DJS Vol. 38 (2017) 53- 62

Delta Journal of Science

Available online at

https://djs.journals.ekb.eg/

Research Article MATHEMATICS

On the dynamics of Kirschner tumor-immune model

A.Zaghrout[1], M.M.A.El-Sheikh[2], A.R. El-Namoury[3], and A.El-Ashry[3]

[1]Faculty of Science for girls, Department of Mathematics, Al-Azhar University, Egypt.
[2]Faculty of Science, Department of Mathematics, Menoufia University, Egypt..
E-mail: msheikh_1999@yahoo.com
[3]Faculty of Science, Department of Mathematics, Tanta University, Egypt..
E-mail: asmaa_el_ashry@yahoo.com

Abstract: A tumor-immune model of Kirschner type is considered. The boundedness of solutions are discussed. Criteria for existence and the stability of equiliria are established. Using similar technique to that we used before in the literature, we study the existence of Hopf-Andronov-Poincaré bifurcation. Using Liapunov function sufficient conditions are guaranteed the existence of a unique periodic asymptotically stable solution for the system are established. Numerical simulations are given to illustrate the results.

Key words: *Kirschner model, Equilibrium points, Global stability, Hopf bifurcation.*

1-Introduction:

Cancer still considered as one of major causes of death world wide. Cancer starts when unbounded growth of normal cells in the body happens fast. It can also occur when cells lose their ability to die. There are many known causes of cancers that have been documented to date including exposure to chemicals, drinking excess alcohol, excessive sunlight exposure, and genetic differences [10]. The most common cause of cancer-related death is lung cancer. However, the cause of many cancers still remains unknown. The kind of cancers differs from country to another for example, in Japan, there are many cases of stomach cancer, but this is not the case in other countries (see [12]). In 1920's Lotka and Volterra introduced the idea of using the qualitative theory of ordinary differential equations in mathematical biology, population models, and tumor-immune dynamics (for a good summry of this subject see [1], and [9]). In 1998 Kirschner and Panetta [7] improved the above works and introduced a 3-dimentinal model. They discussed stability analysis and bifurcation theory to classify behavior of equiliriaof the system. In 2009 Kirschner et al [8] established sufficient conditions that guarantee asymptotic convergence of concentrations of tumor cells using quasi-Liapunov functions technique. In 2012, Tsygvintsev et al [13], derived sufficient conditions for the global stability of the cancer-free equilibrium point.

In this paper we discuss Kirschner and Panetta model, analytically and numerically in a fashion like the work of El-Owaidy and El-Sheikh [5] , El-Sheikh and Mahrouf [2] and [3], Zaghrout and El-Sheikh [17] and El-Sheikh et al [4].The model in this paper can be summarized briefly as follows, tumor cells are tracked as a continuous variable as they are large and generally homogeneous; they are defined as y(t). Immune cells are those cells that have been stimulated and are ready to respond to the foreign matter (known as effector cells); they are defined as x(t) and assumed also to be large in number. Finally, effector molecules are represented by z(t).These are self-stimulating proteins for effector cells which produce them. The equations that describe the interactions of these state variables are given by the following mathematical system (see[7]):

$$\frac{dx}{dt} = cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1 \quad (1a)$$

$$\frac{dy}{dt} = r_2 y(1 - by) - \frac{\alpha xy}{g_2 + y} \quad (1b)$$

$$\frac{dz}{dt} = \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2. \quad (1c)$$

In equation (1a), the first term represents stimulation by the tumor to generate effector immune cells. The parameter c is known as the antigenicity or strength of this characteristic. The second term in (1a) represents natural death and the third is the proliferative enhancement effect of IL-2. s_1 represents a treatment term where by a physician administers effector cells that have been taken from a patient, stimulated to a large degree, and then subsequently infused back into the patient. In equation (1b), the first term is a logistic growth term for tumor growth, and the second is a clearance term by the effector cells. In equation (1c), IL-2 is produced by effector cells (in a Michaelis-Menton fashion, i.e. dose response) and decays via a known half-life (third term). The second term, s_2 is a treatment term that represents administration of IL-2 (manufactured) by a physician to a patient, to again stimulate effector cell growth and proliferation. To help with interpretation of the mathematical results, we present a table of parameters for ease of parameter interpretation:

c (antigenicity)
P_1 (proliferation rate of immune cells)
r_2 (cancer growth rate)
μ_3 (half-life of effector molecule)
g_1 (half sat. for proliferation term)
μ_2 (death rate of immune cells)
g_2 (half-sat. for cancer clearance)
b (logistic growth of cancer capacity)
p_2 (production rate of effector molecule)
α (cancer clearance term)
t (time)

Table 1.Parameter Values.

In the present paper we consider the case of immunotherapy with ACI and IL-Z (i.e. $s_1 > 0$, $s_2 > 0$). Our main aim is to discuss analytically the existence, stability, and bifurcation of the steady states and to improve some known results obtained for the Kirschner Panetta system (1). The paper is organized as follows, in Section 2, we discuss the dissipativeness and the existence of equiliria of the system . In Section 3, we study the stability in the neighborhood of each critical points. In Section 4 we give sufficient conditions for the permanence. In section 5 we establish sufficient conditions for existence of a unique asymptotically periodic solution using liapunov function. Our technique used in Sections 4 and 5 depends on those of [15]. Finally, in Section 6, we give numerical simulations to illustrate our theoretical results.

2-Existence and Dissipativeness

It is clear that the components of the right hand side of the system (1) have continuous partial derivatives on the space $R_+^3 = \{(x(t), y(t), z(t)) : x(t) \geq 0, y(t) \geq 0, z(t) \geq 0\}$. Therefore, the solution of the system (1) with non-negative initial conditions, exists and is unique.

Theorem 1 *The model system (1) is dissipative.*

Proof By (1b), we have

$$\frac{dy}{dt} \leq y(r_2(1 - by)$$

i.e.

$$y(t) \leq \frac{1}{b + k\exp(-r_2 t)}, \quad \text{for all } t \geq 0, \text{ where } k = \frac{1}{y(0)} - b.$$

Thus

$$y(t) \leq \frac{1}{b} \text{ as } t \to \infty.$$

This means that $y(t) \leq \frac{1}{b}$, for large $t > 0$. In fact this is consistent with [8].

Now putting

$W = x + y + z$, then

$$\frac{dW}{dt} \leq cy - \mu_2 x + \frac{p_1 x(g_1 + z)}{g_1 + z} + s_1 + r_2 y(1 - by) + \frac{p_2 x(g_3 + y)}{g_3 + y} - \mu_3 z + s_2.$$

But since $y \leq \frac{1}{b}$, we have

$$\frac{dW}{dt} + \theta W \leq s_1 + s_2 + \frac{r_2}{b}, \text{ where } \theta = \min(\mu_3, \mu_2 - (p_1 + p_2), r_2 - c).$$

So by comparison lemma we obtain,

$$W(t) \leq \frac{(s_1 + s_2 + \frac{r_2}{b})}{\theta} - \left(\frac{(s_1 + s_2 + \frac{r_2}{b})}{\theta} - W(\tilde{T})\right) \exp - \theta(t - \tilde{T}),$$

for all $t \geq T \geq 0$,

If $\tilde{T} = 0$, then

$$W(t) \leq \frac{(s_1 + s_2 + \frac{r_2}{b})}{\theta} - \frac{(s_1 + s_2 + \frac{r_2}{b})}{\theta} - W(0)\exp - \theta t$$

i.e.

$$W(t) < \frac{(s_1 + s_2 + \frac{r_2}{b})}{\theta} \qquad \forall t \geq 0.$$

So, it follows that all solutions of the system (1) that start in R^3_+ are confined to the region Ω, where

$$\Omega = \{(x,y,z) \in R^3_+ : W = \frac{(s_1+s_2+\frac{r_2}{b})}{\theta} + \varepsilon \text{ for } \varepsilon > 0\} \text{(see[6], and [14])}.$$

It is clear that the tumor free equilibrium point $E_1(x_1, 0, \frac{s_2}{\mu_3})$,

where $x_1 = \frac{s_1(g_1\mu_3+s_2)}{\mu_2(g_1\mu_3+s_2)-p_1s_2}$, exists if $p_1s_2 < \mu_2((g_1\mu_3+s_2)$.

Moreover there may exist multiple positive non-trivial steady states, depending on the choice of parameters, $E_i = (x_i, y_i, z_i)$ where i can range from 1 to 3. namel y

3- Local Stability and Hopf bifurcation

Since the Jacobian of the system (1) at any endemic point (x,y,z)

$$J(x,y,z) = \begin{bmatrix} \frac{p_1 z}{g_1+z} - \mu_2 & c & \frac{p_1 g_1 x}{(g_1+z)^2} \\ -\frac{\alpha y}{g_2+y} & r_2(1-2by) - \frac{\alpha g_2 x}{(g_2+y)^2} & 0 \\ \frac{p_2 y}{g_3+y} & \frac{g_3 p_2 x}{(g_3+y)^2} & -\mu_3 \end{bmatrix}.$$

The characteristic equation at the tumor free equilibrium point $E_1(x_1, 0, \frac{s_2}{\mu_3})$ is

$$[\frac{p_1 s_2}{g_1\mu_3+s_2} - \mu_2 - \lambda][r_2 - \frac{\alpha x_1}{g_2} - \lambda][-\mu_3 - \lambda].$$

The eigenvalues are

$$\lambda_1 = \frac{p_1 s_2}{g_1\mu_3+s_2} - \mu_2, \lambda_2 = r_2 - \frac{\alpha x_1}{g_2}, \lambda_3 = -\mu_3.$$

Then clearly equilibrium point E_1 is asymptotically stable

if $s_2 < \frac{\mu_2\mu_1 g_1}{p_1-\mu_2}$, and $s_1 > \frac{g_2\mu_2}{\alpha}[\frac{\mu_2\mu_3 g_1 + s_2(\mu_2-p_1)}{\mu_3 g_1 + s_2}]$, *and* unstable otherwise (This is consistent with [7]).

Now choosing c as a bifurcation parameter for the system (1). Let c_c be the value of c at which the characteristic equation on the neighborhood of E_i, has two pure imaginary roots $\lambda_{1,2}$.

In the following result, we deduce sufficient conditions that guarantee the occurrence of Hopf bifurcation.

Theorem 2 Suppose that the following conditions hold

(A_1) $\frac{p_1 z_i}{g_1+z_i} < \mu_2$

(A_2) $r_2(1-2by_i) < \frac{\alpha g_2 x_i}{(g_2+y_i)^2}$, and

(A_3) $\frac{p_1 p_2 x_i(g_2+y_i)}{c\alpha} < (g_1+z_i)^2(g_3+y_i)$

$< \frac{p_1 z_i(g_1+z_i)(g_3+y_i) + p_2 p_1 g_1 x_i y_i}{\mu_3\mu_2}$,

then at $c = c_c$ there exists a one parameter family of periodic solutions bifurcating from the critical point $E_i \equiv (x_i, y_i, z_i)$ with period T, where $T \to T_\circ$ as $c \to c_\circ$ and where $T_\circ = 2\pi/\omega_\circ = 2\pi/\sqrt{traceJ^c}$.

Proof. Since by the assumptions $(A_1)-(A_3)$, there exists at least one real root λ_3 of the cubic equation

$$\lambda^3\text{-}(traceJ)\,\lambda^2 + (traceJ^c)\,\lambda - \det J = 0, \quad (2)$$

where the matrix J^c is the first compound of J.

Now since

$$traceJ = \frac{p_1 z_i}{g_1+z_i} - \mu_2 - \mu_3 + r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2},$$

$$traceJ^c = \mu_3[\mu_2 - \frac{p_1 z_i}{g_1+z_i}] + [r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2}]$$
$$[\frac{p_1 z_i}{g_1+z_i} - \mu_2 - \mu_3] - \frac{p_2 p_1 x_i y_i}{(g_1+z_i)^2(g_3+y_i)} + \frac{c\alpha y_i}{g_2+y_i}, \text{ and}$$

$$\det J = -[\mu_3(\frac{p_1 z_i}{g_1+z_i} - \mu_2) + \frac{p_2 p_1 x_i y_i}{(g_1+z_i)^2(g_3+y_i)}]$$
$$[r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2}] - \frac{c\alpha y_i\mu_3}{g_2+y_i} -$$
$$\frac{\alpha g_1 g_3 p_2 p_1 x_i^2 y_i}{(g_1+z_i)^2(g_3+y_i)^2(g_2+y_i)}.$$

So we have the following factorization

$$(\lambda - \lambda_3)[\lambda^2 + (\lambda_3 - traceJ)\lambda + (\lambda_3^2 - (traceJ)\lambda + traceJ^c)] = 0. \quad (3)$$

But since by (2), we have

$$\lambda_1 + \lambda_2 + \lambda_3 = traceJ$$

Therefore the remaining roots λ_1, λ_2 of (2) are of the form

$$\lambda_{1,2} = \tfrac{1}{2}\{-[\lambda_3 - traceJ] \pm \sqrt{([\lambda_3 - traceJ]^2 - 4(\lambda_3^2 - (traceJ)\lambda + traceJ^c)}\}. \quad (4)$$

Going through as in [5] and [11], we see that at $c = c_c$ $\lambda_3 = traceJ$, $\lambda_1 = \overline{\lambda_2}$, moreover Eq (2) can be written as

$$F_c(traceJ) = (traceJ)(traceJ^c) - \det J = 0. \quad (5)$$

It is clear that $\lambda_3 = traceJ < 0$, $traceJ^c > 0$ and $\det J < 0$, since $\det J < 0, c > 0$, and $c = c_c > 0$ is a solution of the critical equation (5). In fact Eq (5) can be represented by the following straight line.

$a + bc = F_c(traceJ) = 0$, where

$$a=-[\frac{p_1 z_i}{g_1+z_i} - \mu_2][r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2}]$$
$$[\frac{p_1 z_i}{g_1+z_i} - \mu_2 - 2\mu_3 + r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2}] +$$
$$\mu_3^2[\frac{p_1 z_i}{g_1+z_i} - \mu_2 + r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2}] +$$
$$\frac{\alpha g_1 g_3 p_2 p_1 x_i^2 y_i}{(g_1+z_i)^2(g_3+y_i)^2(g_2+y_i)}[\frac{p_1 z_i}{g_1+z_i} - \mu_2 - \mu_3 +$$
$$r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2}] - [\frac{p_1 z_i}{g_1+z_i} - \mu_2]$$
$$[\mu_3(\frac{p_1 z_i}{g_1+z_i} - \mu_2) + \frac{g_1 p_2 p_1 x_i y_i}{(g_1+z_i)^2(g_3+y_i)}], \text{ and}$$
$$b=[\frac{p_1 z_i}{g_1+z_i} - \mu_2 - \mu_3 + r_2(1-2by_i) - \frac{\alpha g_2 x_i}{(g_2+y_i)^2}].$$

Conversely, knowing that

$\det J < 0$ and $traceJ < 0, c > 0$, we can solve equation (5) for $c_c > 0$, we then know that $traceJ^c_{c_c} > 0$, $\lambda_3 = traceJ_{c_c}$ and λ_1, λ_2 are conjugate imaginary.

Since $b > 0, \lim_{c\to\infty} F_c(traceJ) = -\infty$, and $\lim_{c\to-\infty} F_c(traceJ) = +\infty$,

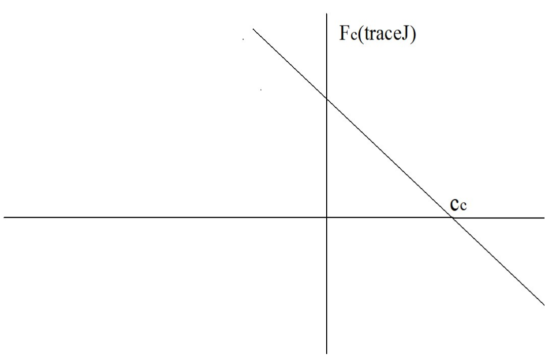


Fig.1. The uniqueness of the bifurcation parameter c_c

Now, since by (2), $\lambda_3 = traceJ$, and

$$F_{c_c}(traceJ) = [traceJ - \lambda_3][\lambda_1\lambda_2 + (traceJ)\lambda_3]$$
$$\operatorname{sgn} F_{c_c}(traceJ) = \operatorname{sgn}(traceJ).$$

Consequent ly if $c > c_c$ then $\operatorname{Re}\lambda_{1,2} = \frac{1}{2}(traceJ - \lambda_3) < 0$,

and for $c < c_c$, $\operatorname{Re}\lambda_{1,2} > 0$ (see Fig.1.)

By the above discussion, we see that as c increased through c_c, there exists a pair of complex conjugate imaginary eigenvalues $\lambda_{1,2}$ of the Jacobian matrix J^c.

Since at $c = c_c$, then $\lambda_3 = traceJ$, and $\lambda_{1,2} = \pm\sqrt{traceJ^c} = \pm i\omega_\circ$, where it is clear that $\omega_\circ > 0$.

Now, Since for $\lambda_1 = \overline{\lambda_2}$, we have

$\operatorname{Re}\lambda_{1,2} = \frac{1}{2}(\lambda_1 + \overline{\lambda_2}) = 0$ at $c = c_c$.

So, we have $\operatorname{Re}\lambda_{1,2} > 0$ for $c < c_c$,

$\operatorname{Re}\lambda_{1,2} > 0$ for $c < c_c$.

Moreover

$$\frac{d}{dc}(\operatorname{Re}\lambda_{1,2})\Big|_{c=c_c} = -\frac{1}{2}(\lambda_3 - trace)\Big|_{c=c_c} = \operatorname{Re}(\frac{d}{dc}\lambda_{1,2})\Big|_{c=c_c} < 0.$$

This completes the proof.

4-Permanence

We first give the following preliminaries.

Definition 1[15] We say that the system (1) is permanent if there are positive constants m and M such that for each positive solution $(x_1(t), x_2(t), x_3(t))$ of the system (1) satisfies $m \le \liminf_{t\to\infty} x_i(t) \le \limsup_{t\to\infty} x_i(t) \le M$, where $i = 1,2,3$.

Definition 2 [15] A solution $X(t, t_\circ, \phi)$ is called ultimately bounded. If there exists $B > 0$ such that for any, $t_\circ \ge 0, \phi \in C$, there exists $T = T(t_\circ, \phi) > 0$ when $t \ge t_\circ + T, |X(t, t_\circ, \phi| \le B$.

Lemma 1[15] If

$a > 0, b > 0$, and $\frac{dx}{dt} \ge x(b - ax)$, for $t \ge 0$, and $x(0) > 0$,

we have $\liminf_{t\to\infty} x(t) \ge \frac{b}{a}$, while if

$a > 0, b > 0$, and $\frac{dx}{dt} \le x(b - ax)$, for $t \ge 0$, and $x(0) > 0$,

we have $\limsup_{t\to\infty} x(t) \ge \frac{b}{a}$.

Now we give the following permanence result.

Theorem 3 Let M_1, M_2, M_3, m_1, m_2, and m_3 be defined by

$$M_1 = \frac{\frac{c}{b} + s_1}{\mu_2 - p_1}, M_2 = \frac{1}{b}, M_3 = \frac{p_2\mu_1 + s_1}{\mu_3}, m_1 = \frac{s_1}{\mu_2}, m_2 = \frac{g_2 r_2 - \alpha\mu_1}{g_2 r_2 b},$$

and $m_3 = \frac{s_2}{\mu_3}$. Further assume that

$(H_1): p_1 < \mu_2$, and

$(H_2): g_2 r_3 > \alpha M_1$, hold,

Then the system (1) is permanent. This means that there exist positive constants $m_i, M_i (i = 1,2,3)$ which are independent of the solutions of the system (1), such that for any positive solution $(x_1(t), x_2(t), x_3(t))$ of the system with the initial conditions

$$x_i(0) \geq 0 \; (i = 1,2,3),$$

we have

$$m_i \leq \liminf_{t\to\infty} x_i(t) \leq \limsup_{t\to\infty} x_i(t) \leq M_i.$$

Proof. Let $(x_1(t), x_2(t), x_3(t))$ be any positive solution of the system (1) with the initial value $(x_1(0), x_2(0), x_3(0))$. It follows from the first equation of (1) that

$$\frac{dx_1}{dt} = cx_2 - \mu_2 x_1 + \frac{p_1 x_1 x_3}{g_1 + x_3} + s_1.$$

Now by Theorem 1, we have

$$\frac{dx_1}{dt} \leq \frac{c}{b} + s_1 + (p_1(\frac{g_1 +_1 x_3}{g_1 + x_3}) - \mu_2)x_1.$$

i.e.

$$\frac{dx_1}{dt} - (p_1 - \mu_2)x_1 \leq \frac{c}{b} + s_1.$$

According to the theory of differential inequality , we get

$$x = \frac{\frac{c}{b} + s_1}{\mu_2 - p_1} + [\frac{\frac{c}{b} + s_1}{\mu_2 - p_1} + x(0)] \exp(p_1 - \mu_2)t.$$

Further since $p_1 < \mu_2$, then

$$\limsup_{t\to\infty} x_1(t) \leq \frac{\frac{c}{b} + s_1}{\mu_2 - p_1} = M_1. \qquad (6)$$

Thus for any positive constant $\varepsilon > 0$, it follows from (6) that there exists a $T_1 > 0$ such that for all $t > T_1$, we have

$$x_1 \leq M_1 + \varepsilon. \qquad (7)$$

Similarly by the second equation of the system , we have by Lemma 1,

$$\limsup_{t\to\infty} x_2(t) \leq \frac{1}{b} = M_2. \qquad (8)$$

Consequently for $\varepsilon > 0$, it follows that there exists a $T_2 > 0$ such that for all $t > T_2$, we get

$$x_2 \leq M_2 + \varepsilon \qquad (9)$$

Similarly from the third equation, we have

$$x_2 \leq M_3 + \varepsilon \qquad (10)$$

But since from (1.a)

$$\frac{dx_1}{dt} = cx_2 - \mu_2 x_1 + \frac{p_1 x_1 x_3}{g_1 + x_3} + s_1 \geq s_1 - \mu_2 x_1.$$

It follows that

$$\liminf_{t\to\infty} x_1(t) = \frac{s_1}{\mu_2} = m_1. \qquad (11)$$

Similarly, from (1.b) and (1.c) , we can easily show that

$$\liminf_{t\to\infty} x_2(t) = \frac{g_2 r_2 - \alpha M_1}{g_2 r_2 b} = m_2. \qquad (12)$$

and

$$\liminf_{t\to\infty} x_3(t) = \frac{s_2}{\mu_3} = m_3. \qquad (13)$$

Thus the system (1) is permanent.

5-Existence and Uniqueness of Asymptotically Periodic Solution

Following [15] we consider the asymptotically periodic system as follows,

$$\frac{dx}{dt} = f(t, x_t) \qquad (14)$$

where $f \in C([-r,0], R^n)$ and for any $x_t \in C$. Define $x_t(\theta) = x(t+\theta), \theta \in [-r,0]$. For any $x = (x_1, x_2, \ldots x_n) \in R_n$ we define $|x| = \sum_{i=1}^{n} |x_i|$, from sec 4, it is easy to see that there exists $H > 0$, such that $|x| \leq nM_i < H$. For any $\phi \in C$, define $\|\phi\| = \sup_{-r\leq\theta\leq 0} |\phi(\theta)|$.

Let $C_H = \{\phi \in C, \|\phi\| < H\}$, and $S_H = \{x \in R^n, |x| < H\}$.

In this section we use the same technique [15] to discuss the existence and uniqueness of asymptotically periodic solution of system (14), we consider the adjoint system

$$\frac{dx}{dt} = f(t, x_t)$$
$$\frac{dy}{dt} = f(t, y_t) \qquad (15)$$

The following lemma is needed

Lemma 2 (Yuan [15,16]) Let $V \in (R_+ \times S_H \times S_H, R_+)$ satisfy

(i) $a(|x-y|) \leq V(t,x,y) \leq b(|x-y),|$ where $a(r)$ and $b(r)$ are are continuously positively increasing functions;

(ii) $|V(t,x_1,y_1) - V(t,x_2,y_2)| \leq l(|x_1 - x_2| + |y_1 - y_2|)$, where l is a constant and satisfies $l > 0$;

(iii) there exists continuous non-increasing function $P(s)$, such that for $s > 0, P(s) > s$, and as $P(V(t,\phi(0),\phi(0)) > (V(t+\theta,\phi(\theta),\phi(\theta)), \theta \in [-r,0]$, it follows that $V'_{(16)}(t,\phi(0),\phi(0)) \leq -\delta V(t,\phi(0),\phi(0))$, where δ is a constant and satisfies $\delta > 0$. Furthermore, the system (15) has a solution $\zeta(t)$ for $t > t_\circ$ and satisfies $\|\zeta(t)\| \le H$. Then system (14) has a unique asymptotically periodic solution, which is uniformly asymptotically stable.

Theorem 4 Let $\theta_1, \theta_2, \theta_3$ and δ are defined by

$$\theta_1 = M_1[\frac{cM_2}{M_1^2} + \frac{s_1}{M_1^2} + \frac{\alpha g_2}{(g_2+M_2)^2} - \frac{p_2 M_2(1+g_3)}{m_3(g_3+m_2)^2}], \quad (16)$$

$$\theta_2 = M_2[r_2 b - \frac{c}{m_1} - \frac{p_2 M_1 g_3}{m_3(g_3+m_2)^2}], \text{and} \quad (17)$$

$$\theta_3 = M_3[\frac{s_2}{M_3^2} - \frac{p_1 g_1}{(g_1+m_3)^2} + \frac{p_1 m_1 m_2(m_2+g_3)}{M_3^2(g_1+M_2)^2}]. \quad (18)$$

$$\delta = \min\{\theta_1, \theta_2, \theta_3\}. \quad (19)$$

respectively. In addition to the conditions (H_1) and (H_2), we assume further that $\delta > 0$, then there exists a unique asymptotically periodic solution of system (1) which is uniformly asymptotically stable.

Proof. By Theorem, we know that the solution of the system (1) is ultimately bounded. Consider the adjoint system of the system (1) as follows

$$\frac{dx_1}{dt} = cx_2 - \mu_2 x_1 + \frac{p_1 x_1 x_3}{g_1 + x_3} + s_1$$
$$\frac{dx_2}{dt} = r_2 x_2(1 - bx_2) - \frac{\alpha x_1 x_2}{g_2 + x_2}$$
$$\frac{dx_3}{dt} = \frac{p_2 x_1 x_2}{g_3 + x_2} - \mu_3 x_3 + s_2 \quad (20)$$
$$\frac{du_1}{dt} = cu_2 - \mu_2 u_1 + \frac{p_1 u_1 u_3}{g_1 + u_3} + s_1$$
$$\frac{du_2}{dt} = r_2 u_2(1 - bu_2) - \frac{\alpha u_1 u_2}{g_2 + u_2}$$
$$\frac{du_3}{dt} = \frac{p_2 u_1 u_2}{g_3 + u_2} - \mu_3 u_3 + s_2.$$

For $X(t) = (x_1(t), x_2(t), x_3(t))$ and $U(t) = (u_1(t), u_2(t), u_3(t))$ are the solutions of system (20) in $\Omega \times \Omega$. Let $x_i^*(t) = \ln x_i(t), u_i^* = \ln u_i(t), i = 1,2,3.$

Consider a Liapunov functional in the form

$$V(t) = \sum_{i=1}^{3} |x_i^*(t) - u_i^*(t)|. \quad (21)$$

By taking $a(r) = b(r) = \sum_{i=1}^{n} |x_i^*(t) - u_i^*(t)|$ and using the inequality $\||a| - |b|\| \le |a - b|$ the proof of condition (i), and (ii) of Lemma 2 be as [15]. Now to prove (iii) of Lemma 2. It follows from (21) that

$$D^+V(t) = \sum_{i=1}^{n} (\frac{x_i^{\cdot}(t)}{x_i(t)} - \frac{u_i^{\cdot}(t)}{u_i(t)}) \times sign(x_i(t) - u_i(t)),$$

then we have

$$D^+V(t) \le \quad c\frac{x_2}{x_1} - \mu_2 + \frac{p_1 x_3}{g_1 + x_3} + \frac{s_1}{x_1} - c\frac{u_2}{u_1} + \mu_2 -$$
$$\frac{p_1 u_3}{g_1 + u_3} - \frac{s_1}{u_1} + r_2 - r_2 b x_2 - \frac{\alpha x_1}{g_2 + x_2} - r_2 + r_2 b u_2 - \frac{\alpha u_1}{g_2 + u_2}$$
$$+ \frac{p_2 x_1 x_2}{x_3(g_3 + x_2)} - \mu_3 + \frac{s_2}{x_3} - \frac{p_2 u_1 u_2}{u_3(g_3 + u_2)} + \mu_3 - \frac{s_2}{u_3}.$$

Furthermore,

$$D^+V(t) \le |x_1 - u_1| \{\frac{-cx_2}{u_1 x_1} - \frac{s_1}{u_1 x_1} - \frac{\alpha g_2}{(g_2 + x_2)(g_2 + x_2)} +$$
$$\frac{p_2 x_2 u_2}{u_3(g_3 + u_2)(g_3 + x_2)} + \frac{p_2 g_3 u_2}{x_3(g_3 + u_2)(g_3 + x_2)}\} + |x_2 - u_2|$$
$$\{\frac{c}{u_1} - r_2 b + \frac{p_2 g_3 x_1}{x_3(g_3 + u_2)(g_3 + x_2)}\} + |x_3 - u_3| \{-\frac{s_2}{x_3 u_3} +$$
$$\frac{p_1 g_1}{(g_1 + u_3)(g_1 + x_3)} - \frac{p_2 x_1 x_2 u_2}{x_3 u_3(g_3 + u_2)(g_3 + x_2)} -$$
$$\frac{p_2 g_3 u_1 u_2}{x_3 u_3(g_3 + u_2)(g_3 + x_2)}\}.$$

Using Lemma 2, we get

$$D^+V(t) \le |x_1 - u_1| \{\frac{-cm_2}{M_1^2} - \frac{s_1}{M_1^2} - \frac{\alpha g_2}{(g_2 + M_2)^2} +$$
$$\frac{p_2 M_2^2}{m_3(g_3 + m_2)^2} + \frac{p_2 g_3 M_2}{m_3(g_3 + m_2)^2}\} + |x_2 - u_2| \{\frac{c}{m_1} -$$
$$r_2 b + \frac{p_2 g_3 M_1}{m_3(g_3 + m_2)^2}\} + |x_3 - u_3| \{-\frac{s_2}{M_3^2} + \frac{p_1 g_1}{(g_1 + m_3)^2}$$
$$- \frac{p_2 m_1 m_2^2}{M_3^2(g_3 + M_2)^2} - \frac{p_2 g_3 m_1 m_2}{M_3^2(g_3 + M_2)^2}\}. \quad (22)$$

Since

$$|x_i(t) - u_i(t)| = |\exp(x_i^*(t)) - \exp(u_i^*(t))|$$
$$= |\exp \zeta_i(t)| |x_i^*(t) - u_i^*(t)|, \quad (23)$$

where $\zeta_i(t)$ lies between $x_i(t)$ and $u_i(t)$ then, we have

$$m_i |x_i^*(t) - u_i^*(t)| < |x_i(t) - u_i(t)| < M_i |x_i^*(t) - u_i^*(t)|, i=1,2,3. \quad (24)$$

Substituting from (25) into (23), we get

$$D^{+}V(t) \le -\{\frac{cm_2}{M_1^2}+\frac{s_1}{M_1^2}+\frac{\alpha g_2}{(g_2+M_2)^2}-\frac{p_2 M_2^2}{m_3(g_3+m_2)^2}-\frac{p_2 g_3 M_2}{m_3(g_3+m_2)^2}\}M_1\left|x_1^*(t)-u_1^*(t)\right|-\{r_2 b-\frac{c}{m_1}-\frac{p_2 g_3 M_1}{m_3(g_3+m_2)^2}\}M_2\left|x_2^*(t)-u_2^*(t)\right|-\{\frac{s_2}{M_3^2}-\frac{p_1 g_1}{(g_1+m_3)^2}+\frac{p_2 m_1 m_2^2}{M_3^2(g_3+M_2)^2}+\frac{p_2 g_3 m_1 m_2}{M_3^2(g_3+M_2)^2}\}M_3\left|x_3^*(t)-u_3^*(t)\right|.$$

This can be written as

$$D^{+}V(t) \le -\theta_1\left|x_1^*(t)-u_1^*(t)\right|-\theta_2\left|x_2^*(t)-u_2^*(t)\right|-\theta_3\left|x_3^*(t)-u_3^*(t)\right|, \qquad (25)$$

where θ_1, θ_2, and θ_3 are defined in (16)-(18).

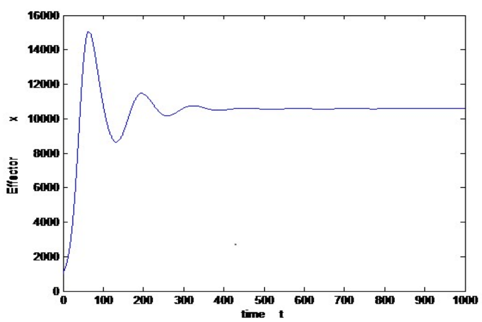
Consider δ as defined in (19). It follows

$$D^{+}V(t) \le -\delta V(t). \qquad (26)$$

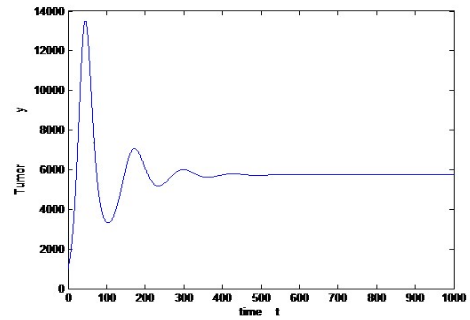
Then (iii) of Lemma 2 is fulfilled. Therefore the system (1) has a unique positive asymptotically periodic solution in the domain Ω, which is uniformly asymptotically stable. This completes the proof.

6- Numerical Results

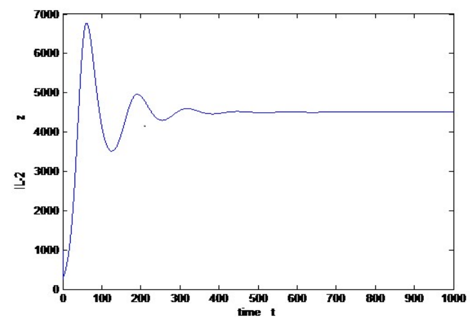
In this section, we perform numerical simulations with the help of parameter values taken from experimental data from published literature. Using Fourth order Runge-Kutta method through out matlab programme. For this purpose we consider the following parameter values $c = .05, \mu_2 = .03, p_1 = .1245, g_1 = 2\times 10^7, r_2 = .1, b = 1\times 10^{-9}, \alpha = 1, g_2 = 1\times 10^5, p_2 = 5, g_3 = 1000, m_3 = 10, s_1 = 30$, and $s_2 = 20$ with the initial conditions $x_\circ = 1000, y_\circ = 1000$, and $z_\circ = 1000$. It clear Fig.2. that the system (1) is a stable spiral .



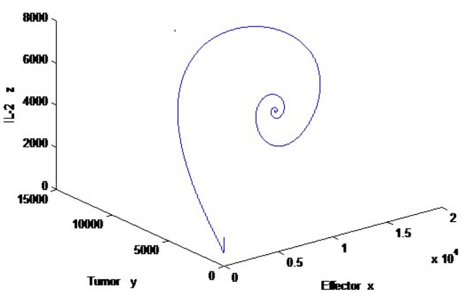
(2-a) The time response of effector cells



(2-b) The time response of tumor cells



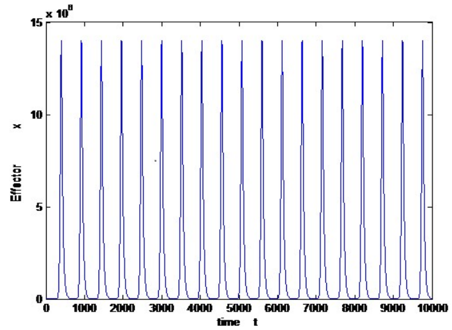
(2-c) The time response of IL-2



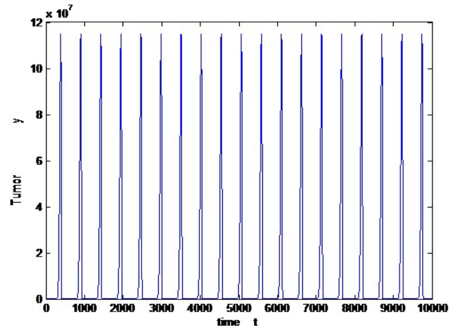
(2-d) Spiral focus of system (1)

Fig.2.The dynamical behavior and the projection of the solution of the system (1).

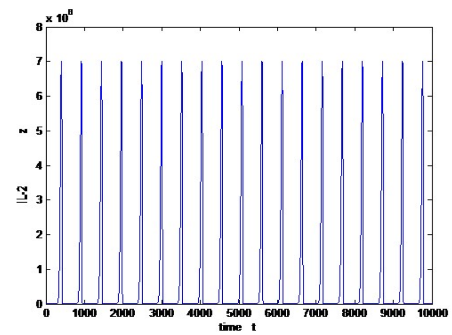
For the initial conditions $x_\circ = 200, y_\circ = 1\times 10^{-7}$, *and* $z_\circ = 1\times 10^{-7}$ and parameter values $c = .005, \mu_2 = .03, p_1 = .02, g_1 = 2\times 10^7$, $r_2 = .1, b = 1\times 10^{-9}, \alpha = 1, g_2 = 1\times 10^7, p_2 = 5, g_3 = 1000, \mu_3 = 10$, $s_1 = 30$, *and* $s_2 = 20$ the conditions H_1, and H_2 hold. Moreover, Fig.3 Shows that the system (1) has a unique positive periodic solution which is globally asymptotically stable.



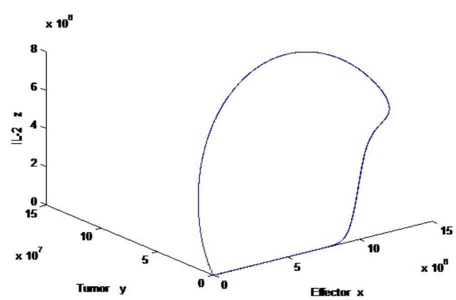
(3-a) The time response of effector cell



(3-b) The time response of tumor cells

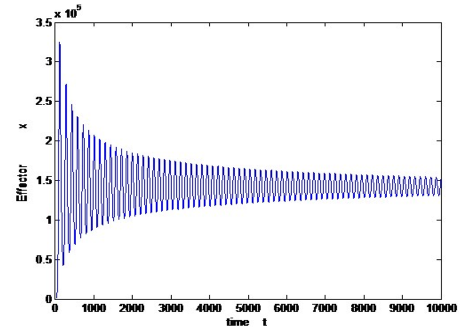


(3-c) The time response of IL-2

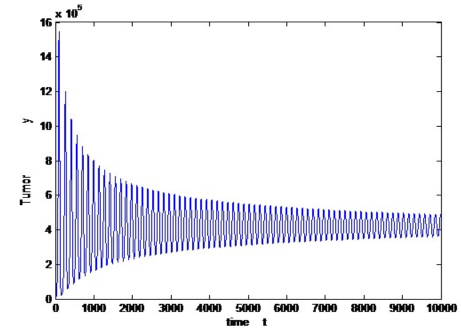


(3-d) Limit cyclic of the system (1)

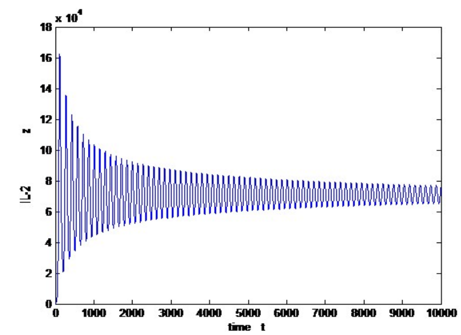
Fig.3. The dynamical behavior and the projection of the solution of the system (1).



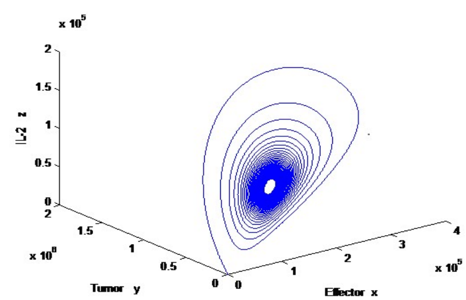
(4-a) The time response of effector cells



(4-b) The time response of tumor cells



(4-c) The time response of IL-2



(4-d) Chaotic attractor of the system (1)

Fig.4. The dynamical behavior and the projection of the solution of the system (1)

Fig.4. represents the chaotic attractor of system (1) at the the initial conditions $x_\circ = 1000$, $y_\circ = 1000$, and $z_\circ = 1000$. with the parameter values $c = .01, \mu_2 = .03, p_1 = .02,$ $g_1 = 2\times10^7, r_2 = .1, b = 1\times10^{-9}, \alpha = 1, g_2 = 1\times10^6, p_2 = 5,$ $g_3 = 1000, \mu_3 = 10, s_1 = 30,$ *and* $s_2 = 20.$

7-Conclusions

In this paper, we discuss a tumor-immune dynamical Kirschner model . We improve some results in literature. We focus on the case of immunotherapy with ACI and

IL-Z. We established the local asymptotic stability of the tumor-free equilibrium point E_1. Our results are consistent with those obtained by Denise Kirschner et al. [7]. We prove the existence of Hopf-Andronov-Poincaré bifurcation using the technique of Pimbley [11], El-Sheikh.[2],and [3]. Also, we used a technique similar to that used by Changjin Xu, and Qiing Zhang [15] to obtain sufficient conditions for the permanence of the system. By constructing a suitable Liapunov function, we give sufficient conditions guarantee the system has a unique asymptotically periodic solution which is globally asymptotically stable, see Fig.3.

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حول ديناميكيه نموذج كيرشنار للأورام

أ.د عفاف ذغروت
قسم الرياضيات- كلية العلوم بنات - جامعة الأزهر
أ.د محمد الشيخ
قسم الرياضيات- كلية العلوم - جامعة المنوفية
أ.د أحمد النموري
قسم الرياضيات- كليه العلوم- جامعة طنطا
أسماء العشري
قسم الرياضيات - كلية العلوم - جامعة طنطا

لازال السرطان يعتبر إحدى أسباب الوفاة بين البشر.ومن أسبابه المعروفة هو النمو السريع غير المحدود للخلايا أو عندما تفقد الخلايا قدرتها علي الفناء وهناك أسباب أخري للسرطان مثل التعرض للكيماويات أو الإفراط في تناول الكحوليات أو التعرض الزائد لضوء الشمس أو اختلاف الجينات كما أن من أشهر السرطانات المؤدية للوفاة سرطان الرئة ألا أن سبب كثير من السرطانات غير معلوم حتى الآن ومن الجدير بالذكر ان نوع السرطان قد يختلف من منطقه لآخري.

في 1920 قام كل من Lotka و Volterra بعمل نموذج رياضي يصف العملية السكانية وفي 1998 قام Kirschner و Panetta بتطبيق ذلك في تطوير النماذج المعرفة لنموذج السرطان وقد قاما بدراسة سلوك الاستقرار والتشعب لنقط الاتزان في حاله الخلو من المرض وتبع هذا البحث الكثير من الانجازات في دراسة خواص النموذج عدديا وتحليايا

في هذا البحث ندرس تحليليا نموذج Kirschner بطريقة مشابهة لنتائجنا في مساهماتنا السابقة في مجال الرياضيات الحيوية حيث ندرس في هذا البحث بعض الخواص الوصفيه لنقاط الاتزان مثل المحدودية والوجود والاستقرار والتشعب وحصلنا علي شروط كافيه لوجود حل دوري مستقر واحد وقد منا بعض التطبيقات والأمثلة العددية لتوضيح النتائج التي حصلنا عليها .