COMPARISON ON VIRUS DYNAMICS MODELS WITH DIFFERENT FUNCTIONAL RESPONSES INCLUDING TIME DELAYS

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Abstract – A virus can be identified as an infectious mediator consisting a core of genetic material and an envelope of protein. The behavior of viruses can be modelled through mathematics, and those viral dynamics can consist a class of differential equations which describe the effect of the virus on uninfected and infected cells, in a body compartment over a period of time. Even though many mathematical models have been proposed for various viral infections, a proper assessment on them has not been done throughout the literature. In this paper, dynamics models with bilinear, Michaelis

Menten, saturated and Beddignton-DeAngelis functional responses have been compared, with respective to the time delays and the basic reproductive rate (0). For the considered models, the populations of uninfected cells, infected cells and free virus were calculated to find solutions for respective infection free and infected equilibriums. By carrying out numerical simulations through literature reported parameter values, the effect of intracellular and maturation time delays on the corresponding reproductive rate of each model was analyzed. Since a reproductive rate, less than unity represents an infection free host, the primary target of the treatments for viral infections is to decrease

the reproductive rate as possible. The graphical representation showed that the model with Beddignton-DeAngelis functional response, possessed a greater capacity in reducing 0, with the effect of time delays. This qualitative analysis on models will have the capability to give the drug producers more significant guidance in recognizing the most appropriate viral dynamics model.

Keywords - viral dynamics, delay differential, reproductive rate

I. INTRODUCTION

A virus can be described as a micro parasite, consisting a core of genetic material, either RNA or DNA and a surrounding envelope of protein, lipid and glycoprotein. It possesses the capability to infect any form of life, including animals, plants and microorganisms (Koonin at el. 2006). Viruses are incompetent of multiplying within them, thus they acquire the assistance of a host cell to be spread. Although certain viruses hold some important functions, substantial amount of viruses including the human immunodeficiency virus (HIV), common cold, influenza, chickenpox, hepatitis A/B/C and human papilloma virus (HPV) are considered to be pathogenic (Zahler 1979).

With numerous researchers finding a way to cure these viruses, virus dynamical modelling has also given a considerable contribution in epidemiology. Even though many mathematical models have been proposed for various viral infections, a proper assessment on them has not been done throughout the literature. Viral dynamics can consist a collection of mathematical models which describe the behavior in the populations of targeted uninfected cells, infected cells and the virus over a period of time. Thus a three dimensional model has been used (Bonhoeffer et al. 1997; Nowak & May 2000) to describe the phenomena as on model (1).

$$\dot{u}(t) = \alpha - \beta u(t)v(t) - ju(t);$$
$$\dot{r}(t) = \beta u(t)v(t) - kr(t);$$
$$\dot{v}(t) = mr(t) - lv(t). \qquad \text{Model (1)}$$

Considering a body compartment, the concentrations of uninfected target cells, infected cells with the aptitude of

producing new virus and free virus at time are represented by , and respectively. The constant (> 0) is the rate which uninfected target cells are recruited to the compartment. (≥ 0) is the constant characterizing the infection of cells. The infected cells produce (> 0) number of free virus in during their life. The constants (> 0), (> 0) and (> 0) denotes the death rates of uninfected cells, infected cells and clearance rate of virus from the system.

In the recent times, there has been an extensive effort in the mathematical modelling of virus dynamics, mainly encouraged by the model (1). These models have been used to study HIV (Li & Ma 2007; Wang et al. 2010; Perelson & Ribeiro 2013; Pradeep & Ma 2014; Pradeep et al. 2015), hepatitis B virus (Ciupe et al. 2007) and hepatitis C virus (Neumann et al. 1998; Chatterjee et al. 2013) among other infections.

In model (1), it has not been considered any of the time delays which occur in the viral progression biologically. In accordance to do the comparison of more realistic virus dynamics models, time delays have been incorporated to compare models with delay differential equations.

The intracellular delay, indicating the time between the viral entry and the new virus production was initially proposed by (Herz et al. 1996) and numerous models representing the intracellular delay were developed later (Li & Ma 2007; Huang et al. 2010; Huang et al. 2011; Pradeep et al. 2015; Pradeep & Ma 2014).

Maturation time delay denotes the time period which the virus acquired after its rise, to develop the ability to infect the target cells. Mathematical models representing the maturation time delay were also developed in the recent years (Huang et al. 2010; Pradeep et al. 2015).

II. METHODOLOGY

In this paper, the followings models, with different functional responses were compared, with respective to the time delays and the reproductive rate (0) which denotes the average number of infected cells produced by one infected cell over the course of its infectious period (Fraser et al. 2009).

In the following models, ≥ 0 is the intracellular time delay while − accounts for the probability of surviving from time − to, ≥ 0 is the maturation time delay while − accounts for the probability of surviving from time − to and the parameters and are positive constants.

1 Bilinear functional response/ Holling type I functional response (Nowak et al. 1997; Nowak & May 2000; Herz et al. 1996; Perelson et al. 1996)

$$\dot{u}(t) = \alpha - \beta u(t)v(t) - ju(t);$$
$$\dot{r}(t) = e{-}k\tau\beta u(t-\tau)v(t-\tau) - kr(t);$$
$$\dot{v}(t) = e{-}l\sigma mr(t-\sigma) - lv(t).$$

2. Michaelis - Menten functional response/ Holling Type II functional response

$$\dot{u}(t) = \alpha - \frac{\beta u(t)v(t)}{1+au(t)} - ju(t);$$
$$\dot{r}(t) = e^{-k\tau}\frac{\beta u(t-\tau)v(t-\tau)}{1+au(t-\tau)} - kr(t);$$
$$\dot{v}(t) = e^{-l\sigma}mr(t-\sigma) - lv(t).$$

Model (3)

3. Saturated incidence rate (Li & Ma 2007)

$$\dot{u}(t) = \alpha - \frac{\beta u(t)v(t)}{1+bv(t)} - ju(t);$$
$$\dot{r}(t) = e^{-k\tau}\frac{\beta u(t-\tau)v(t-\tau)}{1+bv(t-\tau)} - kr(t);$$
$$\dot{v}(t) = e^{-l\sigma}mr(t-\sigma) - lv(t).$$

Model (4)

4. Beddignton-DeAngelis infection rate (Wang et al. 2010; Huang et al. 2011; Pradeep & Ma 2014; Huang et al. 2009)

$$\dot{u}(t) = \alpha - \frac{\beta u(t)v(t)}{1+au(t)+bv(t)} - ju(t);$$
$$\dot{r}(t) = e^{-k\tau}\frac{\beta u(t-\tau)v(t-\tau)}{1+au(t-\tau)+bv(t-\tau)} - kr(t);$$
$$\dot{v}(t) = e^{-l\sigma}mr(t-\sigma) - lv(t)$$

Model (5)

Table 1 - Solutions of Infected Equilibria for the above mentioned Models with time delays

Model	R_0	u^*	v^*	v^*
2	$\frac{\alpha\beta m\, e^{-k\tau-l\sigma}}{jkl}$	$\frac{\alpha}{j}\frac{1}{R0}$	$\frac{jle^{-l\sigma}}{\beta}(R_0-1)$	$\frac{j}{\beta}(R_0-1)$
3	$\frac{\alpha(\beta m\, e^{-k\tau-l\sigma}-alk)}{jkl}$	$\frac{\alpha}{j}\frac{1}{R0}$	$\frac{\alpha e^{-k\tau}}{k}(1-\frac{1}{R_0})$	$\frac{jm\, e^{-k\tau-l\sigma}}{\beta m\, e^{-k\tau-l\sigma}-akl}(R_0-1)$
4	$\frac{\alpha\beta m\, e^{-k\tau-l\sigma}}{jkl}$	$\frac{\alpha}{j}\frac{1}{R0}(1+br^*)$	$\frac{jl(R_0-1)}{me^{-l\sigma}(\beta+jb)}$	$\frac{j}{\beta+jb}(R_0-1)$
5	$\frac{\alpha m\, e^{-k\tau-l\sigma}(\beta m\, e^{-k\tau-l\sigma}-akl)}{jkl}$	$\frac{lk(1+bv^*)}{j\beta m\, e^{-k\tau-l\sigma}-akl}$	$\frac{uv^*}{me^{-l\sigma}}$	$\frac{j}{\beta m\, e^{-k\tau-l\sigma}-akl+jb}(R_0-1)$

III. RESULTS AND DISCUSSION

For all the models, numerical simulations were done using literature reported parameter values, and the following graphs were obtained.

First, the intracellular time delay ( ) was kept fixed at the value of 15, and the maturation time delay ( ) was varied ranging from 0-20, and the deviations of the reproductive rate (0) was attained.

For model (2), 0 deviates from 0-5, for model (3) and model (4) 0 deviates from 0-4.5, and for the model (5), 0 deviates from 0-1.8. These graphical representations verify the fact that model (5) has a greater ability and potential in reducing 0, by reducing the maturation time delay ( ) compared to other models.

Then, the maturation time delay ( ) was kept fixed at the value of 2, and the maturation time delay ( ) was varied ranging from 0-20, and the deviations of the reproductive rate (0) was attained

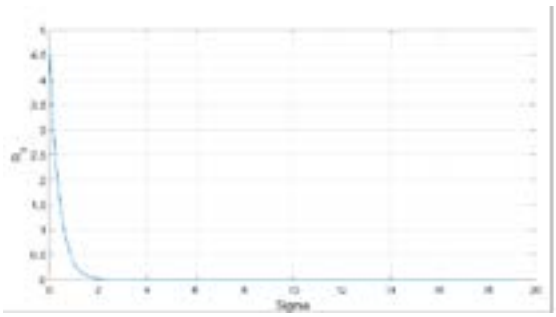

Figure 1 - 0 versus σ for Model 2

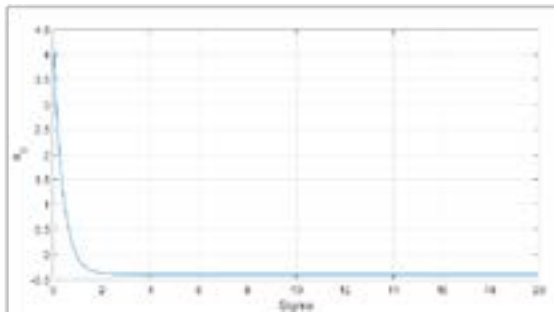

Figure 2 - versus σ for Model 3 and 4

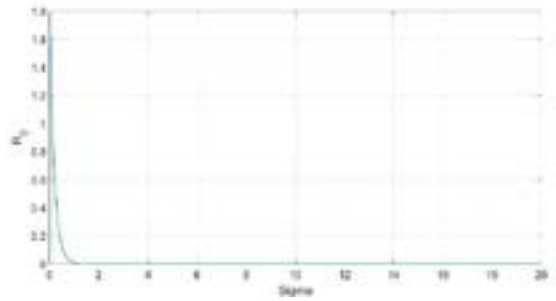

Figure 3 - 0 versus σ for Model 5

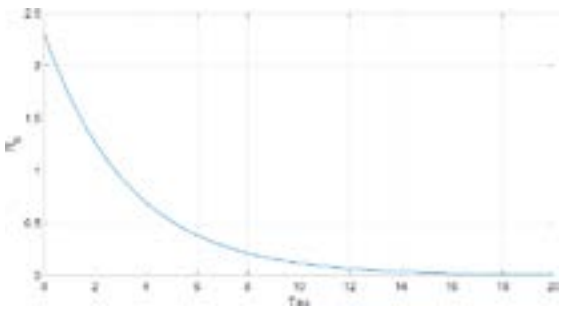

Figure 4 -R_0 versus τ for model 2

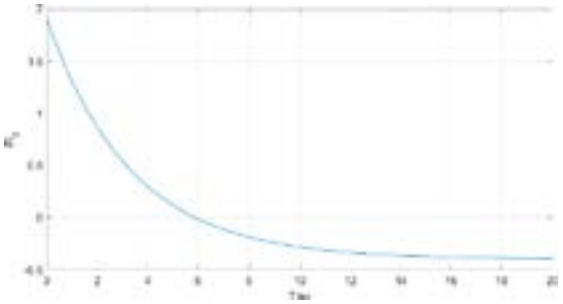

Figure 5 - R_0 versus τ for model 3 and 4

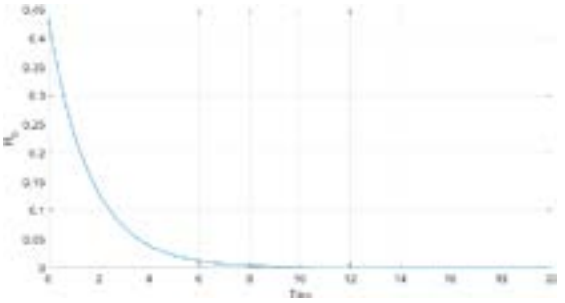

Figure 6 - R_0 versus τ for model 5

IV. CONCLUSION

0 is the limiting factor in determining if the disease has been spread or died out within a host. Thus the reproductive rate should be less than unity in order to recognize as the host is free of infection. Therefore, as to reduce 0, various parameters should be increased or decreased. But, looking at the scenario biologically, it has been identified that the parameters which could be changed by the influence of humans are the intracellular and the maturation time delays. It is certain, from the gained results that the model with Beddignton-DeAngelis functional response carries a greater capacity in reducing 0, with the effect of time delays. Consequently, this comparison can help the drug producers in recognizing the most appropriate viral dynamics model for their identification purposes of parameters more significantly.

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