Mathematical modeling and analysis of tumor-immune system interaction by using Lotka-Volterra predator-prey like model with piecewise constant arguments

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Abstract

In this study, we present a Lotka-Volterra predator-prey like model for the interaction dynamics of tumor-immune system. The model consists of system of differential equations with piecewise constant arguments and based on the model of tumor growth constructed by Sarkar and Banerjee. The solutions of differential equations with piecewise constant arguments leads to system of difference equations. Sufficient conditions are obtained for the local and global asymptotic stability of a positive equilibrium point of the discrete system by using Schur-Cohn criterion and a Lyapunov function. In addition, we investigate periodic solutions of discrete system through Neimark-Sacker bifurcation and obtain a stable limit cycle which implies that tumor and immune system undergo oscillation.

Keywords: tumor growth, piecewise constant arguments, difference equation, stability

1. Introduction

Modeling tumor-immune interaction has attracted much attention in the last decades. This interaction is very complex and mathematical models can help to shape our understanding of dynamics this biological phenomenon. Most of the models consist of two main populations: tumor cells and effector cells such as hunting predator cells (Cytotoxic T lymphocytes) and resting predator cells (T-Helper cells) which are main struggle of immune system. Cytotoxic T lymphocytes (CTLs) responsible to kill tumor cells and resting predator cells account for to activity the native Cytotoxic T lymphocytes.

In order to describe tumor and effector cells interaction, many authors [1-16] have used Lotka-Volterra terms and logistic terms. While some of these models [1-9] consist of ordinary differential equations, the others [10-16] consist of delay differential equations. A familiar model included ordinary differential equations is constructed Kuznetsov and Taylor [1]. They have studied interaction between Cytotoxic T lymphocyte and immunogenic tumor and have obtained a threshold for the tumor growth. Kirschner and Panetta [2] have generalized this model to study the role of IL-2 in tumor dynamics. Another familiar tumor growth model has been proposed by Sarkar and Banerjee [3]. The model explains spontaneous tumor regression and progression under immunological activity.

On the other hand, there exists a discrete time delay in the mitosis phase (cell division phase) since tumor cells need a resting time for a proliferation. This biological phenomenon is explained much better by using delay differential equations instead of ordinary differential equations [10]. Therefore, many authors have considered delay differential equation included time delay factor for modeling tumor growth [10-16]. Sarkar and Banerjee [11] have constructed the model by using the time delay factor as follows:

$$\begin{cases} \dfrac{dM}{dt} = r_1 M \left(1 - \dfrac{M}{k_1}\right) - \alpha_1 MN, \\[2mm] \dfrac{dN}{dt} = \beta NZ(t - \tau) - d_1 N - \alpha_2 MN, \\[2mm] \dfrac{dZ}{dt} = r_2 Z \left(1 - \dfrac{Z}{k_2}\right) - \beta NZ(t - \tau) - d_2 Z, \end{cases} \quad (1)$$

where $M(t)$, $N(t)$ and $Z(t)$ are the number of tumor, hunting and resting cells respectively.

Since stability and bifurcations analysis of delay differential equations is more difficult, numerical analysis may be needed for such equations. In study [17], Cooke and Györi show that differential equation with piecewise constant arguments can be used to obtain good approximate solution of delay differential equations on the infinite interval $[0, \infty)$. Therefore, there has been great interest in studying differential equation with piecewise constant arguments which combine properties

of both differential and difference equations [18-26]. I. Ozturk et al. [18] have modeled bacteria population by using differential equation

$$\frac{dx(t)}{dt} = rx(t)\{1 - \alpha x(t) - \beta_0 x(\llbracket t \rrbracket)$$
$$- \beta_1 x(\llbracket t - 1 \rrbracket)\}. \quad (2)$$

which includes both continuous and discrete time for a bacteria population.

These types of models also allow us to describe both microscopic and macroscopic level events that occur simultaneously. For the tumor-immune system interactions, microscopic interaction refers proliferation and activation of tumor cells together with their competition while macroscopic interaction refers to cancer invasion and metastases [27]. When one considers the both microscopic level interaction which needs a discrete time and macroscopic level interaction which needs continuous time simultaneously, there are two events in a population: a continuity and discrete time. Modeling tumor growth using differential equation with piecewise constant arguments, Bozkurt [19] have considered a more general case of equation (2) as follows:

$$\frac{dx(t)}{dt} = x(t)\{r(1 - \alpha x(t) - \beta_0 x([t]) - \beta_1 x([t-1]))$$
$$+ \gamma_1 x([t]) + \gamma_2 x([t-1])\}. \quad (3)$$

In the present paper, due to above biological facts, we replace the model (1) by adding piecewise constant arguments and get a system of differential equations

$$\begin{cases} \frac{dM}{dt} = r_1 M(t)\left(1 - \frac{M(t)}{k_1}\right) - \alpha_1 M(t)N(\llbracket t \rrbracket), \\ \frac{dN}{dt} = \beta N(t)Z(\llbracket t-1 \rrbracket) - d_1 N(t) - \alpha_2 M(\llbracket t \rrbracket)N(t), (4) \\ \frac{dZ}{dt} = r_2 Z(t)\left(1 - \frac{Z(t)}{k_2}\right) - \beta N(\llbracket t \rrbracket)Z(t) - d_2 Z(t), \end{cases}$$

where $\llbracket t \rrbracket$ denotes the integer part of $t \epsilon [0, \infty)$, $M(t)$, $N(t)$ and $Z(t)$ are the number of tumor, hunting and resting cells respectively. The parameter r_1 represents the growth rate and k_1 represents the maximum carrying capacity of tumor cells, r_2 is the growth rate and k_2 is the maximum carrying capacity of resting cells. The term $-d_1 N(t)$ is natural death of hunting cell. The competition term $-\alpha_1 M(t)N(\llbracket t \rrbracket)$ represents the loss of tumor cells due to encounter with hunting cells and $-\alpha_2 M(\llbracket t \rrbracket)N(t)$ represents the loss of hunting cells due to encounter with the tumor cells. The conversion rate from resting to hunting cells is represented parameter β. There exist a discrete delay time in this conversion which is represented term $Z(\llbracket t - 1 \rrbracket)$. The term $\beta N(t)Z(\llbracket t-1 \rrbracket)$

represents growth of hunting T-cells and the term $-\beta N(\llbracket t \rrbracket)Z(t)$ represents loss of resting cells.

2. Local and global stabilty analysis of the system

An integration of each equation in system (4) on an interval $t \epsilon [n, n+1)$, $n = 0,1,2, \dots$, give us

$$\begin{cases} \frac{dM}{dt} - M(t)\{r_1 - \alpha_1 N(n)\} = -r_1 K_1 (M(t))^2, \\ \frac{dN}{N(t)} = \{\beta Z(n-1) - d_1 - \alpha_2 M(n)\}N(t)dt, \quad (5) \\ \frac{dZ}{dt} - Z(t)\{r_2 - \beta N(n) - d_2\} = -r_2 K_2 (Z(t))^2. \end{cases}$$

where $\frac{1}{k_1} = K_1$, $\frac{1}{k_2} = K_2$. If we solve each equations of system (5) and letting $t \rightarrow n+1$, we get a system of difference equations

$$\begin{cases} M(n+1) = \frac{M(n)[r_1 - \alpha_1 N(n)]}{[r_1 - \alpha_1 N(n) - r_1 K_1 M(n)]e^{-[r_1 - \alpha_1 N(n)]} + r_1 K_1 M(n)}, \\ N(n+1) = N(n)e^{\beta Z(n) - d_1 - \alpha_2 M(n)}, \quad (6) \\ Z(n+1) = \frac{Z(n)[r_2 - \beta N(n) - d_2]}{[r_2 - \beta N(n) - d_2 - r_2 K_2 Z(n)]e^{-[r_2 - \beta N(n) - d_2]} + r_2 K_2 Z(n)}. \end{cases}$$

In order to analysis system (6), we need to find positive equilibrium point of the system. If

$$\alpha_1 < \frac{4d_2 K_2 r_1 r_2}{d_2^2 - 2d_2 r_2 + r_2^2}, \quad \beta > \frac{d_1 K_1 K_2 r_2 + K_2 r_2 \alpha_2}{K_1(r_2 - d_2)}, (7)$$

$$K_1 > \frac{\alpha_2}{d_1} \quad \text{and} \quad r_2 > d_2 \quad (8)$$

then, positive equilibrium point of the system is determined as $\overline{E} = (\overline{M}, \overline{N}, \overline{Z})$ where

$$\overline{M} = \frac{\beta^2 r_1 + \alpha_1(\beta d_2 - \beta r_2 + d_1 K_2 r_2)}{\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2},$$

$$\overline{N} = \frac{r_1(-\beta K_1 d_2 + \beta K_1 r_2 - d_1 K_1 K_2 r_2 - K_2 r_2 \alpha_2)}{\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2},$$

$$\overline{Z} = \frac{\beta(d_1 K_1 r_1 + r_1 \alpha_2) - (r_2 - d_2)\alpha_1 \alpha_2}{\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2}.$$

The linearized system of (6) about positive equilibrium point $\overline{E}$ is $w(n+1) = Aw(n)$, where A is

8

$$A = \begin{pmatrix} e^{-K_1 r_1 \bar{M}} & -\dfrac{(1 - e^{-K_1 r_1 \bar{M}})\alpha_1}{K_1 r_1} & 0 \\ -\alpha_2 \bar{N} & 1 & \beta \bar{N} \\ 0 & -\dfrac{(1 - e^{-K_2 r_2 \bar{Z}})\beta}{K_2 r_2} & e^{-K_2 r_2 \bar{Z}} \end{pmatrix}. \qquad (9)$$

The characteristic equation of matrix A is

$$p(\lambda) = (a_{11} - \lambda)[(1 - \lambda)(a_{33} - \lambda) - a_{23}a_{32}]$$
$$- a_{12}[a_{21}(a_{33} - \lambda)]. \qquad (10)$$

Under the assumption

$$a_{11} = a_{55}, \qquad (11)$$

an eigenvalue of (10) are computed as $\lambda_1 = e^{-K_1 r_1 \bar{M}} < 1$. Solving equation (11) with the fact $r_1 > r_2$ and considering inequalities (7) and (8) we have

$$\alpha_1 = \frac{\beta r_1 (K_1(-\beta r_1 + d_1 K_2 r_2) + K_2 r_2 \alpha_2)}{d_2(\beta K_1 r_1 - K_2 r_2 \alpha_2) + r_2(K_1(-\beta + d_1 K_2)r_1 - K_2 r_2 \alpha_2)}.$$

Thus, characteristic equation $p(\lambda)$ can be reduced second order equation

$$p_1(\lambda) = \lambda^2 + \lambda(-1 - e^{-K_1 r_1 \bar{M}}) + e^{-K_1 r_1 \bar{M}}$$
$$+ \frac{\bar{N}(1 - e^{-K_1 r_1 \bar{M}})(\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2)}{K_1 r_1 K_2 r_2} \qquad (12)$$

Now we can determine stability conditions of discrete system (6) through the equation (12).

Theorem 1. Let $\bar{E}$ the positive equilibrium point of system (6). Suppose that

$$\alpha_1 = \frac{\beta r_1 (K_1(\beta r_1 - d_1 K_2 r_2) - K_2 r_2 \alpha_2)}{r_2(K_1(\beta - d_1 K_2)r_1 - K_2 r_2 \alpha_2)},$$

$$\frac{\alpha_2}{d_1} < K_1 < \frac{r_2 d_1}{r_2 + d_1} \text{ and } r_1 > r_2 > d_2.$$

$\bar{E}$ is local asymptotic stable if

$$\beta > \frac{d_1 K_1 K_2 r_2 + K_2 r_2 \alpha_2}{K_1(r_2 - d_2)} \text{ and } \alpha_1 < \frac{4 d_1 K_2 r_1 r_2}{d_2{}^2 - 2 d_2 r_2 + r_2{}^2}.$$

Proof. By using Schur-Cohn criterion, we obtain that $\bar{E}$ is locally asymptotically stable if and only if

$$\left| -1 - e^{-K_1 r_1 \bar{M}} \right| < 1 + e^{-K_1 r_1 \bar{M}}$$

$$+ \frac{\bar{N}(1 - e^{-K_1 r_1 \bar{M}})(\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2)}{K_1 r_1 K_2 r_2} < 2. (13)$$

The inequality (13) can be written

(a) $\left| -1 - e^{-K_1 r_1 \bar{M}} \right| < 1 + e^{-K_1 r_1 \bar{M}}$
$$+ \frac{\bar{N}(1 - e^{-K_1 r_1 \bar{M}})(\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2)}{K_1 r_1 K_2 r_2}$$

and

(b) $1 + e^{-K_1 r_1 \bar{M}}$
$$+ \frac{\bar{N}(1 - e^{-K_1 r_1 \bar{M}})(\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2)}{K_1 r_1 K_2 r_2} < 2.$$

If we consider condition (7) and (8), it can be easily seen that (a) is always holds. From (b), we hold

$$\frac{\bar{N}(1 - e^{-K_1 r_1 \bar{M}})(\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2) + K_1 r_1 K_2 r_2 e^{-K_1 r_1 \bar{M}}}{K_1 r_1 K_2 r_2} < 1$$

which reveal

$$\beta > \frac{K_1 K_2 r_2 + d_1 K_1 K_2 + K_2 \alpha_2}{r_2 - d_2}.$$

Under the condition

$$K_1 < \frac{r_2 d_1}{r_2 + d_1}$$

we can write

$$\beta > \frac{d_1 K_1 K_2 r_2 + K_2 r_2 \alpha_2}{K_1(r_2 - d_2)} > \frac{K_1 K_2 r_2 + d_1 K_1 K_2 + K_2 \alpha_2}{r_2 - d_2}$$

This completes the proof.

Example 1. The parameter values which are taken from [11] as $r_1 = 0.18$, $r_2 = 0.1045$, $k_1 = 5 \times 10^6$, $k_2 = 3 \times 10^6$, $\beta = 4.32 \times 10^{-8}$, $\alpha_2 = 3.422 \times 10^{-9}$, $d_1 = d_2 = 0.0412$ and the determined value $\alpha_1 = 2.27721 \times 10^{-7}$ provide the conditions of Theorem 1. It can be seen that under the conditions given in Theorem 1, the positive equilibrium
point $\bar{E} = (9.99394 \times 10^5, 6.32449 \times 10^5, 1.03287 \times 10^6)$
of system (6) is local asymptotic stable (see Figure 1a), where blue, red and black graphs represent M(n), N(n) and Z(n) population densities respectively.

Theorem 2. Let the conditions of Theorem 1 hold. Moreover, assume that $r_1 - \alpha_1 N(n) > 0$,
$r_2 - \beta N(n) - d_2 > 0$, $\beta Z(n-1) - d_1 - \alpha_2 M(n) < 0$.

If

9

$$r_1 K_1 M(n) < r_1 - \alpha_1 N(n) < \ln\left(\frac{2\overline{M} - M(n)}{M(n)}\right),$$

$$r_2 K_2 Z(n) < r_2 - \beta N(n) - d_2 < \ln\left(\frac{2\overline{Z} - Z(n)}{Z(n)}\right),$$

and $M(n) < \overline{M}$, $N(n) > 2\overline{N}$, $Z(n) < \overline{Z}$ then the positive equilibrium point $\overline{E}$ is globally asymptotically stable.

Proof. Let

$$V(n) = [E(n) - \overline{E}]^2 \ , n = 0,1,2 \dots$$

is a Lyapunov function with the positive equilibrium point $\overline{E} = (\overline{M}, \overline{N}, \overline{Z})$. The change along the solutions of the system is

$$\Delta V(n) = V(n + 1) - V(n)$$
$$= \{E(n + 1) - E(n)\}\{E(n + 1) + E(n) - 2\overline{E}\}.$$

In addition, the change along the solutions of the first equation in system (6) is

$$\Delta V_1(n) = [M(n + 1) - M(n)][M(n + 1) + M(n) - 2\overline{M}].$$

It can be seen that if $r_1 K_1 M(n) < r_1 - \alpha_1 N(n)$, $A_1 < \ln\left(\frac{2\overline{M} - M(n)}{M(n)}\right)$ and $M(n) < \overline{M}$ then $\Delta V_1(n) < 0$. Similarly, it can be shown that $\Delta V_2(n) = [N(n + 1) - N n[Nn+1+Nn-2N]<0$ and $\Delta V_3(n) = [Z(n + 1) - Z(n)][Z(n + 1) + Z(n) - 2\overline{Z}] < 0$. As a result, we obtain $\Delta V(n) = (\Delta V_1(n), \Delta V_2(n), \Delta_3 V(n)) < 0$.

Example 2. In order to try the conditions of Theorem 2, initial conditions can be determined as $M(1) = 4 \times 10^5$, $N(1) = 1 \times 10^5$, $Z(1) = 1 \times 10^5$ and parameter values can be taken Example 1. Figure 1b shows that under the conditions given in Theorem 2 the positive equilibrium point is global asymptotic stable, where blue, red and black graphs represent $M(n)$, $N(n)$ and $Z(n)$ population densities respectively.
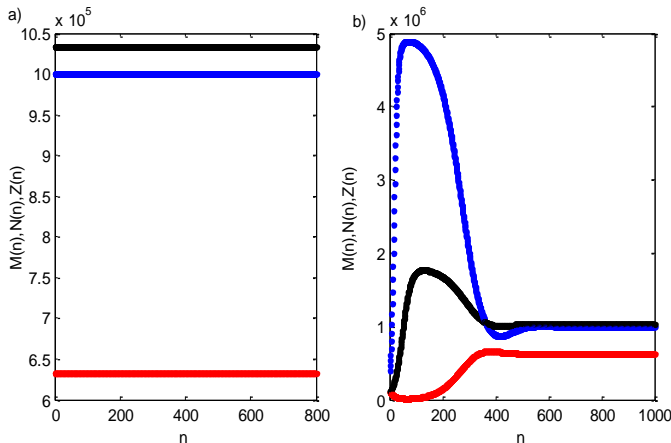
Figure 1. The iteration solution of $M(n)$, $N(n)$ and $Z(n)$ for different initial conditions.

3. Neimark-Sacker bifurcation analysis

In this section, we try to determine Neimark-Sacker bifurcation point of the system by using Schur-Cohn criterion that is given as follows.

Theorem A ([28])**.** A pair of complex conjugate roots of

$$p(\lambda) = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 \tag{14}$$

lie on the unit circle and the other roots of $p(\lambda)$ all lie inside the unit circle if and only if

(a) $p(1) = 1 + p_2 + p_1 + p_0 > 0$ and

$$p(-1) = 1 - p_2 + p_1 - p_0 > 0,$$

(b) $D_2^+ = 1 + p_1 - p_0{}^2 - p_0 p_2 > 0,$

(c) $D_2^- = 1 - p_1 - p_0{}^2 + p_0 p_2 = 0.$

If we rearranged the equation (10), characteristic equation can be obtained as the form (14) where

$$p_2 = -1 - e^{-K_1 r_1 \overline{M}} - e^{-K_2 r_2 \overline{Z}},$$

$$p_1 = e^{-K_1 r_1 \overline{M}} + e^{-K_2 r_2 \overline{Z}} + e^{-K_1 r_1 \overline{M} - K_2 r_2 \overline{Z}}$$
$$+ \frac{\beta^2}{K_2 r_2}\overline{N}\left(1 - e^{-K_2 r_2 \overline{Z}}\right) - \frac{\alpha_1 \alpha_2}{K_1 r_1}\overline{N}\left(1 - e^{-K_1 r_1 \overline{M}}\right),$$

$$p_0 = -\frac{\beta^2}{K_2 r_2}\overline{N}e^{-K_1 r_1 \overline{M}}\left(1 - e^{-K_2 r_2 \overline{Z}}\right) - e^{-K_1 r_1 \overline{M} - K_2 r_2 \overline{Z}}$$
$$+ \frac{\alpha_1 \alpha_2}{K_1 r_1}\overline{N}e^{-K_2 r_2 \overline{Z}}\left(1 - e^{-K_1 r_1 \overline{M}}\right).$$

By using these results, bifurcation point can be determined as the following example.

Example 3. Solving equation c of Theorem A, we get $\overline{\beta} = 2.94043 \times 10^{-7}$. Moreover, we have also $p(1) = 0.000386701 > 0$, $p(-1) = 7.47232 > 0$ ve $D_2^+ = 0.488065 > 0$ for this point. Figure 2 shows that $\overline{\beta}$ is the Neimark-Sacker bifurcation point of the system with the eigenvalues $\lambda_1 = 0.869464$ and $|\lambda_{2,3}| = |0.998519 \pm 0.0544078i = 1$ where blue, red and black graphs represent $M(n)$, $N(n)$ and $Z(n)$ population densities respectively.
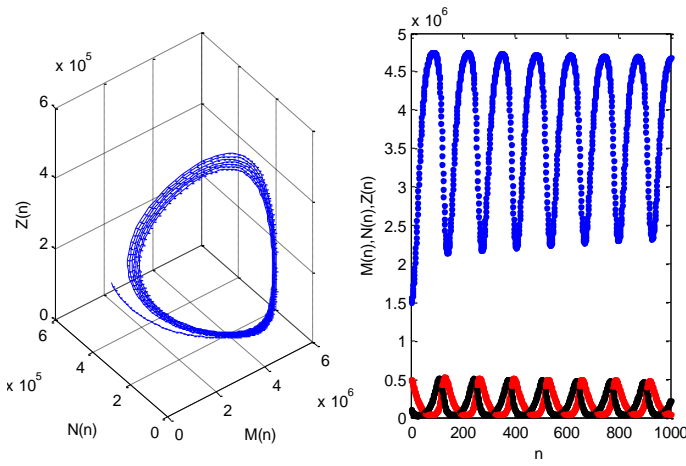
Figure 2. Neimark-Sacker bifurcation of system (6) for $\bar{\beta} = 2.94043x10^{-7}$, where $M(1) = 1.5x10^6$, $N(1) = 5x10^5$, $Z(1) = 1x10^5$. The other parameters are taken Example 1.

As seen in Figure 2, a stable limit cycle occurs at the bifurcation point $\bar{\beta}$ as a result of Neimark-Sacker bifurcation. This result leads to stable periodic solutions around the positive equilibrium point. Determining bifurcation point is very important issue for the control of the tumor cell population. After the bifurcation point, tumor and immune system will exhibit unstable oscillatory behavior, thus resulting uncontrolled tumor growth. The solutions of the system at the point $\beta = 1.14043x10^{-7} < \bar{\beta}$ can be seen in Figure 3, where the system has damped oscillation and the positive equilibrium point is local asymptotic stable. At the point $\beta = 4.34043x10^{-7} > \bar{\beta}$, system (6) has unstable oscillation and the positive equilibrium point is unstable (see Figure 4).

Finally, we can compare our theoretical results to the system (4) that is given in [11]. In study [11], a hopf bifurcation that is continuous case of Neimark-Sacker bifurcation is occurred around positive equilibrium point through stable limit cycle. Thus, we can say that bifurcation results of system (6) and system (4) are similar.
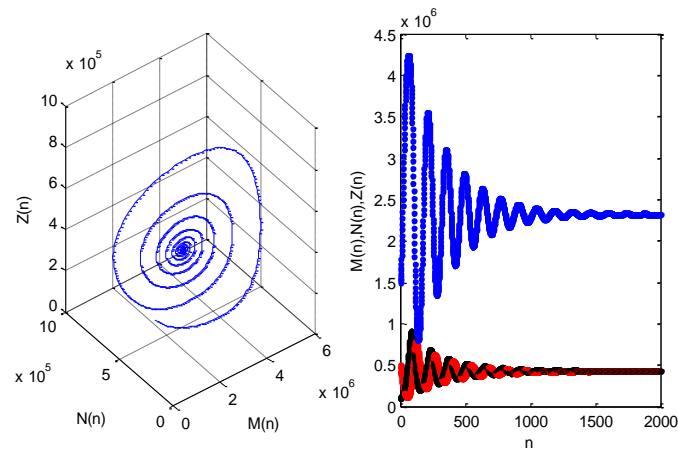

Figure 3. The iteration solution of the system for $\beta = 1.14043x10^{-7}$. The other parameters and initial conditions are the same as Figure 2.
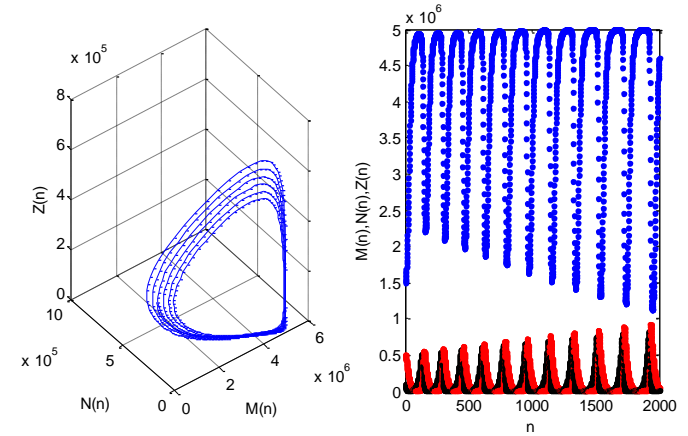

Figure 4. The iteration solution of the system for $4.34043x10^{-7}$. The other parameters and initial conditions are the same as Figure 2.

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