A MATHEMATICAL MODEL OF CANCER TREATMENT BY CHEMOTHERAPY

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1 Introduction  The ultimate role of mathematical modelling in cancer chemotherapy is to provide a basis for chemotherapy regimes and to make qualitative predictions about the dynamic evolution of the disease based on the cytokinetic parameters of the tumor/patient and the drug parametric configuration. Models for cancer chemotherapy can be deterministic or stochastic and at the same time can be cell cycle specific or nonspecific. Here, we consider a cell cycle independent model, which may be found in [7, 17, 18].

The deterministic theory of cancer cell and chemotherapy dynamics presupposes that the population sizes of normal and cancer cells are large enough to be described by continuous variables which are not affected by random cellular fluctuations. In this paper, cell-cycle independent cytokinetic cancer chemotherapy models are developed using the format found in [12]. The main thrust is to model the interactions between normal cells, cancer cells and a chemotherapy agent in a confined area under several protocols, a single chemotherapy injection continuous chemotherapy and periodic chemotherapy introductions. In each case, we determine the equilibria and discuss their stabilities.

A simplified version of such models was considered by Gatenby [11], who used Lotka-Volterra dynamics to model the competition between normal and cancer cells. A competitive model with periodic inputs was also considered in [13].

2 The model  We take as our model of cancer treatment by chemotherapy a system of three ordinary differential equations of “ecological type,” where \( x_1(t) \) represents the concentration of normal cells, \( x_2(t) \) represents the concentration of cancer cells, and \( y(t) \) represents the concentration of chemotherapy agent in the affected region at time \( t \geq 0 \).
We think of $x_1$ and $x_2$ as competing for nutrients, oxygen, etc. and we think of $y$ as a predator capable of destroying both $x_1$ and $x_2$, but selectively is more lethal to $x_2$.

We suppose that the normal and cancer cells are in a state of competition when the chemotherapy agent is introduced into the body at time $t = 0$, and that the chemotherapy agent takes $\tau$ to reach the affected tissues. We further suppose that the cancer is concentrated in a fixed region of the body. The case where the cancer is metastasize to other parts of the body is discussed using one chemotherapy protocol in [14].

The model then takes the form

\begin{align}
\dot{x}_1 &= B_1(x_1) - D_1(x_1) - x_1x_2q_1(x_1, x_2) - p_1(x_1)h(y) \\
\dot{x}_2 &= B_2(x_2) - D_2(x_2) - x_1x_2q_2(x_1, x_2) - p_2(x_2)h(y) \\
\dot{y} &= \begin{cases} 0, & 0 \leq t < \tau \\ \varphi(x_1, x_2, y; t), & \tau \leq t, \end{cases}
\end{align}

\begin{align}
x_1(0) &= x_{10} > 0, \\
x_2(0) &= x_{20} > 0.
\end{align}

Here, $\dot{} = d/dt$, $B_i(x_i)$ and $D_i(x_i)$ are the birth and death rates, respectively, of the normal and cancer cells, $q_i(x_1, x_2)$ is the respective competition function, $p_i(x_i)$ is the “predator functional response” or cell-killing rate per agent of the chemotherapy, $h(y) = u(y)H(t - \tau)$, where $H(t)$ is the Heaviside unit step function, and $u(y)$ is the density dependent chemotherapy effect. Finally, $\varphi(x_1, x_2, y, t)$ is the rule which governs the concentration of chemotherapy agent in the affected region. Clearly, it depends on the injection strategy and the body’s reaction to the agent both before and after reaching the affected region.

Specifically, we assume the following properties for the defined functions.

(H1) $B_i(0) = D_i(0) = 0$, $0 \leq D'_i(0) < B'_i(0)$, $B'_i(x_i) > 0$, $D'_i(x_i) > 0$. There exists $K_i > 0$ such that $B_i(K_i) = D_i(K_i)$ and $B'_i(K_i) < D'_i(K_i), i = 1, 2$. Further, $B_2(x) > B_1(x)$.

The above conditions imply that both normal cells and cancer cells can grow to their carrying capacities in the absence of other factors, but that cancer in general tends to grow more rapidly.

(H2) $q_i(x_1, x_2) \geq 0$, $\frac{\partial q_i}{\partial x_j} \geq 0$, $x_i \geq 0$, $i, j = 1, 2$. 

(H3) \( p_i(0) = 0, p'_i(x_i) > 0 \). Further, \( p'_2(x) > p'_1(x) \) due to the selectivity of the chemotherapy agent.

(H4) \( u(0) = 0, u'(y) > 0 \). Further, \( \lim_{y \to -\infty} u(y) = \pi < \infty \).

The existence of \( \pi \) is due to empirical observations of the effect of body enzymes on chemotherapy agents; see \([1, 6]\).

We assume that the chemotherapy agent is initially injected at time \( t = 0 \) and initially reaches the affected region at time \( \tau \). Hence the form of equation (2.1c). The function \( \varphi(x_1, x_2, y, t) \) represents the rate of change of chemotherapy agent after time \( \tau \). We consider three strategies for chemotherapy treatment: I, a short infusion over time \( \sigma > 0 \); II, a continuous constant infusion; III, a periodically varying infusion.

According to the three above mentioned strategies, the function \( \varphi \) takes the following forms:

I: \[
\varphi(x_1, x_2, y, t) = \begin{cases} 
\delta e^{-kt} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), & \tau \leq t < \tau + \sigma, \\
- [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), & \tau + \sigma \leq t.
\end{cases}
\]

II: \[
\varphi(x_1, x_2, y, t) = \delta e^{-kt} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), & \tau \leq t.
\]

III: \[
\varphi(x_1, x_2, y, t) = f(t - \tau) \delta e^{-kt} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y) & \tau \leq t,
\]

where \( f(t + \omega) = f(t) \) for some \( \omega > 0 \) (the period).

Model (2.1) is analyzed throughout the remainder of this paper. However, before doing so, we need to consider the interaction of normal and cancer cells when there is no treatment. This is done in the next section.

3 The no treatment case In this section, we consider the case where there is no treatment for the cancer, i.e., \( \delta = 0, y = 0 \) for all \( t > 0 \). Our model then takes the form

\[
\begin{align*}
\dot{x}_1 &= B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2), \\
\dot{x}_2 &= B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2),
\end{align*}
\]

with \( x_1(0) \geq 0, x_2(0) \geq 0 \). (Note that \( \delta \) is the dose.)

The equilibria are \((0, 0), (K_1, 0), (0, K_2)\) and possibly \((\bar{x}_1, \bar{x}_2)\). It is well known, \([2, 9]\), that the dynamics of this system are trivial, i.e., all solutions approach an equilibrium. We assume that the dynamics are
such that \( x_2 \) always wins in competition with \( x_1 \) (or there is no need for treatment). Hence, in this case, \( (\tilde{x}_1, \tilde{x}_2) \) does not exist, and \( (0, K_2) \) is a global attractor.

Computing the variational matrix of system (3.1) about \( (0, K_2) \) gives that the eigenvalues are 
\[
\lambda_1 = B'_1(0) - D'_1(0) - K_2 q_1(0, K_2) \quad \text{and} \quad \lambda_2 = B'_2(0) - D'_2(0) - K_2 q_1(0, K_2).
\]
Hence, the condition that \( (0, K_2) \) is a local attractor implies that
\[
(3.2) \quad B'_1(0) - D'_1(0) - K_2 q_1(0, K_2) < 0.
\]
Hence, if (3.2) is satisfied and the additional hypothesis that the system
\[
(3.3) \quad B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) = 0,
\]
\[
B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) = 0
\]
has no positive solutions, then by the trivial dynamics of competitive systems, \( (0, K_2) \) is a global attractor. We assume that this is so in the remainder of the paper.

4 The single treatment case In this section, we consider the case where \( \varphi(x_1, x_2, y, t) \) is given by I. Then for \( t \geq \tau + \sigma \), equation (2.1c) becomes
\[
(4.1) \quad \dot{y} = -[\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]u(y) < 0,
\]
and since there are no positive steady states, \( \lim_{t \to \infty} = 0 \) and so the equilibrium \( (0, K_2, 0) \) is a global attractor.

Note that if instead of a single treatment, a finite number of discrete treatments are given, the net results are the same for this model.

5 The continuous treatment case Here, we consider the case where chemotherapy is applied continuously. In this case, \( \varphi(x_1, x_2, y, t) \) is given by II and equation (2.1c) for \( t \geq \tau \) is given by
\[
(5.1) \quad \dot{y} = \delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]u(y).
\]

Now the equilibria for system (2.1) are as follows:
\[
\bar{E}(0, 0, \bar{y}), \quad \hat{E}_1(\tilde{x}_1, 0, \tilde{y}_1), \quad \hat{E}_2(0, \tilde{x}_2, \tilde{y}_2) \quad \text{and} \quad E^*(x_1^*, x_2^*, y^*),
\]
where \( \bar{y} \) is the positive solution of \( h(y) = \gamma^{-1} \delta e^{-k\tau} \), provided it exists.
In order for $E_1$ to exist, the algebraic system

\begin{align}
B_1(x_1) - D_1(x_1) - p_1(x_1)u(y) &= 0, \\
\delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1)]u(y) &= 0
\end{align}

must have a positive solution. From $u(y) = \frac{e^{-k\tau}}{\gamma + \eta_1 p_1(x_1)}$, this reduces to

\begin{align}
B_1(x_1) - D_1(x_1) &= \frac{\delta e^{-k\tau} p_1(x_1)}{\gamma + \eta_1 p_1(x_1)}.
\end{align}

We write this as $\varphi(x_1) = \psi(x_1)$.

Since $\varphi(0) = \varphi(K_1) = 0$ and $\varphi(x_1) > 0$ for $0 < x_1 < K_1$, and since $\psi(0) = 0$, $\psi(x_1) > 0$ for $x_1 > 0$, there will be a positive intersection of the curves $z = \varphi(x_1)$ and $z = \psi(x_1)$ provided $\psi'(0) < \varphi'(0)$. But $\psi'(0) = \gamma^{-1} \delta e^{-k\tau} p'_1(0)$ and $\varphi'(0) = B'_1(0) - D'_1(0)$. Hence, we assume that

\begin{align}
\gamma^{-1} \delta e^{-k\tau} p'_1(0) < B'_1(0) - D'_1(0),
\end{align}

which guarantees that $E_1$ exists. If we wish $E_1$ to be unique, we further assume that $z = \varphi(x_1)$ is concave down, i.e., that $B''(x_1) - D''(x_1) < 0$ for $0 \leq x_1 \leq K_1$.

Note that if (5.4) is violated, it is still possible for $E_1$ to exist, but no easily stated sufficient condition is available.

Similarly, $E_2$ exists if

\begin{align}
\gamma^{-1} \delta e^{-k\tau} p'_2(0) < B'_2(0) - D'_2(0).
\end{align}

We note that from a biological standpoint, neither $E$ nor $E_2$ can occur, for in either case, there are no healthy cells left (presumably death has occurred or surgery has removed the organ in question).

Before discussing the existence question for $E^*$, the interior equilibrium, we analyze the stability of the boundary equilibria. The variational matrix $M(x_1, x_2, y)$ is of the form $M(x_1, x_2, y) = [m_{ij}(x_1, x_2, y)]_{3 \times 3}$
where

\[
m_{11} = B'_1(x_1) - D'_1(x_1) - x_1x_2q_1x_1(x_1, x_2) - x_2q_1(x_1, x_2) - p'_1(x_1)u(y),
\]

\[
m_{12} = -x_1x_2q_1x_2(x_1, x_2) - x_1q_1(x_1, x_2),
\]

\[
m_{13} = -p_1(x_1)u'(y),
\]

\[
m_{21} = -x_1x_2q_2x_1(x_1, x_2) - x_2q_2(x_1, x_2),
\]

\[
m_{22} = B'_2(x_2) - D'_2(x_2) - x_1x_2q_2x_2(x_1, x_2) - x_1q_2(x_1, x_2) - p'_2(x_2)u(y),
\]

\[
m_{23} = -p_2(x_2)u'(y),
\]

\[
m_{31} = -\eta_1p'_1(x_1)u(y),
\]

\[
m_{32} = -\eta_2p'_2(x_2)u(y),
\]

\[
m_{33} = -[\gamma + \eta_1p_1(x_1) + \eta_2p_2(x_2)]u'(y).
\]

Letting the variational matrices about \(E_0\), \(\hat{E}_1\) and \(\hat{E}_2\) be \(\mathbf{M}\), \(\hat{M}_1\) and \(\hat{M}_2\), respectively, we get

\[
\mathbf{M} = \begin{bmatrix}
B'_1(0) - D'_1(0) & 0 & 0 \\
-p'_1(0)u(y) & 0 & 0 \\
0 & B'_2(0) - D'_2(0) & 0 \\
-\eta_1p'_1(0)u(y) & -\eta_2p'_2(0)u(y) & -\gamma u'(y)
\end{bmatrix}
\]

\[
\hat{M}_1 = \begin{bmatrix}
B'_1(x_1) - D'_1(x_1) & -\hat{x}_1q_1(\hat{x}_1, 0) & -p_1(\hat{x}_1)u'(\hat{y}_1) \\
-p'_1(\hat{x}_1)u(\hat{y}_1) & 0 & -\hat{x}_1q_2(\hat{x}_1, 0) - p'_2(0)u(\hat{y}_1) \\
-\eta_1p'_1(\hat{x}_1)u(\hat{y}_1) & -\eta_2p'_2(0)u(\hat{y}_1) & -[\gamma + \eta_1p_1(\hat{x}_1)]u'(\hat{y}_1)
\end{bmatrix}
\]

\[
\hat{M}_2 = \begin{bmatrix}
B'_1(0) - D'_1(0) & 0 & 0 \\
-\hat{x}_2q_1(0, \hat{x}_2) - p'_1(0)u(\hat{y}_2) & 0 & 0 \\
B'_2(\hat{x}_2) - D'_2(\hat{x}_2) & -\hat{x}_2q_2(0, \hat{x}_2) - p_2(\hat{x}_2)u(\hat{y}_2) & 0 \\
-p'_2(\hat{x}_2)u(\hat{y}_2) & -\eta_1p'_1(0)u(\hat{y}_2) & -\eta_2p'_2(\hat{x}_2)u'(\hat{y}_2) \\
-\eta_1p'_1(0)u(\hat{y}_2) & -\eta_2p'_2(\hat{x}_2)u(\hat{y}_2) & -[\gamma + \eta_2p_2(\hat{x}_2)]u'(\hat{y}_2)
\end{bmatrix}
\]
From the above we can conclude the following:

(i) If $B'(0) - D'(0) - p'(0)u(\bar{y}) < 0$ and $B''(0) - D''(0) - p''(0)u(\bar{y}) < 0$, then the chemotherapy agent kills all cells including the normal cells.

(ii) Suppose that at least

\[ \frac{B}{0} \frac{D}{0} \frac{p}{0} \frac{u}{y} < 0 \]

so that the normal cells can possibly survive. Consider $\hat{E}_1$. The eigenvalues of $\hat{E}_1$ are given by

\[ \lambda = B'(0) - D'(0) - \tilde{x}_1g_2(\tilde{x}_1, 0) - p'(0)u(\tilde{y}_1) \]

and the solutions of

\[ \det \left| \lambda I - \begin{bmatrix} \hat{\ell}_{11} & \hat{\ell}_{12} \\ \hat{\ell}_{21} & \hat{\ell}_{22} \end{bmatrix} \right| = 0, \]

where

\[ \hat{\ell}_{11} = B'(\tilde{x}_1) - D'(\tilde{x}_1) - p'(\tilde{x}_1)u(\tilde{y}_1), \]
\[ \hat{\ell}_{12} = -p_1(\tilde{x}_1)u'(\tilde{y}_1) < 0, \]
\[ \hat{\ell}_{21} = -\eta p_1'(\tilde{x}_1)u'(\tilde{y}_1) < 0, \]
\[ \hat{\ell}_{22} = -[\gamma + \eta p_1'(\tilde{x}_1)]u'(\tilde{y}_1) < 0. \]

This leads to the characteristic equation

\[ \lambda^2 - (\hat{\ell}_{11} + \hat{\ell}_{22})\lambda + (\hat{\ell}_{11}\hat{\ell}_{22} - \hat{\ell}_{12}\hat{\ell}_{21}) = 0 \]

or

\[ \lambda = \frac{1}{2}(\hat{\ell}_{11} + \hat{\ell}_{22}) \pm \frac{1}{2} \sqrt{(\hat{\ell}_{11} - \hat{\ell}_{22})^2 + 4\hat{\ell}_{12}\hat{\ell}_{21}}. \]

These latter eigenvalues are clearly real. Writing them as

\[ \lambda = \frac{1}{2}(\hat{\ell}_{11} + \hat{\ell}_{22}) \pm \frac{1}{2} \sqrt{(\hat{\ell}_{11} + \hat{\ell}_{22})^2 - 4(\hat{\ell}_{11}\hat{\ell}_{22} - \hat{\ell}_{12}\hat{\ell}_{21})}, \]

we see that they are both negative if and only if

\[ \hat{\ell}_{11} < 0 \quad \text{and} \quad \hat{\ell}_{11}\hat{\ell}_{22} > \hat{\ell}_{12}\hat{\ell}_{21}. \]
We now wish to examine criteria for there to be no limit cycles in the $x_1y$-plane.

System (2.1) in the continuous treatment case, restricted to the $x_1y$-plane takes the form

\begin{equation}
\begin{aligned}
\dot{x}_1 &= B_1(x_1) - D_1(x_1) - p_1(x_1)u(y) \equiv f_1(x_1, y), \\
\dot{y} &= \delta e^{-kr} - (\gamma + \eta_1p_1(x_1))u(y) = g_1(x_1, y).
\end{aligned}
\end{equation}

Using Dulac’s negative criterion [3], we define

\begin{equation}
D(x_1, y) = \frac{\partial}{\partial x} [p_1(x_1)^{-1}f_1(x_1, y)] + \frac{\partial}{\partial y} [p_1(x_1)^{-1}g_1(x_1, y)].
\end{equation}

Then

\begin{equation}
D(x_1, y) = \frac{d}{dx} \left[ \frac{B_1(x_1) - D_1(x_1)}{p_1(x_1)} \right] - \left[ \frac{\gamma + \eta_1p_1(x_1)}{p_1(x_1)} \right] u' (y).
\end{equation}

Clearly, $D(x_1, y) < 0$ for $x_1, y > 0$ if $\frac{B_1(x_1) - D_1(x_1)}{p_1(x_1)}$ is a decreasing function of $x_1$. This would be the case if the cancer interactions were modeled by $B_1(x_1) = D_1(x_1) = x_1g_1(x_1)$ where $g_1(x_1)$ decreases and $p_1(x_1) = k_1x_1$ or $p_1(x_1) = k$ [16, pp. 185–187], [17, pp. 152–156], or if, e.g., $g(x_1) = 1 - bx_1$, $p_1(x_1) = x_1/(a + x_1)$, $ab > 1$.

In any of the above cases, or more generally if $D(x_1, y) < 0$ for $x_1, y > 0$, then there are no periodic solutions in the $x_1y$-plane for system (5.9).

Similar mathematical statements may be said about the corresponding system in the $x_2y$-plane.

The final analysis in the $x_1x_2$-plane will involve criteria for $\bar{E}_1$ to be globally asymptotically stable. For this purpose, we utilize the Liapunov function

\begin{equation}
V(x_1, x_2, y) = x_1 - \hat{x}_1 - \hat{x}_1 \ln \frac{x_1}{\hat{x}_1} + \frac{1}{2}k_1x_2^2 + \frac{1}{2}k_2(y - \hat{y}_1)^2,
\end{equation}

where $k_1, k_2 > 0$ may be chosen later. Taking the derivative along solutions, we get

\begin{equation}
\dot{V}(x_1, x_2, y) = (x_1 - \hat{x}_1)[g_1(x_1) - x_2q_1(x_1, x_2) - r_1(x_1)u(y)] + k_1x_2^2[y_2(x_2) - x_1q_2(x_1, x_2) - r_2(x_2)u(y)] + k_2(y - \hat{y}_1)[\delta e^{-kr} - (\gamma + \eta_1x_1r_1(x_1)] + \eta_2x_2r_2(x_2)u(y)].
\end{equation}
where we have set
\[ B_i(x_i) - D_i(x_i) = x_ig_i(x_i), \]
\[ p_i(x_i) = x_i r_i(x_i), \quad i = 1, 2. \]

We note that \( g_i(x_i) \) and \( r_i(x_i) \) are well defined, and that
\[ g_i(0) > 0, \quad g'_i(x_i) < 0, \quad r_i(0) > 0. \]

After some algebraic manipulations and utilizing the definition of \( \hat{x}_1 \) and \( \hat{y}_1 \), we may obtain that
\[ V(x_1, x_2, y) = a_{11}(x_1 - \hat{x}_1)^2 + 2a_{12}(x_1 - \hat{x}_1)x_2 \]
\[ + 2a_{13}(x_1 - \hat{x}_1)(y - \hat{y}_1) \]
\[ + a_{22}x_2^2 + 2a_{23}x_2(y - \hat{y}_1) + a_{33}(y - \hat{y}_1)^2, \]

where
\[ a_{11} = \frac{g_1(x_1) - r_1(x_1)u(\hat{y}_1)}{x_1 - \hat{x}_1}, \]
\[ a_{12} = \frac{1}{2} q_1(x_1, x_2) + \frac{1}{2} k_1(\hat{x}_1 q_2(\hat{x}_1, x_2) - x_1 q_2(x_1, x_2))x_2, \]
\[ a_{13} = \frac{1}{2} r_1(x_1) \frac{u(\hat{y}_1) - u(y)}{y - \hat{y}_1} + \frac{1}{2} k_2 \eta_1 (\hat{x}_1 r_1(\hat{x}_1) - x_1 r_1(x_1)), \]
\[ a_{22} = k_1 [q_2(x_2) - \hat{x}_1 q_2(\hat{x}_1, x_2) - r_2(x_2)u(\hat{y}_1)], \]
\[ a_{23} = k_1 x_2 r_2(x_2) \frac{u(\hat{y}_1) - u(y)}{y - \hat{y}_1} - k_2 \eta_2 r_2(x_2)u(y), \]
\[ a_{33} = \frac{k_2 \delta e^{-kt} - (\gamma + \eta_1 \hat{x}_1 r_1(\hat{x}_1))u(y)}{y - \hat{y}_1}. \]

We first note that since \( u(y) \) is an increasing function, \( a_{33} < 0 \). However, it does not follow automatically that \( a_{11} < 0 \) and/or \( a_{22} < 0 \) unless \( r_1(x_1) \) and/or \( r_2(x_2) \) are nondecreasing functions, which in general may not be the case.

From the above, we have the following result.

**Theorem 5.1.** Let the \( a_{ij}(x_1, x_2, y) \) be defined by (5.16). Let \( a_{11} < 0 \) and \( a_{22} < 0 \) hold. Then if \( k_1 > 0 \) and \( k_2 > 0 \) can be chosen so that the matrix \( A(x_1, x_2, y) \triangleq (a_{ij}(x_1, x_2, y))_{3 \times 3} \) is negative definite, it follows that \( E_1 \) is globally asymptotically stable.
The conditions of this theorem are very difficult to satisfy. But then, they correspond to the case where the cancer is completely destroyed, which is also a rare occurrence.

We may now address the question of an interior equilibrium in \( x_1x_2y \)-space.

Suppose that \( x_1y \) - and \( x_2y \) - planes do not contain nontrivial periodic solutions. Suppose further that

\[
\begin{align*}
B'(0) - D'_{2}(0) - \tilde{x}_{1}q_{1}(\tilde{x}_{1}, 0) - \tilde{p}'_{2}(0)u(\tilde{y}_{1}) > 0, \\
B'(0) - D'_{1}(0) - \tilde{x}_{2}q_{1}(0, \tilde{x}_{2}) - \tilde{p}'_{1}(0)u(\tilde{y}_{2}) > 0
\end{align*}
\]

hold, and that \( \tilde{E}_1 \) and \( \tilde{E}_2 \) are asymptotically stable in their planes. Then by the techniques in [10], the system is persistent, and hence, by the results in [4], the system is uniformly persistent and \( E_{*} \) exists. The stability of \( E_{*} \) is given by the eigenvalues of \( M^{*} \), which are in general not computable in terms of tractable expressions.

However, in the case that \( E_{*} \) is asymptotically stable for low values of \( x_{2} \), that case would correspond to the situation where the cancer is controlled at an acceptable low level.

6 The periodic treatment case

In this section, we consider model (2.1) where \( \varphi(x_{1}, x_{2}, y, t) \) is given by case III, i.e.,

\[
\begin{align*}
\varphi(x_{1}, x_{2}, y, t) &= f(t - \tau)\delta e^{-k\tau} - [\gamma + \eta_{1}p_{1}(x_{1}) + \eta_{2}p_{2}(x_{2})]h(y), \quad \tau \leq t, \\
\text{where } 0 \leq f(t + \omega) &= f(t) \in C[0, \infty) \text{ for some } \omega > 0 \text{ and } f(t) > 0 \text{ on a set of positive measure.}
\end{align*}
\]

We first consider the existence and stability of periodic solutions in the \( x_{1}y \)-plane and then obtain criteria for the persistence and extinction of the cancer cells.

6.1 The \( x_{1}y \)-plane

We first show that under a mild assumption, all solutions initiating in the \( x_{1}y \)-plane are bounded and enter an attracting set in finite time.

In the \( x_{1}y \)-plane, system (2.1c) becomes

\[
\begin{align*}
\dot{x}_{1} &= B_{1}(x_{1}) - D_{1}(x_{1}) - p_{1}(x_{1})u(y), \quad x_{1}(0) = x_{10}, \\
\dot{y} &= f(t - \tau)\delta e^{-k\tau} - [\gamma + \eta_{1}p_{1}(x_{1})]u(y), \quad y(0) = y_{0}, \quad t \geq \tau,
\end{align*}
\]

and let \( 0 \leq m \leq f(t) \leq M \).
Lemma 6.1. Assume that

\[(6.3) \quad \gamma \mathcal{M} > M \delta e^{-k\tau}\]

holds, where \(\mathcal{M} = \lim_{t \to -\infty} u(y)\). Then

(i) \(x_1(t) \leq \max(K_1, x_{10}), y(t) \leq \max(\mathcal{M}, y_0)\), where \(\mathcal{M}\) is such that

\[(6.4) \quad \gamma u(\mathcal{M}) = M \delta e^{-k\tau}.\]

(ii) \(\limsup_{t \to -\infty} (x_1(t), y(t)) \subseteq A\) where

\[A = \{(x_1, y) : 0 \leq x_1 \leq K_1, 0 \leq y \leq \mathcal{M}\}.\]

Assume that the treatment begins at \(t = 0\) and hence \(y_0 > 0\).

Proof. If \(x_{10} = 0\), then \(x_1(t) \equiv 0\). If \(x_{10} > 0\), then \(\dot{x}_1 < B_1(x_1) - D_1(x_1)\), and so by standard comparison theory, since \(B_1(K_1) = D_1(K_1)\) and \(B_1(x_1) < D_1(x_1)\) for \(x_1 > K_1\), we have that \(x_1(t) \leq \max(K_1, x_{10})\).

Further, since \(\dot{x}_1 < 0\) for \(x_1 > K_1\), we get that \(\limsup_{t \to -\infty} x_1(t) \leq K_1\).

Now,

\[
\dot{y} = f(t - \tau)\delta d^{-k\tau} - [\gamma + \eta_1 p_1(x_1)]u(y) \\
< M\delta e^{-k\tau} - \gamma u(y).
\]

Hence, by (6.4) and standard comparison theory, \(y(t) \leq \max(\mathcal{M}, y_0)\) and when \(y = \mathcal{M}\), then \(\dot{y} < 0\), we get that \(\limsup_{t \to -\infty} y(t) \leq \mathcal{M}\), and thus the lemma is proved.

The above shows that all solutions initiating in the positive octant are eventually uniformly bounded (and hence, system (6.2) is dissipative) and so all solutions are continueable for positive \(t\). Hence, by Massera’s theorem [15] and the fact that system (6.2) has no equilibria, we have shown the following.

Theorem 6.2. If inequality (6.3) holds, then there exists a nonnegative periodic solution of (6.2) of period \(\omega\).

Unfortunately, by the same token, the equation

\[(6.5) \quad \dot{y} = f(t - \tau)\delta e^{-k\tau} - \gamma u(y)\]

has a periodic solution, \(y = \psi_0(t), \psi_0(t + \omega) = \psi_0(t)\) and so the periodic solution of (6.2) found by Theorem (6.2) could be \((0, \psi_0(t))\), which is not interior to the \(x_1y\)-plane.

We now show that \(\psi_0(t)\) is unique.
Theorem 6.3. Let \( y_1(t) \) and \( y_2(t) \) be periodic solutions of period \( \omega \) of (6.5) such that \( y_i(\tau) = \psi_0(\tau), \ i = 1, 2 \). Then \( y_1(t) \equiv y_2(t) \).

Proof. Let \( y(t) = y_1(t) - y_2(t) \). Then \( \dot{y}(t) = \gamma (u(y_2) - u(y_1)) \) and \( y(t) = \gamma \int_0^t (u(y_2) - u(y_1)) \, dt \). Since \( u(y_i) \) is differentiable (and hence Lipschitzian), there exists \( L > 0 \) such that \( |u(y_2) - u(y_1)| \leq L|y_1 - y_2| \). Hence, \( |y(t)| \leq \gamma \int_0^t L|y(s)| \, ds \), and so by Gronwall’s inequality, \( y(t) \equiv 0 \).

Having established the above, we can now formulate criteria for there to exist (and not to exist) an interior (to the \( xy \)-plane) periodic solution.

Theorem 6.4. Define \( \mu_0 = \frac{1}{\omega} \int_0^\omega u(\psi_0(s)) \, ds \), where \( \psi_0 \) is the unique nontrivial \( \omega \)-periodic solution of (6.5). Let

\[
\nu \triangleq \max_{0 \leq x_1 \leq K_1} [B_1'(x_1) - D_1'(x_1) - p_1'(x_1)u(\beta)],
\]

where \( \beta = \min_{t \in [0, \omega]} \psi_0(t) \). Then

(i) If \( \mu_0 > \frac{B_1'(0) - D_1'(0)}{p_1'(0)} \), then the \( \omega \)-periodic solution \((0, \psi_0(t))\) of (6.2) is asymptotically stable.

(ii) If in addition \( \nu < 0 \), then \((0, \psi_0(t))\) is globally asymptotically stable.

Proof. (i) The Jacobian matrix due to linearization about \((0, \psi_0)\) is

\[
M_0 = J_F(0, \psi_0) = \begin{bmatrix}
B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0) & 0 \\
-\mu p_1'(0)u(\psi_0) & -\gamma u'(\psi_0)
\end{bmatrix}
\]

The Floquet multipliers are

\[
\rho_1 = e^{\int_0^\omega [B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0(s))] \, ds}
\]

and

\[
\rho_2 = e^{-\int_0^\omega \gamma u'(\psi_0(s)) \, ds} \quad \text{where} \quad u'(\psi_0(s)) > 0
\]

which implies that \( |\rho_2| < 1 \).

Hence, \((0, \psi_0)\) is locally asymptotically stable if

\[
\int_0^\omega [B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0(s))] \, ds < 0
\]
and unstable if
\[(6.8) \quad \int_{0}^{\infty} \left[ B'_1(0) - D'_1(0) - p'_1(0)u(\psi_0(s)) \right] ds > 0.\]
However, (6.7) and (6.8) can be written as
\[
\mu_0 > \frac{B'_1(0) - D'_1(0)}{p'_1(0)} \implies \text{stability},
\]
\[
\mu_0 < \frac{B'_1(0) - D'_1(0)}{p'_1(0)} \implies (0, \psi_0) \text{ is unstable.}
\]
(ii) Let \(F(x_1) = B_1(x_1) - D_1(x_1) - p_1(x_1)u(y)\). Then \(F \in C^1([0, \omega] \times [0, K_1], \mathbb{R}_+)\) and \(F(0) = 0\). Clearly, \(\nu\) as defined in (6.6) satisfies \(\nu = \max_{x_1 \in [0, K_1]} F'(x_1)\). Then
\[
\frac{\dot{x}_1}{x_1} < \frac{F(x_1)}{x_1}, \quad x_1 \in (0, K_1]
\]
\[
\leq \max_{x_1 \in [0, K_1]} F'(x_1) \leq \nu.
\]
Hence, \(x_1 \leq x_{10}e^{\nu t}\).
If \(\nu < 0\), then \(\lim_{t \to -\infty} x_1(t) = 0\).
Hence, all solutions initiating in the interior approach the \(y\)-axis, and so approach \((0, \psi_0(t))\). \(\Box\)

We now wish to obtain criteria for there to exist an interior periodic solution. We first show that if \(\mu_0 < 0\), then \(x_{10} > 0 \implies \) there exists \(\theta > 0\) such that \(\limsup_{t \to -\infty} x_1(t) \geq \theta\).
To see this, consider the system linearized about \(x_1 = 0\) and \(y = \psi_0(t)\). Then the linearized system can be written as
\[
\dot{v} = \left[ B'_1(0) - D'_1(0) - p'_1(0)u(\psi_0(t)) \right] v,
\]
\[
\dot{w} = -\eta p'_1(0)u(\psi_0(t))v - \gamma u'(\psi_0(t))w.
\]
Hence, \(v(t) = v_0e^{\left[ B'_1(0) - D'_1(0) - p'_1(0)u(\psi_0(t)) \right] t} e^{-\eta \int_{0}^{t} p'_1(s)u(\psi_0(s))ds} \). We are given that \(B'_1(0) - D'_1(0) > 0\). Hence, if \(\mu_0 < 0\), by standard persistence theory \([4, 10]\), this statement holds true.
We then reexamine Theorem (6.2) for large \(t > 0\) in the region \(x_1 \geq \theta, y \geq 0\). Then Massera’s Theorem gives a nontrivial positive periodic solution.

By the above, we have shown the following corollary.
Corollary 6.5. Let (6.3) and $\mu_0 < 0$ hold. Then there exists a nontrivial $\omega$-periodic solution lying in the region \{$(x_1, y) : 0 < x_1 \leq K_1, 0 < y \leq \overline{y}$\}.

We have now established the existence of a positive periodic solution interior to the positive quadrant of the $x_1y$-plane. Mathematically we could also establish such a periodic solution in the $x_2y$-plane in an entirely similar manner, but physiologically, an organ containing only cancer cells and no normal cells means that the organism no longer exists.

At this time, we wish to discuss the stability of the periodic solution found above. In order to do this, we recall the definition of Lozinskii measure [5, p. 41] which in the case of a $2 \times 2$ matrix $(a_{ij})$ is

$$
\mu(A) = \max\{a_{11} + |a_{21}|, a_{22} + |a_{12}|\}.
$$

Theorem 6.6. Let

$$
(6.11) \quad \hat{\mu}(t) \triangleq \max\{B'_1(\varphi_1(t)) + D'_1(\varphi(t))
+ (\eta_1 - 1)p'_1(\varphi_1(t))u(\psi(t)), [\gamma + (\eta_1 - 1)p_1(\varphi_1(t))]u'(\psi(t))\},
$$

where $(\varphi_1(t), \psi(t))$ is the periodic solution found by Theorem 6.4.

(i) If $\int_0^\infty \hat{\mu}(s)ds = -\infty$, then $(\varphi_1(t), \psi(t))$ is asymptotically stable.
(ii) If $\hat{\mu}(t) \leq -\alpha < 0$, then $(\varphi_1(t), \psi(t))$ is uniformly asymptotically stable.

Proof. Let $A(t)$ be the Jacobian matrix of system (6.22) about $(\varphi_1(t), \psi(t))$. Then $A(t) = (a_{ij}(t))_{2 \times 2}$ where

$$
a_{11}(t) = B'_1(\varphi_1(t)) - D'_1(\varphi_1(t)) - p'_1(\varphi_1(t))u(\psi(t)),
a_{12}(t) = -p'_1(\varphi_1(t))u'(\psi(t)),
a_{21}(t) = -\eta_1p'_1(\varphi_1(t))u(\psi(t)),
a_{22}(t) = -[\gamma + \eta_1p_1(\varphi_1(t))]u'(\psi(t)).
$$

Then the function $\hat{\mu}(t)$ defined by (6.11) is just the Lozinskii measure $\mu(A(t))$. The theorem then follows from the stability criteria of Coppel [5, p. 59].

In the following corollary, we give explicit criteria for $\mu(A(t)) < 0$ and therefore for $(\varphi_1(t), \psi(t))$ to be uniformly asymptotically stable.
Corollary 6.7. Define \( \overline{x} = \text{sup}\{x_1 : B'_1(x_1) = D'_1(x_1)\} \). Assume that the following hold:

(H) \( \eta_1 < 1, \overline{\varphi}_1 < \varphi_1(t) < K_1, u'(y) \geq u'_0 \) (where \( u'_0 \) is a positive constant), \( \gamma < (1 - \eta_1)p_1(\overline{\varphi}_1) \). Define \( \overline{\mu} = \text{min}\{|B'_1(\varphi_1(t)) - D'_1(\varphi_1(t))|\} \).

Then \( \mu(A(t)) = \overline{\mu}(t) \leq -\alpha < 0 \).

Proof. Since \( \eta_1 < 1 \) and \( \varphi_1(t) > \overline{\varphi}_1 \),

\[
B'_1(\varphi_1) - D'_1(\varphi_1) + (\eta_1 - 1)p'_1(\varphi_1)u(\psi) < B'_1(\varphi_1) - D'_1(\varphi_1) \leq -\overline{\mu}.
\]

Further,

\[
\gamma + (\eta_1 - 1)p_1(\varphi_1) \leq \gamma + (\eta_1 - 1)p_1(\overline{\varphi}_1) < 0
\]

since \( \gamma < (1 - \eta)\overline{p}_1(\overline{\varphi}_1) \). Hence,

\[
[\gamma + (\eta_1 - 1)p_1(\varphi_1)]u'(\psi) \leq [\gamma + (\eta_1 - 1)p_1(\overline{\varphi}_1)]u'_0 < 0.
\]

Therefore, taking \( \alpha = \text{min}\{\gamma, [\gamma + (\eta_1 - 1)p_1(\overline{\varphi}_1)]u'_0\} \), the corollary is proved. \( \square \)

6.2 \( x_1x_2y \)-space We now consider the dynamics of chemotherapy agent interaction with both normal and cancer cells. Our first result gives criteria for the cancer to be completely eliminated from the site under consideration. Since physiologically this is not the most likely outcome, the mathematical criteria are fairly restrictive as expected. For easy reference in this section, we repeat system (2.1) with \( \varphi(x_1, x_2, y, t) \) given by (6.1) for \( t > \tau \).

\[
\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1x_2q_1(x_1, x_2) - p_1(x_1)u(y),
\]

\[
\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1x_2q_2(x_1, x_2) - p_2(x_2)u(y),
\]

\[
\dot{y} = f(t - \tau)e^{-k\tau} - [\gamma + \eta_1p_1(x_1) + \eta_2p_2(x_2)]u(y).
\]

Theorem 6.8. Let \( \underline{\varphi}, \overline{\varphi} \) and \( \overline{\varphi} \) be such that

(6.13) \( \underline{\varphi}y \leq u(y) \leq \overline{\varphi}y \), \( \overline{\varphi}y \geq M\delta E^{-k\tau} \)

hold for \( 0 \leq y \leq \overline{\varphi} \). Let

\[
\Upsilon = \max_{0 \leq x_2 \leq K_2} (B'_2(x_2) - D'_2(x_2)), \quad \underline{\varphi} = \min_{0 \leq x_2 \leq K_2} p'_2(x_2).
\]

Let

\[
\Upsilon' = \frac{m\delta e^{-k\tau}}{[\gamma + \eta_1p_1(K_1) + \eta_2p_2(K_2)]\overline{\varphi}},
\]

where \( 0 < m \leq f(t) \leq M \). Then if \( \underline{\Upsilon} - \Pi \Upsilon' < 0 \), \( x_2(t) \to 0 \) as \( t \to \infty \).
Proof. From (6.12) and (6.13) we have that
\[ m \delta e^{-kr} - [\gamma + \eta_1 p_1(K_1) + \eta_2 p_2(K_2)]y \leq \dot{y} \leq M \delta e^{-kr} - \gamma y. \]
Since \( y(t) = 0 \) for \( t > \tau \), we obtain by Kanke's comparison theorem,
\[ m \delta e^{-kr} \leq y \leq \frac{m \delta e^{-kr}}{\sigma}, \]
that is, \( U \leq u(y) \leq M \delta e^{-kr}. \)
From (6.12), we have
\[ \dot{x}_2 \leq B_2(x_2) - D_2(x_2) - p_2(x_2)u(y) \leq B_2(x_2) - D_2(x_2) - p_2(x_2)U = F(x_2). \]
But \( F(0) = 0 \) and \( F'(x_2) = B'_2(x_2) - D'_2(x_2) - p'_2(x_2)U \leq \overline{T} - \overline{U}U < 0 \), and so \( x_2(t) \to 0 \) as \( t \to \infty \). \qed

In an analogous manner, the following theorem may be proved.

**Theorem 6.9.** Let \( \overline{T}_\varepsilon = \max_{\varepsilon \leq x_2 \leq K_2}(B'_2(x_2) - D'_2(x_2)) \) and \( \underline{U}_\varepsilon = \min_{\varepsilon \leq x_2 \leq K_2} p'_2(x_2) \). Then if \( \overline{T}_\varepsilon - \underline{U}_\varepsilon U < 0 \), then \( \limsup_{t \to \infty} x_2(t) \leq \varepsilon \).

Note that \( \overline{T}_\varepsilon \) is a nonincreasing function of \( \varepsilon \) whereas \( \underline{U}_\varepsilon \) is a nondecreasing function of \( \varepsilon \).

The last theorem gives a criterion for the control of the cancer cells, i.e., a criterion to eventually force the cancer level to below a prescribed level. From another point of view, for a given \( f(t) \), the value of \( \varepsilon \) such that \( \overline{T}_\varepsilon - \underline{U}_\varepsilon U = 0 \) is an upper limit to the level of eventual cancer concentration.

Our next goal is to obtain criteria for the existence of a periodic solution in \( x_1, x_2, y \)-space. Of course, if the hypotheses of Theorem 6.9 are satisfied, this periodic solution will have only small values of \( x_2 \) for small \( \varepsilon > 0 \).

The results here depend on the ability of the solution \((\varphi_1(t), 0, \psi(t))^T\) to change stability. Hence, we require the following lemma.

For convenience of notation, let
\[ (6.14) \quad B_2(x_2) = b \tilde{B}_2(x_2) \]
and
\[ g(t, b) = b \tilde{B}_2'(0) - D_2'(0) - \varphi_1(t)q_2(\varphi_1(t), 0) - p_2'(0)u(\psi(t)). \]
Lemma 6.10. Let \((\varphi_1(t), 0, \psi(t))^T\) be the periodic solution in the \(x_1y\)-plane found in Theorem 6.4 and assume \(\int_{0}^{\infty} \tilde{p}(t) \, dt = -\infty\). Then this periodic solution is asymptotically stable (resp. unstable) if
\[
\int_{0}^{\infty} g(t, b) \, dt < 0 \quad (\text{resp.} \ > 0).
\]

Proof. If one computes the variational matrix about this periodic solution, one gets from \(\int_{0}^{\infty} \tilde{u}(t) \, dt = -\infty\), that it is stable in the \(x_1y\)-plane. The second row of this matrix has a nonzero term only in the 22 spot, and it is \(g(t, b)\). Hence, the Floquet multiplier corresponding to the \(x_2\)-direction is \(e^{\int_{0}^{\infty} g(t, b) \, dt}\), giving the theorem \[\square\]

Note that \(g(t, 0) < 0\), whereas \(g(t, +\infty) = +\infty\). Hence, \(\int_{0}^{\infty} g(t, b) \, dt\) can be both negative and positive for various \(b\). Further, since \(g(t, b)\) is a strictly increasing function of \(b\), there exists a unique \(b_0\) such that
\[
\int_{0}^{\infty} g(t, b_0) \, dt = 0. \tag{6.15}
\]

The technique used in establishing criteria for the existence of a three-dimensional positive periodic solution is to bifurcate from the planar periodic solution to the interior with \(b\) as the bifurcation parameter. As \(b\) passes through \(b_0\), since the planar solution loses its stability, one would expect under the right circumstances for a bifurcation into a stable interior periodic solution.

Unfortunately, the criteria for this to occur are very complicated and encompass several cases to consider involving cases of the implicit function theorem. We discuss these in some detail in the Appendix. However, for the reader not interested in the gruesome details, we hereby state that criteria do exist guaranteeing such a positive periodic solution.

As to the stability of this solution, it involves a further degree of difficulty and is not discussed here.

7 Numerical examples In this section, we describe some examples to illustrate some of our results. In the first two examples, there is a linear dependence on \(y\), whereas in the next four examples, there is a Michaelis-Menten dependence on \(y\). In either case, parameter values are chosen to illustrate the mathematical results, and may not correspond to any actual medical possibility.
7.1 Examples 1–2 (adjuvant chemotherapy) In this section, both examples will be of the form

\begin{align}
\dot{x}_1 &= a_{11}x_1 - a_{12}x_1^2 - a_{13}x_1x_2 - a_{14}x_1y, \\
\dot{x}_2 &= a_{21}x_2 - a_{22}x_2^2 - a_{23}x_1x_2 - a_{24}x_2y, \\
\dot{y} &= a_3f(t) - (a_{33} + a_{34}x_1 + a_{35}x_2)y.
\end{align}

(7.1)

Example 1. In this example, we set

\begin{align*}
a_{11} &= 3.645, & a_{12} &= 0.0025, & a_{13} &= 0.0025, & a_{14} &= 0.00807, \\
a_{21} &= 6.405, & a_{22} &= .008, & a_{23} &= .00075, & a_{24} &= .00985, \\
a_3 &= 4500, & a_{33} &= .02, & a_{34} &= .125, & a_{35} &= .225, & f(t) &= 1.
\end{align*}

The initial conditions are \(x_{10} = 1000, \ x_{20} = 200\) and \(y_0 = 0\).

This example represents a constant input of chemotherapy agent. Very quickly normal cells, cancer cells and the chemotherapy agent to to a steady state (see Figure 7.1).

Example 2. The constant and initial conditions are the same as in Example 1. However, in this example, \(f(t)\) is a periodic function, \(f(t) = 5 + 5 \sin \frac{\pi}{2} t\).

The solution rapidly approaches a periodic function (see Figure 7.2) which looks to be globally stable.

7.2 Examples 3–6 In this section, all examples are of the form

\begin{align}
\dot{x}_1 &= a_{11}x_1 - a_{12}x_1^2 - a_{13}x_1x_2 - \frac{a_{14}x_1y}{1 + y}, \\
\dot{x}_2 &= a_{21}x_2 - a_{22}x_2^2 - a_{23}x_1x_2 - \frac{a_{24}x_2y}{1 + y}, \\
\dot{y} &= a_3f(t) - \left(a_{33} + a_{34}x_1 + a_{35}x_2\right)\frac{y}{1 + y}.
\end{align}

Example 3. In this example, the coefficients are

\begin{align*}
a_{11} &= 3.645, & a_{12} &= 0.0025, & a_{13} &= 0.0025, & a_{14} &= 0.00807, \\
a_{21} &= 6.405, & a_{22} &= 0.008, & a_{23} &= 0.00075, & a_{24} &= 0.01085, \\
a_3 &= 450, & a_{33} &= 0.02, & a_{34} &= 0.4125, & a_{35} &= 0.5225, \\
x_{10} &= 1000, & x_{20} &= 200, & y_0 &= 0.
\end{align*}
FIGURE 7.1: Constant chemotherapy input with linear uptake. Constants, initial conditions and $f(t)$ given in the text.
FIGURE 7.2: Periodic chemotherapy input with linear uptake. Constants, initial conditions and $f(t)$ given in the text.
FIGURE 7.3: Constant chemotherapy input with Michaelis-Menten uptake. Constants, initial conditions and \( f(t) \) given in the text.
Here, $f(t) \equiv 1$ is the constant input. All solutions rapidly approach a constant steady state (see Figure 7.3).

**Example 4.** Here $f(t)$ is a periodic function of period 2 such that

$$f(t) = \begin{cases} 
1, & 0 \leq t \leq 0.5, \\
0, & 0.5 < t \leq 2.
\end{cases}$$

All solutions rapidly approach a steady state which is periodic in $x_2$ with small amplitude and constant in $x_1$ (see Figure 7.4). The values of the constants are

$$a_{11} = 1.98, \quad a_{12} = .005, \quad a_{13} = .0055, \quad a_{14} = .00025,$$

$$a_{21} = 2.5, \quad a_{22} = .05, \quad a_{23} = .005, \quad a_{24} = .25,$$

$$a_3 = 800, \quad a_{33} = .45, \quad a_{34} = 1.25, \quad a_{35} = 2.25,$$

The initial conditions are $x_{10} = 1000, x_{20} = 100, y_0 = 0.$

**Example 5.** In this example,

$$a_{11} = 1.98, \quad a_{12} = .005, \quad a_{13} = .085, \quad a_{14} = .07,$$

$$a_{21} = 3.5, \quad a_{22} = .008, \quad a_{23} = .01, \quad a_{24} = .085,$$

$$a_3 = 1140, \quad a_{33} = .05, \quad a_{34} = .45, \quad a_{35} = .9,$$

Here $f(t)$ is a periodic function similar to the last example, but with period 3 such that

$$f(t) = \begin{cases} 
1, & 0 \leq t \leq 0.5, \\
0, & 0.5 < t \leq 3.
\end{cases}$$

Initial conditions are $x_{10} = 1000, x_{20} = 15, y_0 = 0.$ From Figure 7.5, one can see that the cancer takes over, i.e., it approaches a period function of high values whereas the normal cells are driven extinct.

**Example 6.** All constants and $f(t)$ are as in Example 5 except for $x_{20} = 14.$ Now, $x_1$ approaches a steady state with the cancer cells going extinct. Note the periodic accumulation of chemotherapy agent (see Figure 7.6).
FIGURE 7.4: Periodic chemotherapy input with Michaelis-Menten uptake. Constants, initial conditions and $f(t)$ given in the text.
FIGURE 7.5: Periodic chemotherapy input with Michaelis-Menten uptake. Normal cells driven to extinction. Constants, initial conditions and $f(t)$ given in the text.
FIGURE 7.6: Periodic chemotherapy input with Michaelis-Menten uptake. Cancer cells driven to extinction. Constants, initial conditions and $f(t)$ given in the text.
8 Conclusion  In this paper, we have proposed a model of chemotherapy on cancer cells in competition with normal cells, consisting of three interacting ordinary differential equations. We have analyzed the solutions for various types of chemostat inputs including a finite number of constant inputs, a sustained constant input and sustained periodic inputs.

Our models show that the following scenarios are possible: cancer causes the normal cells to go extinct (presumably resulting in death); cancer cells go extinct; cancer cells kept at a low level; all cells approach a steady state which is high for the cancer cells; all cells and chemotherapy approach periodic oscillations.

An interesting case is shown in comparing Examples 5 and 6. These examples are identical except for the cancer cell starting values. In the latter case, with \( x_{20} = 14 \), the cancer is driven to extinction whereas in the former case, the cancer drives the normal cells to extinction with \( x_{20} = 15 \). This shows that outcomes could be very sensitive on cancer values immediately before treatment, which means that early detection and treatment may be instrumental to survival.

9 Appendix  In this appendix, we indicate the process leading to a bifurcation of the planar periodic solution \((\varphi_1(t), 0, \psi(t))\) of system (6.2) into an interior periodic solution. The idea is to set up a period time map and use the implicit function theorem to establish a second periodic solution.

Step 1. First we define \( \tilde{B}_2(x_2) \) and the constant \( b \) by \( B_2(x_2) = b\tilde{B}_2(x_2) \). \( b \) will be our bifurcation parameter. Under the assumption that \((\varphi_1(t), 0, \psi(t))^T\) is a periodic solution of period \( \omega \) of (6.2), we define

\[
g(t, b) = b\tilde{B}_2'(0) - D_1'(0) - \varphi_1(t)q_2(\varphi_1(t), 0) - p'_2(0)u(\psi(t))
\]

and

\[
\Phi(t) = (\varphi_1(t), 0, \psi(t))^T.
\]

Then computing the variational matrix \( M \) about \( \Phi(t) \), we get

\[
M(\Phi(t)) = \begin{bmatrix}
b\tilde{B}_2'(\varphi(t)) - D_1'(\varphi_1(t)) & -\varphi(t)q_1(\varphi_1(t), 0) & -p_1(\varphi_1(t))u'(\psi(t)) \\
-p_1'(\varphi_1(t))u(\psi(t)) & -p_1(\varphi_1(t))u'(\psi(t)) & 0 \\
0 & g(t, b) & 0 \\
-\eta_1p_1'(\varphi_1(t))u(\psi(t)) & -\eta_2p_2'(0)u(\psi(t)) & -[\gamma + \eta_1p_1(\varphi_1(t))]u'(\psi(t))
\end{bmatrix}
\]
From $M(\Phi(t))$, we see that if $\int_0^\omega g(t, b) \, dt < 0$ (resp. $> 0$), then there is local stability (resp. instability) in the $x_2$-direction. Bifurcation will occur if by changing $b$, the system loses stability.

**Step 2.** We now move the periodic solution $\Phi(t)$ to the origin by a change of variables and then separate off the linear part of the resulting system.

Let

\begin{equation}
(9.3) \quad w_1 = x_1 - \varphi_1(t), \quad w_2 = x_2, \quad z = y - \psi(t).
\end{equation}

This results in the system

\begin{equation}
(9.4) \quad \begin{aligned}
\dot{w}_1 &= B_1(w_1 + \varphi_1(t)) - B_1(\varphi_1(t)) - D_1(w_1 + \varphi_1(t)) + D_1(\varphi_1(t)) \\
&\quad - (w_1 + \varphi_1(t))w_2q_1(w_1 + \varphi_1(t), w_2) \\
&\quad - p_1(w_1 + \varphi_1(t))u(z + \psi(t)) + p_1(\varphi_1(t))u(\psi(t)) \\
&\quad \equiv \Theta_1(t, w_1, w_2, z, b), \\
\dot{w}_2 &= bB_2(w_2) - D_2(w_2) - (w_1 + \varphi_1(t))w_2q_2(w_1 + \varphi_1(t), w_2) \\
&\quad - p_2(w_2)u(z + \psi(t)) \\
&\quad \equiv \Theta_2(t, w_1, w_2, z, b), \\
\dot{z} &= -[\gamma + \eta_1p_1(w_1 + \varphi_1(t)) + \eta_2p_2(w_2)]u(z + \psi(t)) \\
&\quad + [\gamma + \eta_3p_1\varphi_1(t)]u(\psi(t)) \\
&\quad \equiv \Theta_3(t, w_1, w_2, z, b).
\end{aligned}
\end{equation}

Note that $\Theta_1(t, 0, 0, 0, b) = 0$ and so $E_0 = (0, 0, 0)^T$ is a periodic solution of system (9.3).

Let $A(t) = M(\Phi(t)) = (a_{ij}(t), u = (w_1, w_2, z)^T$, $\Theta = (\Theta_1, \Theta_2, \Theta_3)^T$ and $N(t, u, b) = \Theta(t, w_1, w_2, z, b) - A(t)u$. Then $N(t, 0, b) = \Theta(t, 0, 0, 0, b)$

$\equiv 0 = 0$, $\frac{\partial N}{\partial u}(t, 0, b) = A(t) - A(t) = 0$. Hence, system (9.4) can be written as

\begin{equation}
(9.5) \quad \dot{u} = A(t)u + N(t, u, b),
\end{equation}

where $N(t, u, b)$ is nonlinear in $u$.

**Step 3.** First note that by a result of Poicaré (see [8]) if the system

\begin{equation}
(9.6) \quad \dot{u} = A(t)u
\end{equation}

has no nontrivial solutions of period $\omega$, then system (9.5) has a unique periodic solution of period $\omega$, and since $E_0$ is such a solution, there can be no bifurcation. Hence we assume
System (9.6) has one or more nontrivial periodic solutions of period $\omega$.

In preparation for bifurcation using the implicit function theorem, note that $g(t, 0) < \infty$ while $\lim_{b \to \infty} g(t, b) > 0$. Further, $\frac{\partial g(t, b)}{\partial b} = \tilde{B}'(0) > 0$. Hence, there exists a unique $b_0 > 0$ such that $\int_0^\omega g(t, b_0) \, dt = 0$.

Finally, we define $\varepsilon$ by

$$\varepsilon = b - b_0.$$

**Step 4.** Let $u(t, \xi, \varepsilon)$ be that solution of (9.5) such that $u(0, \xi, \varepsilon) = \xi$. Note that $u(t, 0, 0) = 0$. Define the vector function $F(\xi, \varepsilon)$ by

$$F(\xi, \varepsilon) = u(\omega, \xi, \varepsilon) - \xi.$$

If the equation $F(\xi, \varepsilon) = 0$ can be solved for $\xi$ as a function of $\varepsilon$ such that $\lim_{\xi \to 0} \xi(\varepsilon) = 0$, then we will have found a periodic solution.

Now $F(0, 0) = u(\omega, 0, 0) = 0$. $F_\xi(0, 0) = u_\xi(\omega, 0, 0) - I$. But $u_\xi(t, \xi, \varepsilon)$ satisfies

$$\dot{u}_\xi = A(t)u_\xi + N_\omega(t, u, b)u_\xi, \quad u_\xi(0, \xi, \varepsilon) = I.$$

Hence at $\xi = 0$, $\varepsilon = 0$, we get

$$\dot{u}_\xi = A(t)u_\xi + N_\omega(t, 0, b_0)u_\xi, \quad u_\xi(0, 0, 0) = I,$$

or

$$\dot{u}_\xi = A(t)u_\xi, \quad u_\xi(0, 0, 0) = I$$

since $N$ is nonlinear in $u$.

Let $\Psi(t)$ be that fundamental matrix solution of (9.6) such that $\Psi(0) = I$. Then

$$F_\xi(0, 0) = \Psi(\omega) - I,$$

and by hypothesis (H), we obtain that $\det F_\xi(0, 0) = 0$. Hence, we are in the required singular case of the implicit function theorem.

We will also need to compute $F_\varepsilon(0, 0)$. $F_\varepsilon(\xi, \varepsilon) = u_\varepsilon(\omega, \xi, \varepsilon)$. Now $u_\varepsilon(t, \xi, \varepsilon)$ satisfies

$$\dot{u}_\varepsilon = A(t)u_\varepsilon + N_\omega(t, u, b)u_\varepsilon + N_b(t, u, b), \quad u_\varepsilon(0, \xi, \xi) = 0.$$

At $\xi = \varepsilon = 0$, $u_\varepsilon(t, 0, 0)$ satisfies

$$\dot{u}_\varepsilon = A(t)u_\varepsilon + N_b(t, 0, b_0), \quad u_\varepsilon(0, 0, 0) = 0.$$
Hence,

\[(9.8) \quad u_\varepsilon(t, 0, 0) = \Psi(t) \int_0^t \Psi(s)^{-1} N_b(s, 0, b_0) \, ds,\]

and so

\[F_\varepsilon(0, 0) = \Psi(0) \int_0^\omega \Psi(s)^{-1} N_b(s, 0, b_0) \, ds.\]

Note that \(N_b(s, 0, b_0) = (0, \hat{B}_2'(0), 0)^T\) is a constant vector.

**Step 5.** Here we discuss the first of three generic cases.

**Case (i):** \(F_\xi(0, 0) = 0, F_\varepsilon(0, 0) = 0.\)

In this case, \(F(\xi, \varepsilon)\) begins with quadratic or higher terms. We begin by defining the vector \(\eta\) by

\[(9.9) \quad \xi = \eta \varepsilon\]

and setting

\[G(\eta, \varepsilon) = \begin{cases} 
\varepsilon^{-2}F(\eta \varepsilon, \varepsilon), & \varepsilon \neq 0, \\
\frac{1}{2} F_{\xi\xi}(0, 0) \eta^2 + F_{\xi\varepsilon}(0, 0) \eta + \frac{1}{2} F_{\varepsilon\varepsilon}(0, 0), & \varepsilon = 0.
\end{cases}\]

In order to solve \(G(\eta, \varepsilon) = 0\) for \(\eta\) as a function of \(\varepsilon\), we first must find a vector \(\eta_0\) such that \(G(\eta_0, 0) = 0\), i.e.,

\[(9.10) \quad \frac{1}{2} F_{\xi\xi}(0, 0) \eta_0^2 + F_{\xi\varepsilon}(0, 0) \eta_0 + \frac{1}{2} F_{\varepsilon\varepsilon}(0, 0) = 0.\]

Computing the second derivative in a similar manner as the above, we get

\[(9.11) \quad F_{\xi\xi}(0, 0) = \Psi(0) \int_0^\omega \Psi(s)^{-1} N_{uu}(s, 0, b_0) \Psi^{-1}(s)^2 \, ds,\]

\[(9.11) \quad F_{\xi\varepsilon}(0, 0) = \Psi(0) \int_0^\omega \Psi(s)^{-1} N_{uu}(s, 0, b_0) u_\varepsilon(s, 0, 0) u_\varepsilon(s, 0, 0) \, ds,\]

\[(9.11) \quad F_{\varepsilon\varepsilon}(0, 0) = \Psi(0) \int_0^\omega \Psi(s)^{-1} N_{uu}(s, 0, b_0) u_\varepsilon(s, 0, 0)^2 \, ds,\]

Note that \(F_{\varepsilon\varepsilon}\) is a vector, \(F_{\xi\xi}\) is a \(3 \times 3\) matrix and \(F_{\xi\xi}\) is a \(3 \times 3 \times 3\) tensor. Hence, (9.11) is equivalent to solving three quadratic equations in three unknowns (the components of \(\eta\)). It can have up to nine distinct solutions.

If (9.11) has no real solution, then \(\xi\) cannot be solved for \(\varepsilon\). Hence we make the following assumptions.
(H2) Equation (9.11) has at least one real distinct solution \( \eta_0 \).

With assumption (H2) we get that \( G(\eta_0, 0) = 0 \). Now we compute \( G_\eta(\eta_0, 0) \) and \( G_\varepsilon(\eta_0, 0) \).

\[
G_\eta(\eta_0, 0) = \lim_{\varepsilon \to 0} \frac{F_\xi(\eta_0 \varepsilon, \varepsilon)}{\varepsilon} = F_\xi(0, 0) \eta_0 + F_\xi(0, 0),
\]

\[
G_\varepsilon(\eta_0, 0) = \lim_{\varepsilon \to 0} \frac{d}{d\varepsilon} \left( \frac{F(\eta \varepsilon, \varepsilon)}{\varepsilon^2} \right)
= \frac{1}{3} \lim_{\varepsilon \to 0} \frac{F_\xi(\eta \varepsilon, \varepsilon) + F_\varepsilon(\eta \varepsilon, \varepsilon)}{\varepsilon^2},
\]

which in light of (H2) give

\[
G_\varepsilon(\eta_0, 0) = \frac{1}{3} F_\xi(0, 0) \eta_0^3 + F_\xi(0, 0) \eta_0^2 + F_\varepsilon(0, 0) \eta_0 + \frac{1}{3} F_\varepsilon(0, 0),
\]

where these derivatives are computed similar to the second derivatives.

(H3) Hence, if \( \det G_\varepsilon(\eta_0, 0) \neq 0 \), we can solve for \( \eta \) as a function of \( \varepsilon \), i.e.,

\[
\eta = \eta_0 - G_\eta(\eta_0, 0)^{-1} G_\varepsilon(\eta_0, 0) \varepsilon + o(\varepsilon),
\]

or

(9.12) \[
\xi = \eta_0 \varepsilon - G_\eta(\eta_0, 0)^{-1} G_\varepsilon(\eta_0, 0) \varepsilon^2 + o(\varepsilon^2).
\]

**Step 6.** Since \( u(t, \xi, \varepsilon) \) is a periodic perturbation of \( \Phi(t) \), \( w_1(t, \xi, \varepsilon) \) and \( z(t, \xi, \varepsilon) \) are positive for \( \xi \) sufficiently small.

With respect to \( w_2 \), we note that \( u(t, \xi, \varepsilon) \) can be written as

\[
u(t, \xi, \varepsilon) = u(t, 0, 0) + u_\xi(t, 0, 0) \xi + u_\varepsilon(t, 0, 0) \varepsilon + \text{H.O.T.}
\]

\[
= \Psi(t) \begin{bmatrix} \eta_0 + \int_0^t \Psi(s)^{-1} (0, \tilde{E}_2'(0), 0)^T \varepsilon + o(\varepsilon) \\ \chi(t) \varepsilon + o(\varepsilon) \end{bmatrix}
\]

Hence for \( w_2 > 0 \) for \( \varepsilon > 0 \), we require that the middle component of \( \chi(t) \) be positive, \( 0 \leq t \leq \omega \).
Step 7.

Case (ii): $F_{\xi}(0, 0) = 0, F_{\varepsilon}(0, 0) \neq 0$. In this case, we assume that there exists $n \geq 2$ such that $\det(F_{\xi}(0, 0)) \neq 0$. To illustrate the technique, assume $n = 2$.

First we set $\varepsilon = \tau^2$ and

$$H(\xi, \tau) = F(\xi, \tau^2).$$

Then as before, we set $\xi = \eta \varepsilon$ and define

$$J(\eta, \varepsilon) = \begin{cases} H(\eta \varepsilon, \tau) \varepsilon^{-2}, & \varepsilon \neq 0, \\ \frac{1}{2}H_{\xi \xi}(0, 0)\eta^2 + H_{\xi \tau}(0, 0)\eta + \frac{1}{2}H_{\tau \tau}(0, 0), & \varepsilon = 0, \end{cases}$$

where

$$H_{\xi \xi}(0, 0) = F_{\xi \xi}(0, 0),$$

$$H_{\xi \tau}(0, 0) = 0,$$

$$H_{\tau \tau}(0, 0) = 2F_{\varepsilon}(0, 0).$$

Hence, as in Step 5, one requires a real distinct solution to the system

$$F_{\xi \xi}(0, 0)\eta^2 + 2F_{\varepsilon}(0, 0) = 0.$$  

If such a real solution, $\eta_0$, does not exist, then instead of $\varepsilon = \tau^2$, one can try $\varepsilon = -\tau^2$, and that may work, otherwise no bifurcation occurs.

If $\eta_0$ exists (in which case there are two or no branches for $\xi$ as a function of $\varepsilon$), the rest proceeds as in Steps 5 and 6.

Step 8.

Case (iii) $\det(F_{\xi}(0, 0)) = 0, F_{\xi}(0, 0) \neq 0$. This case is somewhat complicated. First, by a linear change of variables, we assume that $F_{\xi}(0, 0)$ is in Jordan canonical form with all zero eigenvalues on the upper left on the diagonal. We then define all rows which consist only of zero to be the singular rows and all such columns to be the exceptional columns. Then if $F(\xi, \varepsilon)$ is broken into singular and nonsingular parts, $F_s$ and $F$, respectively, and $\xi$ into exceptional and nonexceptional components, $\xi_e$ and $\xi_0$, respectively, one can see that $\det(F_{\xi}(0, 0)) \neq 0$.

Hence, $\tilde{F}(\xi, \varepsilon)$ can be solved for $\tilde{\xi}$ as a function of $\xi_e$ and $\varepsilon$. We then substitute into $F_s(\xi, \varepsilon)$, giving a system of the form $F_s(\xi_e, \varepsilon) = 0$, where now $F_s(0, 0) \equiv 0$. Then we proceed as in Steps 5 and 6, or Step 7. See [8] for complete details of this technique.
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