $e_i = e_i(\epsilon)$, with the properties $\underline{x}(t;0) = \underline{x}_1(e_i(c))$, $e_i(0) = e_i(c)$, but $\underline{x}(t;\epsilon) = \underline{x}_1(e_i(\epsilon))$ for all sufficiently small $\epsilon \neq 0$. $\underline{x}(t;\epsilon)$ and $e_i(\epsilon)$ are analytic at each point $(t;0)$ and $\epsilon = 0$, respectively. The period of oscillation $T(0) = \lim_{\epsilon \to 0} T(\epsilon) = \frac{2\pi}{|\omega(e_i(c))|}$ is also analytic at $\epsilon = 0$.*

In more informal terms, $e_i(c)$ is a bifurcation value of the eigenvalues of the Jacobian matrix such that $\mu(e_i(c)) = 0, \omega(e_i(c)) \neq 0$, and as $e_i$ varies through $\dot{e}_i(c)$, the real parts of the eigenvalues change sign (transversality condition). Under these circumstances, $e_i = e_i(c)$ may correspond to a center, with infinitely many neutrally stable concentric closed orbits surrounding $\underline{x} = \underline{x}_1$; or a single closed orbit (limit cycle) surrounding $\underline{x} = \underline{x}_1$ for $e_i$ in some range $e_i(c) < e_i < e_i(\max)$, or $e_i(\min) < e_i < e_i(c)$. In each case the diameter of the limit cycle varies like $|e_i - e_i(c)|^{1/2}$ as $e_i$ changes. The former range corresponds to supercritical bifurcation; the latter corresponds to subcritical bifurcation (see [3]). The Hopf bifurcation theorem gives no information about the stability of such limit cycle solutions, though in [5] a stability criterion is derived. It is pointed out in [6], however, that in the case of a simple eigenvalue (as here), if a solution branch $(\underline{x}_1; e_i)$, asymptotically stable for $e_i < e_i(c)$, loses its stability through a simple eigenvalue at $e_i = e_i(c)$ (i.e., $\mathrm{Re}(\lambda \lesseqgtr 0$ as $e_i \lesseqgtr e_i(c))$, then supercritical bifurcating branches are stable, and subcritical bifurcating branches are unstable.

Obtaining more precise analytic properties for a limit cycle is a rather involved process (see [7]). More recent work [8], based on an algorithm in [9], discusses the stability and asymptotic form of such small amplitude periodic solutions.

## REFERENCES


1. C. DeLisi and A. Rescigno, Immune surveillance and neoplasia—I. A minimal mathematical model, *Bull. Math. Biol.* **39**, 201–221 (1977).
2. R. May, Limit cycles in predator-prey communities, *Science* **177**, 900–902 (1972).
3. L. Edelstein-Keshet, *Mathematical Models in Biology*, Chapter 8, Random House, New York, (1988).
4. M. Eisen, *Mathematical Methods and Models in the Biological Sciences*, Chapter 4, Prentice-Hall, Englewood Cliffs, NJ, (1988).
5. J.E. Marsden and M. McCracken, *The Hopf Bifurcation and its Applications*, p. 136, Springer-Verlag, New York, (1976).
6. G. Nicolis and I. Prigogine, *Exploring Complexity*, Chapter 3, W.H. Freeman & Co., (1989).
7. N. Minorsky, *Nonlinear Oscillations*, Van Nostrand, Princeton, NJ, (1977).
8. N.D. Kazarinoff and P. Van Den Driessche, A model predator-prey system with functional response, *Math. Biosci.* **39**, 125–134 (1978).
9. B. Hassard and Y.H. Wan, Bifurcation formulae derived from center manifold theory, *J. Math. Anal. Appl.* **63**, 297–312 (1978).
10. R.T. Prehn, Perspectives in oncogenesis: Does immunity stimulate or inhibit neoplasia?, *J. Reticuloendothel Soc.* **63**, 1–18 (1971).
11. J.A. Adam, The dynamics of growth-factor-modified immune response to cancer growth: One dimensional models, *Mathl. Comput. Modelling* **17** (3), 83–106 (1993).
12. A. Rescigno and C. DeLisi, Immune surveillance and neoplasia—II. A two-stage mathematical model, *Bull. Math. Biol.* **39**, 487–497 (1977).
13. N. Bellomo and G. Forni, Dynamics of tumor interaction with the host immune system, *Mathl. Comput. Modelling* **20** (1), 107–122 (1994).
14. J.A. Adam, Complementary levels of description in applied mathematics: II. Mathematical models in cancer biology, *Intl. J. Math. Ed. Sci. Tech.* **19**, 519–535 (1988).