Numerical approximation to time-delayed model of tumor and immune cells interaction

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Abstract. In this paper, we recreate the results of S.Kartal [4] and improve on his work by providing clear reasoning for the assumptions and eliminating unnecessary requirements. The main focus is in analyzing the solutions to a numerical approximation of a delayed Lotka-Volterra predator-prey like model for the interaction of tumor-immune system presented by Sakar & Banerjee [8]. The approximated model, with piecewise constant arguments, results in a set of difference equations with multiple equilibria whose existence and stability conditions are discussed. The equilibrium of interest is the interior/positive equilibrium where all cells have non-zero values. Necessary conditions are placed on the parameters for the existence as well as the local and global stability of the interior equilibrium. Using Schur-Cohn criterion, a Neimark-Sacker bifurcation analysis is conducted and Jeff's Phenomenon [9], periodic oscillations of tumor cells without any treatment, is observed.

Keywords: Tumor Growth · Piecewise Constant Arguments · Difference Equations · Stability · Neimark-Sacker bifurcation.

1   Introduction

Several models have been developed over the past 20 years to explain the interaction between cancer cells and normal as well as effector cells. Eftimie et al. [1] have outlined models consisting of interaction between cancer cells with one to four generic effector cells. The paper also states that a model with a set of three ODEs (for cancer cells and two generic effector cells), can sufficiently explain the "most essential mechanisms". Therefore, we will be focusing on a model with three ODEs to explain the macroscopic interaction of cancer cells with generic effector cells. In his paper, S. Kartal [4] has modelled the relationship between cancer cells, hunting cells and resting cells using a time-delayed set of ODEs. His analysis has shown the existence of a Neimark-Sacker bifurcation with a stable limit cycle. The author has outlined the difficulty of performing stability analysis of delay differential equations, hence he performed the stability analysis on a discrete time delay approximation to the original equation using numerical methods.

2   Related Previous Work

The time-delayed three equations model for interaction among tumor cells, normal effector (hunting) cells and resting effector cells has been proposed and discussed by

R. Sarkar and S. Banerjee [8] and Merola et. al [6]. The three-equation model can be written as:

$$\frac{dM(t)}{dt} = r_1 M(t) \left(1 - \frac{M(t)}{k_1} \right) - \alpha_1 M(t)N(t),$$

$$\frac{dN(t)}{dt} = \beta N(t)Z(t - \tau) - \alpha_2 M(t)N(t) - d_1 N(t), \tag{1}$$

$$\frac{dZ(t)}{dt} = r_2 Z(t) \left(1 - \frac{Z(t)}{k_2} \right) - \beta N(t)Z(t - \tau) - d_2 Z(t),$$

where $M(t)$, $N(t)$ and $Z(t)$ correspond to the population of tumor cells, hunting cells and resting cells respectively.

The parameters in the equation are,

r_1	Growth rate of tumor cells
r_2	Growth rate of resting cells
$k_1 = 1/K_1$	Maximum capacity of tumor cells
$k_2 = 1/K_2$	Maximum capacity of resting cells
d_1	Natural death rate of hunting cells
d_2	Natural death rate of resting cells
α_1	Death rate of tumor cells from hunting cells interactions
α_2	Death rate of hunting cells from tumor cells interactions
β	Conversion rate from resting to hunting cells

Sarkar and Banerjee [8] utilize perturbation methods to analyze the existence of a Hopf bifurcation where the parameter of interest is the time delay in the conversion from resting to hunting cells. I. Gyori [3] has shown that differential equations with piecewise constant arguments provide a good approximaiton to delayed differential equations. Ozturk et al. [7] have modelled bacteria population by:

$$\frac{dx(t)}{dt} = rx(t) \left[1 - \alpha x(t) - \beta_0 x([t]) - \beta_1 x([t - 1]) \right] \tag{2}$$

which utilizes both discrete and continunous time dependence to study allee effects. The [t] term represents the integer part of t ∈ [0,∞).

Based on I. Gyori's [3] premise and Ozturk et al. 's work [7], S. Kartal [4] has altered the model (1) and analyzed its numerical approximation

$$\frac{dM(t)}{dt} = r_1 M(t) \left(1 - \frac{M(t)}{k_1} \right) - \alpha_1 M(t)N([t]),$$

$$\frac{dN(t)}{dt} = \beta N(t)Z([t - 1]) - \alpha_2 M([t])N(t) - d_1 N(t), \tag{3}$$

$$\frac{dZ(t)}{dt} = r_2 Z(t) \left(1 - \frac{Z(t)}{k_2} \right) - \beta N([t])Z(t) - d_2 Z(t),$$

The results in [4] show the presence of a Neimark-Sacker bifurcation as the value for the resting-hunting cell onversion rate (β) is varied.

3　Modelling & Analysis

3.1　Model Approximation

We propose that a small alteration of Eq (3)

$$\frac{dM(t)}{dt} = r_1 M(t)\left(1 - K_1 M(t)\right) - \alpha_1 M(t)N([t]),$$

$$\frac{dN(t)}{dt} = \beta N(t)Z([t]) - \alpha_2 M([t])N(t) - d_1 N(t), \qquad (4)$$

$$\frac{dZ(t)}{dt} = r_2 Z(t)\left(1 - K_2 Z(t)\right) - \beta N([t])Z(t) - d_2 Z(t),$$

can be used to approximate a slightly modified version of Eq (1)

$$\frac{dM(t)}{dt} = r_1 M(t)\left(1 - K_1 M(t)\right) - \alpha_1 M(t)N(t - v),$$

$$\frac{dN(t)}{dt} = \beta N(t)Z(t - \tau) - \alpha_2 M(t - v)N(t) - d_1 N(t), \qquad (5)$$

$$\frac{dZ(t)}{dt} = r_2 Z(t)\left(1 - K_2 Z(t)\right) - \beta N(t - \tau)Z(t) - d_2 Z(t),$$

where we introduce a hunting delay (v) for the interaction between the hunting and tumor cells. The assumption being that the hunting delay is the same for both tumor and hunting cells. Similar age dependent Lotka-Volterra predator prey models have been studied by T. Faria [2] and Li et. al [10], where one of the time delays (v or τ) or their sum ($v + \tau$) can be used as the critical parameter in the Hopf bifurcation for the model:

$$u'(t) = u(t)[r_1 - a_1 u(t) - a_2 v(t - v)] \quad v'(t) = v(t)[-r_2 + a_3 u(t - \tau) - a_4 v(t)]$$

In addition to the assumptions on the hunting delay stated above, the discretized model (4) makes the simplification of (5) where the time delay in the conversion of resting cells to hunting cells is considered to be the same as that of the hunting delay ($\tau = v$).

We can then rewrite the approximate model (4) on an interval $t \in [n, n + 1)$ for $n = 0, 1, 2 \dots$

$$\frac{dM(t)}{dt} = r_1 M(t)\left(1 - K_1 M(t)\right) - \alpha_1 M(t)N(n),$$

$$\frac{dN(t)}{dt} = \beta N(t)Z(n) - \alpha_2 M(n)N(t) - d_1 N(t), \qquad (6)$$

$$\frac{dZ(t)}{dt} = r_2 Z(t)\left(1 - K_2 Z(t)\right) - \beta N(n)Z(t) - d_2 Z(t),$$

and solve the equations with respect to t on $[n, t)$. By taking the limit as $t \to n + 1$, we get a difference equation of the form

$$M(n+1) = \frac{M(n)(r_1 - \alpha_1 N(n))}{(r_1 - \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)}$$

$$N(n+1) = N(n)e^{\beta Z(n) - d_1 - \alpha_2 M(n)} \tag{7}$$

$$Z(n+1) = \frac{Z(n)(r_2 - \beta N(n) - d_2)}{(r_2 - \beta N(n) - d_2 - r_2 K_2 Z(n))e^{-(r_2 - \beta N(n) - d_2)} + r_2 K_2 Z(n)}.$$
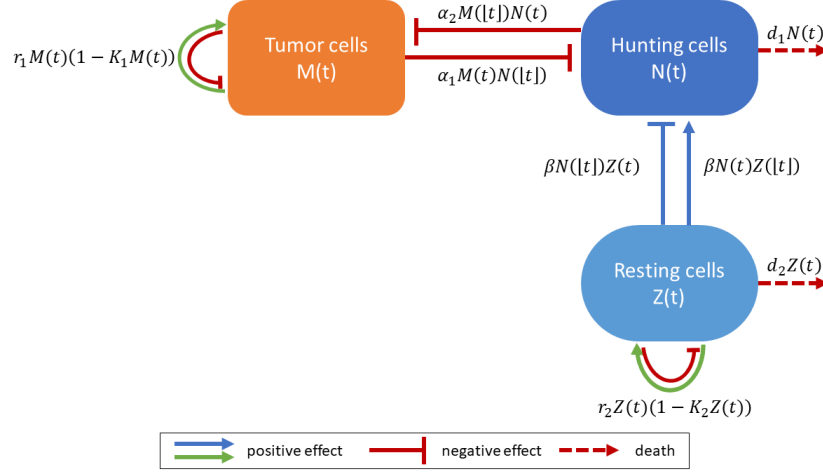

Fig. 1: Interactions in system 4

3.2   Local Stability Analysis

To analyze the stability of this system of difference equations (7), we first need to find the equilibrium points. We will only consider equilibrium points that are biologically feasible, which means they have to be non-negative. Under this restriction, system (7) permits four kinds of equilibria:

1. Equilibrium at the origin:

   $E_0 = (0,0,0)$

2. Equilibria on the boundary of an octant:

   $E_1 = \left(\frac{1}{K_1}, 0, 0\right)$ and $E_2 = \left(0, 0, \frac{r_2 - d_2}{r_2 K_2}\right)$

3. M-Z and N-Z planar equilibria:

   $E_3 = \left(\frac{1}{K_1}, 0, \frac{r_2 - d_2}{r_2 K_2}\right)$ and $E_4 = \left(0, \frac{\beta(r_2 - d_2) - K_2 r_2 d_1}{\beta^2}, \frac{d_1}{\beta}\right)$

4. Interior equilibrium:

$$E_5 = \bar{E} = (\bar{M}, \bar{N}, \bar{Z}) \text{ where}$$

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

$$\bar{N} = \frac{r_1}{\alpha_1}(1 - K_1 \bar{M})$$

$$\bar{Z} = \frac{d_1 + \alpha_2 \bar{M}}{\beta}$$

For E_2 and E_3 to exist we need $r_2 > d_2$, E_4 exists if $\beta > \frac{K_2 r_2 d_1}{(r_2 - d_2)}$. The equilibrium we are most interested in is the interior equilibrium. The existence of $\bar{E}$ is guaranteed, if

$$r_2 > d_2$$
$$\beta > \frac{K_2 r_2 (\alpha_2 + d_1 K_1)}{K_1 (r_2 - d_2)} \tag{8}$$
$$\alpha_1 < \min\left(\frac{\beta^2 r_1}{\beta(r_2 - d_2) - r_2 d_1 K_2}, \frac{\beta^2 r_1 K_1}{\alpha_2 K_2 r_2}\right) = \frac{\beta^2 r_1}{\beta(r_2 - d_2) - r_2 d_1 K_2}.$$

The lower bound on β guarantees $\bar{N} > 0$ by having $\bar{M} < 1/K_1$. The upper bound on α_1 will guarantee $\bar{M} > 0$ by making both its numerator and denominator > 0. If $\bar{M} > 0$, $\bar{Z}$ will always be positive.

Theorem 1. *Suppose the interior equilibrium $\bar{E}$ of system (7) exists, then the non-negative equilibria E_0, E_1, E_2, E_3 and E_4 as defined above are all unstable.*

Equilibrium	*Stability*
E_0	*unconditionally unstable*
E_1	*unstable if E_2 exists*
E_2	*unconditionally unstable*
E_3	*unstable if $\bar{E}$ exists*
E_4	*unstable if $\bar{E}$ exists*

Proof. We compute the linearized system of (7).

$$a_{11} = \frac{\mathrm{d}}{\mathrm{d}M(n)} \frac{M(n)(r_1 - \alpha_1 N(n))}{(r_1 - \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)}$$

$$= \frac{r_1 - \alpha_1 N(n) - M(n+1)\left(K_1 r_1 - K_1 r_1 e^{\alpha_1 N(n) - r_1}\right)}{(r_1 - \alpha_1 N(n) - r_1 K_1 M(n))e^{\alpha_1 N(n) - r_1} + K_1 r_1 M(n)}$$

$$a_{12} = \frac{\mathrm{d}}{\mathrm{d}N(n)} \frac{M(n)(r_1 - \alpha_1 N(n))}{(r_1 - \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)}$$

$$= \frac{-M(n+1)\left(\alpha_1 e^{\alpha_1 N(n) - r_1}(-\alpha_1 N(n) - K_1 r_1 M(n) + r_1) - \alpha_1 e^{\alpha_1 N(n) - r_1}\right) - \alpha_1 M(n)}{e^{\alpha_1 N(n) - r_1}(\alpha_1 N(n) - K_1 r_1 M(n) + r_1) + K_1 r_1 M(n)}$$

$$a_{13} = \frac{d}{dZ(n)} \frac{M(n)(r_1 - \alpha_1 N(n))}{(r_1 - \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)}$$

$$= 0$$

$$a_{21} = \frac{d}{dM(n)} N(n)e^{\beta Z(n) - d_1 - \alpha_2 M(n)}$$

$$= -\alpha_2 N(n+1)$$

$$a_{22} = \frac{d}{dN(n)} N(n)e^{\beta Z(n) - d_1 - \alpha_2 M(n)}$$

$$= e^{\beta Z(n) - d_1 - \alpha_2 M(n)}$$

$$a_{23} = \frac{d}{dZ(n)} N(n)e^{\beta Z(n) - d_1 - \alpha_2 M(n)}$$

$$= \beta N(n+1)$$

$$a_{31} = \frac{d}{dM(n)} \frac{Z(n)(r_2 - \beta N(n) - d_2)}{(r_2 - \beta N(n) - d_2 - r_2 K_2 Z(n))e^{-(r_2 - \beta N(n) - d_2)} + r_2 K_2 Z(n)}$$

$$= 0$$

$$a_{32} = \frac{d}{dN(n)} \frac{Z(n)(r_2 - \beta N(n) - d_2)}{(r_2 - \beta N(n) - d_2 - r_2 K_2 Z(n))e^{-(r_2 - \beta N(n) - d_2)} + r_2 K_2 Z(n)}$$

$$= \frac{-Z(n+1)\left(\beta e^{\beta N(n) + d_2 - r_2}(-\beta N(n) - d_2 - K_2 r_2 Z(n) + r_2) - \beta e^{\beta N(n) + d_2 - r_2}\right) - \beta Z(n)}{e^{\beta N(n) + d_2 - r_2}(-\beta N(n) - d_2 - K_2 r_2 Z(n) + r_2) + K_2 r_2 Z(n)}$$

$$a_{33} = \frac{d}{dZ(n)} \frac{Z(n)(r_2 - \beta N(n) - d_2)}{(r_2 - \beta N(n) - d_2 - r_2 K_2 Z(n))e^{-(r_2 - \beta N(n) - d_2)} + r_2 K_2 Z(n)}$$

$$= \frac{-\beta N(n) - d_2 + r_2 - Z(n+1)\left(K_2 r_2 - K_2 r_2 e^{\beta N(n) + d_2 - r_2}\right)}{e^{\beta N(n) + d_2 - r_2}(-\beta N(n) - d_2 - K_2 r_2 Z(n) + r_2) + K_2 r_2 Z(n)}$$

The variational matrix of the system is

$$A(M, N, Z) = \begin{pmatrix} a_{11} & a_{12} & 0 \\ -\alpha_2 N(n+1) & e^{\beta Z(n) - d_1 - \alpha_2 M(n)} & \beta N(n+1) \\ 0 & a_{32} & a_{33} \end{pmatrix}$$

Evaluating this at the equilibria leads to the following matrices and eigenvalues:

$$A(E_0) = \begin{pmatrix} e^{r_1} & 0 & 0 \\ 0 & e^{-d_1} & 0 \\ 0 & 0 & e^{r_2 - d_2} \end{pmatrix}$$

which has eigenvalues $\{e^{r_1}, e^{-d_1}, e^{r_2 - d_2}\}$. We can see that $e^{r_1} > 1$ and $e^{-d_1} < 1$, hence E_0 is an unstable saddle point.

$$A(E_1) = \begin{pmatrix} e^{-r_1} & \frac{\alpha}{K_1 r_1}\left(e^{-r_1} - 1\right) & 0 \\ 0 & e^{-d_2 - \frac{\alpha_2}{K_1}} & 0 \\ 0 & 0 & e^{r_2 - d_2} \end{pmatrix}$$

which has eigenvalues $\left\{ e^{-r_1}, e^{-d_2 - \frac{\alpha_2}{K_1}}, e^{r_2 - d_2} \right\}$. If equilibrium point E_2 exists ($r_2 > d_2$), then $e^{-r_1} < 1, e^{-d_2 - \frac{\alpha_2}{K_1}} < 1$ and $e^{r_2 - d_2} > 1$. Therefore, if E_2 exists then E_1 is an unstable saddle point.

$$A(E_2) = \begin{pmatrix} e^{r_1} & 0 & 0 \\ 0 & e^{\beta \frac{r_2 - d_2}{r_2 K_2} - d_1} & 0 \\ 0 & \frac{\beta}{r_2 K_2}\left(e^{d_2 - r_2} - 1\right) & e^{r_2 - d_2} \end{pmatrix}$$

which has eigenvalues $\left\{ e^{r_1}, e^{\beta \frac{r_2 - d_2}{r_2 K_2} - d_1}, e^{r_2 - d_2} \right\}$. We can see that $e^{r_1} > 1$, $e^{r_2 - d_2} > 1$. Therefore E_2 is unstable.

$$A(E_3) = \begin{pmatrix} \frac{e^{-r_1}}{r_1} & -\frac{\alpha_1\left(1 - e^{-r_1}\right)}{r_1 K_1} & 0 \\ 0 & e^{\frac{\beta(r_2 - d_2) - K_2 d_1 r_2 - \alpha_2 r_2}{r_2 K_2}} & 0 \\ 0 & -\frac{\beta\left(1 - e^{-(r_2 - d_2)}\right)}{r_2 K_2} & \frac{e^{-(r_2 - d_2)}}{r_2 - d_2} \end{pmatrix}$$

which has eigenvalues $\left\{ \frac{e^{-r_1}}{r_1}, e^{\frac{\beta(r_2 - d_2) - K_2 d_1 r_2 - \alpha_2 r_2}{r_2 K_2}}, \frac{e^{-(r_2 - d_2)}}{r_2 - d_2} \right\}$. We can see that $\frac{e^{-r_1}}{r_1} < 1$ and $\frac{e^{-(r_2 - d_2)}}{r_2 - d_2} < 1$. However, if the interior equilibrium $\bar{E}$ exists, then $\beta > \frac{K_2 r_2(\alpha_2 + d_1 K_1)}{K_1(r_2 - d_2)}$ and the eigenvalue $e^{\frac{\beta(r_2 - d_2) - K_2 d_1 r_2 - \alpha_2 r_2}{r_2 K_2}} > 1$. Hence, if $\bar{E}$ exists, then E_3 is an unstable saddle point.

$$A(E_4) = \begin{pmatrix} e^{r_1 - \alpha_1\left(\frac{\beta(r_2 - d_2) - K_2 r_2 d_1}{\beta^2}\right)} & 0 & 0 \\ -\alpha_2\left(\frac{\beta(r_2 - d_2) - K_2 r_2 d_1}{\beta^2}\right) & 1 & \beta\left(\frac{\beta(r_2 - d_2) - K_2 r_2 d_1}{\beta^2}\right) \\ 0 & -\beta\frac{\left(1 - e^{\frac{-K_2 r_2 d_1}{\beta}}\right)}{K_2 r_2} & e^{-\frac{r_2 K_2 d_1}{\beta}} \end{pmatrix}$$

The characteristic polynomial of matrix $A(E_4)$ is

$$p(\lambda) = (a_{11} - \lambda)(\lambda^2 - (a_{33} + 1)\lambda + a_{33} - a_{23}a_{32})$$

where the eigenvalues are:

$$\lambda_1 = e^{r_1 - \alpha_1\left(\frac{\beta(r_2 - d_2) - K_2 r_2 d_1}{\beta^2}\right)} \tag{9}$$

$$\lambda_{2,3} = \frac{1 + e^{-\frac{r_2 K_2 d_1}{\beta}}}{2} \pm \frac{\sqrt{(a_{33} - 1)^2 + 4a_{23}a_{32}}}{2} \tag{10}$$

We can show that if the interior equilibrium exists, then E_4 is an unstable saddle point with $Re(\lambda_1) > 1, 0 < Re(\lambda_2) < 1$ and $0 < Re(\lambda_3) < 1$.
The existence of the interior equilibrium is conditioned on (8), which imply that,

$$\lambda_1 = e^{r_1 - \alpha_1 \left(\frac{\beta(r_2 - d_2) - K_2 r_2 d_1}{\beta^2} \right)} = e^{\frac{r_1 \beta^2 - \alpha_1 (\beta(r_2 - d_2) - K_2 r_2 d_1)}{\beta^2}} > e^0 = 1$$

and

$$(1 - a_{33})^2 + 4a_{23}a_{32} = (1 - e^{-\frac{r_2 K_2 d_1}{\beta}}) \left(1 - e^{-\frac{r_2 K_2 d_1}{\beta}} - \frac{4\beta(r_2 - d_2)}{K_2 r_2} + 4d_1 \right)$$

$$< (1 - e^{-\frac{r_2 K_2 d_1}{\beta}}) \left(1 - e^{-\frac{r_2 K_2 d_1}{\beta}} - \frac{4\alpha_2}{K_1} \right)$$

$$< \left(1 - e^{-\frac{r_2 K_2 d_1}{\beta}} \right)^2$$

Therefore, $Re(\lambda_2) > 0, Re(\lambda_3) > 0$ and

$$Re(\lambda_2) < \frac{1 + e^{-\frac{r_2 K_2 d_1}{\beta}} + 1 - e^{-\frac{r_2 K_2 d_1}{\beta}}}{2} = 1$$

$$Re(\lambda_3) \leqslant \frac{1 + e^{-\frac{r_2 K_2 d_1}{\beta}}}{2} < 1$$

Hence, if the interior equilibrium $\bar{E}$ exists, then the equilibrium point E_4 is an unstable saddle point.

$\square$

To analyze the stability of the interior equilibrium $\bar{E}$, we have to look at the following matrix:

$$\bar{A} = A\left(\bar{E}_5\right) = \begin{pmatrix} e^{-K_1 r_1 \bar{M}} & -\alpha_1 \frac{(1 - e^{-K_1 r_1 \bar{M}})}{K_1 r_1} & 0 \\ -\alpha_2 \bar{N} & 1 & \beta \bar{N} \\ 0 & -\beta \frac{(1 - e^{-K_2 r_2 \bar{Z}})}{K_2 r_2} & e^{-K_2 r_2 \bar{Z}} \end{pmatrix}$$

The characteristic polynomial of matrix $\bar{A}$ is

$$p(\lambda) = (\bar{a}_{11} - \lambda)((1 - \lambda)(\bar{a}_{33} - \lambda) - \bar{a}_{23}\bar{a}_{32}) - \bar{a}_{12}\bar{a}_{21}(\bar{a}_{33} - \lambda). \qquad (11)$$

The stability of the equilibrium point depends on the values of α_1 and β. Since we want to analyze the stability based on the values of β alone, we will fix the value of α_1. However, the $\bar{E}$ existence requirement for α_1 depends on β. We can ensure the requirement (8) on α_1 won't be violated as β is varied by finding the minimum of

$$f(\beta) = \frac{\beta^2 r_1}{\beta(r_2 - d_2) - r_2 d_1 K_2} \implies f_{min} = \frac{4 K_2 r_2 r_1 d_1}{(r_2 - d_2)^2}.$$

Therefore, a stricter bound can be set on α_1

$$\alpha_1 < \frac{4K_2r_2r_1d_1}{(r_2-d_2)^2}. \tag{12}$$

Then we can fix alpha by making the assumption,

$$\bar{a}_{11} = \bar{a}_{33} \tag{13}$$

which implies $\lambda_1 = e^{-K_1r_1\bar{M}} < 1$ is an eigenvalue of $\bar{A}$. With the biological fact that $r_1 > r_2$ we get

$$\alpha_1 = \frac{\beta r_1 \left(K_1(-r_1\beta + d_1r_2K_2) + \alpha_2K_2r_2\right)}{d_2(K_1r_1\beta - \alpha_2K_2r_2) + r_2(K_1r_1(-\beta + d_1K_2) + K_2\alpha_2r_2)}. \tag{14}$$

Under assumption (13) we can reduce the characteristic polynomial $q(\lambda)$ to a second order equation

$$q(\lambda) = \lambda^2 + \lambda(-1 - \bar{a}_{33}) + \bar{a}_{33} - \bar{a}_{23}\bar{a}_{32} - \bar{a}_{12}\bar{a}_{21}$$

$$= \lambda^2 + \lambda(-1 - e^{-K_1r_1\bar{M}}) + e^{-K_1r_1\bar{M}} + \frac{\bar{N}\left(1 - e^{-K_1r_1\bar{M}}\right)\left(\beta^2K_1r_1 - K_2r_2\alpha_1\alpha_2\right)}{K_1r_1K_2r_2}. \tag{15}$$

Theorem 2. *Let $\bar{E}$ be the interior equilibrium point of system (7). Suppose that $\bar{E}$ exists and*

$$\alpha_1 = \frac{\beta r_1 \left(K_1(-r_1\beta + d_1r_2K_2) + \alpha_2K_2r_2\right)}{d_2(K_1r_1\beta - \alpha_2K_2r_2) + r_2(K_1r_1(-\beta + d_1K_2) + K_2\alpha_2r_2)}.$$

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

$$\beta < \frac{K_2r_2(K_1 + K_1d_1 + \alpha_2)}{K_1(r_2 - d_2)}.$$

Proof. We use the Schur-Cohn criterion for the characteristic polynomial (15). Define q_1, q_0 such that

$$q(\lambda) = \lambda^2 + q_1\lambda + q_0.$$

Then by Schur-Cohn criterion $\bar{E}$ is stable if and only if the coefficents of

$$Q(\lambda) = (1 + q_1 + q_0)\lambda^2 + (2 - 2q_0)\lambda + (1 - q_q + q_0)$$

are of the same sign. Since

$$q_1 = (-1 - e^{-K_1r_1\bar{M}}) < 0 \text{ and}$$

$$q_0 = e^{-K_1r_1\bar{M}} + \frac{\bar{N}\left(1 - e^{-K_1r_1\bar{M}}\right)\left(\beta^2K_1r_1 - K_2r_2\alpha_1\alpha_2\right)}{K_1r_1K_2r_2} > 0$$

it follows that

$$1 - q_1 + q_0 > 0.$$

Using (8) yields

$$1 + q_1 + q_0 = 1 + (-1 - e^{-K_1 r_1 \bar{M}}) + e^{-K_1 r_1 \bar{M}} + \frac{\bar{N} \left(1 - e^{-K_1 r_1 \bar{M}}\right) \left(\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2\right)}{K_1 r_1 K_2 r_2}$$

$$= \frac{\bar{N} \left(1 - e^{-K_1 r_1 \bar{M}}\right) \left(\beta^2 K_1 r_1 - K_2 r_2 \alpha_1 \alpha_2\right)}{K_1 r_1 K_2 r_2} > 0.$$

Hence we need

$$2 - 2q_0 > 0$$

$$\Leftrightarrow \qquad 1 > q_0$$

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

$$\Leftrightarrow \quad K_1 K_2 r_1 r_2 \left(1 - e^{-K_1 r_1 \bar{M}}\right) > (\beta(K_1 r_1 r_2 - K_1 r_1 d_1) - d_1 K_1 K_2 r_1 2_2 - K_2 r_1 r_2 \alpha_2) \left(1 - e^{-K_1 r_1 \bar{M}}\right)$$

$$\Leftrightarrow \qquad K_1 K_2 r_2 > \beta(K_1 r_1 r_2 - K_1 r_1 d_1) - d_1 K_1 K_2 r_1 2_2 - K_2 r_1 r_2 \alpha_2$$

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

This completes the proof.   □

3.3   Global Stability Analysis

Theorem 3. *Let the conditions of Theorem 2 hold. Furthermore, assume that*

$$r_1 - \alpha_1 N(n) > 0, \qquad\qquad (16)$$
$$r_2 - \beta N(n) - d_2 > 0, \qquad\qquad (17)$$
$$\beta Z(n) - d_1 - \alpha_2 M(n) < 0. \qquad\qquad (18)$$

If

$$r_1 K_1 M(n) < r_1 - \alpha_1 N(n) < \ln\left(\frac{2\bar{M} - M(n)}{M(n)}\right), \qquad\qquad (19)$$

$$r_2 k_2 Z(n) < r_2 - \beta N(n) - d_2 < \ln\left(\frac{2\bar{Z} - Z(n)}{Z(n)}\right), \qquad\qquad (20)$$

$$N(n) > 2\bar{N}, \qquad\qquad (21)$$

then the positive equilibrium point $\bar{E}$ is globally asymptotically stable.

Proof. Let

$$V(E(n)) = \left(E(n) - \bar{E}\right)^2 \text{ for } n = 0, 1, 2 \ldots$$

Then $V(E(n))$ is a Lyapunov function with positive isolated equilibrium point $\bar{E} = \left(\bar{M}, \bar{N}, \bar{Z}\right)$. It is gobally positive definite and radially unbounded. Computing the change along the solutions of the system yields

$$\begin{aligned}
\Delta V(E(n)) &= V(E(n+1)) - V(E(n)) \\
&= \left(E(n+1) - \bar{E}\right)^2 - \left(E(n) - \bar{E}\right)^2 \\
&= (E(n+1) - E(n))\left(E(n+1) + E(n) - 2\bar{E}\right).
\end{aligned}$$

Using assumption (19) we get for the first component

$$\begin{aligned}
\Delta V(E_M(n)) &= (M(n+1) - M(n))\left(M(n+1) + M(n) - 2\bar{M}\right) \\
&< (M(n+1) - M(n))\left(M(n+1) - M(n)e^{r_1 - \alpha_1 N(n)}\right) \\
&= \frac{M(n)^2\left(r_1 K_1 M(n) - r_1 K_1 M(n)e^{r_1 - \alpha_1 N(n)}\right)}{(r_1 \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)} \\
&\quad \cdot \frac{\left(r_1 - \alpha_1 N(n) - (r_1 - \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)\right)}{(r_1 \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)} \\
&= \frac{M(n)^2\left(r_r K_1 M(n)(r_1 - \alpha_1 N(n) + (r_1 K_1 M(n))^2\right)\left(2 - e^{-(r_1 - \alpha_1 N(n))} - e^{r_1 - \alpha_1 N(n)}\right)}{\left((r_1 \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)\right)^2} \\
&< \frac{M(n)^2\left((r_1 - \alpha_1 N(n))^2 + (r_1 K_1 M(n))^2\right)\left(2 - e^{-(r_1 - \alpha_1 N(n))} - e^{r_1 - \alpha_1 N(n)}\right)}{\left((r_1 \alpha_1 N(n) - r_1 K_1 M(n))e^{-(r_1 - \alpha_1 N(n))} + r_1 K_1 M(n)\right)^2}.
\end{aligned}$$

Since $f(x) = 2 - e^{-x} - e^x$ has a global maximum at 0, it follows

$$\Delta V(E_m(n)) < 0.$$

Similarly using assumption (20) it can be shown that

$$\Delta V(E_Z(n)) = (Z(n+1) - Z(n))\left(Z(n+1) + Z(n) - 2\bar{Z}\right) < 0.$$

Computing $\Delta V(E_N(n))$ with assumptions (18) and (21) yields

$$\begin{aligned}
\Delta V(E_N(n)) &= (N(n+1) - N(n))\left(N(n+1) + N(n) - 2\bar{N}\right) \\
&= \left(N(n)\left(e^{\beta Z(n) - d_1 - \alpha_2 M(n)} - 1\right)\right)\left(N(n)\left(e^{\beta Z(n) - d_1 - \alpha_2 M(n)} + 1\right) - 2\bar{N}\right) \\
&< 0.
\end{aligned}$$

Thus, $\Delta V(E(n)) = (\Delta V(E_M(n)), \Delta V(E_N(n)), \Delta V(E_Z(n))) < 0$ and the equilibrium $\bar{E}$ is globally asymptotically stable.

$\square$

3.4 Bifurcation Analysis

We will employ the Schur-Cohn criterion to determine the Neimark-Sacker bifurcation point for our system (6) and the equilibrium point $\bar{E}$. Given the simplifications presented by (13), which fixes α_1, we will treat β as our bifurcation parameter.

Theorem 4. *[5] A pair of complex conjugate roots of equation*

$$p(\lambda) = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 \tag{22}$$

lie on the unit circle and the other roots of equation (22) *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) $D_2^- = 1 - p_1 - p_0^2 + p_0 p_2 = 0.$

The coefficients stated above map to that of the characteristic equation for $\bar{A}$ (11) as,

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

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

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

The bifurcation point $\bar{\beta}$ can now be determined by solving (c) $D_2^- = 0$ in the above theorem and checking conditions (a) and (b).

4   Results and Discussion

To discuss the stability conditions for our model derived by the previous analysis, we will fix all parameters, except for α_1 and β, using the estimations given by R. Sarkar & S. Banerjee [8]:

Parameters	Estimated Values
r_1	0.18 / day
r_2	0.1045 / day
k_1	5.0×10^6 cells
k_2	3.0×10^6 cells
d_1	0.0412 / day
d_2	0.0412 / day
α_2	3.422×10^{-9} / cells / day

With this set of parameter values, the interior equilibrium $\bar{E}$ will exist and be locally stable, if

$$3.2087 \times 10^{-8} < \beta < 5.8238 \times 10^{-7}$$

where the lower bound guarantees existence and the upper bound guarantees local stability. We will fix α_1 to be the minimum of the function $\alpha_1(\beta)$ as given in (14), to ensure it meets the strict bound (12). That results in α_1 taking the value 2.2683×10^{-7}.

The bifurcation point $\bar{\beta}$ can then be determined by solving $D_2^- = 0$ in theorem 4. We will use Matlab to solve this treating the equilibrium point $\bar{E}$ as a function of β. This gives:

$$\bar{\beta} = 2.9503 \times 10^{-7}$$
$$\bar{E}(\bar{\beta}) = (3.785 \times 10^6, 0.193 \times 10^6, 0.184 \times 10^6)$$

This $\bar{\beta}$ also meets the conditions (a) and (b) of theorem 4:

$$p(1) = 3.8788 \times 10^{-4} \quad > 0$$
$$p(-1) = 7.4713 \quad\quad\quad > 0$$
$$D_2^+ = 0.4889 \quad\quad\quad > 0$$

The lower bound on β implies that the conversion rate from resting to hunting cell should not be too small such that the immune system cannot respond quickly to the presence of tumor cells thereby resulting in uncontrolled tumor growth. Fixing α_1 at 2.2683×10^{-7}, we observe the stability change from a stable attractor to a limit cycle to uncontrolled oscillatory tumor growth when increasing β.

We find that if $3.2087 \times 10^{-8} < \beta < \bar{\beta}$ there exists a non-zero equilibrium, where tumor, hunting and resting cells can coexist. Fig. 2 shows an example where $\beta = 1 \times 10^{-7}$.
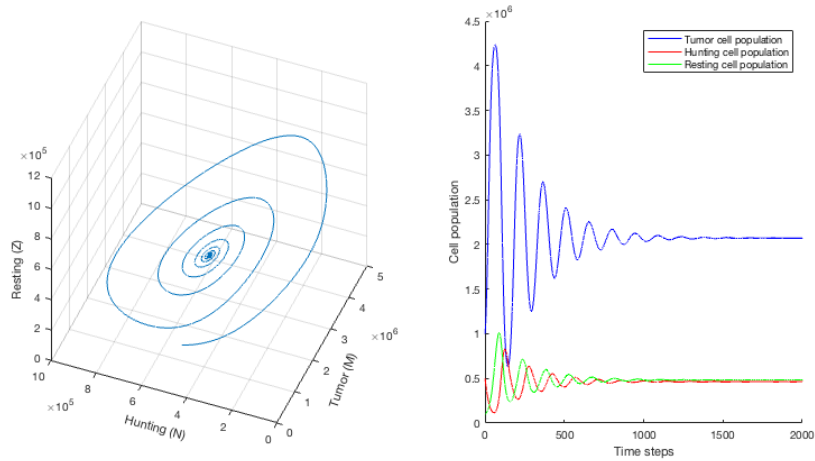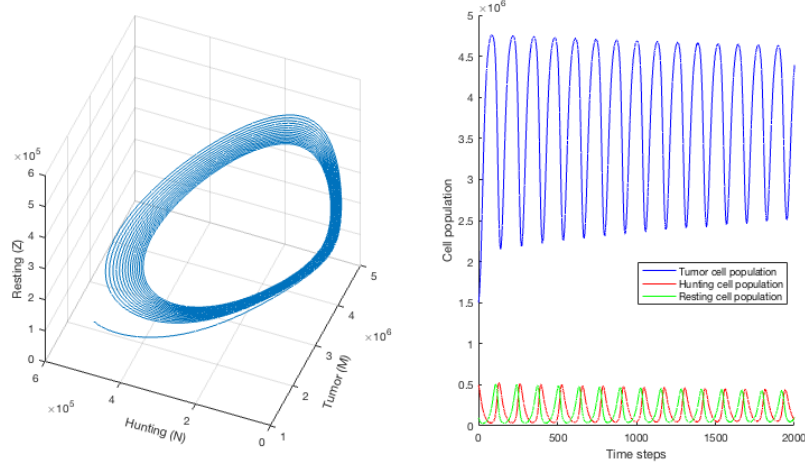

Fig. 2: Neimark-Sacker bifurcation of system (7) for $\bar{\beta} = 1 \times 10^{-7}$, $\alpha_1 = 2.27 \times 10^{-7}$, starting at $(1.5 \times 10^6, 5 \times 10^5, 1 \times 10^5)$

When the resting-hunting cell conversion rate is at the threshold $\bar{\beta}$ (i.e $\beta \approx 2.95 \times 10^{-7}$), then we observe a limit cycle. The results in Fig. 3 shows that the tumor and immune cells exhibit oscillatory behaviour even in the absence of any external treatment. Such periodic solutions labelled **"Jeff's Phenomenon"** or **"self-regression of tumor"** have

been observed clinically [9]. Fig. 4 shows that at $\bar{\beta}$, the convergence of the system to the actual limit cycle state takes about 2×10^5 time steps.

Fig. 3: Neimark-Sacker bifurcation of system (7) for $\bar{\beta} = 2.95 \times 10^{-7}, \alpha_1 = 2.27 \times 10^{-7}$, starting at $(1.5 \times 10^6, 5 \times 10^5, 1 \times 10^5)$
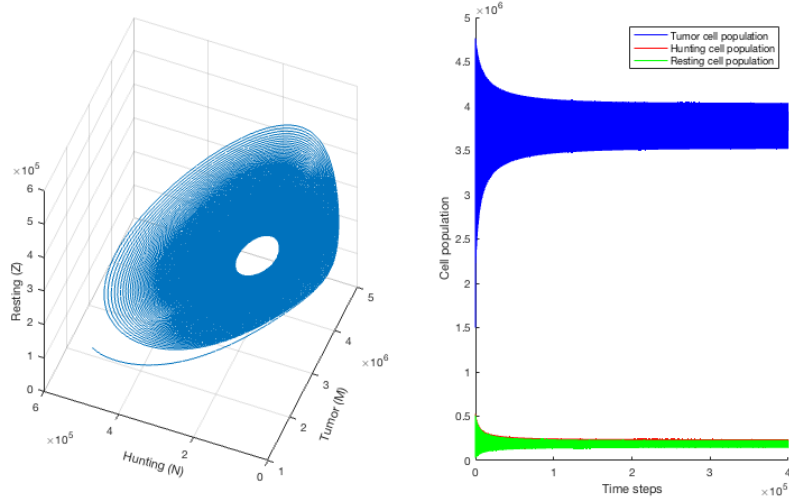

Fig. 4: Neimark-Sacker bifurcation of system (7) for $\bar{\beta} = 2.95 \times 10^{-7}, \alpha_1 = 2.27 \times 10^{-7}$, starting at $(1.5 \times 10^6, 5 \times 10^5, 1 \times 10^5)$ after 4×10^5 time steps

As the resting-hunting cell conversion rate exceeds the threshold ($\bar{\beta}$), we observe uncontrolled oscillatory tumor growth, up to the carrying capacity ($k_1 = 5 \times 10^6$). When the upper bound is exceeded, almost all the resting cells are depleted and cannot regenerate quickly enough to transform into hunting cells thereby resulting in sporadic unbounded hunting cell and tumor growth which (in either case) causes damage to the host[1]. It

is worth noting that the interior equilibrium point depends on β and as such changes as the value of β is varied.
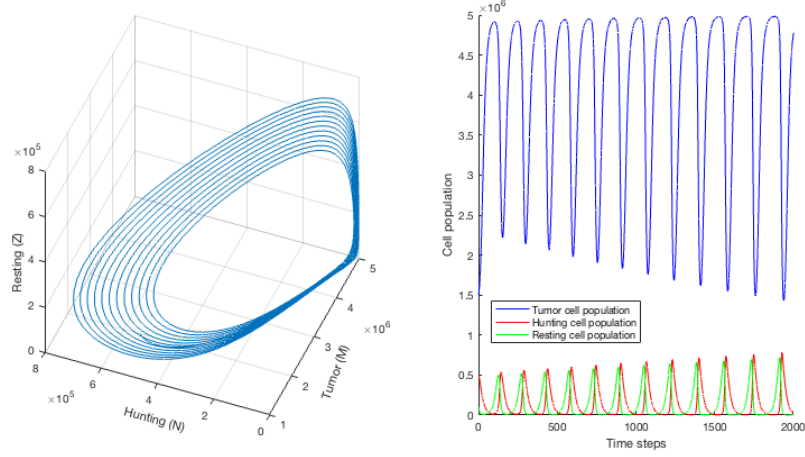

Fig. 5: Neimark-Sacker bifurcation of system (7) for $\bar{\beta} = 4 \times 10^{-7}$, $\alpha_1 = 2.27 \times 10^{-7}$, starting at $(1.5 \times 10^6, 5 \times 10^5, 1 \times 10^5)$
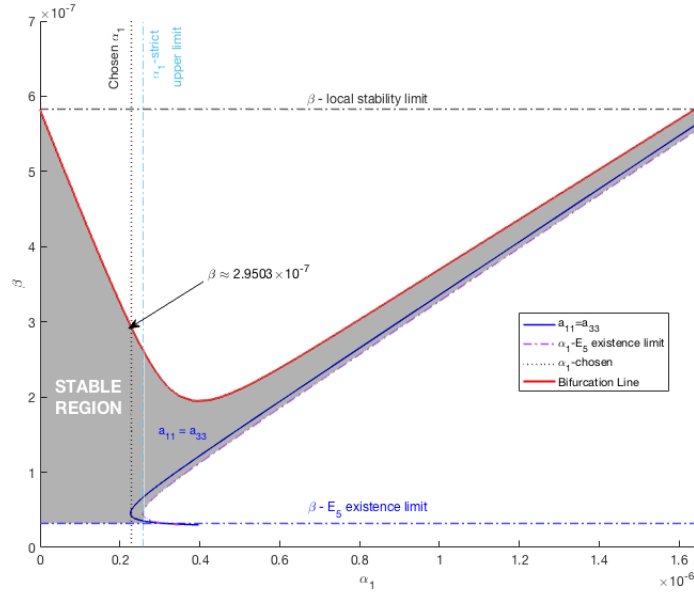

Fig. 6: Region of stability for choices of (α_1, β)

Combining our analysis regarding existence, local and global stability of the interior equilibrium $\bar{E}$, we find the region of stability regarding to the choice of α_1 and β to be the grey area shown in Fig. 6. The bifurcation line is determined by numerically solv-

ing $D_2^- = 0$ for different values of α_1 using Matlab. Due to the instability of the solver ("vpasolve") when evaluating the solution for $\alpha_1 > 1 \times 10^{-6}$, a linear interpolating curve is used to extend the curve up to α_1 value of 1.6×10^{-7}.

Additional work on the local stability analysis without the assumption (14) might yield an inequality constraint on α_1 and improved numerical methods could help better characterize the bifurcation line. Furthermore, an investigation that compares the quantitative results of this paper with that of R. Sarkar S. Banerjee [8] can assess the potential to use our approximation as a replacement of the time-delayed model (5).

5   Conclusion

In this paper we explore the effects and interactions of tumor cells and immune cells through a system of difference equations following [4]. We investigate all biologically feasible equilibria for the populations of tumor, hunting and resting cells and examine their existence and local stability criteria. For the interior equilibrium, we find an upper limit for the resting-hunting cell conversion rate such that the equilibrium is local asymptotically stable. We show that local stability conditions on the parameters outlined in [4] are incorrect and also remove his assumptions we believe to be unnecessary. As the equilibrium of interest, the interior equilibrium is investigated further and limits on the resting-hunting cell conversion rate are calculated to achieve global stability. Based on our results of the stability analysis, we determine the Neimark-Sacker bifurcation point for our system. Depending on the value of resting-hunting cell conversion rate, we observe a different behavior of the system and replicate the results of S. Kartal [4]. Our final results are consistent with that of R. Sarkar & S. Banerjee [8] and T. Faria [2] who show the existence of a Hopf bifurcation around a positive equilibrium point.

Our work differs from S.Kartal [4] in that we combine our analysis of the interior equilibrium to find the region in which the equilibrium is stable as a function of the death rate of tumor cells from hunting cells interactions and the resting-hunting cell conversion rate. Additionally, we attempt to provide clear explanations for assumptions that have been outlined in [4] and rationalize the numerical approximation in [4], by providing an alternate but very similar base model (5).

6   Contributions

This section describes the contribution of each author.

1. Abenezer Teklemariam
    a) Literature review
    b) Alternate model and approximation
    c) Calculation of other equilibrium points
    d) Application of Schur-Cohn criterion
    e) Bifurcation diagrams
2. Marie Kuhn
    a) Literature review
    b) Figure explaining modelled interactions
    c) Calculations for local stability analysis
    d) Calculation of final results given parameters
3. Elisabeth Kluth
    a) Literature review
    b) Linearization of the system of difference equations
    c) Calculations for local stability analysis
    d) Global stability analysis

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