9

Modeling Cancer Treatment Using Competition: A Survey *

H.I. Freedman

Summary. Several models are proposed to simulate the treatment of cancer by various techniques including chemotherapy, immunotherapy and radiotherapy. The interactions between cancer and normal cells are viewed as competitions for resources. Using ordinary differential equations, we model these treatments as constant and periodic.

9.1 Introduction

In North America, cancer is the second largest cause of human mortality, and as such, is of great concern to the population at large. Despite the billions of dollars poured into research to date, a "cure for cancer" is still out of reach, although significant progress has been made in many types of cancers. Such progress has led to greater understanding of the cancers and their effects and in improvements in treatments leading to a better quality of life and in some cases to a cure.

Mathematics has contributed in a small way to the understanding of cancer by analysis and simulation of cancer models in a hope of discovering new insights. This is well evidenced by the publication of a special issue of the journal, *Discrete and Continuous Dynamical Systems Series B* (Horn and Webb 2004), titled "Mathematical Models in Cancer", which contains twenty-one papers concerned with modelling various types and aspects of cancer. It is interesting to note, however, that in all these works (and others) there is hardly any modelling or mention of treatment.

It is the purpose of this chapter to briefly survey how treatment may be included in cancer modelling. However, we restrict ourselves to models which treat the interactions between cancer and normal cells as a competition for bodily resources (nutrients, oxygen, space, etc.).

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The organization of the chapter is as follows. In Sect. 9.2 we consider our model with no treatment and state the conditions for cancer to always win. This is followed by modelling treatment by radiation using control theory in Sect. 9.3. Section 9.4 deals with chemotherapy treatment and Sect 9.5 with immunotherapy treatment. In Sect. 9.6 we look at the case where cancer metastasizes (spreads). Finally a short discussion will be in Sect. 9.7.

9.2 The no treatment case

We model the interaction between normal and cancer cells as a competition for bodily resources. Let $x_1(t)$ be the concentration of normal cells and $x_2(t)$ be the concentration of cancer cells at a given site. Then in the absence of treatment, our model takes the form

$$\begin{aligned} \dot{x}_1(t) &= \alpha_1 x_1(t)\Big(1 - \frac{x_1(t)}{K_1}\Big) - \beta_1 x_1(t)x_2(t)\,, \qquad x_1(0) \geq 0 \\ \dot{x}_2(t) &= \alpha_2 x_2(t)\Big(1 - \frac{x_2(t)}{K_2}\Big) - \beta_2 x_1(t)x_2(t)\,, \qquad x_2(0) \geq 0\,, \end{aligned} \tag{1}$$

where $\cdot = \frac{\mathrm{d}}{\mathrm{d}t}$, α_i is the proliferation coefficient, β_i is the competition coefficient and K_i is the carrying capacity for the ith cell population, $i = 1, 2$.

For this model, the following boundary (with respect to the positive quadrant) equilibria always exist, $E_0(0,0), E_1(K_1,0)$ and $E_2(0,K_2)$. It is well known (see Freedman and Waltman 1984) that for the general dynamics of solutions initiating in the nonnegative quadrant at nonequilibrium values, there are four possible outcomes, (i) x_1 always wins, (ii) x_2 always wins, (iii) there is an interior equilibrium $\widehat{E}(\widehat{x}_1, \widehat{x}_2)$, where $\widehat{x}_1 > 0, \widehat{x}_2 > 0$, and $\widehat{E}$ is asymptotically stable (and hence globally stable for strictly positive solutions), (iv) $\widehat{E}$ exists and is a saddle point, i. e. E_1 and E_2 are both locally stable, and whether x_1 or x_2 wins depends on the initial conditions.

According to our cancer assumption that cancer always wins, we require that only case (ii) occurs. Criteria for this to happen are given in Freedman and Waltman (1984), and are

$$\alpha_1 < K_2\beta_1\,, \quad \alpha_2 > K_1\beta_2\,. \tag{2}$$

Throughout the rest of this chapter, we assume that (2) holds.

We will modify system (1) in this paper to simulate various treatments.

9.3 Treatment by radiation

The material in this section is taken (with permission) from the Masters Thesis of Belostotski (2004). In general system (1) may be modified so as to

include a harvesting of cells due to radiation. The general form of the new system is then given by

$$\begin{aligned} \dot{x}_1 &= \alpha_1 x_1\Big(1-\frac{x_1}{K_1}\Big) - \beta_1 x_1 x_2 - \eta_1(t,x_1,x_2)\,, \qquad x_1(0)\geq 0 \\ \dot{x}_2 &= \alpha_2 x_2\Big(1-\frac{x_2}{K_2}\Big) - \beta_2 x_1 x_2 - \eta_2(t,x_1,x_2)\,, \qquad x_2(0)\geq 0\,, \end{aligned} \tag{3}$$

where η_i, $i=1,2$, is the effect of radiation on the cell populations.

In the first instance we suppose that the radiation is ideal, i. e. it targets only cancer cells. This may be effected by setting $\eta_1(t,x_1,x_2)=0$. In the second instance we can look at the case of a minor spillover to normal cells, by writing $\eta_1(t,x_1,x_2)=\varepsilon\overline{\eta}_1(t,x_1,x_2)$, and use perturbation theory. Then at the third stage of analysis, one can consider fully system (3).

In this paper, we only consider the case where $\eta_1(t,x_1,x_2)=0$. For the perturbation case, see Belostotski (2004). Four types of control are feasible:

$$\text{(i) } \eta_2=\gamma=\text{const.}\,; \quad \text{(ii) } \eta_2=\gamma x_2\,; \quad \text{(iii) } \eta_2=\gamma\frac{x_2}{x_1}\,;$$

$$\text{(iv) } \eta_2=\begin{cases}\gamma & \text{for} \quad nkT\leq t<(nk+1)T \\ 0 & \text{for} \quad (nk+1)T\leq t<(nk+2)T\,, \quad n\in N\,. \end{cases}$$

Here we will analyze in some detail case (i). The other cases may be found in Belostotski (2004).

9.3.1 Existence of equilibria

In case (i), system (3) becomes

$$\begin{aligned} \dot{x}_1 &= \alpha_1 x_1\Big(1-\frac{x_1}{K_1}\Big) - \beta 1 x_1 x_2 \\ \dot{x}_2 &= \alpha_2 x_2\Big(1-\frac{x_2}{K_2}\Big) - \beta_2 x_1 x_2 - \gamma\,. \end{aligned} \tag{4}$$

Let

$$a=\alpha_1\alpha_2-\beta_1\beta_2 K_1 K_2\,.$$

In the absence of radiation, i. e. $\gamma=0$, system (4) generates the following isoclines:

$$\begin{aligned} \Gamma_1 &: x_1 = K_1 - \frac{\beta_1 K_1}{\alpha_1}x_2 \\ \Gamma_2 &: x_1 = \frac{\alpha_2}{\beta_2} - \frac{\alpha_2}{\beta_2 K_2}\,x_2\,. \end{aligned} \tag{5}$$

The sign of a describes the nature of the interaction between healthy and

cancer cells. Consider the slopes of Γ_1 and Γ_2 in (5). If

$$\begin{aligned} &\text{(i)} \quad -\frac{\alpha_2}{\beta_2 K_2} > -\frac{\beta_1 K_1}{\alpha_1} \implies a < 0\,, \\ &\text{(ii)} \quad -\frac{\alpha_2}{\beta_2 K_2} = -\frac{\beta_1 K_1}{\alpha_1} \implies a = 0\,, \\ &\text{(iii)} \quad -\frac{\alpha_2}{\beta_2 K_2} < -\frac{\beta_1 K_1}{\alpha_1} \implies a > 0\,. \end{aligned} \tag{6}$$

When $a \neq 0$, the isoclines (5) do not intersect since we restrict our analysis to the case when cancer wins the competition (conditions (2)). When radiation is introduced, the equations of isoclines (5) will change to:

$$\begin{aligned} \Gamma_1 &: x_1 = K_1 - \frac{\beta_1 K_1}{\alpha_1} x_2 \\ \Gamma_3 &: x_1 = \frac{\alpha_2}{\beta_2} - \frac{\alpha_2}{\beta_2 K_2} x_2 - \frac{\gamma}{\beta_2 x_2}\,. \end{aligned} \tag{7}$$

Notice that on Γ_3 as $x_2 \to 0^+$, then x_1 approaches $-\infty$. In addition, on Γ_3, $\frac{\mathrm{d}x_1}{\mathrm{d}x_2} = -\frac{\alpha_2}{\beta_2 K_2} + \frac{\gamma}{\beta_2 x_2^2}$ and $\frac{\mathrm{d}^2 x_1}{\mathrm{d}x_2^2} = -\frac{2\gamma}{\beta_2 x_2^3}$. Thus Γ_3 will have the shape as depicted in Figs. 9.1 and 9.2 with the vertex (maximum value of x_1) at:

$$(x_1, x_2) = \Big(\frac{\alpha_2}{\beta_2} - \frac{2}{\beta_2}\sqrt{\frac{\alpha_2\gamma}{K_2}}\,, \sqrt{\frac{K_2\gamma}{\alpha_2}}\Big)\,.$$

In the positive x_1, x_2 plane these isoclines may intersect twice, once, or zero times as in Figs. 9.1 and 9.2. The number of intersections depends on the size of γ and the dynamics of the cancer-healthy tissue interaction represented by a.

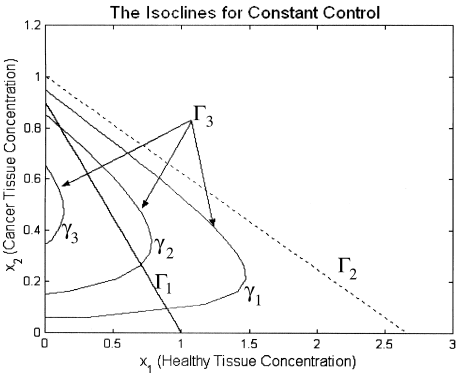

Fig. 9.1. Isoclines of (6): $a < 0$. Changes in shape of Γ_3 for different values of $\gamma : \gamma_1 < \gamma_2 < \gamma_3$

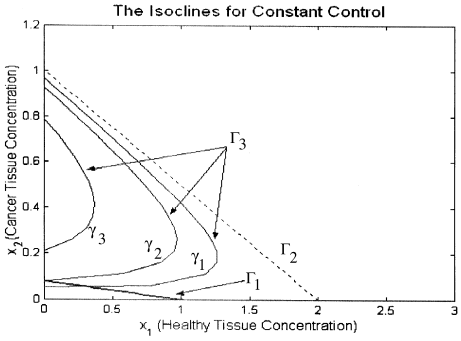

Fig. 9.2. Isoclines of (6): $a < 0$. Changes in shape of Γ_3 for different values of $\gamma : \gamma_1 < \gamma_2 < \gamma_3 < \gamma_4 < \gamma_5$

The boundary equilibria on the x_2 axis will exist if $0 = \frac{\alpha_2}{\beta_2} - \frac{\alpha_2}{\beta_2 K_2} x_2 - \frac{\gamma}{\beta_2 x_2}$ or, equivalently, $0 = \alpha_2 x_2^2 - K_2 \alpha_2 x_2 + \gamma K_2$ has positive solutions. Therefore,

$$\begin{aligned}
\gamma < \frac{\alpha_2 K_2}{4} &\implies \text{two positive real solutions } 0 < x_2 < \frac{K_2}{2}\,,\ \frac{K_2}{2} < x_2 < K_2 \\
\gamma = \frac{\alpha_2 K_2}{4} &\implies \text{one positive real solution } x_2 = \frac{K_2}{2} \\
\gamma < \frac{\alpha_2 K_2}{4} &\implies \text{no positive real solutions}\,.
\end{aligned} \tag{8}$$

To develop conditions necessary for an internal equilibrium first we solve system (7) by substituting for x_1 from the first equation into the second to obtain

$$a x_2^2 - b x_2 + \alpha_1 K_2 \gamma = 0\,, \tag{9}$$

where $a = \alpha_1 \alpha_2 - \beta_1 \beta_2 K_1 K_2$ and $b = K_2 \alpha_1 (\alpha_2 - K_1 \beta_2)$. The solutions of this quadratic equation are given by

$$x_2 = \frac{b \pm \sqrt{b^2 - 4 a \alpha_1 K_2 \gamma}}{2a}\,. \tag{10}$$

This x_2 defines the location of an internal equilibrium. The equilibrium from now on is labeled as $E^* = (x_1^*, x_2^*)$.

Conditions (2) $\implies b > 0$ since $\beta_2 K_1 < \alpha_2$. Variable a, however, may be positive, negative, or zero. Therefore, by conditions (6), the solution to (9) are:

$$\begin{aligned}
a < 0 \implies x_2^* &= \frac{b - \sqrt{b^2 - 4 a \alpha_1 K_2 \gamma}}{2a} && \text{is the only potential solution}\,, \\
a = 0 \implies x_2^* &= \frac{\gamma}{\alpha_2 - \beta_2 K_1} && \text{is the only possible solution}\,, \\
a > 0 \implies x_2^* &= \frac{b \pm \sqrt{b^2 - 4 a \alpha_1 K_2 \gamma}}{2a} && \text{gives two potential solutions}\,.
\end{aligned} \tag{11}$$

There may also be a single solution when Γ_3 is tangent to Γ_1. In this case, $x_2^* = \frac{b}{2a}$ and $\gamma = \frac{b^2}{4a\alpha_1 K_2} = \frac{\alpha_1 K_2}{4a}(\alpha_2 - \beta_2 K_1)^2$, or $\gamma = \frac{a(x_2^*)^2}{K_2\alpha_1}$. In order to have a solution in the first quadrant, x_1^* should also satisfy: $0 < x_1^* < K_1$. Thus (7) $\Longrightarrow 0 < x_2^* < \frac{\alpha_1}{\beta_1}$. We obtain the following further restrictions on γ:

$$
\begin{aligned}
&a < 0 \implies 0 < \gamma < \frac{\alpha_1\alpha_2}{\beta_1 K_2}\left(K_2 - \frac{\alpha_1}{\beta_1}\right), \\
&a = 0 \implies 0 < \gamma < \frac{\alpha_1\alpha_2 - \alpha_1\beta_2 K_1}{\beta_1}, \\
&a > 0 \implies \begin{cases} 0 < \gamma < \dfrac{\alpha_1\alpha_2}{\beta_1 K_2}\left(K_2 - \dfrac{\alpha_1}{\beta_1}\right), & \text{(one solution)} \\ \dfrac{\alpha_1\alpha_2}{\beta_1 K_2}\left(K_2 - \dfrac{\alpha_1}{\beta_1}\right) < \gamma < \dfrac{\alpha_1 K_2}{4a}(\alpha_2 - \beta_2 K_1)^2, & \text{(two solutions)}. \end{cases}
\end{aligned}
\tag{12}
$$

Note that (12) must be satisfied concurrently with (2), (8) and (6) since the existence of internal solutions must guarantee the existence of solutions on the axis.

9.3.2 Stability of internal equilibria

The local stability of the internal equilibria may be determined by considering the variational matrix of system (3). Let M represent the variational matrix. Then

$$
\begin{aligned}
M &= \begin{bmatrix} \dfrac{\partial \dot{x}_1}{\partial x_1} & \dfrac{\partial \dot{x}_1}{\partial x_2} \\ \dfrac{\partial \dot{x}_2}{\partial x_1} & \dfrac{\partial \dot{x}_2}{\partial x_2} \end{bmatrix} \\
&= \begin{bmatrix} \alpha_1\left(1 - 2\dfrac{x_1}{K_1}\right) - \beta 1 x_2 & -\beta_1 x_1 \\ -\beta_2 x_2 & \alpha_2\left(1 - 2\dfrac{x_2}{K_2}\right) - \beta_2 x_1 \end{bmatrix}.
\end{aligned}
\tag{13}
$$

We would like to study the stability of the internal equilibrium, $E^* = (x_1^*, x_2^*)$. This equilibrium is found at the intersection of isoclines Γ_1 and Γ_3. Notice that when $\dot{x}_1 = 0, \beta_1 x_2 = \alpha_1\left(1 - \frac{x_1}{K_1}\right)$; and when $\dot{x}_2 = 0, \beta_2 x_1 + \frac{\gamma}{x_2} = \alpha_2\left(1 - \frac{x_2}{K_2}\right)$. Therefore, matrix (13) evaluated at $E^* = (x_1^*, x_2^*)$ is simplified to:

$$
M^* = \begin{bmatrix} -\alpha_1\dfrac{x_1^*}{K_1} & -\beta_1 x_1^* \\ -\beta_2 x_2^* & \dfrac{\gamma}{x_2^*} - \alpha_2\dfrac{x_2^*}{K_2} \end{bmatrix}. \tag{14}
$$

The eigenvalues are the solutions of the equation

$$\begin{aligned} 0 &= \det(\lambda I - M^*) \\ &= \lambda^2 + \lambda\Big(\alpha_1 \frac{x_1^*}{K_1} + \alpha_2 \frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*}\Big) \\ &\quad + \alpha_1 \frac{x_1^*}{K_1}\Big(\alpha_2 \frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*}\Big) - \beta_1\beta_2 x_1^* x_2^* \,. \end{aligned} \tag{15}$$

If $\alpha_2 \frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*} < 0$, then the eigenvalues are of opposite signs and the equilibrium is a saddle point. However if $\alpha_2 \frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*} > 0$, then $\alpha_1 \frac{x_1^*}{K_1}\left(\alpha_2 \frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*}\right) - \beta_1\beta_2 x_1^* x_2^*$ may be negative (a saddle point equilibrium), or positive. We simplify the expression

$$\begin{aligned} &\alpha_1 \frac{x_1^*}{K_1}\Big(\alpha_2 \frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*}\Big) - \beta_1\beta_2 x_1^* x_2^* \\ &= \frac{x_1^*}{x_2^* K_1 K_2}[{x_2^*}^2(\alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2) - \alpha_1 K_2 \gamma] \\ &= \frac{x_1^*}{x_2^* K_1 K_2}[{x_2^*}^2 a - \alpha_1 K_2 \gamma] \,. \end{aligned}$$

Since the equilibrium is located at x_2^* given by (10), we obtain the following:

$$\begin{aligned} &\frac{x_1^*}{x_2^* K_1 K_2}\Big[\Big(\frac{b \pm \sqrt{b^2 - 4a\alpha_1 K_2 \gamma}}{2a}\Big)^2 a - \alpha_1 K_2 \gamma\Big] \\ &= \frac{x_1^*}{x_2^* K_1 K_2}\Big[\frac{2b^2 \pm 2b\sqrt{b^2 - 4a\alpha_1 K_2\gamma} - 4a\alpha_1 K_2\gamma}{4a} - \alpha_1 K_2 \gamma\Big] \\ &= \frac{x_1^*}{2a x_2^* K_1 K_2}[b^2 \pm b\sqrt{b^2 - 4a\alpha_1 K_2\gamma} - 4a\alpha_1 K_2\gamma] \\ &= \frac{x_1^*}{2a x_2^* K_1 K_2}\Big[\Big(\sqrt{b^2 - 4a\alpha_1 K_2\gamma}\Big)^2 \pm b\sqrt{b^2 - 4a\alpha_1 K_2\gamma}\Big] \\ &= \frac{x_1^*\sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a x_2^* K_1 K_2}\Big(\sqrt{b^2 - 4a\alpha_1 K_2\gamma} \pm b\Big) \,. \end{aligned}$$

In the case where $a > 0$,

$$\begin{aligned} &\frac{x_1^*\sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a x_2^* K_1 K_2}\Big(\sqrt{b^2 - 4a\alpha_1 K_2\gamma} + b\Big) > 0 \,, \\ &\frac{x_1^*\sqrt{b^2 - 4a\alpha_1 K_2\gamma}}{2a x_2^* K_1 K_2}\Big(\sqrt{b^2 - 4a\alpha_1 K_2\gamma} - b\Big) < 0 \,. \end{aligned}$$

These expressions correspond to $x_2^* = \frac{b+\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ and to $x_2^* = \frac{b-\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ respectively. In the case where $a < 0$,

$$\frac{x_1^*\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2ax_2^* K_1 K_2}\left(\sqrt{b^2-4a\alpha_1 K_2\gamma}-b\right) < 0\,.$$

This expression corresponds to the only possible internal equilibrium when $a < 0$ located at $x_2^* = \frac{b-\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$.

Therefore, the equilibrium at $x_2^* = \frac{b-\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ is a saddle point for both $a < 0$ and $a > 0$.

The equilibrium at $x_2^* = \frac{b+\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ corresponds to positive $\alpha_2\frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*}$. Here

$$\alpha_1\frac{x_1^*}{K_1} + \alpha_2\frac{x_2^*}{K_2} - \frac{\gamma}{x_2^*} > 0 \Longrightarrow \mathrm{Re}(\lambda_{1,2}) < 0\,.$$

Therefore, the equilibrium at $x_2^* = \frac{b+\sqrt{b^2-4a\alpha_1 K_2\gamma}}{2a}$ is stable.

9.3.3 Conclusion

This model describes what is known, namely that the larger the value of γ, the better the control of the cancer cells. However, at the same time, the larger the γ, the greater the spillover to the healthy cells. In practical terms, a great deal of time is spent by medical researchers in finding the correct balance for radiation to control the cancer cells without doing too much damage to the normal cells.

9.4 Treatment by chemotherapy

The material from this section is based upon the Ph.D. work of Nani (1998). In the case that chemotherapy treatment is warranted, the chemotherapy agent acts like a predator on both healthy and cancer cells, by binding to them and killing them. The action of the agent on the cancer cells is desirable, but on the healthy cells is undesirable causing so-called side effects such as extreme nausea and hair loss. The object then is to design the chemotherapy agent where possible to maximize its effects on specific cancers at specific sites and to minimize the side effects.

We take as our model the system

$$\begin{aligned}
\dot{x}_1 &= \alpha_1 x_1\left(1-\frac{x_1}{K_1}\right) - \beta_1 x_1 x_2 - p_1(x_1)h(y)\,, \qquad x_1(0) \geq 0\\
\dot{x}_2 &= \alpha_2 x_2\left(1-\frac{x_2}{K_2}\right) - \beta_2 x_1 x_2 - p_2(x_2)h(y)\,, \qquad x_2(0) \geq 0\\
\dot{y} &= \varphi(x_1, x_2, y, t)\,, \qquad y(0) > 0
\end{aligned} \tag{16}$$

where $p_i(x_i)$ is the chemotherapic functional response on x_i, φ is the treatment strategy, $y(t)$ is the concentration of chemotherapy agent. $h(y)$ will be described below. All other parameters and functions are as in system (3).

Since $p_i(x_i)$ is the effect of a single chemotherapy binding site on $x_i, h(y)$ is the cumulative effects of a concentration of y binding sites. Generally $h(y)$ is nonlinear, but has the properties $h(0) = 0, h'(y) > 0$ for $y \geq 0$, there exists $0 < \overline{h} < \infty$ such that

$$\lim_{y \to \infty} h(y) = \overline{h} \tag{17}$$

(see Agur et al. 1992).

As for $p_i(x_i)$, they have the usual predator functional response properties

$$p_i(0) = 0\,, \quad p_i'(x_i) > 0 \quad \text{for} \quad x_i \geq 0\,, \tag{18}$$

(see Freedman and Waltman 1984).

$\varphi(x_1, x_2, y, t)$ will depend on the treatment strategy. We focus here on two types of treatments, namely continuous and periodic. We will discuss the continuous case in some detail, and very briefly discuss the periodic case. Details may be found in Nani (1998).

9.4.1 The continuous treatment case

In this case we take

$$\varphi(x_1, x_2, y, t) = \delta - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y)\,. \tag{19}$$

Here δ is the continuous infusion of chemotherapy concentration to the affected site in question, γ is the natural washout rate, and $\eta_i, i = 1, 2$ are the binding coefficients between the chemotherapy agent and the cells.

There are four possible equilibria in this case, namely

$$E_0(0, 0, y_0), \widehat{E}_1(\widehat{x}_1, 0, \widehat{y}_1), \widehat{E}_2(0, \widehat{x}_2, \widehat{y}_2), E^*(x_1^*, y_2^*, y_3^*)$$

where y_0 is the positive solution of $h(y) = \gamma^{-1}\delta$, providing it exits.

We now show that $\widehat{E}_1$ and $\widehat{E}_2$ always exist.

Theorem 1. *$\widehat{E}_i$ always exists with $0 < \widehat{x}_i < K_i$, $\widehat{y}_i > 0, i = 1, 2$, provided $\alpha_i \gamma > \delta p_i'(0)$ and $\overline{h} > \delta\gamma^{-1}$.*

Proof. We prove this for the case $i = 1$. The case $i = 2$ follows analogously.

$\widehat{x}_1$ and $\widehat{y}_1$ satisfy the system

$$\begin{aligned} \alpha_1 \widehat{x}_1 \Big(1 - \frac{\widehat{x}_1}{K_1}\Big) - p_1(\widehat{x}_1)h(\widehat{y}) &= 0 \\ \delta - [\gamma + \eta_1 p_1(\widehat{x}_1)]h(\widehat{y}) &= 0\,. \end{aligned} \tag{20}$$

Substituting

$$h(\widehat{y}) = \frac{\delta}{\gamma + \eta_1 p_1(\widehat{x}_1)} \tag{21}$$

into the first equation of (20) and writing $p_1(\widehat{x}_1) = \widehat{x}_1\widetilde{p}_1(\widehat{x}_1)$ (since $p_1(0) = 0$ and $p_1'(0)$ exists), we get that for $\widehat{x}_1 > 0$,

$$\alpha_1\Big(1 - \frac{\widehat{x}_1}{K_1}\Big)\left(\gamma + \eta_1\widehat{x}_1\widetilde{p}_1(\widehat{x}_1)\right) = \delta\widetilde{p}_1(\widehat{x}_1)\,. \tag{22}$$

Note that $\widetilde{p}_1(0) = p_1'(0) > 0$. Writing (22) as $F_1(\widehat{x}_1) = G_1(\widehat{x}_1)$, we easily see that $F_1(0) = \alpha_1\gamma > 0, F_1(K_1) = 0, G_1(0) = \delta p_1'(0), G_1(K_1) = \delta\widetilde{p}_1(K_1) > 0$. Since by hypothesis $F_1(0) > G_1(0)$ and $F_1(K_1) < G_1(K_1)$, there exists a $0 < \widehat{x}_1 < K_1$ such that (22) holds. Then from (21), $h(\widehat{y}) > 0$ exists and therefore $\widehat{y} > 0$ exists.

To check whether E^* exists, one must solve the full algebraic system, writing $p_i(x_i) = x_i\widetilde{p}_i(x_i), i = 1, 2,$

$$\begin{aligned}
\alpha_1\Big(1 - \frac{x_1}{K_1}\Big) - \beta_1 x_2 - \widetilde{p}_1(x_1)h(y) &= 0\\
\alpha_2\Big(1 - \frac{x_2}{K_2}\Big) - \beta_2 x_1 - \widetilde{p}_2(x_2)h(y) &= 0\\
\delta - [\gamma + \eta_1 x_1\widetilde{p}_1(x_1) + \eta_2 x_2\widetilde{p}_2(x_2)]h(y) &= 0\,.
\end{aligned} \tag{23}$$

Substituting

$$h(y) = \frac{\delta}{\gamma + \eta_1 x_1\widetilde{p}_1(x_1) + \eta_2 x_2\widetilde{p}_2(x_2)} \tag{24}$$

into the first two equations of (23) gives the algebraic system

$$\begin{aligned}
\Big[\alpha_1\Big(1 - \frac{x_1}{K_1}\Big) - \beta_1 x_2\Big][\gamma + \eta_1 x_1\widetilde{p}_1(x_1) + \eta x_2\widetilde{p}_2(x_2)] &= \delta\widetilde{p}_1(x_1)\\
\Big[\alpha_2\Big(1 - \frac{x_2}{K_2}\Big) - \beta_2 x_1\Big][\gamma + \eta_1 x_1\widetilde{p}_1(x_1) + \eta_2 x_2\widetilde{p}_2(x_2)] &= \delta\widetilde{p}_2(x_2)\,.
\end{aligned} \tag{25}$$

As before, if $x_1^*, x_2^* > 0$ exists, then from (24) so does $y^* > 0$.

It is extremely difficult to see whether or not system (25) has a positive solution. Hence we take a different approach to obtain criteria for the existence of E^*, namely persistence theory. In order to do so, we will need the variational matrices about $E_0, \widehat{E}_1$, and $\widehat{E}_2$.

The general variational matrix about an equilibrium $(\overline{x}_1, \overline{x}_2, \overline{y})$ is given by

$$\overline{M} = \begin{bmatrix}
\alpha_1\Big(1 - \frac{2\overline{x}_1}{K_1}\Big) - \beta_1\overline{x}_2 & -\beta_1\overline{x}_1 & -p_1(\overline{x}_1)h'(\overline{y})\\
-p_1'(\overline{x}_1)h(\overline{y}) & & \\
-\beta_2\overline{x}_2 & \alpha_2\Big(1 - \frac{2\overline{x}_2}{K_2}\Big) - \beta_2\overline{x}_1 & -p_2(\overline{x}_2)h'(\overline{y})\\
 & -p_2'(\overline{x}_2)h(\overline{y}) & \\
-\eta_1 p_1'(\overline{x}_1)h(\overline{y}) & -\eta_2 p_2'(\overline{x}_2)h(\overline{y}) & -[\gamma + \eta_1 p_1(\overline{x}_1)\\
 & & +\eta_2 p_2(\overline{x}_2)]h'(\overline{y})
\end{bmatrix}.$$

This implies, after some simplifications

$$M_0 = \begin{bmatrix} \alpha_1 - p_1'(0)h(y_0) & 0 & 0 \\ 0 & \alpha_2 - p_2'(0)h(y_0) & 0 \\ -\eta_1 p_1'(0)h(y_0) & -\eta_2 p_2'(0)h(y_0) & -\gamma h'(y_0) \end{bmatrix}$$

$$\widehat{M}_1 = \begin{bmatrix} -\frac{\alpha_1 \widehat{x}_1}{K_1} + \{\widetilde{p}_1(\widehat{x}_1 & -\beta_1 \widehat{x}_1 & -p_1(\widehat{x}_1)h'(\widehat{y}_1) \\ -p_1'(\widehat{x}_1)\}h(\widehat{y}_1) & & \\ 0 & \alpha_2 - \beta_2 \widehat{x}_1 - p_2'(0)h(\widehat{y}_1) & 0 \\ -\eta_1 p_1'(\widehat{x}_1)h(\widehat{y}_1) & -\eta_2 p_2'(0)h(\widehat{y}_1) & -[\gamma + \eta_1 p_1(\widehat{x}_1)]h'(\widehat{y}_1) \end{bmatrix}$$

$$\widehat{M}_2 = \begin{bmatrix} \alpha_1 - \beta_1 \widehat{x}_2 - p_1'(0)h(\widehat{y}_2) & 0 & 0 \\ -\beta_2 \widehat{x}_2 & -\frac{\alpha_2 \widehat{x}_2}{K_2} + \{\widetilde{p}_2(\widehat{x}_2) & -p_2(\widehat{x}_2)h'(\widehat{y}_2) \\ & -p_2'(\widehat{x}_2)\}h(\widehat{y}_2) & \\ -\eta_1 p_1(0)h(\widehat{y}_2) & -\eta_2 p_2'(\widehat{x}_2)h(\widehat{y}_2) & -[\gamma + \eta_2 p_2(\widehat{x}_2)]h'(\widehat{y}_2) \end{bmatrix}.$$

First we examine M_0. The eigenvalues of M_0 are given by

$$\alpha_1 - p_1'(0)h(y_0)\,, \quad \alpha_2 - p_2'(0)h(y_0) \quad \text{and} \quad -\gamma h'(y_0)\,.$$

From this, E_0 is clearly locally stable in the y direction and is locally stable or unstable in the x_i direction according to whether $\alpha_i - p_i'(0)h(y_0)$ is negative or positive.

The important concern is with $\alpha_2 - p_2'(0)h(y_0)$, for if this expression is negative, then cancer can be eradicated if caught in time. However, at the same time we would want $\alpha_1 - p_1'(0)h(y_0) > 0$ so that the healthy cells survive.

Finally for persistence to hold according to techniques developed in Freedman and Waltman (1984), we would require E_0 to be unstable, and for $\widehat{E}_i$ to be unstable locally in the j direction, $i, j = 1, 2, j \neq i$. Hence the criteria for persistence are as follows:

$$\begin{aligned} \alpha_1 - \beta_1 \widehat{x}_2 - p_1'(0)h(\widehat{y}_2) > 0\,, \\ \alpha_2 - \beta_2 \widehat{x}_1 - p_2'(0)h(\widehat{y}_1) > 0\,, \end{aligned} \tag{26}$$

and one of

$$\alpha_i - p_i'(0)h(y_0) > 0\,, \quad i = 1, 2\,.$$

Finally from results given in Butler et al. (1986), if (26) holds, then E^* exists.

9.4.2 Periodic treatment

In actual practice, a form of periodic treatment is employed. Typically, the cancer patient is given a fixed number of doses over a fixed period of time at regular intervals. This may be approximated by a periodic step function.

In general, we let

$$\varphi(x_1, x_2, y, t) = f(t) - [\delta + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y) \,, \tag{27}$$

where $f(t) \geq 0$ and $f(t + \omega) = f(t)$. With this form of $\varphi(x_1, x_2, y, t)$ as given by (27), there can be no interior equilibrium. Hence if cancer cannot be forced to extinction (which is the usual case), criteria need to be developed for there to exist a positive periodic solution to system (16) with low values of x_2. I will now briefly describe how to develop these criteria, but due to their complexity, will not state them here.

First note that by Massera's theorem (see Pliss (1966)) there is a positive periodic solution on the y-axis. Then using some standard bifurcation theory, one obtains criteria for a positive periodic solution in the $x_1 - y$ plane.

Now comes the tricky part. The idea is to develop criteria for this solution to bifurcate away from the plane into the positive $x_1 - x_2 - y$ space. One way of doing this is to use critical cases of the implicit function theorem (see Nani (1998)) and so obtain the required criteria.

9.4.3 Conclusion

Under appropriate circumstances, a periodic application of chemotherapy may force a periodic behaviour in the interactions between healthy and cancer cells and the chemotherapy agent. Again, this would be most likely if the cancer is detected at an early stage.

9.5 Treatment by immunotherapy

The material in this section is based on work done in Nani and Freedman (2000).

When cancer cells proliferate to a detectable threshold number at a given site, the body's own natural immune system is triggered into a search-and-destroy mode. Unfortunately, the process of natural immune attack against immunogenic cancer is not always sustainable nor eventually successful and can always be terminated or downgraded due to various reasons, including insufficient lymphocytes, evasion by cancer cells or release of inhibitory substances by the cancer cells (Toledo-Pereya 1988), and for these reasons, the natural immune system cannot provide a therapeutically successful anti cancer attack.

This can be overcome to some extent by clinically extracting lymphocytes from the body, incubating these so called LAK cells outside the body for at least 48 hours, and then reintroducing them into the body.

This leads to the following model consisting of four ODEs:

$$\begin{aligned}
\dot{x}_1 &= \alpha_1 x_1\Big(1 - \frac{x_1}{K_1}\Big) - \beta_1 x_1 x_2\,, & x_1(0) \geq 0 \\
\dot{x}_2 &= \alpha_2 x_2\Big(1 - \frac{x_2}{K_2}\Big) - \beta_1 x_1 x_2 - h(x_3, w)\,, & x_2(0) \geq 0 \\
\dot{w} &= Q_1 - \gamma_1 e_1(w) + f(w, z) - \delta h(x_2, w)\,, & w(0) \geq 0 \\
\dot{z} &= Q_2 - \gamma_2 e_2(z) - \eta f(w, z)\,, & z(0) \geq 0\,.
\end{aligned} \tag{28}$$

Here $w(t)$ is the concentration of lymphocytes $z(t)$ is the concentration of LAC cells, $f(w, z)$ is the rate of lymphocyte proliferation due to the influence of LAC cells, $h(x_2, z)$ is the rate of cancer destruction by lymphocytes and Q_i are the respective rates of infusion of lymphocytes and LAC cells into the body. $\gamma_1 e_1(w)$ and $\gamma_2 e_2(z)$ are the natural death or washout rates of the lymphocytes and LAC cells respectively. δ is the proportionate combination of lymphocytes with cancer cells, and η is the proportionate influence of the lymphocytes on LAC cells. It is shown in Nani and Freedman (2000) that solutions of system (28) enter into a bounded invariant region and that the system is dissipative.

There are four possible equilibria for system (28) of the form

$$E_0(0, 0, \mathring{w}, \mathring{z})\,, \quad E_1(\overline{x}_1, 0, \overline{w}, \overline{z})\,, \quad E_2(0, \widehat{x}_2, \widehat{w}, \widehat{z})$$

and

$$E_3(x_1^*, x_2^*, w^*, z^*)\,.$$

The equilibrium of interest is E_1, for if E_1 is locally stable in the x_2 direction, then cancer could be eradicated if caught early enough. The variational matrix of system (28) about E_1, assuming it exists is

$$\begin{bmatrix}
-\alpha_1 & -\beta_1 K_1 & 0 & 0 \\
0 & \big(\alpha_2 - \beta_2 K_1 - h_{x_2}(0, \overline{w})\big) & -h_w(0, \overline{w}) & 0 \\
0 & -\delta h_{x_2}(0, \overline{w}) & -\gamma_1\, \mathrm{e}_1'(\overline{w}) + f_w(\overline{w}, \overline{z}) - \delta h_w(0, \overline{w}) & f_z(\overline{w}, \overline{z}) \\
0 & 0 & -\eta f_w(\overline{w}, \overline{z}) & -\gamma_2\, \mathrm{e}_2'(\overline{z}) - \eta f_z(\overline{w}, \overline{z})
\end{bmatrix}.$$

Then the local stability in the x_2 direction is given by $g(\overline{w}) = \alpha_2 - \beta_2 K_1 - h_{x_2}(0, \overline{w})$ assuming $h_w(0, w) = 0$ given the definition of $h(x_2, w)$. Hence if $g(\overline{w}) < 0$, cancer can be eradicated if caught early enough.

System (28) is analyzed in detail in Nani and Freedman (2000).

9.6 Metastasis

Metastasis means that the cancer has spread from one site to another. Usually the metastasis occurs one way only. It is very often the case that the cancer at the second site is much more deadly than at the first site. The material from this section is taken from Pinho et al. (2002).

We consider cancer at two sites treated by chemotherapy. This requires a system of six ODE's. We let $x_1(t)$ and $x_2(t)$ be the concentration of healthy and cancer cells respectively at the primary site and $u_1(t)$ and $u_2(t)$ be the concentration of healthy cells and cancer cells respectively at the secondary site. We further let $y(t)$ and $z(t)$ be the concentration of chemotherapy agent at the primary and secondary sites respectively. Thus our model becomes

$$\begin{aligned}
\dot{x}_1(t) &= \alpha_1 x_1(t)\left(1-\frac{x_1(t)}{K_1}\right) - \beta_1 x_1(t)x_2(t) - \frac{p_1 x_1(t)y(t)}{a_1+x_1(t)}\,,\\
&\quad x_1(0)\geq 0\\
\dot{x}_2(t) &= \alpha_2 x_2(t)\left(1-\frac{x_2(t)}{K_2}\right) - \beta_2 x_1(t)x_2(t) - \frac{p_2 x_2(t)y(t)}{a_2+x_2(t)} - \theta x_2(t)\,,\\
&\quad x_2(0)\geq 0\\
\dot{y}(t) &= \Delta - \Big[\xi + \frac{c_1 x_1(t)}{a_1+x_1(t)} + \frac{c_2 x_2(t)}{a_2+x_2(t)}\Big]y(t)\,,\\
&\quad y(0)\geq 0\\
\dot{u}_1(t) &= \gamma_1 u_1(t)\left(1-\frac{u_1(t)}{L_1}\right) - \delta_1 u_1(t)u_2(t) - \frac{s_1 u_1(t)z(t)}{b_1+u_1(t)}\,,\\
&\quad u_1(0)\geq 0\\
\dot{u}_2(t) &= \gamma_2 u_2(t)\left(1-\frac{u_2(t)}{L_2}\right) - \delta_2 u_1(t)u_2(t) - \frac{s_2 u_2(t)z(t)}{b_2+u_2(t)} + \varepsilon\theta x_2(t-\tau)\,,\\
&\quad u_2(0)\geq 0\\
\dot{z}(t) &= \Phi - \Big[\eta + \frac{d_1 u_1(t)}{b_1+u_1(t)} + \frac{d_2 u_2(t)}{b_2+u_2(t)}\Big]z(t)\,,\\
&\quad z(0)\geq 0\,,
\end{aligned} \tag{29}$$

where we have chosen specific functional responses for simplicity and all other constants have similar interpretations as before.

Here the new feature in this model is the introduced delay term in the fifth equation, $\varepsilon\theta x_2(t-\tau)$, which represents the fact that it takes time τ for the cancer growth to be triggered at the secondary site. Here θ is the proportion of cancer cells from the first site that are activated at the secondary site, a_i are the respective Michaelis-Menton growth constants for x_i, and b_i are similar for u_i. Note that system (29) simulates the continuous treatment case.

System (29) has nine possible equilibria of the form

$$F_0(0,0,\xi^{-1}\Delta,0,0,\eta^{-1}\Phi)\,, \qquad F_1(\widehat{x}_1,0,\widehat{y},0,0,\eta^{-1}\Phi)$$
$$F_2(0,0,\xi^{-1}\Delta,\widehat{u}_1,0,\widehat{z})\,, \qquad F_3(\widehat{x}_1,0,\widehat{y},\widehat{u}_1,0,\widehat{z})\,,$$
$$F_4(\widehat{x}_1,0,\widehat{y},0,\overline{u}_2,\overline{z})\,, \qquad F_5(0,\check{x}_2,\check{y},0,\check{u}_2,\check{z})$$
$$F_6(x_1^*,x_2^*,y^*,0,u_2^{\#},z^{\#})\,, \qquad F_7(0,\check{x}_2,\check{y},u_1^{\dagger},u_2^{\dagger},z^{\dagger})\,,$$
$$F_8(x_1^*,x_2^*,y^*,u_1^*,u_2^*,z^*)\,.$$

These are extremely difficult to analyze analytically. Here we will give some numerical results. A more detailed analysis can be found in Pinho et al. (2002).

The following three figures indicate a variety of behaviours of solutions, depending on parameters and initial conditions.

In Fig. 9.3, we see that at the primary site, cancer is eradicated, but at the secondary site after time τ, the cancer takes over and drives the healthy cells to extinction. Unfortunately, this is all too often the case.

In Fig. 9.4, the behaviour at the primary site is the same as in Fig. 9.3, but at the secondary site, wild chaotic oscillations occur. This unpredictability makes it extremely difficult to prescribe treatment. This corresponds to cases where cancer seems to go in and out of remission until the body succumbs.

Finally Fig. 9.5 shows that for certain cancers and chemotherapies, the cancer can be controlled at both sites.

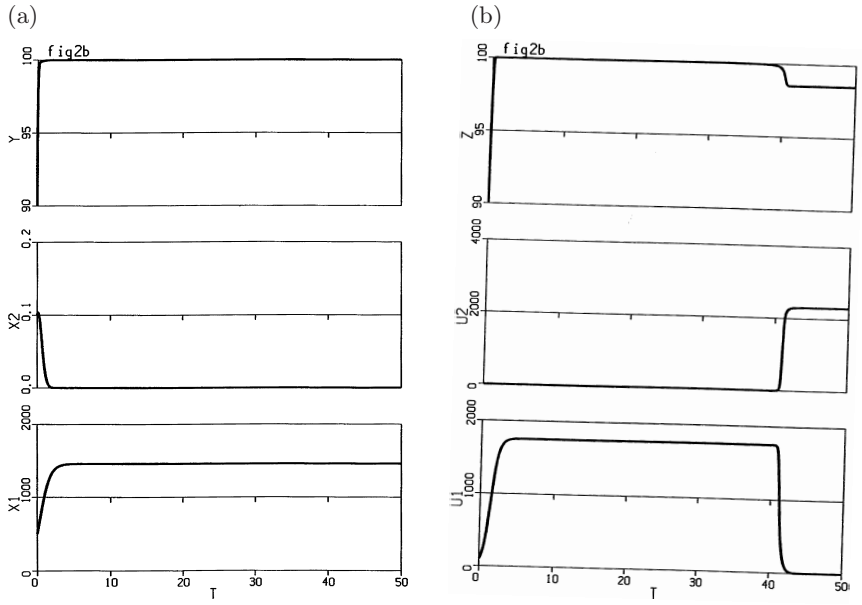

Fig. 9.3. a Cancer eradicated at primary site. **b** Cancer outcompetes normal cells at secondary site

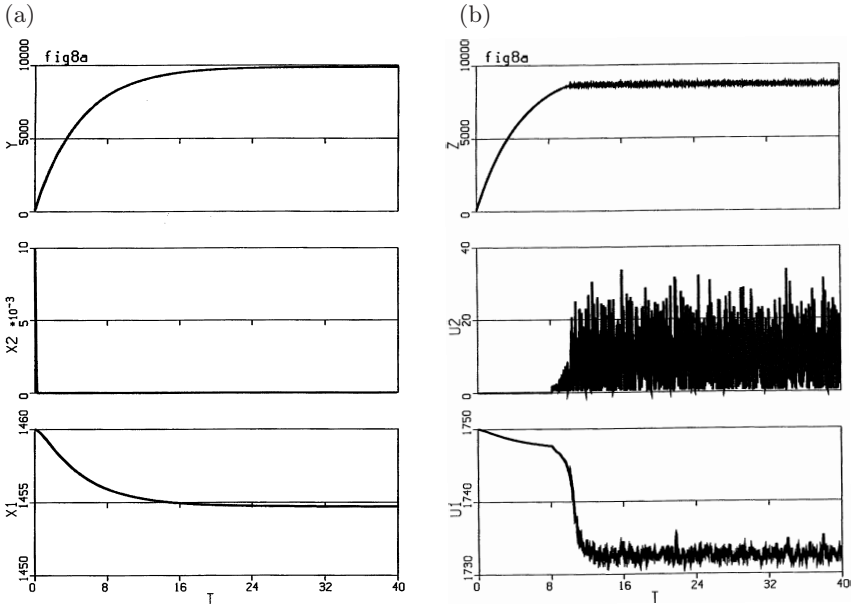

Fig. 9.4. a Cancer eradicated at primary site. **b** Chaotic behavior at secondary site

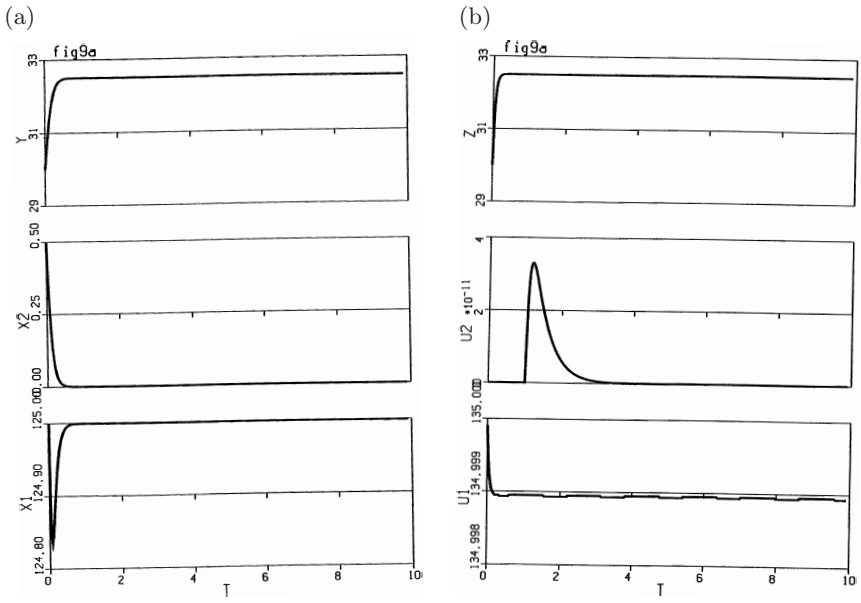

Fig. 9.5. Cancer eradicated at both primary and secondary sites

9.7 Discussion

In this paper we have briefly described various models of cancer treatment by radiotherapy, chemotherapy and immunotherapy. In all cases, we have shown that it is possible to drive the cancer extinct provided that it is caught early enough, and depending on the type of cancer.

However, we note that there are certain types of cancers, such as leukemia, for which these models do not apply. It is the purpose of future investigations to develop more robust models which do apply to other cancers.

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