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DYNAMICAL ANALYSIS AND NUMERICAL SOLUTION OF A TUMOR MODEL

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ABSTRACT.

Significant advancements have been achieved in understanding the complex behaviours of tumor cells and their interactions with the immune system through theoretical, experimental, and clinical approaches in recent years. These developments have accelerated the development of crucial methods for treating cancer, including immunotherapy, chemotherapy, targeted pharmacotherapy, and others. Simultaneously, significant progress has been made in the fields of analytical and computer modeling, with the aim of understanding clinical observations. In this paper, we introduces a tumorâĂŞimmune interaction model consisted of tumor cells, activated T cells, and anti PD-1 drug, represented as three-dimensional Ordinary differential equation model. We assume the tumor growth to be exponential, due to their unrestrained growth in the absence of an immune response and drug therapy. In the absence of drug application, the model has a tumor-free equilibrium and maximum one tumorous equilibrium . We further discussed the stability analysis of the equilibrium and conducted numerical simulations to validate the obtained findings.

Keywords: Tumor-immune system interaction model, Numerical approximation, Stability.

1. INTRODUCTION

An equation comprises one or more functions with their derivatives, is regarded to be a differential equation. Now a days, the differential equations are used to study biology, cancer modelling, physics, engineering, heat flow, population growth and so on. The primary motivation behind solving numerous differential equations is to acquire profound understanding of the fundamental physical processes, that are represented by the equations. The fact that even the most straightforward equations resemble practical physical models and contributes to our understanding of differential equations.

To comprehend mathematical models effectively, a solid grasp of stability and instability is crucial, as expounded by. While linear equations are suitable for many applications, nonlinear equations are indispensable for understanding the majority of real-world phenomena. However, interpreting nonlinear equations is generally more challenging than linear ones, leading to numerous unique and complex scenarios.

In situations where a local solution is sufficient, such as for a limited time period or specific parameter values, nonlinear equations can often be approximated through linearization techniques utilizing the jacobian matrix. A diverse range of literature exists that elucidates physical and biological phenomena through the application of nonlinear ordinary differential equations

Differential equations are essential tools in modeling complex biological systems, such as tumor growth and its interactions with the immune system and therapies. This paper presents a three-dimensional differential equation model that focuses on tumor-immune interactions. The model includes three main components: tumor cells, activated T cells, and an anti-PD-1 drug, which is an immunotherapy used to inhibit certain pathways that tumors use to evade the immune response.

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The model is described as follows:

$$\begin{aligned}\frac{dG}{dt} &= rG - \eta GE,\\ \frac{dE}{dt} &= (M+NE)\left(1+\frac{kP(E+\alpha_G G)}{K_{EQ}}\right)^{-1} - d_E E,\\ \frac{dC}{dt} &= \gamma_C - \mu_{PC}(\rho_P - \gamma C)EC - d_C C.\end{aligned} \tag{1.1}$$

where G(t)and E(t) indicates the population densities of tumor cells and active T cells at the time t, respectively. C(t) indicates the anti PD-1 treatment at time t and r > 0 is the pace of tumor growth in cells, η > 0 is tumour cell death rate by T cells where M > 0 and N > 0 indicates the activation rate of naive T cells by IL-12 and the explosive growth rate of T cells caused by IL-12 , respectively. The mortality rate of T cells is dE > 0. The function

$$\left(1+\frac{kP(E+\alpha_G G)}{K_{EQ}}\right)^{-1},$$

reflects the reduction in the activation of T cells and proliferation by PD-1-PD-L1 complex, where αG > 1 is the ratio of expressions of PD-L1 in tumor cells and T cells, whereas $\frac{1}{KEQ}$>0 measures the functions level of inhibition of T cells by PD-1-PD-L1 complex, k > 0 is the rate of PD-1 expression on T cells. The intravenous, constantly injection is called γC. PD-1 has a ωP C rate of binding to anti PD-1. Anti PD-1 naturally deteriorates at a rate of dC . The function P = (ρP − γC)E depicts the frequency of the free PD-1, where ρP indicates that there is a set amount of PD-1 in each activated T cells. PD-1 is depleted at a rate of γC as anti PD-1 is given and the medication binds to PD-1.Firstly, nondimensionalize the model using following scaling,

$$G = \frac{\kappa_{EQ}\eta}{\kappa\rho_P\alpha_G r}\phi, \quad E = \frac{r}{\eta}\theta, \quad C = \frac{\rho_P}{\gamma}\epsilon, \quad t = \frac{1}{r}\tau.$$

The system (1.1) can be represented as written below, (we will still express τ with t):

$$\begin{aligned}\frac{d\phi}{dt} &= \phi(1-\theta),\\ \frac{d\theta}{dt} &= \frac{a_1 + a_2\theta}{1+(1-\epsilon)(a_3\theta^2+\phi\theta)} - a_4\theta,\\ \frac{d\epsilon}{dt} &= \sigma - \zeta(1-\epsilon)\theta\epsilon - \omega\epsilon.\end{aligned} \tag{1.2}$$

in which

$$a_1 = \frac{\eta M}{r^2},\ a_2 = \frac{N}{r},\ a_3 = \frac{k\rho_P r^2}{K_{TQ}\eta^2},\ a_4 = \frac{d_T}{r},\ \sigma = \frac{\gamma\gamma_C}{r\rho_P},\ \zeta = \frac{\omega_{PC}\rho_P}{\eta},\ \omega = \frac{d_C}{r}, \tag{1.3}$$

whereas a_1, a_2, a_3, a_4, σ, ζ, ω all are positive as well as constants.

2. STABILITY ANALYSIS OF MODEL WITHOUT TREATMENT

We initially examine the case in which anti PD-1 therapy is not implemented in order to better understand the dynamics of the entire system (1.2) and to get insight into the interaction of the natural tumor immune system. Assume = 0 (which means C = 0 in the model (1.1)) in the entire system (1.2). Consequently, the no treatment models reduced structure is as follows

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$$\begin{aligned} \frac{d\phi}{dt} &= \phi(1-\theta), \\ \frac{d\theta}{dt} &= \frac{a_1 + a_2\theta}{1 + a_3\theta^2 + \phi\theta} - a_4\theta. \end{aligned} \tag{2.1}$$

whereas a_1, a_2, a_3, a_4 are defined in (1.3). We shall only take into consideration the dynamics of system (2.1) in a closed first quadrant of the (φ, θ) plane due of its biological aspects. Firstly, we will identify all of the stable situations in order to examine the dynamics of the system (2.1). Fix

$$\begin{aligned} &\phi(1-\theta) = 0, \\ &\frac{a_1 + a_2\theta}{1 + a_3\theta^2 + \phi\theta} - a_4\theta = 0, \end{aligned}$$

which results

$$\begin{cases} N_0(\theta) = a_3a_4\theta^3 - (a_2 - a_4)\theta - a_1 = 0; \quad for \quad \phi = 0, \\ or \\ \phi = \dfrac{a_1 + a_2 - (1+a_3)a_4}{a_4}; \quad for \quad \theta = 1. \end{cases} \tag{2.2}$$

Note that $N0(\theta) = 0$ has a single positive root as determined by the relationships between the coefficients and roots of the third-order algebraic equation, θ0. As a result, system (2.1) only has one tumor-free equilibrium $F0 = (0, \theta_0)$, and one tumorous equilibrium. Also,

$F = (\varphi^*, \theta^*) = \left(\frac{a1 + a2 - (1 + a3)a4}{a4}, 1\right)$ if and only if $a_1 + a_2 - (1+a_3)a_4 > 0$. Now, we want to look into the local stability of the equilibria F0 and F^*. We linearized the system (2.1) and calculated the jacobian matrix at equilibrium F(φ, θ) for the system (2.1):

$$J(F) = \begin{pmatrix} 1-\theta & -\phi \\ -\dfrac{(a_1 + a_2\theta)\theta}{(1 + a_3\theta^2 + \theta\phi)^2} & -\dfrac{a_2a_3\theta^2 + 2a_1a_3\theta + a_1\phi - a_2}{(1 + a_3\theta^2 + \theta\phi)^2} - a_4 \end{pmatrix}. \tag{2.3}$$

Then, we concluded the following results.

Result 1

(1) If $a2 < (a3 + 1)a4 - a1$, then the system (2.1) has F_0 as saddle point.

(2) If $a2 > (a3 + 1)a4 - a1$, then the system (2.1) has F_0 as stable node and F^* as saddle point.

Proof: The jacobian matrix (2.3) at $F0 = (0, \theta_0)$ becomes

$$J(F_0) = \begin{pmatrix} 1-\theta_0 & 0 \\ -\dfrac{(a_1 + a_2\theta_0)\theta_0}{(1 + a_3\theta_0^2)^2} & -\dfrac{a_2a_3\theta_0^2 + 2a_1a_3\theta_0 - a_2}{(1 + a_3\theta_0^2)^2} - a_4 \end{pmatrix},$$

which has two eigenvalues

$$\lambda_1 = 1 - \theta_0, \ \lambda_2 = -\frac{a_2a_3\theta_0^2 + 2a_1a_3\theta_0 - a_2}{(1 + a_3\theta_0^2)^2} - a_4,$$

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and the Det of $J(F_0)$ is

$$det(J(F_0)) = \lambda_1\lambda_2 = (1-\theta_0)\left[-\frac{a_2a_3\theta_0^2 + 2a_1a_3\theta_0 - a_2}{(1+a_3\theta_0^2)^2} - a_4\right].$$

From $N_0(\theta_0) = 0$ in (2.2) we have;

$$a_2 = \frac{a_3a_4\theta_0^3 + e\theta_0 - a_1}{\theta_0},$$

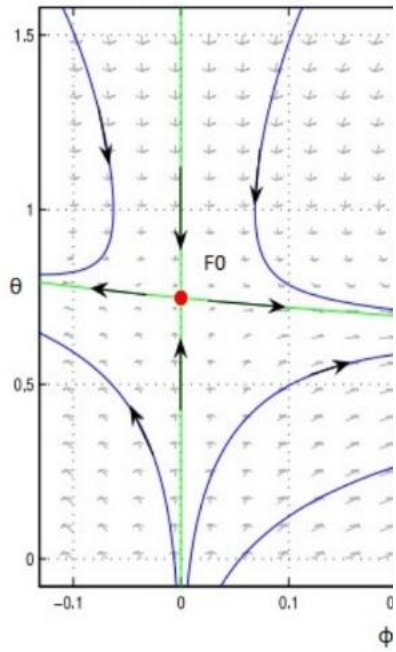

Figure 1. If $a_2 < (a_3 + 1)a_4 - a1$ then F0 is the saddle point.

by substituting (2) in det(J(F0)), we get

$$\begin{aligned} det(J(F_0)) = \lambda_1\lambda_2 &= \frac{(\theta_0-1)(a_1 + 2a_3a_4\theta_0^3)}{\theta_0(1+a_3\theta_0^2)} \\ &= \frac{(\theta_0-1)}{\theta_0(1+a_3\theta_0^2)}[\theta_0N_0'(\theta_0) - N_0(\theta_0)] \qquad (2.4) \\ &= \frac{\theta_0-1}{(1+a_3\theta_0^2)}N_0'(\theta_0). \end{aligned}$$

On the one hand, we posses with $N'_0(\theta_0) > 0$ whereas on the other hand, we get $a_2 < (a_3 + 1)a_4 - a_1 \Longleftrightarrow N_0(1) > 0 \Longleftrightarrow \theta_0 < 1$. Therefore, it is quite easy to visualize that the equilibrium $F_0(0, \theta_0)$ is a saddle if $a_2 < (a_3 + 1)a_4 - a_1$, and if $a_2 > (a_3 + 1)a_4 - a1$, then $\theta_0 > 1$, which gives $det(J(F_0) > 0$. We also possess with $det(J(F0)) = \lambda1\lambda2$ and $\lambda1 < 0$,then it is easy to get that $\lambda2 < 0$. Thus, $F_0(0, \theta_0)$ is stable node if $a_2 > (a_3 + 1)a_4 - a_1$. At $F^* = (\varphi^*, \theta^*)$, the jacobian matrix will become

$$J(F^*) = \begin{pmatrix} 0 & \frac{(1+a_3)a_4 - (a_1+a_2)}{a_4} \\ -\frac{a_4^2}{a_1+a_2} & -\frac{(a_3a_4 + 2a_1 + a_2 - a_4)a_4}{a_1+a_2} \end{pmatrix}$$

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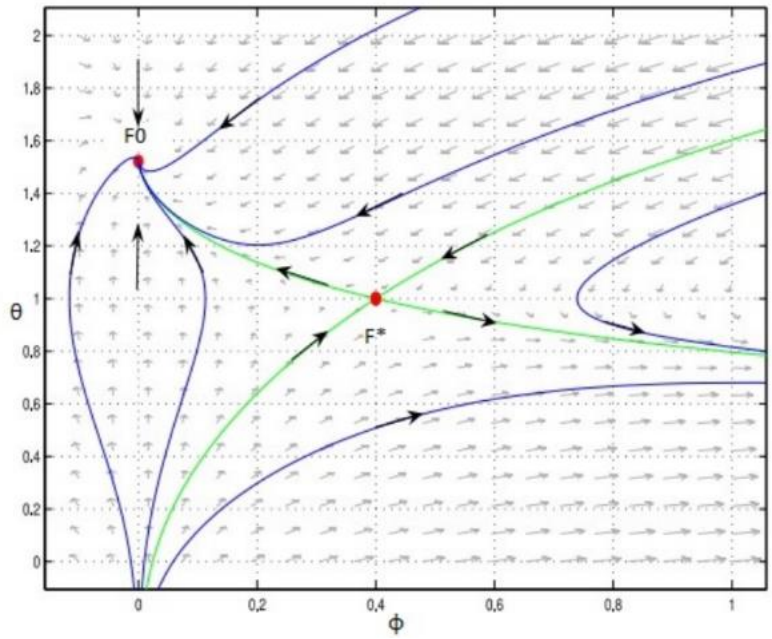

Figure 2. If $a_2 > (a_3 + 1)a_4 - a_1$, then F_0 is a stable node and F^* is a saddle point.

The det of J(F^*) is

$$det(J(F^*)) = \frac{a_4[(1 + a_3)a_4 - (a_1 + a_2)]}{(a_1 + a_2)}.$$

Note that det(J(F)) < 0 therefore $a_1 + a_2 - (a_3 + 1)a_4 > 0$. Therefore, F^* is a saddle point.

3. NUMERICAL SOLUTIONS

In the following section, we will find the numerical solutions of system (1.2). Before studying numerical solutions firstly we will notice that after nondimensionalize φ represents the population densities of tumor cells at time t, θ depicts activated cells at time t and depicts the anti PD-1 treatment at time t.

The model will now be visualized through the use of graphs and phase portraits, which will be constructed using MATLAB. This visualization process relies on the selection of specific parameter values for the model.

The numerical solution of the system (1.2) and corresponding phase portrait for different parameter values are shown as follow:

- In Fig.3, If we assume a1 = 6, a2 = 1.2, a3 = 1.1, a4 = 4, ζ = 1.3, ω = 3, σ = 3. Where this set of parameters satisfying the conditions σ = ω, a2 < a4.
- In Fig.4, If we assume a1 = 0.19, a2 = 1.7, a3 = 0.2, a4 = 1.9, ζ = 0.4, μ = 1.6, σ = 1.66. Where this set of parameters satisfying the conditions ω > ζ.
- In Fig.5, If we assume a1 = 0.38, a2 = 0.35, a3 = 0.51, a4 = 0.68, ζ = 2.6, ω = 2.1, σ = 2.024. Where this set of parameters satisfying the conditions ω < ζ.
- In Fig.6, If we assume a1 = 0.38, a2 = 0.35, a3 = 0.6, a4 = 0.68, ζ = 2.6, ω = 2.1, σ = 2.0245. Where this set of parameters satisfying the conditions ζ(2B − 1) < ω < ζ.

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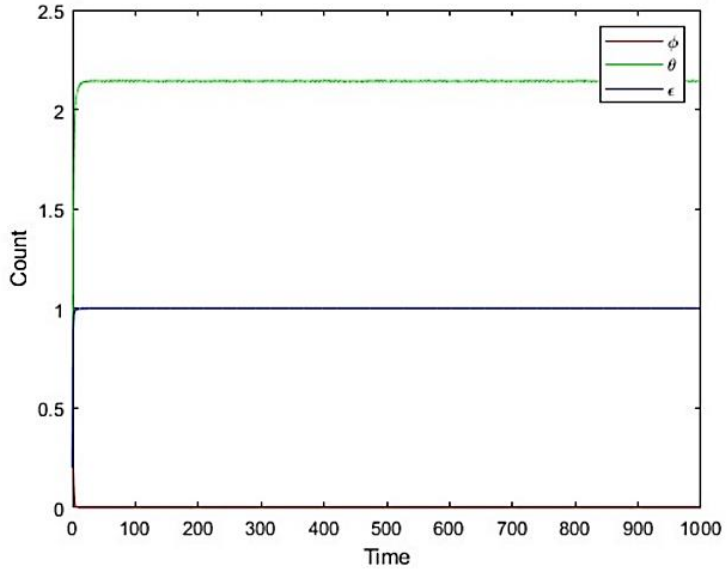
The phase portraits of system (2.1) are shown in Figure 1 and Figure 2, showing the dynamic behaviour and trajectories of the system throughout time. The findings of Result 2 displayed in these figures give a visual depiction of the stability, equilibrium points, and general behaviour of the system under the given circumstances.

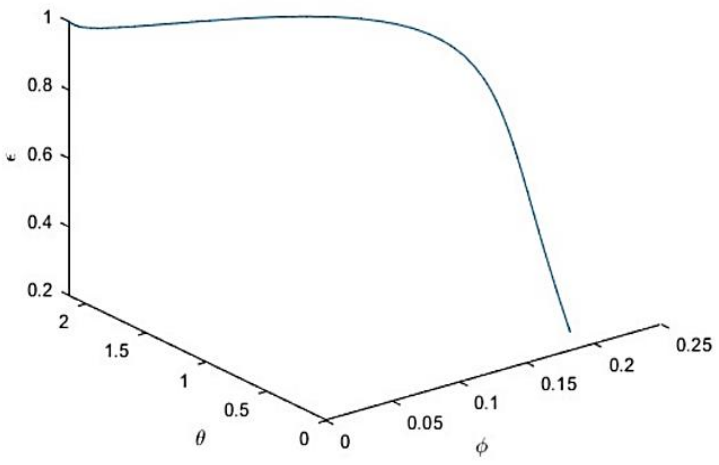
The Figure 6, Figure 4, Figure 5, and Figure 3 represent the solution trajectories and solutions of the system (1.2) with respect to mentioned initial conditions and parameter values.

4. CONCLUSION

In this article, the graphs and phase portraits depicts the change in tumor cells with respect to time, under the influence of anti drug. Through, this procedure we can see how much drug is needed for the further improvement and how it is helping in decreasing the tumor cells because above figures gives us the proper visualize of stability or non-stability in person condition, where count represents the tumor cells present in human body with respect to time.



(A)



(B)

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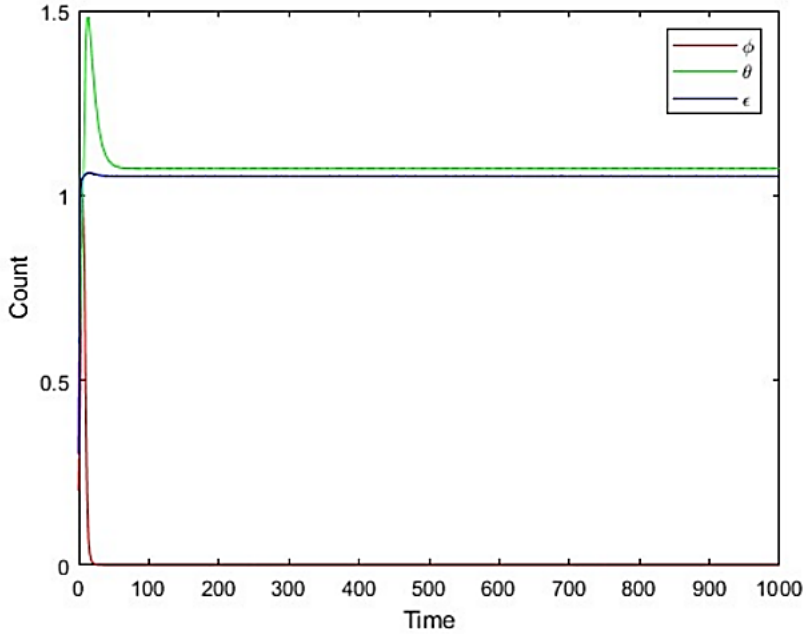
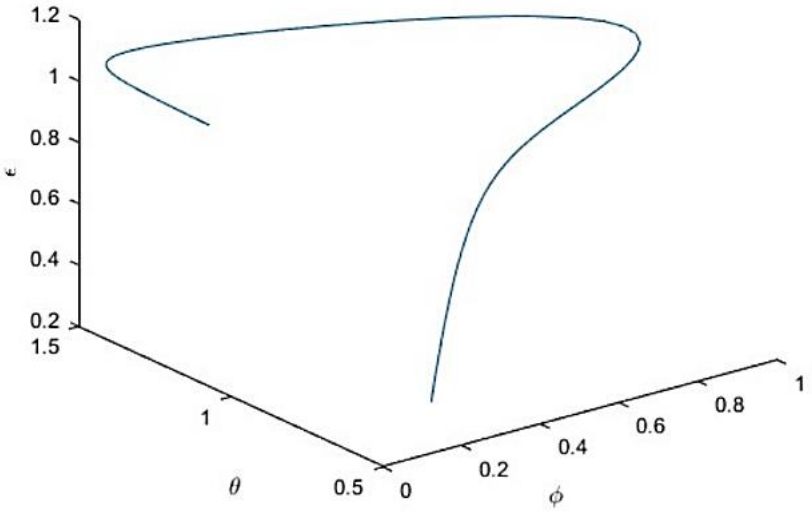
Figure 3. (A) The solution of system (1.2) where initial point is taken as(0.2, 0.2, 0.2), and (B) Phase portrait of system (1.2) depicts instability.



(A)



(B)

Figure 4. (A) The solution of system (1.2) where initial point is taken as (0.2, 0.6, 0.3), and (B) Phase portrait of system (1.2) depicts asymptotically stability.

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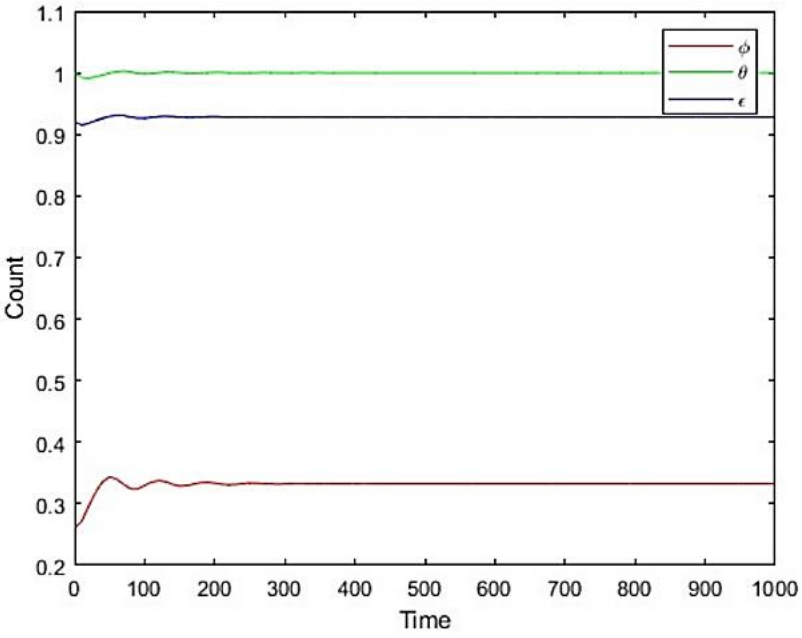
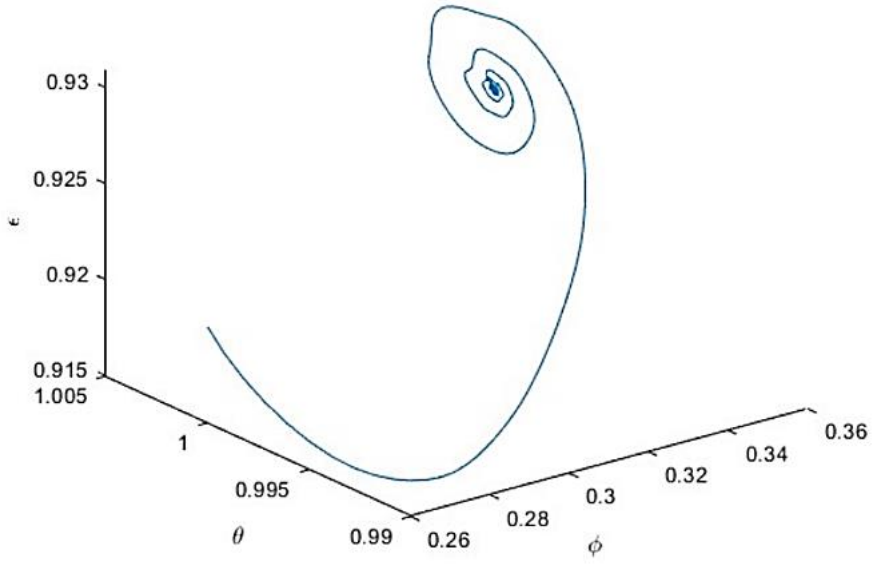


(A)



(B)

Figure 5. (A) The solution of system (1.2) where the initial point is taken as (0.26, 1, 0.92), and (B) Phase

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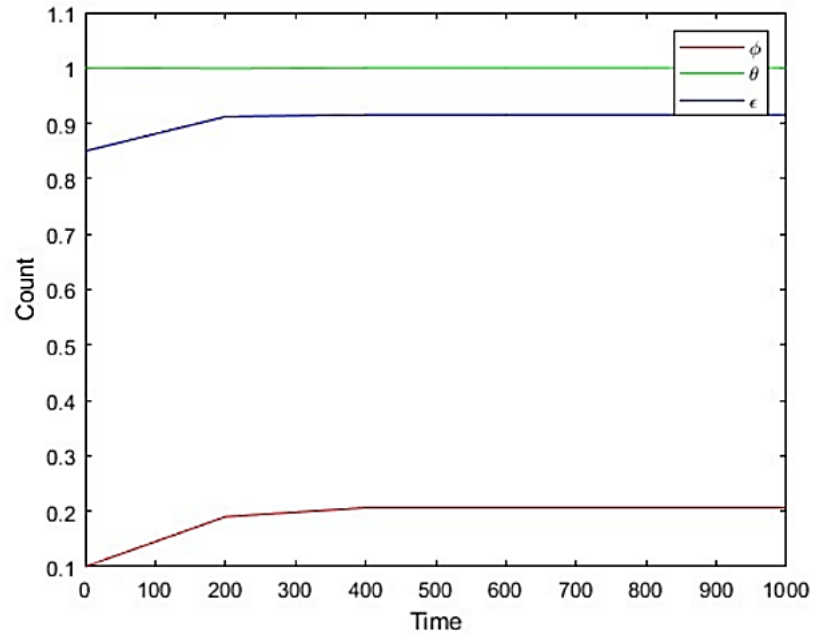
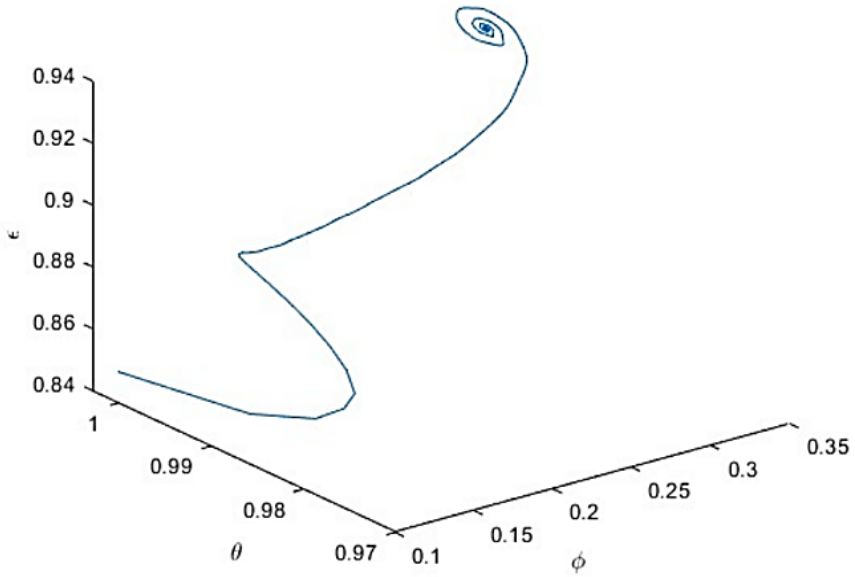
portrait of system (1.2) depicts asymptotically stable.



(A)



(B)

Figure 6. (A) The solution of system (1.2) where the initial point is taken as (0.1, 1, 0.85), and (B) Phase portrait of system (1.2) depicts asymptotically stable.

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