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Mathematical analysis of the global dynamics of a power law model for HIV infection of CD4+ T cells

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Abstract

We analyze a mathematical power law model that describes HIV infection of CD4+ T cells. We report that the number of critical points depends on n, where n is a positive integer. We show that for any positive integer n the infection – free equilibrium is asymptotically stable if the reproduction number $R_0 < 1$ and unstable if $R_0 > 1$. The method of proof involves Rene Descartes' theory of positive solutions. The graph of X(uninfected T cells), T*(infected T cells) and V(HIV virus) against time t shows how the groups- the infected, the susceptible and the virus vary with time for various values of the parameter in the model. The results show that the positive integer n has a considerable effect on the variations of the groups with time.

Keywords: CD4+ T cells, critical / equilibrium points, reproduction number, asymptotic stability.

1.0 Introduction

The Human Immune deficiency Virus (HIV) is a retrovirus that can lead to Acquired Immune Deficiency Syndrome (AIDS), a condition in humans which the immune system begins to fail, leading to life – threatening opportunistic infections. HIV primarily infects vital cells in the human immune system specifically the CD4+ T Cells. When CD4+T cell numbers decline below a critical level, cell – mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infection which may eventually leads to Acquired Immune Deficiency Syndrome (AIDS). The count of CD4 + T Cells is a primary indicator used to measure progression of HIV infection. In a normal person, the level of CD4+T cells in peripheral blood is regulated at a level between 800 cells / mm3 and 1200 cells /mm^3 [1].

The dynamics of CD4 + T cells and HIV infections has been a subject of vigorous research among many researchers [2-6] . In particular [1] proposed the following models;

$$\frac{dT}{dt} = S - \alpha T + rT\left(1 - \frac{T^*}{T_{max}}\right) - KVT \quad (1.1)$$

$$\frac{dT^*}{dx} = KVT - \beta T^* \quad (1.2)$$

$$\frac{dV}{dx} = N\beta T^* - \gamma V \quad (1.3)$$

Where

S: the constant production rate at which the body produces CD4 +T Cells from the precursor in the bone marrow and thymus; α : natural turnover rate of uninfected T cells; r: rate at which T cells multiply though mitosis; T_{max}: maximum level of CD4+ T cells concentration in the body; β : natural turnover rates of infected T cells; γ : natural turnover rates of virus practices; k > 0: is the infection rate; N: virus particles produced by infected CD4 + T cells during its life time; T: concentration of the susceptible CD 4 + T cells; T^*: concentration of infected CD4 + T cells by the HIV virus; V: free HIV virus particles in the blood

2.0 Mathematical formulation

A model of HIV infection similar to equation (1.2) but using $\frac{dT^*}{dx} = KVT - \beta T^{*n}$ where n is a positive integer is proposed in this paper. Thus our model is

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$$\left.\begin{aligned}\frac{dT}{dt} &= S - \alpha T + rT\left(1 - \frac{T^*}{T_{max}}\right) - KVT \\ \frac{dT^*}{dx} &= KVT - \beta T^* \\ \frac{dV}{dx} &= N\beta T^* - \gamma V\end{aligned}\right\} \quad (2.1)$$

We shall consider in this paper the cases $n = 1,2,3, \ldots\ldots m, m+1$.

3.0 Methodology

Let $X = \frac{S}{\alpha - r} - T$, then equation (2.1) becomes [1]

$$\left.\begin{aligned}\frac{dX}{dt} &= -(\alpha - r)X + \frac{rST^*}{(\alpha - r)T_{max}} - \frac{rXT^*}{T_{max}} + \frac{KVS}{(\alpha - r)} - KVS \\ \frac{dT^*}{dt} &= \frac{KVS}{(\alpha - r)} - KXV - \beta T^{*n} \\ \frac{dV}{dt} &= N\beta T^* - \gamma V\end{aligned}\right\} \quad (3.1)$$

3.1 The critical points

3.1.1 The case $n = 1$.

We consider the model from equations (2.1) with $n = 1$ below:

$$\left.\begin{aligned}\frac{dX}{dt} &= -(\alpha - r)X + \frac{rST^*}{(\alpha - r)T_{max}} - \frac{rXT^*}{T_{max}} + \frac{KVS}{(\alpha - r)} - KVS \\ \frac{dT^*}{dt} &= \frac{KVS}{(\alpha - r)} - KXV - \beta T^* \\ \frac{dV}{dt} &= N\beta T^* - \gamma V\end{aligned}\right\} \quad (3.2)$$

The critical points of the system of equations in equation (3.2) by setting $\frac{dX}{dt} = \frac{dT^*}{dt} = \frac{dV}{dt} = 0$ are:

$$P_0 = (0,0,0) \text{ and } P_1 = \left(\frac{ksN - \gamma(\alpha - r)}{kN(\alpha - r)}, \frac{(ksN - \gamma(\alpha - r))T_{\max}}{\gamma r + kN\beta T_{\max}}, \frac{(ksN - \gamma(\alpha - r))N\beta T_{\max}}{\gamma(\gamma r + kN\beta T_{\max})}\right).$$

P_0 is the infection-free critical point and P_1 is the infection critical point.

3.1.2 The case $n = 2$

If $n = 2$ in equation (2.1) we obtain

$$\left.\begin{aligned}\frac{dX}{dt} &= -(\alpha - r)X + \frac{rST^*}{(\alpha - r)T_{max}} - \frac{rXT^*}{T_{max}} + \frac{KVS}{(\alpha - r)} - KVS \\ \frac{dT^*}{dt} &= \frac{KVS}{(\alpha - r)} - KXV - \beta T^{*2} \\ \frac{dV}{dt} &= N\beta T^* - \gamma V\end{aligned}\right\} \quad (3.3)$$

and the critical points for $n = 2$ are obtained as:

$$P_0^* = (0,\ 0,\ 0),$$

$$P_1^* = \left(\frac{2AS + 1 + \sqrt{4AS + 1}}{2A(\alpha - r)},\ \frac{-KN\left(1 + \sqrt{4AS + 1}\right)}{2A\gamma(\alpha - r)},\ \frac{-KN^2\beta\left(1 + \sqrt{4AS + 1}\right)}{2A\gamma^2(\alpha - r)}\right),$$

$$P_2^* = \left(\frac{2AS + 1 - \sqrt{4AS - 1}}{2A(\alpha - r)},\ \frac{-KN\left(1 - \sqrt{4AS + 1}\right)}{2A\gamma(\alpha - r)},\ \frac{-KN^2\beta\left(1 - \sqrt{4AS + 1}\right)}{2A\gamma^2(\alpha - r)}\right)$$

Where $A = \frac{KN(\gamma r + KN\beta T_{\max})}{\gamma^2(\alpha - r)^2 T_{\max}}$

We can continue in this fashion for $n = 3,4, \ldots\ldots m$

3.1.3 The case $n = m$ (where m is a positive integer).

If we let $n = m$ in equation (2.1) we obtain

$$\left.\begin{aligned}\frac{dX}{dt} &= -(\alpha - r)X + \frac{rST^*}{(\alpha - r)T_{max}} - \frac{rXT^*}{T_{max}} + \frac{KVS}{(\alpha - r)} - KVS \\ \frac{dT^*}{dt} &= \frac{KVS}{(\alpha - r)} - KXV - \beta T^{*m} \\ \frac{dV}{dt} &= N\beta T^* - \gamma V\end{aligned}\right\} \quad (3.4)$$

By setting $\frac{dX}{dt} = \frac{dT^*}{dt} = \frac{dV}{dt} = 0$ in equation (3.4) to obtain

$$-(\alpha - r)X + \frac{rST^*}{(\alpha-r)T_{max}} - \frac{rXT^*}{T_{max}} + \frac{KVS}{(\alpha-r)} - KVS = 0 \quad (3.5)$$

$$\frac{KVS}{(\alpha-r)} - KXV - \beta T^{*m} = 0 \quad (3.6)$$

$$N\beta T^* - \gamma V = 0 \quad (3.7)$$

It follows that $V = 0 \quad or \quad V = \frac{N\beta}{\gamma}^{m-1}\sqrt{\frac{KN(S-(\alpha-r))X}{\gamma(\alpha-r)}}$ (3.8)

When $V = 0 \ , T^* = 0 \ and \ X = 0$ i.e. the infection-free equilibrium point is $P_0^{**} = (0,0,0)$

When $V = \frac{N\beta}{\gamma}^{m-1}\sqrt{\frac{KN(S-(\alpha-r))X}{\gamma(\alpha-r)}}$, an equation of degree $(m-1)$ emerges with $(m$-1) roots as solutions which gives $(m-1)$ infection equilibrium points.

3.1.4 The case $n = m + 1$ (where m is a positive integer)

If we let $n = m$ in equation (2.1) we obtain

$$\left.\begin{aligned} \frac{dX}{dt} &= -(\alpha - r)X + \frac{rST^*}{(\alpha-r)T_{max}} - \frac{rXT^*}{T_{max}} + \frac{KVS}{(\alpha-r)} - KVS \\ \frac{dT^*}{dt} &= \frac{KVS}{(\alpha-r)} - KXV - \beta T^{*(m+1)} \\ \frac{dV}{dt} &= N\beta T^* - \gamma V \end{aligned}\right\} \quad (3.9)$$

By setting $\frac{dX}{dt} = \frac{dT^*}{dt} = \frac{dV}{dt} = 0$ in equation (3.4) to obtain

$$-(\alpha - r)X + \frac{rST^*}{(\alpha-r)T_{max}} - \frac{rXT^*}{T_{max}} + \frac{KVS}{(\alpha-r)} - KVS = 0 \quad (3.10)$$

$$\frac{KVS}{(\alpha-r)} - KXV - \beta T^{*(m+1)} = 0 \quad (3.11)$$

$$N\beta T^* - \gamma V = 0 \quad (3.12)$$

It follows that $T^* = 0 \quad or \quad T^* = \frac{N\beta}{\gamma}^{m}\sqrt{\frac{KN(\alpha-r)X-KNS}{\gamma(\alpha-r)}}$ (3.13)

When $T^* = 0 \ , V = 0 \ and \ X = 0$ i.e. the infection-free equilibrium point is $P_0^{***} = (0,0,0)$

When $T^* = \frac{N\beta}{\gamma}^{m}\sqrt{\frac{KN(\alpha-r)X-KNS}{\gamma(\alpha-r)}}$, an equation of degree m emerges with m roots as solutions. This gives m infection equilibrium points.

3.2 The translation to the origin of the infection-free points $P_0, P_0^*, P_0^{**}, P_0^{***}$

Let $y = X - X_1 \ , \ z = T^* - T^*_1 \ , \ w = V - V_1 \ \}$ (3.14) If by differentiating (3.14) with respect to t and the result substituted in (3.2),(3.3),(3.4) and (3.5), we have the translated equations as follows:

$$\left.\begin{aligned} \frac{dy}{dx} &= -(\alpha - r)y + \frac{rSz}{(\alpha-r)T_{max}} + \frac{KSw}{(\alpha-r)} - \frac{ryz}{T_{max}} - Kwy \\ \frac{dz}{dx} &= -\beta z + \frac{KSw}{(\alpha-r)} - Kwy \\ \frac{dw}{dx} &= N\beta z - \gamma w \end{aligned}\right\} \quad (3.15)$$

$$\left.\begin{aligned} \frac{dy}{dx} &= -(\alpha - r)y + \frac{rSz}{(\alpha-r)T_{max}} + \frac{KSw}{(\alpha-r)} - \frac{ryz}{T_{max}} - Kwy \\ \frac{dz}{dx} &= -\beta z + \frac{KSw}{(\alpha-r)} - Kwy^2 \\ \frac{dw}{dx} &= N\beta z - \gamma w \end{aligned}\right\} \quad (3.16)$$

$$\left.\begin{aligned} \frac{dy}{dx} &= -(\alpha - r)y + \frac{rSz}{(\alpha-r)T_{max}} + \frac{KSw}{(\alpha-r)} - \frac{ryz}{T_{max}} - Kwy \\ \frac{dz}{dx} &= -\beta z + \frac{KSw}{(\alpha-r)} - Kwy^m \\ \frac{dw}{dx} &= N\beta z - \gamma w \end{aligned}\right\} \quad (3.17)$$

$$\left.\begin{aligned}\frac{dy}{dx} &= -(\alpha - r)y + \frac{rSz}{(\alpha-r)T_{max}} + \frac{KSw}{(\alpha-r)} - \frac{ryz}{T_{max}} - Kwy \\ \frac{dz}{dx} &= -\beta z + \frac{KSw}{(\alpha-r)} - Kwy^{(m+1)} \\ \frac{dw}{dx} &= N\beta z - \gamma w\end{aligned}\right\} \quad (3.18)$$

The reproduction parameter

The basic reproduction parameter R_o is defined by [7]. In this paper R_o is determined by considering the fate of a single productively infected cell in an otherwise healthy individual. Infact R_o in this case is $R_o = \frac{KNS}{\gamma(\alpha-r)}$.

3.3 Nature of the critical points

We shall need the following theorems in the analysis of the nature of the critical points. The stability theorems for our system of equations in (3.15), (3.16), (3.17) and (3.18) are stated below without proof.

Let $\frac{dx}{dt} = P(x, y)$

$$\frac{dy}{dt} = Q(x, y)$$

$$X = \begin{pmatrix} x \\ y \end{pmatrix}$$

Theorem 3.1 [8]:

Let $X_1 = \begin{pmatrix} x_1 \\ y_1 \end{pmatrix}$ be a critical point of the plane autonomous system

$$X_1 = g(X) = \begin{pmatrix} P(x, y) \\ Q(x, y) \end{pmatrix},$$

Where P(x,y) and Q(x,y) have continuous first partial derivatives in a neighborhood of X_1,

(a) If the eigenvalues of $A = g^1(X_1)$ have negative real part then X_1 is an asymptotically stable critical point.

(b) If $A = g^1(X_1)$ has an eigenvalue with positive real part, then X_1, is an unstable critical point.

Consider the system

$X^1 = HX$

Where $X^1 = \begin{pmatrix} x_1 \\ y_1 \end{pmatrix}$, $X = \begin{pmatrix} x \\ y \end{pmatrix}$, $H = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$

Theorem 3.2 [9]:

Consider the system

$$x^1 = a_{11}x + a_{12}y$$

$$y^1 = a_{21}x + a_{22}y$$

where a_{ij} are real constants and $a_{11}a_{22} - a_{12}a_{21} = 0$, so that the origin (0, 0) is the only critical point.

Let λ_1 and λ_2 be the two roots of the auxiliary equations

$\lambda^2 - (a_{11} + a_{22})\lambda + (a_{11}a_{22} - a_{21}a_{12}) = 0$. Then

(a) The origin is stable if λ_1 and λ_2 are purely imaginary

(b) The origin is asymptotically stable if Re $\lambda_1 < 0$ and Re $\lambda_2 < 0$

(c) The origin is unstable in all other cases

Theorem 3.3 [1] (DESCARTES' RULE OF SIGNS)

The number of positive zeros (negative zeros) of polynomials with real coefficient is either equal to the number of change in sign of the polynomial or less than this by an even number (By counting down by two's).

3.2 The stability of the infection free equilibrium points

The Jacobian matrix of the system of equations in (3.15), (3.16), (3.17) and (3.18) at the points P_0 ,P_0^*, P_0^{**} and P_0^{***} is

$$J(P_0) = J(P_0^*) = J(P_0^{**}) = J(P_0^{***}) = \begin{pmatrix} -(\alpha - r) & \frac{rs}{(\alpha - r)T_{max}} & \frac{KS}{(\alpha - r)} \\ 0 & -\beta & \frac{KS}{(\alpha - r)} \\ 0 & N\beta & -\gamma \end{pmatrix}$$

The eigenvalues are given by $\left(-(\alpha - r) - \lambda\right)\left((-\beta - \lambda)(-\gamma - \lambda) - \frac{kN\beta s}{(\alpha - r)}\right) = 0$ i.e

$\left(-(\alpha - r) - \lambda\right)\left(\lambda^2 + (\gamma + \beta)\lambda + \gamma\beta(1 - R_0)\right) = 0$

$\lambda_1 = -(\alpha - r)$ and $\left(\lambda^2 + (\gamma + \beta)\lambda + \gamma\beta(1 - R_0)\right) = 0$

Then if $\alpha > r > 0$ it follows that $\lambda_1 = -(\alpha - r)$ is less than zero i.e. λ_1 is negative.

When $\left(\lambda^2 + (\gamma + \beta)\lambda + \gamma\beta(1 - R_0)\right) = 0$ we have

$$\lambda_2 = \frac{-(\gamma + \beta) + \sqrt{(\gamma + \beta)^2 - 4(1 - R_0)\gamma\beta}}{2} \text{ and } \lambda_3 = \frac{-(\gamma + \beta) - \sqrt{(\gamma + \beta)^2 - 4(1 - R_0)\gamma\beta}}{2}$$

Now if $\gamma > 0$, $\beta > 0$ *and* $R_0 < 1$. It follows that λ_2 and λ_3 are both less than zero i.e. λ_2 and λ_3 are both negative. There are no changes in sign; hence, all eigenvalues are all negative. Therefore P_0 is asymptotically stable.

Furthermore, if $R_0 > 1$ and $\gamma > 0$, $\beta > 0$ then $\left(\lambda^2 + (\gamma + \beta)\lambda + \gamma\beta(1 - R_0)\right) = 0$ has 1 sign change sothat all eigenvalues are not all negative. Hence P_0 is unstable.

4.0 Numerical solutions

The equation (3.1),(3.5) and the translated equations (3.7), (3.8) and (3.9) were solved numerically using Runge-Kutta-Fehlberg method (RKF45) and results for the cases n=1 and n=2 were compared.

4.1 Numerical solutions of the infection free critical points P0 and P*0

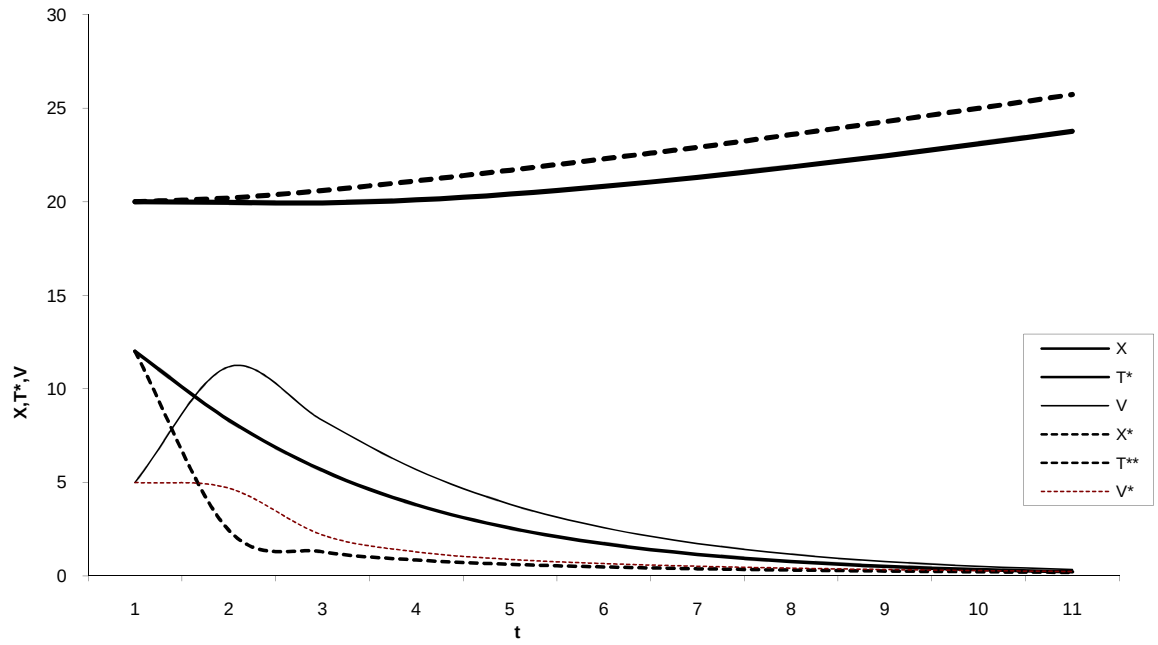

Figure 1. The graph of X(uninfected T cells), T*(infected T cells) and V(HIV virus) against time t for cases n=1 and n=2

5.0 Discussion Of Results

The infection – free equilibrium of (3.2),(3.3),(3.4) and (3.5) are asymptotically stable if $R_0 < 1$ and $r < \alpha$ and unstable if $R_0 > 1$ and $\alpha < r$. Figure 1 shows the stability of the infection – free equilibrium for $n = 1$ and $n = 2$.

5.1 Conclusion

In this paper, we modified an existing HIV/AIDS model. We investigated the characteristic equation and we discussed the stability of equilibrium points that were not previously considered. We solved the mathematical modelled equations numerically (using maple 9 software package which uses the Runge – Kutta-Fehlberg method (RKF45 method)) using realistic values for the parameters and we interpreted the graph that resulted from the numerical solutions.

Conclusively, we found that the number of critical points depends on the value of the positive integer n and that the infection-free equilibriums in all cases considered is P_o= (0, 0, 0) showing that the infection – free equilibrium is independent of n. For any positive integer n, the infection-free equilibrium point is P_o= (0, 0, 0), thus the positive integer n has no effect on P_o= (0, 0, 0).The infection-free equilibrium point P_o= (0, 0, 0) is asymptotically stable if $R_o<1$ and unstable if $R_o>1$ for all positive integer values of n.

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