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DISCRETE TIME MATHEMATICAL MODELLING OF A CELL TO CELL TRANSMISSION MODEL OF VIRUSES

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Abstract:

Humans have been battling viruses even before our species had evolved into its modern form. Viruses are small infectious agents that replicates only inside the living cells of other organisms. Understanding the dynamics of viruses at a cellular level gives us a clear knowledge about the disease spread and helps us to take necessary and more effective preventive measures. Difference equations are a numerical methods approach to getting approximate solutions to differential equations. In this paper, we construct a continuous time model of Cell to Cell transmission of viruses. Using Backward Euler method, we discretize the model. We derive the basic reproduction number, which is a threshold value. We analyse the stability of the model and analyse the conditions in which the model is stable or unstable. Finally, we prove our theoretical results using numerical simulations through MATLAB.

Key Words: Differential Equations, Difference Equations, Basic Reproduction Number, Equilibria & Local Stability

1. Introduction:

Common cold, influenza, chickenpox and cold sores are some of the infectious diseases caused by viruses. We can recognize some specific viruses as causative agents for epidemics that occured hundred or thousand years ago. Viral infections spread based on their ability to overcome multiple barriers and move from cell to cell, tissue to tissue, and person to person and even across species. Cell to cell spread of viruses is more than release and entry. For within-host virus dynamics, mathematical models based on understanding of biological interactions, can provide non intuitive insights into the dynamics of host response to viruses and can suggest new avenues for experimentation. Though the details of virus infection and replication vary greatly with host type, all viruses share 6 basic steps in their replication cycles. They are attachment, penetration, uncoating, replication, assembly and release. In the viral life cycle there are two ways to reproduce. One results in thousands to millions of copies of virus (virions) being released in a few hours. This method results in the death of the host cell because the virions cause the host to lyse. This is the lytic cycle. The other replication method results in only a few virions being released at a time. The advantage is that the virus can survive and replicate inside a host for many years because there is no host cell lysis. This is the lysogenic cycle otherwise called as "Budding". Dynamics of virus was studied by Xiulan Lai in continuous time[7]. viral and immune system dynamics was studied by Alan S. Perelson [8]. In this paper, we construct a cell to cell transmission model of virus in continuous time. We discretize the model using Backward Euler method and analyse the stability. A good reason for studying the discrete models is that, the data is collected in discrete times and hence it might be easier to compare the data with the output of a discrete model. In section 2, we formulate the mathematical model using a system of Differential Equations and discretize the model using Backward Euler method. Basic reproduction number of the model is discussed in section 3. Equilibrium points of the model are given in section 4. We analyse the local stability of the model in section 5. Numerical simulations of the model are given in section 5. Conclusion of the paper is given in section 6.

2. Mathematical Model:

We consider a system of Differential Equations to form our mathematical model:

$$T^{'} = rT\left[1-\frac{T}{K}\right]-\frac{\beta_B V_B T}{1+qA}-\frac{\beta_L V_L T}{1+qA}-d_T T$$

$$V_B^{'} = \frac{\beta_B V_B T}{1+qA}-\eta_B V_B A-d_{V_B} V_B$$

$$V_L^{'} = \frac{\beta_L V_L T}{1+qA}-\eta_L V_L A-d_{V_L} V_L$$

$$A^{'} = \rho\left(V_B+V_L\right)A-\eta_B V_B A-\eta_L V_L A-d_A A$$

By using Backward Euler Scheme, we discretize the model

$$T(t+1) = T(t)+rT(t+1)\left[1-\frac{T(t+1)}{K}\right]-\frac{\beta_B V_B T(t+1)}{1+qA(t+1)}-\frac{\beta_L V_L T(t+1)}{1+qA(t+1)}-d_T T(t+1)$$

$$V_B(t+1) = V_B(t)+\frac{\beta_B V_B T(t+1)}{1+qA(t+1)}-\eta_B V_B A(t+1)-d_{V_B} V_B(t+1)$$

$$V_L(t+1) = V_L(t)+\frac{\beta_L V_L T(t+1)}{1+qA(t+1)}-\eta_L V_L A(t+1)-d_{V_L} V_L(t+1)$$

$$A(t+1) = A(t)+\rho\left(V_B(t+1)+V_L(t+1)\right)A(t+1)-\eta_B V_B A(t+1)-\eta_L V_L A(t+1)-d_A A(t+1)$$

This can be taken as system (I).
Where

$T(t)$ is the density of uninfected target cells at time *t*.

$V_B(t)$ and $V_L(t)$ is the density of virus produced by budding and lytic strategy at time *t* respectively.

$A(t)$ is the density of antibody at time *t*.

β_B and β_L are the infection rates of budding and lytic virus respectively.

ρ is the activation rate of antibodies.

η_B and η_L are the neutralization rates of antibodies for budding and lytic virus respectively.

d_T, d_{V_B}, d_{V_L} and d_A denote the death rates of uninfected target cells, budding virus, lytic virus and antibody respectively.

r is the intrinsic growth rate of the uninfected target cells.

K is the carrying capacity of the uninfected target cells.

q is a positive constant.

We assume the following conditions:

- ✓ We assume that there is a logistic growth rate of uninfected target cells.
- ✓ We consider the transmission rates to be saturated incidence rate.

Our system (I) has initial conditions $\left(T(\theta), V_B(\theta), V_L(\theta), A(\theta)\right)$ which satisfy

$$T(\theta) \geq 0, V_B(\theta) = 0, V_L(\theta) = 0, A(\theta) \geq 0$$

Where $\theta \in \left[-t^*, 0\right]$

That is, there is no infection in $t \in \left[-t^*, 0\right]$ and infection occurs only at time $t = 0$.

$$T(0) > 0, V_B(\theta) > 0, V_L(\theta) > 0, A(\theta) > 0$$

Let us assume that the following conditions hold.

$$0 < d_T, d_{V_B}, d_{V_L}, d_A < 1 \qquad (1)$$

3. Basic Reproduction Number:

The basic reproduction number(Usually denoted by R0), is a significant epidemiological quantity, which plays an important role in the dynamics of disease transmission. It is a useful metric that helps us to predict whether an infectious disease will spread through a population or not. If it is less than one, the infection will die out in the long run, otherwise, the infection will keep persistent in the population.

Let R_B^0 gives the reproductive ratio of the budding virus in the absence of antibody (also referred to as the basic reproductive number). In parallel, R_L^0 is the reproductive ratio of the lytic virus in the absence of antibody. Thus, R_B^1 is the reproductive ratio of budding virus when the antibody for budding virus is established. Similarly, R_L^1 is the reproductive ratio of lytic virus when the antibody for lytic virus is established.Let

$$R_B^0 = \frac{r}{d_T}\left[1 - \frac{d_{V_B}}{K\beta_B}\right], R_L^0 = \frac{r}{d_T}\left[1 - \frac{d_{V_L}}{K\beta_L}\right]$$

$$R_B^1 = d_{V_B} + \frac{d_T}{r} + \frac{K\beta_B^2 d_A}{r(\rho - \eta_B)}, R_L^1 = d_{V_L} + \frac{d_T}{r} + \frac{K\beta_L^2 d_A}{r(\rho - \eta_L)} \qquad (2)$$

4. Equilibrium Points:

The possible equilibria of the system (I) are given below:

- ✓ For system (I), there always exists an infection free equilibrium

$$E^0 = \left(K\left[1 - \frac{d_T}{r}\right], 0, 0, 0\right)$$

- ✓ If $R_B^0 > 1$, there exists an equilibrium $E^{1*} = \left(T^{1*}, V_B^{1*}, 0, 0\right)$

Where $T^{1*} = \dfrac{dV_B}{\beta_B}, V_B^{1*} = \dfrac{dT}{\beta_B}\left(R_0^B - 1\right)$

- ✓ If $R_L^0 > 1$, there exists an equilibrium $E^{11} = \left(T^{11}, 0, V_L^{11}, 0\right)$

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Where $T^{11} = \frac{dV_L}{\beta_L}, V_L^{11} = \frac{dT}{\beta_L}\left(R_0^L - 1\right)$

- ✓ If $R_B^1 > 1$, there exists an equilibrium $E^{2*} = \left(T^{2*}, V_B^{2*}, 0, A^{2*}\right)$

Where $V_B^{2*} = \frac{d_A}{\rho - \eta_B}, T^{2*} = \frac{1}{\beta_B}\left(\eta_B A^{2*} + d_{V_B}\right)\left(1 + qA^{2*}\right)$

A^{2*} is a positive root of the following equation

$B_1 A^{2*^3} + B_2 A^{2*^2} + B_3 A^{2*} + B_4 = 0$

Where

$B_1 = \eta_B q^2, B_2 = 2q\eta_B + q^2 d_{V_B}$

$B_3 = \left(2qd_{V_B} + \eta_B\right) + \left(\frac{d_T}{r} - 1\right)q, B_4 = R_B^1 - 1$

- ✓ If $R_L^1 > 1$, there exists an equilibrium $E_{22} = \left(T^{22}, 0, V_L^{22}, A^{22}\right)$

Where $V_L^{22} = \frac{d_A}{\rho - \eta_L}, T^{22} = \frac{1}{\beta_L}\left(\eta_L A^{22} + d_{V_L}\right)\left(1 + qA^{22}\right)$

A^{22} is a positive root of the following equation $C_1 A^{22^3} + C_2 A^{22^2} + C_3 A^{22} + C_4 = 0$

Where

$C_1 = \eta_L q^2, C_2 = 2q\eta_L + q^2 d_{V_L}$

$C_3 = \left(2qd_{V_L} + \eta_L\right) + \left(\frac{d_T}{r} - 1\right)q, C_4 = R_L^1 - 1$

- ✓ If $R_B^0 = R_L^0 > 1$, then there exists infinitely many equilibria of the form $E^{12} = (T^{12}, V_B^{12}, V_L^{12}, 0)$ such that

$$\beta_L T^{12} = \eta_L A^{12} + d_{V_L}, r\left[1 - \frac{T^{12}}{K}\right] = \beta_B V_B^{12} + \beta_L V_L^{12} + d_T$$

- ✓ If $R_B^1 = R_L^1 > 1$, then there exists infinitely many equilibria of the form $E^{21} = (T^{21}, V_B^{21}, V_L^{21}, A^{21})$ such that

$\beta_L T^{21} = \left(\eta_L A^{21} + d_{V_L}\right)\left(1 + qA^{21}\right), \rho\left(V_B^{21} + V_L^{21}\right) = \eta_B V_B^{21} + \eta_L V_L^{21} + d_A$

5. Local Stability:

Theorem 1:

The disease free equilibrium E^0 is locally asymptotically stable if

$$\beta_B K\left[1 - \frac{d_T}{r}\right] < d_{V_B}, \beta_L K\left[1 - \frac{d_T}{r}\right] < d_{V_L}, r > d_T \tag{3}$$

Theorem 2:

The equilibrium points E^{1*} and E^{11} are non hyperbolic.

Theorem 3:

The equilibrium point E^{12} is locally asymptotically stable if the following conditions are satisfied .

$$1 + r < \frac{2rT^{12^2}}{K} + \frac{\beta_B V_B^{12^2}}{1 + qA^{12^2}} + d_T, 1 + \frac{\beta_B T^{12^2}}{1 + qA^{12^2}} < \eta_B A^{12^2} + dV_B$$

$$1 + (\rho - \eta_B)V_B^{12^2} < d_A, 1 + \frac{\beta_L T^{2*}}{1 + qA^{2*}} - \eta_L A^{2*} < d_{V_L} \tag{4}$$

Theorem 4:

The equilibrium point E^{21} is locally asymptotically stable if the following conditions are satisfied .

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$$1+r<\frac{2rT^{21^2}}{K}+\frac{\beta_L V_L^{21^2}}{1+qA^{21^2}}+d_T, 1+\frac{\beta_L T^{21^2}}{1+qA^{21^2}}<\eta_L A^{21^2}+dV_L$$

$$1+(\rho-\eta_L)V_L^{21^2}<d_A, 1+\frac{\beta_B T^{21^2}}{1+qA^{21^2}}-\eta_B A^{21^2}<d_{V_B} \quad (5)$$

Otherwise unstable.

6. Numerical Simulations:

The simulations have been performed using MATLAB to explain our theoretical results. Let us consider the following set of values:

$$r=1.2, K=5, q=0.3, \beta_B=0.5, \beta_L=0.8, \eta_B=0.7, \eta_L=0.6, p=0.8$$
$$d_T=0.4, d_{V_B}=0.5, d_{V_L}=0.5, d_A=0.1$$

For the given set of values, we obtain the following simulation result:

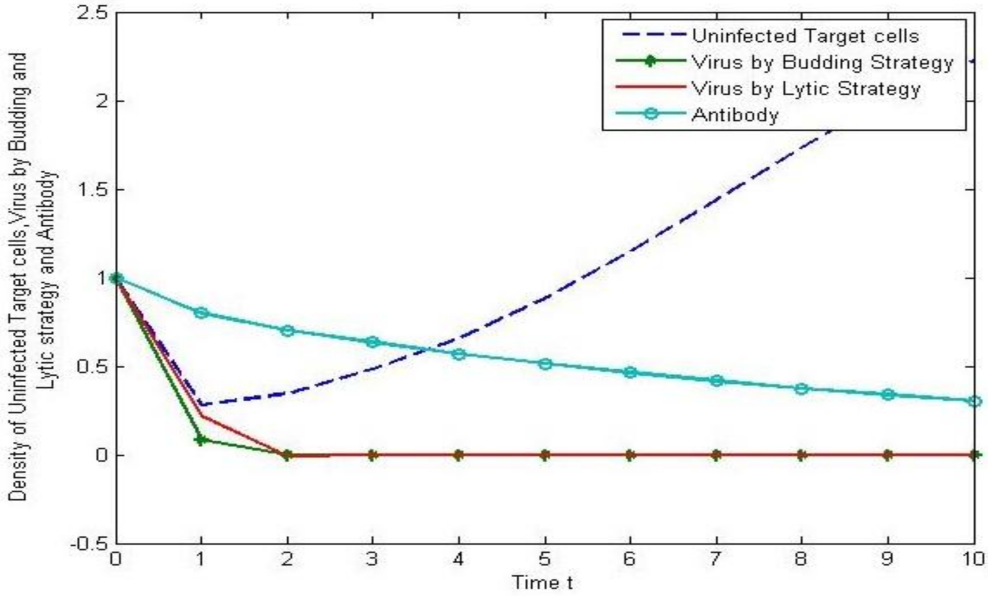

Figure 1: Dynamical Behaviours of system (I)

We change the value of $\beta_L=0.7$, which denotes a decrease in Lytic virus and observe that the density of Lytic virus has decreased.

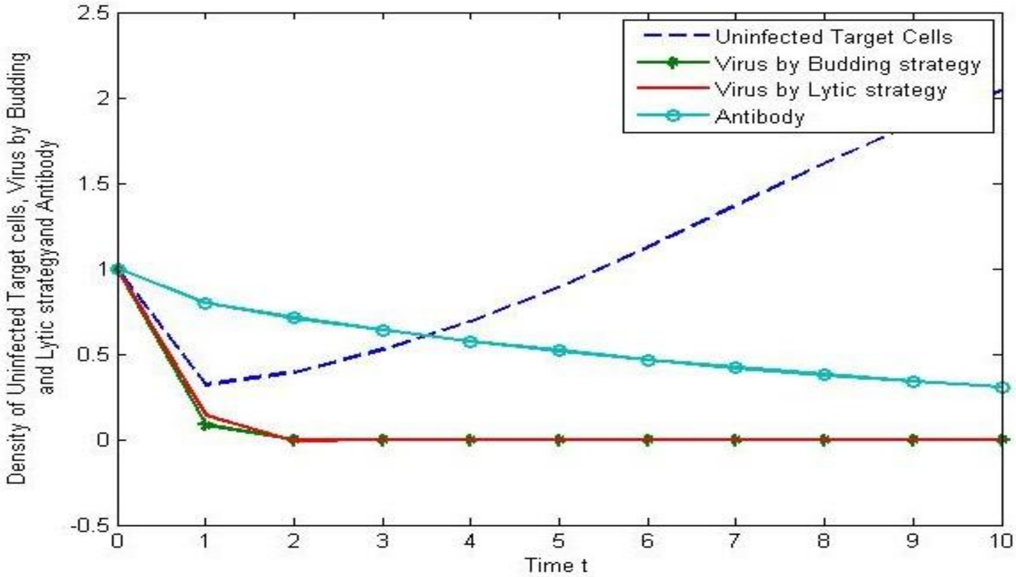

Figure 2: Dynamical Behaviours of system (I) for decreased Lytic Virus

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We change the value of $\beta_B = 0.3$, which denotes a decrease in Budding virus and observe that the density of Budding virus has decreased but there is an increase in density of Lytic virus.

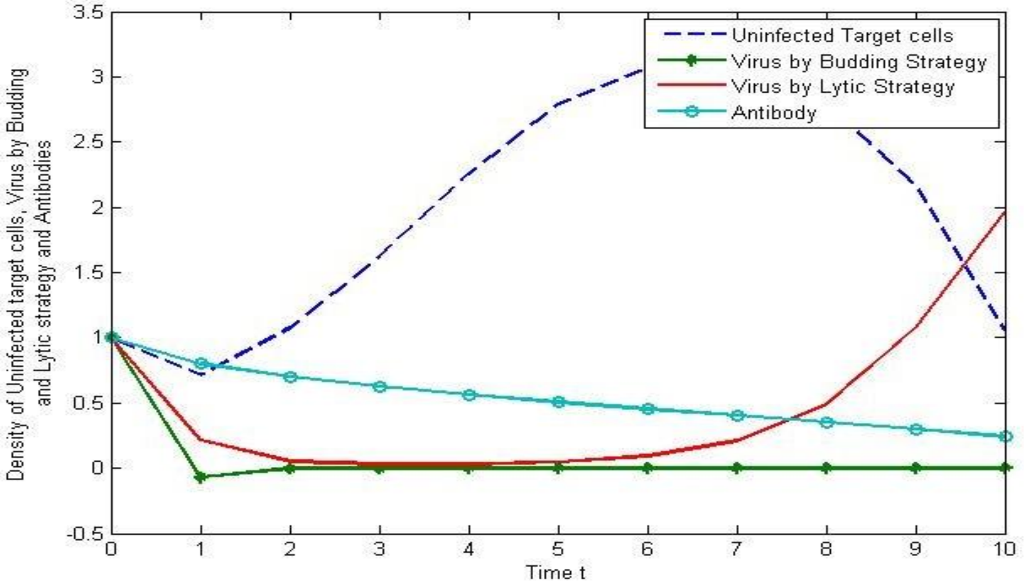

Figure 3: Dynamical Behaviours of system (I) for decreased Budding Virus

From these numerical simulations, we see that the transmission rates play an important role in the dynamics of disease transmission and that the control of transmission rates leads to the decrease in spread of viruses and hence the disease dies out.

8. Conclusion:

In this paper, we construct a mathematical model of cell to cell transmission of viruses and list out all possible equilibrium points. We also derive the Basic reproduction number of the model. We analyse the local stability of the equilibrium points. Finally, we prove our theoretical results using numerical simulations through MATLAB. We conclude that the transmission rates play an important role in disease spread and the control of transmission rates leads to the control of the disease.

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