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Bifurcation Analysis of a Mathematical Model of Tumor Growth in MCF-7 Breast Cancer Cell Line

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Abstract

Breast cancer is the second leading cause of cancer death for women worldwide. In this study, a previously published mathematical model of breast cancer in MCF-7 cell line is considered. The interaction among tumor cells, estradiol, natural killer (NK) cells, cytotoxic T lymphocytes (CTLs) or CD8+ T cells, and white blood cells (WBCs), is described by ordinary differential equations (ODEs). The system exhibits three coexisting stable equilibrium points which resemble the 3 E's (elimination, equilibrium, and escape) of cancer immunoediting. In this paper, a numerical method based on adaptive grid method is employed for bifurcation analysis of the mathematical model. Bifurcation analysis is performed for some important parameters for which changes in value result in changes in the stability of steady states. The results obtained from the bifurcation analysis may provide useful information about treatment strategy in further studies.

1 Introduction

Breast cancer is the second most common cancer in women worldwide [7, 8], and it is a heterogeneous disease. Approximately 75% of breast cancer cases are ER+ [14]. The MCF-7 cell line is a common in vitro model used for studies on ER+ breast cancer. Simms et al. [16] have presented a mathematical model of cell cycle progression and applied the mathematical model to the MCF-7 cell line to investigate cell proliferation and the effect of treatment using tamoxifen. Oke et al. [13] have proposed a mathematical model for ER+ breast cancer with optimal control analysis. Wei [20] has introduced a mathematical model for tumor growth in MCF-7 breast cancer cell line with interaction among the cancer cells and immune cells. This work is motivated by the mathematical model developed by Wei [20]. The model was based on several experiments conducted by Nawata et al. [12], Caragine et al. [3], Müller et al. [10], Chen et al. [4], using MCF-7 breast cancer cells. The mathematical model exhibits multistability where the tumor free, microscopic tumor, and large tumor steady states are stable. The phenomena resemble the 3 E's of cancer immunoediting [6, 11]. Numerical simulation using direct integration has shown that immune system strength is important in determining whether or not an immune system is able to eliminate a small tumor or produce long-term dormancy.

Bifurcation analysis is a powerful tool to study the changes in dynamics as parameter values vary. Identifying the parameters for which changes in value lead to changes in dynamics of the

mathematical model can provide useful information about the treatment strategy. Recently, numerical methods for bifurcation analysis have been developed for ODE systems with periodically pulsed therapies [18, 19, 21]. These numerical methods are based on adaptive grid technique for bifurcations of fixed points in ODE systems with periodically pulsed inputs. In this paper, the numerical methods is to be applied to the mathematical model for the identification of periodic solutions and bifurcation curves where a fixed point changes its stability. Computation of bifurcation curves provides an efficient means to find the sets of parameter values at which the system changes its asymptotic behavior. This can help identify important parameters that affect tumor population dynamics and manage treatment strategy.

To provide details, the numerical approach for locating periodic solutions is presented in Section 2. Numerical examples and discussion are given in Section 3. Finally, a brief conclusion is made in Section 4.

2 Numerical methods for locating the periodic solutions

2.1 Mathematical model

The mathematical model proposed by Wei [20] is as follows:

$$\begin{aligned}
\frac{dT}{dt} &= T(a+\frac{cET}{1+\alpha_1 E+\beta_1 T^2})(1-T/K)-\frac{p_1 TN^2}{1+\alpha_2 T+\beta_2 N^2} \\
&\quad -\frac{p_6 T^2 L}{1+\alpha_6 T^2+\beta_6 L}, \qquad (1)\\
\frac{dN}{dt} &= eC-fN-p_2 NT+\frac{p_3 NT}{1+\alpha_3 T+\beta_3 N}, \qquad (2)\\
\frac{dL}{dt} &= (p_4 L_N+\frac{p_5 I}{\alpha_4+I}L)(1-L/K_L)\frac{T}{\alpha_5+T}-dL, \qquad (3)\\
\frac{dC}{dt} &= \alpha-\beta C, \qquad (4)\\
E(t) &= \tilde{E}(t-n\tau), \quad t\in[n\tau,(n+1)\tau), \qquad (5)
\end{aligned}$$

where $E(t)$ is a periodic function and t is in days. The model consists of five state variables: the MCF-7 tumor cell population T (cells), the circulating level of estradiol E (pmol/L), NK cell population N (cells/L), CTL (or CD8+ T) cell population L (cells/L), and WBC population C (cells/L). Parameters a and K are growth rate and carrying capacity of tumor cells, respectively; I is the concentration of interleukin 2(IL-2) and p_5 is the maximum growth rate of CTLs induced by IL-2; L_N, p_4, K_L, and d represent naive CTL population, the fraction of naive CTLs that become activated, the carrying capacity of CTLs, and the death rate of CTLs, respectively; e, f, and p_2 are fraction of WBCs that become NK cells, death rate of NK cells, and NK cell inactivation rate by tumor cells, respectively; p_3 is related to NK cell recruitment rate and c is related to the growth rate of tumor cells induced by circulating level of estradiol; α_i for $i=1\cdots 6$ and β_i for $i=1,2,3,6$ are related to half saturation constants; p_1 and p_6 are rates of NK- and CTL-induced tumor death, respectively; α and β are production rate and death rate of WBCs, respectively. The parameter values are summarized and shown in Table 1.

Table 1: Parameter values in Eqs. (1)-(5).

Parameter	Value	Units
a	0.3	Day^{-1}
c	1.93×10^{-6}	$\text{L Cell}^{-1}\ \text{Day}^{-1}\ \text{pmol}^{-1}$
α_1	0.507	L pmol^{-1}
β_1	7.08×10^{-8}	Cell^{-1}
K	10^9	Cell
p_1	8.7×10^{-4}	$\text{L}^2\ \text{Cell}^{-2}\ \text{Day}^{-1}$
α_2	7×10^6	Cell^{-1}
β_2	5.4×10^{-5}	$\text{L}^2\ \text{Cell}^{-2}$
β	6.3×10^{-3}	Day^{-1}
α	3.6×10^7	$\text{Cell L}^{-1}\ \text{Day}^{-1}$
e	0.00486	Day^{-1}
f	0.0693	Day^{-1}
p_2	3.42×10^{-6}	Cell Day^{-1}
p_3	1.87×10^{-8}	$\text{Cell}^{-1}\ \text{Day}^{-1}$
α_3	1.6×10^{-5}	Cell^{-1}
β_3	3.27	L Cell^{-1}
p_6	2.04×10^{-3}	$\text{L Cell}^{-2}\ \text{Day}^{-1}$
α_6	0.268	Cell^{-2}
β_6	4343	L Cell^{-1}
L_N	2.3×10^8	Cell L^{-1}
K_L	8×10^8	Cell L^{-1}
p_4	9×10^{-5}	Day^{-1}
I	2.3×10^{-11}	g L^{-1}
α_4	2.3×10^{-11}	g L^{-1}
p_5	4.14	$\text{L Cell}^{-2}\ \text{Day}^{-1}$
d	0.41	Day^{-1}
α_5	1000	Cell

2.2 Stability of the tumor-free equilibrium

The tumor-free equilibrium E_0 of Eqs. (1)-(5) is $(T, N, L, C) = (0, \frac{e\alpha}{f\beta}, 0, \alpha/\beta)$. Let $C_p = \alpha/\beta$ and thus $N_p = eC_p/f$. Then, the Jacobian matrix at E_0 is

$$J(E_0) = \begin{bmatrix} a - \frac{p_1 N_p^2}{1+\beta_2 N_p^2} & 0 & 0 & 0 \\ -p_2 N_p + \frac{p_3 N_p}{1+\beta_3 N_p} & -f & 0 & e \\ p_4/\alpha_5 & 0 & -d & 0 \\ 0 & 0 & 0 & -\beta \end{bmatrix}. \tag{6}$$

The tumor-free equilibrium is stable if $a < \frac{p_1 N_p^2}{1+\beta_2 N_p^2}$.

2.3 Numerical methods for locating periodic solutions

Since the circulation estradiol level $E(t)$ is a periodic function with period $\tau = 29$, the system, Eqs. (1)-(5), has equilibrium point only when $T = 0$. However, the system may have periodic solutions of period τ. In fact, numerical simulation conducted by Wei [20] has shown that the system has stable periodic solutions with small oscillations in population levels. To find periodic solutions, it may be assumed that $C(t)$ has reached its equilibrium population level and thus the system, Eqs. (1)-(5), is reduced to Eqs. (1)-(3) and (5) with $C = \alpha/\beta$. Let

$F(t) = (T(t), N(t), L(t))$. A periodic solution satisfies $F(\tau) - F(0) = 0$ which is to be solved by Newton's method.

Let $T(0) = T_0$, $N(0) = N_0$, and $L(0) = L_0$, and let the Jacobian matrix of the right hand side of Eqs. (1)-(3) be J. The Jacobian matrix

$$A(t) = \begin{bmatrix} \partial T/\partial T_0 & \partial T/\partial N_0 & \partial T/\partial L_0 \\ \partial N/\partial T_0 & \partial N/\partial N_0 & \partial N/\partial L_0 \\ \partial L/\partial T_0 & \partial L/\partial N_0 & \partial L/\partial L_0 \end{bmatrix}. \tag{7}$$

satisfies

$$A'(t) = JA(t), \qquad A(0) = I_{3\times 3}. \tag{8}$$

Recall that the system has a stable tumor-free equilibrium and two stable periodic solutions with small oscillations for the set of parameter values shown in Table 1. This also implies that the system has two unstable periodic solutions. Locating each of the periodic solutions requires solving (8) and an initial guess for Newton's method. In this paper, the initial guess is obtained by finding all the equilibrium points for Eqs. (1)-(3) with $E(t)$ replaced by its average value over $[0, \tau]$, which is $\bar{E} = \int_0^\tau E(t)dt/\tau$. Note that these initial guesses satisfy

$$\begin{aligned} 0 &= (a + \frac{c\bar{E}T}{1 + \alpha_1\bar{E} + \beta_1 T^2})(1 - T/K) - \frac{p_1 N^2}{1 + \alpha_2 T + \beta_2 N^2} \\ &\quad - \frac{p_6 TL}{1 + \alpha_6 T^2 + \beta_6 L}, \end{aligned} \tag{9}$$

$$0 = eC - fN - p_2 NT + \frac{p_3 NT}{1 + \alpha_3 T + \beta_3 N}, \tag{10}$$

$$0 = (p_4 L_N + \frac{p_5 I}{\alpha_4 + I} L)(1 - L/K_L)\frac{T}{\alpha_5 + T} - dL. \tag{11}$$

The variable L can be expressed in terms of T from Eq. (11) and then N can be written in terms of T and L from Eq. (9). Next, consider an evenly spaced grid over $[0, \log K]$. Let x_i be the ith grid point in $[0, \log K]$ and $T_i = 10^{x_i}$. Then, evaluate the right hand side of Eq. (10), and an equilibrium point might exist for $T \in (T_i, T_{i+1})$ if the right hand sides of Eq. (10) have different signs at T_i and T_{i+1}. Use a T value in (T_i, T_{i+1}), an L value obtained from (11), and an N value obtained from Eq. (9) as an initial guess for Newton's method to solve Eqs. (9)-(11). The resulting equilibrium points are then used as initial guesses for solving $F(\tau) - F(0) = 0$.

3 Numerical examples and discussion

It has been reported that a level of ER greater than 5 fmoles/mg protein indicates an ER positive breast cancer [2, 15]. The breast cancer patients may have a level of ER greater than 300 fmoles/mg [1] depending on individual variation. This implies that tumor cell proliferation induced by estradiol stimulation varies in individual patients and c values may vary largely in ER+ breast cancer patients. Recent immunotherapy based on enhancing T cell response to tumor cells, such as anti PD-1 antibody therapy, has shown promising response rates [5]. The parameter p_6 is related to T cell response to tumor cells. Thus, parameters c and p_6 are used as bifurcation parameters in the first numerical example.

Fig. 1(a) shows the regions in which the system has different asymptotic properties on the parameter domain $[10^{-6}, 10^{-3}] \times [10^{-3}, 4 \times 10^{-2}]$. Let E_1 denote the small tumor periodic solution and E_2 denote the large tumor periodic solution. Note that E_0, and E_1, and E_2 are

stable solutions. The immune system is able to eliminate or regress a large tumor when CTLs display strong responses ($p_6 > 0.33$) against tumors. Coexistence of E_0, E_1, and E_3 in a large region shows that a normal immune system is able to eliminate a small tumor or control a small tumor producing long-term dormancy. There are two regions in which E_0 and E_2 exist. Fig. 1(b) shows that the immune system is able to eliminate a tumor of moderate size (2×10^8 cells) in the region with small ER levels while Fig. 1(c) shows that a small tumor of 2×10^6 cells grows to its carrying capacity in the region with small CTL response.

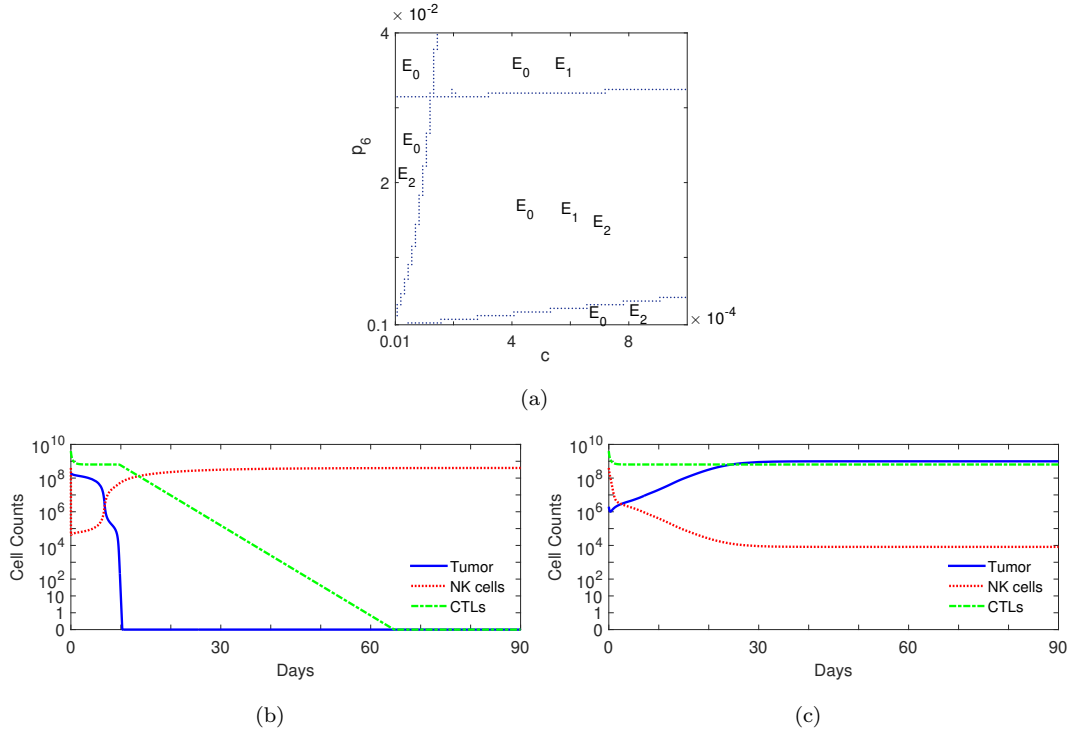

Figure 1: (a) Bifurcation diagram using c and p_6 as bifurcation parameters. Cell population dynamics for (b) $c = 4 \times 10^{-4}$ and $p_6 = 10^{-3}$ with initial condition $(T(0), N(0), L(0)) = (2 \times 10^6, 4 \times 10^8, 4 \times 10^9)$, and (c) $c = 2 \times 10^{-6}$ and $p_6 = 10^{-3}$ with initial condition $(T(0), N(0), L(0)) = (2 \times 10^8, 4 \times 10^8, 4 \times 10^9)$.

Combination therapy with two or more drugs for cancer treatment has been shown to be more effective than monotherapy [22]. It can achieve additive or synergistic effects with lower doses or lower toxicity drugs. Recent clinical trials have suggested combination therapy with a BCL-2 inhibitor and tamoxifen in ER positive breast cancer [9]. Tamoxifen is usually considered to be an estrogen antagonist to block estrogen receptors in mammary gland. BCL-2 is known to inhibit cell apoptosis. A BCL-2 inhibitor inhibits the activity of BCL-2 and restores apoptosis of tumor cells. Assuming that a BCL-2 inhibitor can enhance apoptosis of tumor cells so that the tumor grows less progressively upon the administration of a BCL-2 inhibitor. Consequently, this results in a smaller a values. In this example, parameter c and a are used as bifurcation parameters.

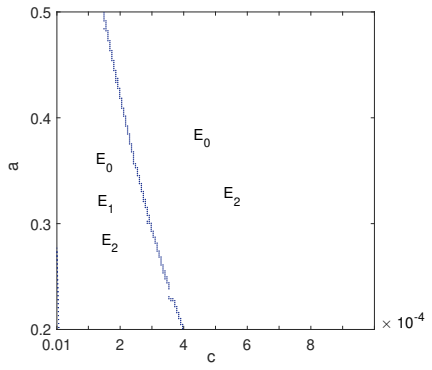

Figure 2: Bifurcation diagram using c and a as bifurcation parameters.

Fig. 2 shows the bifurcation diagram on the parameter domain $[10^{-6}, 10^{-3}] \times [0.2, 0.5]$. The system has stable solutions E_0 and E_2 in the region where the tumor has a high ER level. A small tumor will grow to its carrying capacity. The situation is similar to that shown in Fig. 1(c). The use of drugs that block estrogen receptors can lower c values and consequently decrease tumor proliferation induced by estrogen stimulation. As the c value decreases, it brings the system to the region where E_0, E_1, and E_2 exist. The immune system is able to eliminate a small tumor or produce long term dormancy. Interestingly note that reducing the a value can change the system's asymptotic behavior only when $c \in [2.5 \times 10^{-4}, 4 \times 10^{-4}]$. This implies that drugs, such as a BCL-2 inhibitor, that can reduce tumor growth rate may not be effective when used alone. However, reducing tumor growth rate combines with reducing ER levels may produce synergistic effect. In fact, Vaillant et al. [17] have reported that the administration of ABT-199, a BCL-2 inhibitor, alone is ineffective in ER+ breast cancer but combining ABT-199 with tamoxifen can produce synergistic effect.

4 Conclusion

This paper which is based on a mathematical model previously developed by Wei [20] studies bifurcations of the model. The condition for which the tumor-free equilibrium is stable has been proven. Then, numerical techniques based on an adaptive grid method have been proposed to perform bifurcation analysis. Numerical simulation has shown that enhancing CTL response to tumor cells can help the immune system to control a large tumor. Cancer treatment such as tumor infiltrating lymphocyte (TIL) therapy together with checkpoint inhibitor (such as anti-PD-1 or anti-PD-L1 drugs) may be used to enhance the anti-tumor activity of CTLs. Numerical simulation has also shown that decreases in tumor cell growth rate may be ineffective when the tumor has high ER levels. Combination therapy, such as BCL-2 inhibitor with tamoxifen that slows tumor growth and reduces ER levels may produce synergistic effects.

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