Journal of the Nigerian Association of Mathematical Physics
***Volume* 18 (May, 2011), pp 303 - 306**

The Mathematical Analysis of the Within-Host Dynamics of Plasmodium Falciparum

[1]M.O. Adeniyi, [2]M.K. Kolawole and [3]M.O Olayiwola
[1]Department of Mathematics, Lagos State Polytechnic, Ikorodu.
[2,3]Department of Mathematical & Physical Sciences, College of Science, Engineering & Technology, Osun State University, Osogbo, Nigeria.

Abstract

We analyze a mathematical model of within-host dynamics of plasmodium falciparum. We report that there are two critical points the infection-free equilibrium point and the infection equilibrium point. We show that the infection – free equilibrium is asymptotically stable if the reproduction number $R_0 < 1$ and unstable if $R_0 > 1$. New theorems were formulated using the basic reproduction parameter R_0.

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

1.0 INTRODUCTION

The development of malaria due to Plasmodium falciparum is a complex, multi-stage process. It is usually characterized by an exponential growth in the number of parasite-infected erythrocytes, followed by marked oscillations. This of course has been a subject of various mathematical models. In particular the mathematical model proposed by Anderson, May and Gupta (1989) which attempt to address the blood –stage asexual cycle of Plasmodium falciparum by following the invasion of erythrocytes (RBC) by merozoites and the infected red blood cells (IRBC). In this paper we are interested in the mathematical analysis of the equilibrium points by considering the stability of such points which depend on the basic reproduction parameter R_o as discussed by Oluyo et-al (2007).

2.0 MATHEMATICAL FORMULATION

The model to be discussed in this paper is as presented by Anderson, May and Gupta (1989) given as

$$\left.\begin{aligned} \frac{dx}{dt} &= \gamma - \mu \boldsymbol{x} - \boldsymbol{\beta x s} \\ \frac{dy}{dt} &= \boldsymbol{\beta x s} - \boldsymbol{\alpha y} \\ \frac{ds}{dt} &= \boldsymbol{\alpha r y} - \boldsymbol{\delta s} - \boldsymbol{\beta x s} \end{aligned}\right\} \tag{1}$$

x:the uninfected red blood cells concentration(URBC); y: the infected red blood cells concentration(IRBC); s:the concentration of the merozoites; γ:the fixed rate at which erythropo iesis is produced in the bone marrow; μ:the normal decay of RBCs at constant rate; $\boldsymbol{\alpha}$:rate at which merozoites are released from rupturing IRBCs; $\boldsymbol{r}$:the multiplication rate per cycle; $\boldsymbol{\beta}$:coefficient of merozoites eliminated by the invasion of fresh RBCs at a rate proportional to the concentrations of RBC and merozoites; $\boldsymbol{\delta}$:merozoites eliminated due to loss of infectivity.
It is important to point here that we have replaced $\boldsymbol{\Lambda}$ by $\boldsymbol{\gamma}$ in the model as presented by Anderson et al (1989).

3.0 METHODOLOGY

3.1` THE CRITICAL POINTS

The critical points of equation (1) are:

$$A_o = \left(\frac{\gamma}{\mu}, 0{,}0\right) \text{ and } A^* = \left(\frac{\delta}{\beta(r-1)}, \frac{\gamma\beta r - \gamma\beta - \mu\delta}{\beta(r-1)\alpha}, \frac{\gamma\beta r - \gamma\beta - \mu\delta}{\beta\delta}\right)$$

A_o is the infection-free equilibrium point and A^* the infection equilibrium.

3.2 THE TRANSLATED EQUATIONS TO THE ORIGIN

The translated equations to the origin of the points A_o and $A^*$are:

[1]Corresponding author: M. O. Adeniyi, **E-mail:** ojigweadeniyiarsenal2007@yahoo.com, Tel:+2348033805036

$$\left.\begin{aligned}\frac{dX}{dt} &= -\mu \boldsymbol{X} - \boldsymbol{\beta X S} - \frac{\gamma}{\boldsymbol{\mu}}\boldsymbol{\beta S}\\ \frac{dY}{dt} &= \frac{\gamma}{\boldsymbol{\mu}}\boldsymbol{\beta S} - \boldsymbol{\alpha Y} + \boldsymbol{\beta X S}\\ \frac{dS}{dt} &= -\boldsymbol{\beta X S} + \boldsymbol{\alpha r Y} - \left(\frac{\delta\mu + \beta}{\mu}\right)\mathrm{S}\end{aligned}\right\} \quad (2)$$

and

$$\left.\begin{aligned}\frac{dX}{dt} &= -\frac{\beta}{\delta}(\boldsymbol{r}-\boldsymbol{1})\boldsymbol{X} - \frac{\boldsymbol{\delta}}{(\boldsymbol{r}-\boldsymbol{1})}\boldsymbol{S} - \boldsymbol{\beta X S}\\ \frac{dY}{dt} &= \frac{\gamma\beta r - \gamma\beta - \mu\delta}{\delta}X - \boldsymbol{\alpha Y} + \frac{\boldsymbol{\delta}}{(\boldsymbol{r}-\boldsymbol{1})}\boldsymbol{S} + \boldsymbol{\beta X S}\\ \frac{dS}{dt} &= -\left(\frac{\gamma\beta r - \gamma\beta - \mu\delta}{\delta}\right)X + \boldsymbol{\alpha r Y} - \frac{\boldsymbol{\delta r}}{(\boldsymbol{r}-\boldsymbol{1})}\mathrm{S} - \boldsymbol{\beta X S}\end{aligned}\right\} \quad (3)$$

3.3 THE REPRODUCTION PARAMETER

The basic reproduction parameter R_o is defined by Patrick De Leenheer et al (2003)]. In this paper R_o is determined by considering the fate of a single productively infected cell in an otherwise healthy individual with normal target URBC level $x = x_0$. Infact R_o in this case is$R_o = \frac{\propto\gamma\beta r}{\mu}$.

3.4 STABILITY THEOREMS

We shall need the following theorems in the analysis of the nature of the critical points

THEOREM3.1[2]:

Let $\frac{dx}{dt} = P(x, y), \frac{dy}{dt} = Q(x, y)$ and X = $\begin{pmatrix} x \\ y \end{pmatrix}$.

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.

THEOREM 3.2 [2]:

Consider the system

$$x^1 = a_{11}x + a_{12}y$$
$$y^1 = a_{21}x + a_{22}y$$

where they 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 the origin is stable if λ_1 and λ_2 are purely imaginary:

(a) the origin is asymptotically stable if Re $\lambda_1 < 0$ and Re $\lambda_2 < 0$
(b) the origin is unstable in all other cases.

THEOREM 3.3 (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)

Consequent to the above theorems we shall state and prove new theorems that could be derived from the theorems. We now propose the following theorems:

Theorem3.4 The critical point of the infected-free equilibrium is asymptotically stable if $R_0 < 1$ and if $\mu > 0, \alpha > 0, \delta > 0, \gamma > 0, \beta > 0, r > 0$, otherwise the critical point is unstable.

Proof:
The Jacobian matrix of equation (2) at A_o is (see [3])

$$J(A_o) = \begin{pmatrix} -\mu & 0 & \frac{-\gamma\beta}{\mu} \\ 0 & -\alpha & \frac{\gamma\beta}{\mu} \\ 0 & \alpha r & -\left(\frac{\delta\mu+\lambda\beta}{\mu}\right) \end{pmatrix}$$

So the eigenvalues are given by $(-\mu-\lambda)\left[\lambda^2+\frac{(\propto\mu+\mu\delta+\gamma\beta)}{\mu}\varphi+(\alpha\delta-\frac{\gamma\alpha r\beta}{\mu})\right]=0$ i.e

$$(-\mu-\lambda)\left[\lambda^2+\frac{(\propto\mu+\mu\delta+\gamma\beta)}{\mu}\lambda+(\alpha\delta-R_0)\right] \quad (4)$$

Hence,

$$\lambda_1=-\mu,$$

$$\lambda_2=\frac{1}{2\mu}(-\alpha\mu-\delta\mu-\gamma\beta+\sqrt{\alpha^2\mu^2+2\alpha\mu^2\delta+2\alpha\mu\gamma\beta+\delta^2\mu^2+2\delta\mu\gamma\beta+\gamma^2\beta^2-4\mu^2\alpha\delta+4\mu^2R_0}),$$

$$\lambda_2=\frac{-1}{2\mu}(-\alpha\mu-\delta\mu-\gamma\beta+\sqrt{\alpha^2\mu^2+2\alpha\mu^2\delta+2\alpha\mu\gamma\beta+\delta^2\mu^2+2\delta\mu\gamma\beta+\gamma^2\beta^2-4\mu^2\alpha\delta+4\mu^2R_0})$$

If $\mu>0,\alpha>0,\delta>0,\gamma>0,\beta>0$ and $R_0<1$ in equation (4) then the result follows that there are no change in signs which implies that there are no positive solutions of equation (4). If φ is replaced by $-\varphi$ in equation (4) then

$$-\lambda^3+\left(\frac{\mu^2+(\alpha+\delta)\mu+\gamma\beta}{\mu}\right)\lambda^2-(\alpha\mu+\mu\delta+\gamma\beta+\alpha\delta-R_0)\lambda+\mu(\alpha\delta-R_0)=0 \quad (5)$$

If $\mu>0,\alpha>0,\delta>0,\gamma>0,\beta>0$ and $R_0<1$ then there are 3 sign changes so that equation(5) has 3 negative roots or 1 negative root which implies that all the eigen values $\lambda_1,\lambda_2,\lambda_3$ are all negative. Hence the result follows that the infection-free critical point $A_o$is asymtotically stable

Theorem3.5
The critical point of the infected-free equilibrium is unstable if $R_0>1$and if $\mu>0,\alpha>0,\delta>0,$
$\gamma>0,\beta>0,r>0.$

Proof:
From equations (4) and (5) of the proof of theorem 3.1 if we let $\mu>0,\alpha>0,\delta>0,\gamma>0,\beta>0$ and $R_0>1$ in equation (4) it follows there is only 1 sign change which implies that there is exactly 1 positive root. If φ is replaced by $-\varphi$ as before in equation (4) and that $\mu>0,\alpha>0,\delta>0,\gamma>0,\beta>0$ and $R_0>1$ in equation (5) yields 2 sign changes and there are exactly 2 negative roots or zero root. This implies that there is exactly 1 positive root and 2 negative roots. Therefore, the result follows immediaely that the critical point A_o is unstable.

Theorem3.6 The infection equilibrium is asymptotically stable if $R_0<1$and if$\mu>0,\alpha>0,\delta>0,\gamma>0,\beta>0,r>1$

Proof:
The Jacobian matrix of equation (3) at A^* is

$$J(A^*) = \begin{pmatrix} -\frac{\gamma\beta}{\delta}(r-1) & 0 & \frac{-\delta}{(r-1)} \\ \frac{\gamma\beta r-\gamma\beta-\mu\delta}{\delta} & -\alpha & \frac{\delta}{(r-1)} \\ -\left(\frac{\gamma\beta r-\gamma\beta-\mu\delta}{\delta}\right) & \alpha r & -\frac{-\delta r}{(r-1)} \end{pmatrix}$$

The characteristic equation of the system of equations in equation (3) is

$$\left(\frac{-\gamma\beta(r-1)}{\delta}-\lambda\right)\left((\alpha(r-1)-\lambda)\left(\frac{(\gamma\beta r^2-2\gamma\beta r+\gamma\beta+\mu\delta)}{(r-1)}-\lambda\right)-\mu(r-1)R_0\right)=0 \quad (6)$$

Therefore,

$$\lambda_1=\frac{-\gamma\beta(r-1)}{\delta}$$

$, \lambda_2=\frac{1}{2(r-1)}\Big(-2\alpha r+\gamma\beta r^2-2\gamma\beta r+\alpha+\alpha r^2+\gamma\beta+\mu\delta+(\alpha^2r^4-2\gamma\beta r^4\alpha+\gamma^2\beta^2-2\alpha r^2\mu\delta+\mu^2\delta^2+$
$6\gamma^2\beta^2r^2-4\gamma^2\beta^2r^3+\gamma^2\beta^2r^4+4\mu R_0r^3+\alpha^2-4\gamma^2\beta^2r+6\alpha^2r^2-4\alpha^2r-4\alpha^2r^3+8\alpha r^3\beta-12\alpha r^2\beta+8\alpha r\beta+$
$4\alpha r\mu\delta-2\alpha\beta-2\alpha\mu\delta-4\mu R_0-12\mu R_0r^2+12\mu R_0r+2\beta\mu\delta-4\beta r\mu\delta+2\beta r^2\mu\delta)^{1/2}\Big)$,

$\lambda_3 = -\frac{1}{2(r-1)}\big(-2\alpha r + \gamma\beta r^2 - 2\gamma\beta r + \alpha + \alpha r^2 + \gamma\beta + \mu\delta + (\alpha^2 r^4 - 2\gamma\beta r^4\alpha + \gamma^2\beta^2 - 2\alpha r^2\mu\delta + \mu^2\delta^2 + 6\gamma^2\beta^2 r^2 - 4\gamma^2\beta^2 r^3 + \gamma^2\beta^2 r^4 + 4\mu R_0 r^3 + \alpha^2 - 4\gamma^2\beta^2 r + 6\alpha^2 r^2 - 4\alpha^2 r - 4\alpha^2 r^3 + 8\alpha r^3\beta - 12\alpha r^2\beta + 8\alpha r\beta + 4\alpha r\mu\delta - 2\alpha\beta - 2\alpha\mu\delta - 4\mu R_0 - 12\mu R_0 r^2 + 12\mu R_0 r + 2\beta\mu\delta - 4\beta r\mu\delta + 2\beta r^2\mu\delta)^{1/2}\big)$,

By expanding equation (6) to obtain

$$\lambda^3 + \left(\frac{-\alpha\delta(r-1)^2 - \gamma\beta\delta r^2 + 2\gamma\beta\delta r - \gamma\beta\delta - \mu\delta^2 + \gamma\beta(r-1)^2}{\delta(r-1)}\right)\lambda^2 + \left(\frac{(\gamma\beta r^2 - 2\gamma\beta r + \gamma\beta + \mu\delta)(\alpha\delta - \gamma\beta) - \gamma\beta\alpha(r-1)^2}{\delta}\right)\lambda + \frac{(\gamma\beta r^2 - 2\gamma\beta r + \gamma\beta + \mu\delta)(\alpha\delta - \gamma\beta) - \gamma\beta\alpha(r-1)^2}{\delta} = 0 \qquad (7)$$

If $\mu > 0, \alpha > 0, \delta > 0, \gamma > 0, \beta > 0, r > 1$ and $R_0 < 1$ in equation (7) then the result follows that there are no change in signs which implies that there are no positive solutions of equation (7). If λ is replaced by $-\lambda$ in equation (7) then

$$-\varphi^3 + \left(\frac{-\alpha\delta(r-1)^2 - \gamma\beta\delta r^2 + 2\gamma\beta\delta r - \gamma\beta\delta - \mu\delta^2 + \gamma\beta(r-1)^2}{\delta(r-1)}\right)\varphi^2 - \left(\frac{(\gamma\beta r^2 - 2\gamma\beta r + \gamma\beta + \mu\delta)(\alpha\delta - \gamma\beta) - \gamma\beta\alpha(r-1)^2}{\delta}\right)\varphi + \frac{(\gamma\beta r^2 - 2\gamma\beta r + \gamma\beta + \mu\delta)(\alpha\delta - \gamma\beta) - \gamma\beta\alpha(r-1)^2}{\delta} = 0 \qquad (8)$$

If $\mu > 0, \alpha > 0, \delta > 0, \gamma > 0, \beta > 0, r > 1$ and $R_0 < 1$ then there are 3 sign changes so that equation(8) has 3 negative roots or 1 negative root which implies that all the eigen values $\lambda_1, \lambda_2, \lambda_3$ are all negative. Hence the result follows that the infection critical point A^* is asymtotically stable.

Theorem3.4
The infection equilibrium is unstable if $R_0 > 1$ and if $\mu > 0, \alpha > 0, \delta > 0, \gamma > 0, \beta > 0, r > 1$.

Proof:
From equations (7) and (8) of the proof of theorem 3.3 if we let $\mu > 0, \alpha > 0, \delta > 0, \gamma > 0, \beta > 0, r > 1$ and $R_0 > 1$ in equation (8) it follows there is only 1 sign change which implies that there is exactly 1 positive root. If λ is replaced b$-\lambda$ y as before in equation (7) and that $\mu > 0, \alpha > 0, \delta > 0, \gamma > 0, \beta > 0$, $r > 1$and $R_0 > 1$ in equation (8) yields 2 sign changes and there are exactly 2 negative roots or zero root. This implies that there is exactly 1 positive root and 2 negative roots. Therefore, the result follows immediaely that the infection critical point A^* is unstable.

4.0 RESULTS AND DISCUSSION
The analysis revealed that there are two critical points; the infection- free point and the infection point. The stability criteria shows that the infection-free point is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$

REFERENCES

[1] **Anderson, R.M**., **May, R.M**. **and Gupta, S.** (1989): Non-linear phenomena in host-parasite interactions. Parasitology 99 (Suppl.), S59 - S79

[2] **Dennis G. Zill, Michael R. Cullen**: Differential Equations with Boundary – value Problems pp 395-417

[3] **Labarre A.E. Jr**. (1961): Elementary Mathematical Analysis. Addison – Wesley Publishing Company, Inc. Reading. pp 297 -298

[4] **Oluyo, T.O., Ayeni, R.O**. and **Ayandokun, O.O**. (2007): Mathematical Analysis of the Global Dynamics of a model for HIV Infections of CD4+T cells. Journal of NAMP, Vol. 11, pp. 103 – 110.

[5] **Patrick De Leenheer** and **Hal L. Smith** (2003): Virus Dynamics; A Global analysis: SIAM J. APPL. MATH. Vol. 63, No.4, pp. 1313 – 1327