

A Policy to Eradicate Tumor in a Discrete-Continuous Immune Cell-Tumor Cell-Drug Administration Model with the Help of Stability Analysis and Bifurcation Analysis of the Model

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Abstract

In this paper we have analyzed an immune cell-tumor cell model of Lotka-Volterra type with the control policy in the form of chemotherapy. We derived the conditions for the stability of the tumor free equilibrium point. Investigation regarding the possible bifurcation types was carried out for the system and it was observed that the system exhibits a transcritical bifurcation and undergoes period doubling route to chaos as the control parameter is varied. Combining the results of stability analysis and bifurcation analysis we determined a range for the rate of drug administration to eradicate the tumor completely. Numerical simulations were performed to observe the qualitative behaviour of the system as the control parameter is varied.

Keywords: Lotka-Volterra type, transcritical bifurcation, period doubling route to chaos.

INTRODUCTION:

According to Saini [15], the description of cancer was found in Egyptian papyrus. Until the 19th century, this disease was regarded as an incurable one. In an effort to control this deadly disease, mathematicians joined hands with the biologists to study the tumor dynamics and developed the anti cancer therapies.

Mathematical model of Cancer was first proposed by Thomlinson and Gray [16] using diffusion and utilization of oxygen to supplement an experimental investigation of a few sort of bronchial carcinomas.

In 1950s, immune surveillance hypothesis had been formulated, which suggested that body's own defence system (i.e. immune cells) are capable of inhibiting the developing tumors before they become detectable [4]. This, in fact was the motivational factor for mathematicians to make models and use those for investigating the interactions between tumor cells and the immune cells. The immune system consists of effector cells which are capable of controlling tumor progression such as macrophages, NK cells CD8⁺T cells, dendritic cells etc.

Generally predator-prey type models are used to depict the immune-tumor interactions [7,10,13,17]. The effector immune cells play the role of predator and the tumor cells play the role of prey. The presence of tumor cells biologically stimulates the production of immune cells. Simultaneously, the growth of the tumor cells is retarded by the presence of immune cells. As the tumor cells die of, the

immune cells consequently decrease. But, decrease of immune cells allow the tumor cells to grow once again. Depending on the system parameters, the cycle could continue indefinitely, or eventually spiral to a point of equilibrium. Based on the fact that action of the immune cells significantly effect the dynamics of tumor growth, Pillis et.al. included the interaction of the immune and tumor cells in their model [11].

Proliferation and activation of tumor cells together with their competition with immune system are referred in cellular (microscopic) level while cancer invasion and metastasis are referred in macroscopic level [1]. Many authors used discrete variable to describe tumor-immune interaction considering the microscopic level [1, 2, 5, 6, 14].

Considering the microscopic interaction between tumor cells and immune cells in the model proposed by Gatenby in [8], Gurcan et.al. [9] formulated a tumor cell-Cytotoxic T Lymphocytes (CTLs) model with a discrete time delay factor

$$\frac{dx}{dt} = r_1x(t) \left(1 - \frac{x(t)}{k_1}\right) - \alpha_1x(t)y([t]) + \alpha_2x(t)y([t-1])$$

$$\frac{dy}{dt} = r_2y(t) \left(1 - \frac{y(t)}{k_2}\right) + \alpha_1y(t)x([t]) - \alpha_2y(t)x([t-1]) - d_1y(t)$$

Bozkurt [3] modelled an early brain tumor growth by using differential equation with piecewise constant arguments

$$\frac{dx}{dt} = x(t) \{r (1 - \alpha x(t) - \beta_0x([t]) - \beta_1x([t-1])) + \gamma_1x([t]) + \gamma_2x([t-1])\}$$

In the present study, we construct an immune-cell-tumor cell-drug administration model with piecewise constant arguments.

Model Formulation:

To construct our model we consider a model which is the simplified model developed by Pillis and Radunskay [11] where we have considered the interaction between tumor cells and immune cells only. We amended the model by replacing Michaelis-Menten form of the function in the immune system equation with the Lotka-Volterra form.

Pillis and Radunskaya [11], proposed a model that described the competition between tumor cells, normal cells and

immune system. They proposed the model under certain assumptions as follows:

- (1) There is a normal rate of flow 's' of mature effector cells into tumor region .
- (2) Saturated effect of effector immune response was indicated by Michaelis-Menten form $\frac{\rho xy}{\alpha + y}$.
- (3) Tumor and normal cells follow the logistic growth law.

The model proposed by Pillis and Radunskaya [11] without therapy is as follows:

$$\dot{x} = s + \frac{\rho xy}{\alpha + y} - c_1 xy - d_1 x$$

$$\dot{y} = r_1 y(1 - b_1 y) - c_2 xy - c_3 yz$$

$$\dot{z} = r_2 z(1 - b_2 z) - c_4 yz$$

where, $x(t)$, $y(t)$, $z(t)$ represent population density of immune cells, tumor cells and normal cells respectively, d_1 represent apoptosis of the effector cells.

In the construction of model to be investigated by us, we considered the model proposed by Pillis et.al. [11] where we consider the interaction between immune cells and tumor cells only replacing Michaelis-Menten form of the function in the immune system equation with the Lotka-Voltera form which is as follows:

$$\frac{dx}{dt} = s + c_1 x(t)y(t) - d_1 x(t)$$

$$\frac{dy}{dt} = r_1 y(t)(1 - b_1 y(t)) - c_2 x(t)y(t)$$

where $x(t)$ is the immune cell population and $y(t)$ is the tumor cell population at time t . Constant number of immune cells already present in the body is represented by s , d_1 is the natural death rate of immune cells, r_1 is the intrinsic tumor growth rate, $1/b_1$ is the tumor population carrying capacity.

In contrast to [11], we have extended this continuous model by including discrete time interactions between the immune and tumor cells. Also, we applied a control policy in terms of chemotherapy that follows the logistic rule with a drug administration rate α , maximum drug carrying capacity β and a natural decay rate d_2 (obviously $\alpha > d_2$). We consider the drug administration law to follow discrete time evolution. Further, we assumed that the drug kills both immune cells and tumor cells but with different kill rates.

Thus, our proposed model is:

$$\frac{dx}{dt} = s + c_1 x(t)y[[t]] - d_1 x(t) - a_1 x(t)z[[t]]$$

$$\frac{dy}{dt} = r_1 y(t)(1 - b_1 y(t)) - c_2 x[[t]]y(t) - a_2 y(t)z[[t]]$$

$$z(n + 1) = \alpha z(n)(1 - \beta z(n)) - d_2 z(n) \quad (1)$$

where, $[[t]]$ denotes the integer part of $t \in [0, \infty)$. Here, $x(t)$ is the immune cell population density at time t , $y(t)$ is the tumor cell population density at time t and $z(n)$ is the amount of drug administrated to the patient at time n .

The discrete time $[[t]]$ is added in the competition term $x(t)y(t)$ because the immune cells interact with tumor cells on discrete level. Also, the inclusion of the discrete time $[[t]]$ in the drug interaction term $x(t)z(t)$ and $y(t)z(t)$ are because we assumed that the drug also interact with the immune cells and tumor cells on discrete level.

In our model, we assume that the tumor cells follow the logistic growth law and the kill rate of tumor cells due to drug administration is more than the kill rate of immune cells due to the drug administration of the same amount of drug because otherwise there will be no meaning of drug administration.

Integrating the first two equations of the system (1) in the interval $t \in [n, n + 1)$, we get the solutions as

$$x(t) = x(n) + \int_n^t \{s + c_1 x(u)y(n) - d_1 x(u) - a_1 x(u)z(n)\} du$$

$$y(t) = y(n) e^{\int_n^t \{r_1(1-b_1 y(u)) - c_2 x(n) - a_2 z(n)\} du}$$

Using positive initial conditions i.e. for $x(n) > 0, y(n) > 0$ it can be easily observed that the system (1) has positive solutions $x(t) > 0, y(t) > 0$. This is because in the first solution the integrand is positive and in the second solution the exponential always gives the positive values. Also, the third equation of the system (1) always possess positive values for positive initial conditions. Thus, our proposed model (1) is positive invariant.

For numerical verification of our results we take the following parameter values:

Table 1

Parameters	Values
s (constant number of immune cells already present in the body)	0.05
d_1 (the natural death rate of immune cells)	0.2
r_1 (the intrinsic tumor growth rate)	0.35
$1/b_1$ (the tumor population carrying capacity)	$1/1.5$
β (maximum drug carrying capacity)	1
d_2 (natural decay rate of drug)	0.05
a_1 (immune cell kill rate due to drug)	0.2
a_2 (tumor cell kill rate due to drug)	0.5
c_1 (decay rate of immune cells due to tumor cells)	0.25
c_1 (decay rate of tumor cells due to immune cells)	0.4

Local stability analysis:

On the interval $t \in [n, n + 1)$, the first two equations of system (1) can be written as:

$$\frac{dx}{dt} + [d_1 - c_1y(n) + a_1z(n)]x(t) = s$$

$$\frac{dy}{dt} - [r_1 - c_2x(n) - a_2z(n)]y(t) = -r_1b_1(y(t))^2 \quad \dots(2)$$

Integrating both sides of each equations in (2) with respect to t on the interval $[n, n + 1)$, we get the following:

$$x(n + 1) = \frac{s}{d_1 - c_1y(n) + a_1z(n)} [1 - e^{-[d_1 - c_1y(n) + a_1z(n)]}] + e^{-[d_1 - c_1y(n) + a_1z(n)]} x(n)$$

$$y(n + 1) = \frac{[r_1 - c_2x(n) - a_2z(n)]y(n)}{r_1b_1y(n) + \{r_1 - c_2x(n) - a_2z(n) - r_1b_1y(n)\}e^{-[r_1 - c_2x(n) - a_2z(n)]}}$$

Thus, we get the following set of difference equations which is equivalent to the differential-difference model (1)

$$x(n + 1) = \frac{s}{M} [1 - e^{-M}] + e^{-M}x(n)$$

$$y(n + 1) = \frac{Ny(n)}{r_1b_1y(n) + \{N - r_1b_1y(n)\}e^{-N}}$$

$$z(n + 1) = \alpha z(n)(1 - \beta z(n)) - d_2z(n) \quad \dots(3)$$

where, $M = d_1 - c_1y(n) + a_1z(n)$, $N = r_1 - c_2x(n) - a_2z(n)$

Equilibrium points of the system (3) are given by,

$$\frac{s}{M} [1 - e^{-M}] + e^{-M}x = x \Rightarrow x = \frac{s}{r_1 - c_2x - a_1z}, \text{ if } r_1 - c_2x - a_1z \neq 0$$

$$\frac{Ny}{r_1b_1y + \{N - r_1b_1y\}e^{-N}} = y \Rightarrow y = 0 \text{ or } N = r_1b_1y + \{N - r_1b_1y\}e^{-N}$$

Here, $N = r_1b_1y + \{N - r_1b_1y\}e^{-N}$

$$\Rightarrow e^{-N} = 1 \text{ if } N \neq r_1b_1y$$

$$\Rightarrow N = 0 \text{ if } r_1 - c_2x - a_2z \neq r_1b_1y \Rightarrow x = \frac{r_1 - a_2z}{c_2}$$

i.e. $y = 0$ or $x = \frac{r_1 - a_2z}{c_2}$ if $N \neq r_1b_1y$

$$\text{And } \alpha z(1 - \beta z) - d_2z = z \Rightarrow z = 0 \text{ or } z = \frac{\alpha - d_2 - 1}{\alpha\beta}$$

Thus the four equilibrium points are:

$$E_0\left(\frac{s}{d_1}, 0, 0\right), E_1\left(\frac{s}{d_1 + a_1z_1}, 0, z_1 = \frac{\alpha - d_2 - 1}{\alpha\beta}\right),$$

$$E_2\left(\frac{s}{d_1 - c_1y_2}, y_2, 0\right) \text{ and } E_3\left(\frac{s}{d_1 - c_1y_3 + a_1z_3}, y_3, z_3 = \frac{\alpha - d_2 - 1}{\alpha\beta}\right)$$

$$\text{Here, } y_2 = \frac{d_1}{c_1} - \frac{c_2s}{c_1r_1} \text{ and } y_3 = \frac{d_1}{c_1} + \frac{a_1z_3}{c_1} - \frac{c_2s}{c_1(r_1 - a_2z_3)}$$

Now, the jacobian matrix of (3) at the equilibrium point E_0 is

$$J_{E_0} = \begin{pmatrix} e^{-d_1} & \frac{sc_1}{d_1^2}(1 - e^{-d_1}) & \frac{-sa_1}{d_1^2}(1 - e^{-d_1}) \\ 0 & e^{r_1} & 0 \\ 0 & 0 & \alpha - d_2 \end{pmatrix}$$

The eigen values are $\lambda_1 = e^{-d_1} < 1$, $\lambda_2 = e^{r_1}$, $\lambda_3 = \alpha - d_2$

But, r_1 can't be negative being the intrinsic tumor growth rate which implies $\lambda_2 \geq 1$. So, the equilibrium E_0 is unstable.

At the equilibrium point E_1 ,

$$J_{E_1} = \begin{pmatrix} e^{-(d_1 + a_1z_1)} & \frac{sc_1}{(d_1 + a_1z_1)^2}(1 - e^{-(d_1 + a_1z_1)}) & \frac{-sa_1}{(d_1 + a_1z_1)^2}(1 - e^{-(d_1 + a_1z_1)}) \\ 0 & e^{r_1 - c_2x_1 - a_2z_1} & 0 \\ 0 & 0 & -\alpha + d_2 + 2 \end{pmatrix}$$

Eigen values are $\lambda_1 = e^{-(d_1 + a_1z_1)} < 1$ if $\alpha > \frac{a_1(d_2 + 1)}{\beta d_1 + a_1}$

$$\lambda_2 = e^{r_1 - c_2x_1 - a_2z_1} < 1 \text{ if } r_1 - c_2x_1 - a_2z_1 < 0$$

and $\lambda_3 = -\alpha + d_2 + 2 < 1$ if $\alpha > d_2 + 1$

Thus the tumor free equilibrium point E_1 is locally stable if the above conditions are met.

Thus for the parameter values in table 1, E_1 is locally stable if $\alpha > 2.4581$ which can be clearly observed from the bifurcation diagram of the tumor cells given below:

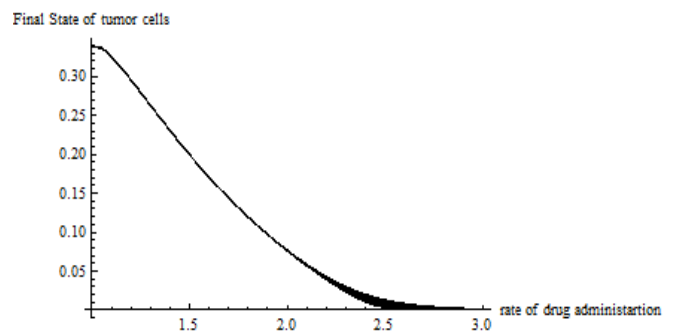


Fig 1: Bifurcation diagram of the number of tumor cells in the range $1 \leq \alpha$ (rate of drug administration) ≤ 3

Bifurcation analysis:

In this section, first we determine the range for the control parameter of the system (3) and then we investigate the possible bifurcation types of the system (3). Since the third equation in (3) is independent of the other two equations and the control parameter (α , the rate of drug administration) is involved directly in the third equation so it will be sufficient to consider the third equation for bifurcation analysis.

We let $f(z) = \alpha z(1 - \beta z) - d_2z$. Then $z^* = \frac{\alpha - d_2}{2\alpha\beta}$ is a point of maximum for the function $f(z)$ which gives:

$$f(z^*) = \frac{(\alpha - d_2)^2}{4\alpha\beta} \in \left[0, \frac{1}{\beta}\right] \Rightarrow \alpha^2 - 2\alpha d_2 + d_2^2 \in [0, 4\alpha]$$

$$\Rightarrow \alpha^2 - 2\alpha d_2 + d_2^2 \geq 0 \text{ and } \alpha^2 - 2\alpha d_2 + d_2^2 \leq 4\alpha$$

$\Rightarrow (\alpha - d_2)^2 \geq 0$ (which always holds) and $0.000609847 \leq \alpha \leq 4.09939$ (as per the values considered in table 1)

But for z^* to be positive we must have, $\alpha > 1 + d_2$ which implies $\alpha \in (1.05, 4.09939]$

The fixed points of $f(z)$ are $z_{1,1} = 0$ and $z_{1,2} = \frac{\alpha - d_2 - 1}{\alpha\beta}$ ($z_{1,2}$ exists only when $\alpha > 1 + d_2$)

Using the stability criteria it is seen that $z_{1,1} = 0$ is unstable for $\alpha < 1 + d_2$ and stable when $\alpha > 1 + d_2$ which confirms

that a transcritical bifurcation takes place at the parameter value $\alpha = 1 + d_2 = 1.05$ (for $d_2 = 0.05$)

$z_{1,2}$ is stable if $|\alpha + d_2 + 2| < 1$ i.e. $1 + d_2 < \alpha < 3 + d_2$ and unstable if $|\alpha + d_2 + 2| > 1$ i.e. $1 + d_2 > \alpha$ or $\alpha > 3 + d_2$. But $z_{1,2}$ does not exist for $\alpha < 1 + d_2$ so it is unstable only when $\alpha > 3 + d_2$.

i.e. $z_{1,2}$ is stable if $1.05 < \alpha < 3.05$ and unstable if $\alpha > 3.05$ for $d_2 = 0.05$.

Therefore, the fixed point $z_{1,2}$ changes its nature from stable to unstable at $\alpha = 3 + d_2$ i.e. at $\alpha = 3.05$ (for $d_2 = 0.05$). So, $\alpha = 3 + d_2$ is a bifurcation point (perhaps the first period doubling bifurcation point) of the drug administration policy in the system (3).

Now to find the points of period-2, it is necessary to consider the equation:

$$f^2(z) = \alpha\{az(1 - \beta z) - d_2z\}[1 - \beta\{az(1 - \beta z) - d_2z\}]$$

The fixed points of $f^2(z)$ are given by, $f^2(z) = z$

$$\Rightarrow \alpha\{az(1 - \beta z) - d_2z\}[1 - \beta\{az(1 - \beta z) - d_2z\}] = z \quad (4)$$

$z_{1,1}$ and $z_{1,2}$ are points of period-1, so they repeat on every second iteration.

Thus we get the other two fixed points of $f^2(z)$ or the points of period-2 of $f(z)$ as:

$$z_{2,1} = \frac{\alpha + \alpha^2 - \alpha d_2 + \alpha \sqrt{-3 - 2\alpha + \alpha^2 + 2d_2 - 2\alpha d_2 + d_2^2}}{2\alpha^2}$$

$$\text{and } z_{2,2} = \frac{\alpha + \alpha^2 - \alpha d_2 - \alpha \sqrt{-3 - 2\alpha + \alpha^2 + 2d_2 - 2\alpha d_2 + d_2^2}}{2\alpha^2}$$

These two points exist iff, $-3 - 2\alpha + \alpha^2 + 2d_2 - 2\alpha d_2 + d_2^2 > 0$

$$\Rightarrow (-3 + \alpha - d_2)(1 + \alpha - d_2) > 0$$

$$\Rightarrow (-3 + \alpha - d_2) > 0 \text{ [since, } 1 + \alpha - d_2 > 0]$$

$$\Rightarrow \alpha > 3 + d_2 = 3.05 \text{ (for } d_2 = 0.05)$$

After calculation it is found to be, $\frac{d}{dz}f^2(z_{2,1}) = \frac{d}{dz}f^2(z_{2,2})$, i.e. it is clear that the nature of stability of the fixed points $z_{2,1}$ and $z_{2,2}$ of $f^2(z)$ which are periodic points of period-2 of the map $f(z)$ are the same.

Using the stability criterion it is found that $z_{2,1}$ and $z_{2,2}$ are stable in the range $3 + d_2 < \alpha < 1 + \sqrt{6} + d_2$ and unstable for $\alpha > 1 + \sqrt{6} + d_2$.

Thus at $\alpha = 3 + d_2$, the final state of the amount of drug present in the body changes its behaviour from a stable period-1 trajectory to a stable period-2 trajectory i.e. $\alpha = 3 + d_2$ is the first period doubling bifurcation point. It can also be shown in a similar way that $\alpha = 1 + \sqrt{6} + d_2$ is the second period doubling bifurcation point of the drug administration policy in the system (3). It will be further difficult to determine the next higher period doubling bifurcation points analytically and so we verified the phenomenon of next higher period doubling bifurcations through bifurcation diagram and time series diagrams. A time series plot to visualise the fact that the amount of drug present in the system (3) shows period-3 behaviour for some values of the control parameter is also drawn. The occurrence of period-3 behaviour confirms that for some parameter value the final state of the amount of drug present in the body will exhibit chaos [12].

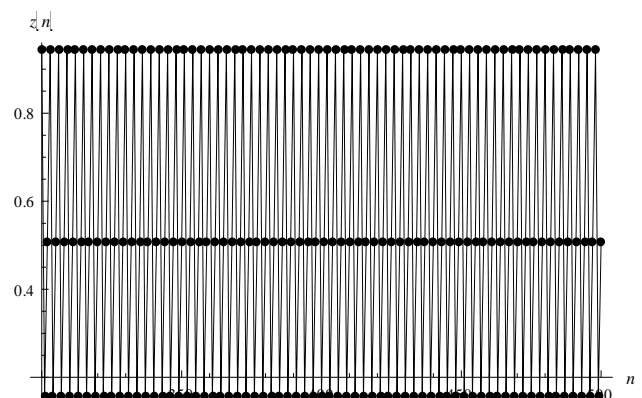
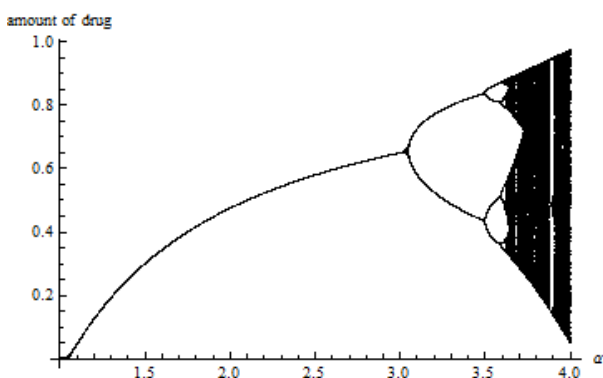


Fig 2: (a) Bifurcation diagram of the amount of drug present in the body for $0 \leq \alpha \leq 4$
 (b) Time series diagram of the final state of drug present showing period-3 behaviour at $\alpha = 1.05 + 2\sqrt{2}$

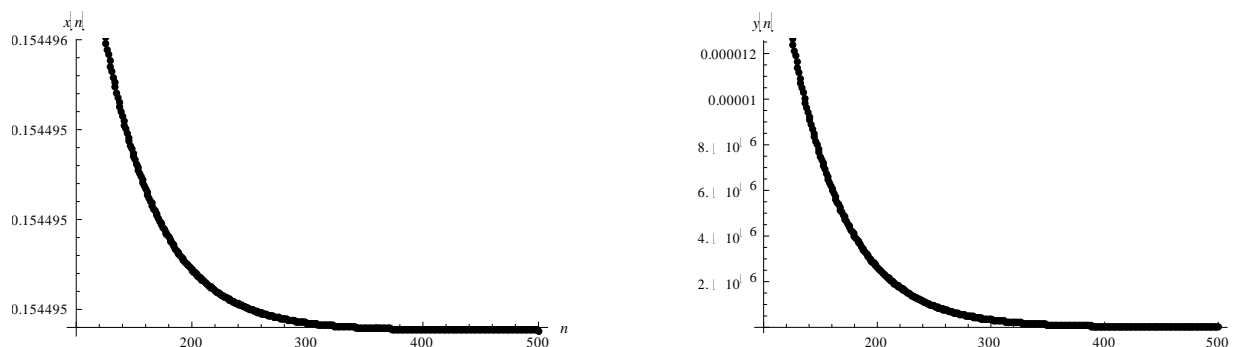


Fig 3: Time series diagram of (a) no. of immune cells (b) no. of tumor cells at $\alpha = 2.75$

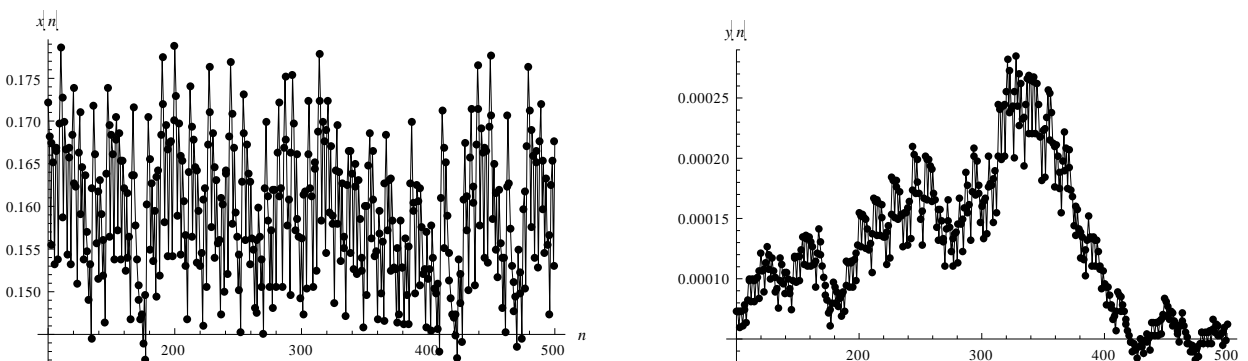


Fig 4: Time series diagram of (a) no. of immune cells (b) no. of tumor cells at $\alpha = 4$

When the final state of the drug present in the body becomes chaotic, the ultimate and obvious effect is that the the control policy given by the system (3) will collapse and the final state of tumor cells will oscillate randomly. Thus to have a sustainable control policy to eradicate the tumor completely one needs the drug administration rate to be in the range where it becomes stable and before the first bifurcation point of the final state of the drug present in the body. As soon as the first bifurcation point $\alpha = 3 + d_2$ is crossed, the final state of tumor cells starts oscillating and the total control in stabilizing the tumor free state is lost. The total system of control policy starts oscillating randomly and will collapse as soon as the control parameter α crosses the value (for the parameter values in table1, $\alpha = 3.6199 \dots$) where the chaos begins.

CONCLUSION:

In this paper we proposed a tumor cell-immune cell model in the form of a combination of difference equation and differential equations with the logistic law of drug administration. Instead of applying the idea of global stability we combined the results of local stability analysis of the tumor free equilibrium point and bifurcation analysis of the system represented by the proposed model to present a control policy to eradicate the tumor completely. Using numerical simulation we verified our results.

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