Mathematical Dynamics For Controling Hepatitis B Virus

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Abstract

Mathematical models have played a significant role in understanding the spread and control of diseases. In this work, we used the SEIR model based on differential equations to propose the viral dynamics of HBV. The existence and stability of the disease-free equilibrium is analyzed and found that the characteristic roots are all negative, hence the disease free equilibrium state is stable by Routh-Hurwitz Criteria.

Keywords: Hepatitis B, thresholds, Mathematical model, Routh-Hurwitz Criteria, Stability

1. Introduction

Hepatitis B is a life-threatening liver infection caused by the hepatitis B virus. It is a major health problem and the most serious type of viral hepatitis. It can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer. Worldwide, estimated two billion people have been infected with the hepatitis B virus (HBV), and more than 350 million have chronic liver infections. In the past decade, therapy for HBV has been revolutionized by the advent of drugs that directly block replication of the HBV genome. All these drugs (to date) are nucleoside or nucleotide analogues that selectively target the viral reverse transcriptase. The first successful drug, lamivudine, emerged from screening for inhibitors of the HBV reverse transcriptase and was introduced into clinical practice for the management of HBV infection.

Recently, mathematical models have been used frequently to study the transmission dynamics of HBV [1–10]. In [1], Anderson and May used a simple mathematical model to illustrate the effects of carriers on the transmission of HBV. In an effort to model HBV infection dynamics and its treatment with the reverse transcriptase inhibitor. Most infectious diseases could be driven towards eradication, if adequate and timely steps (e.g. vaccination, treatment, educational and enlightenment campaign, etc.) are taken in the course of the epidemic.

However, many of these diseases eventually become endemic in our society due to lack of adequate policies and timely interventions to mitigate the spread of the diseases. Consequently, there is the need for proactive steps towards controlling the spread of infectious diseases, particularly those ones for which both vaccine and cure are available. Moreover, it is often cheaper to prevent the occurrence of a disease than to cure it. For a few other diseases, there is no cure but individuals can be vaccinated against getting infected (e.g. Polio).

Surprisingly, it remains a puzzle why diseases for which both treatment and vaccine are available are still endemic in some of our societies.

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Some examples on the use of mathematical model for the analyses of treatment and control of infectious disease can be found in [4, 5, 8–10, 13], etc. For instance, Nelson et al [8], based on results from the analysis and simulations of their HIV model, suggested universal HBV testing followed by an immediate commencement of antiretroviral therapy for those infected as a strategy to drive HBV epidemic towards elimination.

Also, Kuang et al. [5] proposed an improved Hepatitis B virus (HBV) model for the treatment of the disease and they claimed that their model control strategy could help reduce death due to HBV remarkably.

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In this paper, we address the question of how to optimally combine the vaccination and the treatment strategies such that the cost of the implementation of the two interventions is minimized while the disease is eradicated within specified period. It is important to mention here that our work is different from some of the other related works cited in this paper because the model uses bilinear incidence with a variable size total population which tends to an asymptotic limit. Note that in this paper, we shall deal with the mathamatical analysis of the model . This approach is different from the ones in most of the papers cited which concentrate on either of the two parts. Also, most of the papers cited used constant population size but we are considering a variable population size (tending to a limit) which is more realistic.

The paper is organized as follows. In section 2, we present the SEIR model to be investigated. In section 3, we carry out local stability analysis on the model equilibrium. In section 4,we discuss and conclusion.

2. Methodology

There are several variations of models for describing epidemics with different properties with respect to mortality, immunity, and time horizon. In this paper, one of these variations is examined. Precisely, we considered a standard SEIR model with bilinear incidence and variable total population. Suppose S represents the number of Susceptible, E represents the number of Exposed Individuals, I represents the number of individuals who are infected, and R represents the number of individuals who are removed due to vaccination or recovery from the disease which confers permanent immunity to reinfection. It is important to note that this model is applicable to a class of diseases that is fatal, despite the availability of treatment and vaccination. Also, individuals can acquire immunity against the disease either through vaccination or recovery after treatment for the disease.

We now consider the SEIR model below:

Let $\emptyset$ represent the incoming individuals are immunized against infection

μ represents the Natural death

δ represents the Artificial death

α represents the contact rate of infection from Susceptible to Exposed

β represents the contact of Infection

ρ represents the contact rate of Infection from Exposed class to Infected class

σ represents the successful cure of infections rate

u_1 is the proportion of the susceptible that is vaccinated per unit time,

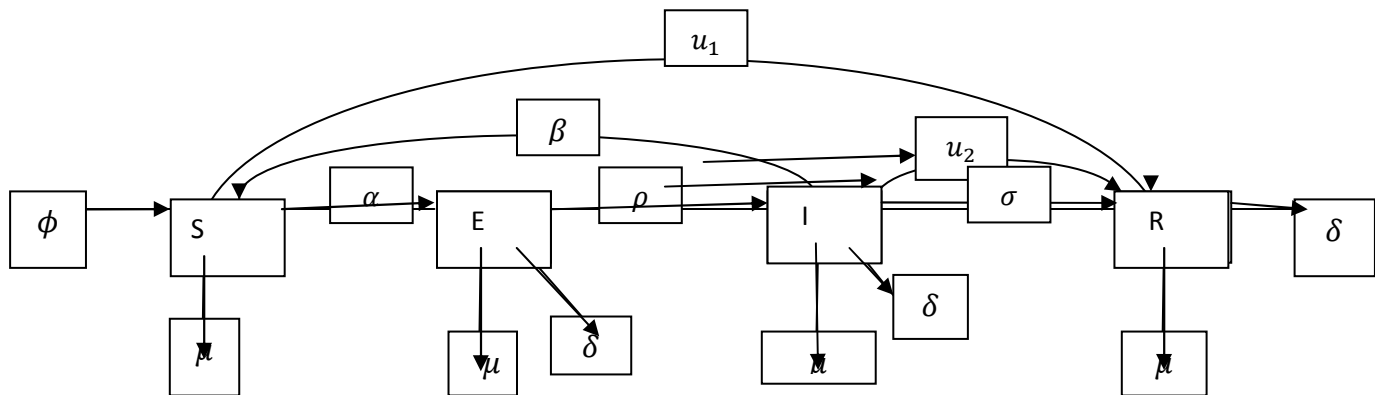u_2 is the proportion of the infective that is treated per unit time.

Figure 1: Schematic representation of the model

Then the equation of the dynamics are given as

$$\frac{dS}{dt} = \emptyset + \beta I - \alpha SI - \mu S - u_1 S \qquad (2.1)$$

$$\frac{dE}{dt} = \alpha SI - \mu E - \rho E - \delta E \qquad (2.2)$$

$$\frac{dI}{dt} = \rho E - \mu I - \beta I - \sigma I - \delta I - u_2 I \qquad (2.3)$$

$$\frac{dR}{dt} = \sigma I - \mu R - \delta R + u_1 S + u_2 I \qquad (2.4)$$

$$S(t) > 0, \quad E(t) > 0, \quad I(t) > 0, R(t) > 0$$

where the total population is

$$N(t) = S(t) + E(t) + I(t) + R(t)$$

Then the equilibrium (Critical) point is obtained from :

$$\frac{dS}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = 0 \qquad (2.5)$$

By rescaling equations (2.1),(2.2), (2.3), and (2.4),

we set $S(t) = a, \quad E(t) = b, \quad I(t) = c, \quad R(t) = d$

Therefore, equation (2.1) to (2.4) becomes

$$\emptyset + \beta c - \alpha ac - \mu a - u_1 a = 0 \qquad (2.6)$$
$$\alpha ac - \mu b - \rho b - \delta b = 0 \qquad (2.7)$$
$$\rho b - \mu c - \beta c - \sigma c - \delta c - u_2 c = 0 \qquad (2.8)$$
$$\sigma c - \mu d - \delta d + u_1 a + u_2 c = 0 \qquad (2.9)$$

Then to obtain the existence of disease free equilibrium state, we look into equation (2.8) and get

$$\rho b = (\mu + \beta + \sigma + \delta + u_2)c$$
$$b = \frac{((\mu + \beta + \sigma + \delta + u_2)c)}{\rho} \qquad (2.10)$$

Substituting equation (2.10) into equation (2.7), we get

$$\alpha ac - (\mu + \rho + \delta)\frac{(\mu + \beta + \sigma + \delta + u_2)c}{\rho} = 0$$
$$c\left[\alpha a - (\mu + \rho + \delta)\frac{(\mu + \beta + \sigma + \delta + u_2)}{\rho}\right] = 0 \qquad (2.11)$$

This implies

$$c = 0, \quad \text{or} \quad \left[\alpha a - (\mu + \rho + \delta)\frac{(\mu + \beta + \sigma + \delta + u_2)}{\rho}\right] = 0 \qquad (2.11a)$$

Substituting $c = 0$ into equation (2.9), we get

$$d = \frac{u_1 \emptyset}{(\mu + \delta)(\mu + u_1)}$$

Also, substituting $c = 0$ into equation (2.10), we get

$$b = 0$$

Substituting $b = 0$, and $c = 0$, into(2.6),we get

$$a = \frac{\emptyset}{\mu + u_1}$$

Hence, the disease free equilibrium state is given as follows:

$$M = (a, b, c, d) = \left(\frac{\emptyset}{\mu + u_1}, 0, 0, \frac{u_1 \emptyset}{(\mu + \delta)(\mu + u_1)}\right) \qquad (2.12)$$

Then to obtain the existence of epidemic equilibrium states, we look into (2.11a) and get

$$\alpha a - (\mu + \rho + \delta)\frac{(\mu + \beta + \sigma + \delta + u_1)}{\rho} = 0$$
$$a = (\mu + \rho + \delta)\frac{(\mu + \beta + \sigma + \delta + u_1)}{\alpha\rho} \qquad (2.13)$$

substituting for equation (2.13) in equation (2.6) ,we get

$$c = \frac{\mu(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1) - \emptyset\alpha\rho}{\beta\alpha\rho - \alpha(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1)} \qquad (2.14)$$

Substituting equation (2.14) into (2.8) ,we get

$$b = \frac{(\mu + \beta + \sigma + \delta + u_2)[\mu(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1) - \emptyset\alpha\rho]}{\rho(\alpha\beta\rho - \alpha(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1))} \qquad (2.15)$$

Substituting equations (2.13), (2.14) into equation (2.9), we get

$$d = \frac{(\sigma + u_2)(\mu(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1) - \emptyset\,\alpha\rho)}{(\mu + \delta)(\alpha\beta\rho - \alpha(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1))} + \frac{\left(u_1((\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1))\right)}{(\mu + \delta)\alpha\rho} \qquad (2.16)$$

Hence the epidemic equilibrium state is given by:
$$M^* = (a^*, b^*, c^*, d^*)$$
Where

$$a^* = (\mu + \rho + \delta) \frac{(\mu + \beta + \sigma + \delta + u_1)}{\alpha\rho} \tag{2.17}$$

$$b^* = \frac{(\mu + \beta + \sigma + \delta + u_2)[\mu(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1) - \emptyset\alpha\rho]}{\rho(\alpha\beta\rho - \alpha(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1))} \tag{2.18}$$

$$c^* = \frac{\mu(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1) - \emptyset\alpha\rho}{\beta\alpha\rho - \alpha(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1)} \tag{2.19}$$

$$d^* = \frac{(\sigma + u_2)(\mu(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1) - \emptyset\,\alpha\rho)}{(\mu + \delta)(\alpha\beta\rho - \alpha(\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1))} + \frac{(u_1((\mu + \rho + \delta)(\mu + \beta + \sigma + \delta + u_1)))}{(\mu + \delta)\alpha\rho} \tag{2.20}$$

$$R_0 = \frac{\rho\alpha\phi}{(\mu + u_1)(\mu + \delta + \rho)(\mu + \beta + \sigma + \delta + u_2)} \tag{2.21}$$

The basic reproduction number R_0 is indeed a threshold quantity that helps to determine whether an outbreak of infectious disease dies out or spreads in a community. When $R_0 < 1$, the disease dies out without any medical interventions but when $R_0 > 1$, the disease becomes endemic and this necessitates the introduction of some control measures in order to curtail the situation.

3.Dynamical behavior of the system
We have already established that the system (2.6), (2.7), (2.8) and (2.9) has disease free equilibrium and epidemic equilibrium.
3.1. Local Stability of the Equilibrium:
Theorem 1: The disease free equilibrium is locally asymptotically stable if $R_0 < 1$
Proof: The Jacobean matrix J of the system Equation (2.6) to (2.9) is given as

$$J = \begin{pmatrix} -(\alpha c + \mu + u_1) & 0 & (\beta - \alpha a) & 0 \\ \alpha c & -(\mu + \rho + \delta) & \alpha a & 0 \\ 0 & \rho & -(\mu + \beta + \sigma + \delta + u_2) & 0 \\ u_1 & 0 & (\sigma + u_2) & -(\mu + \delta) \end{pmatrix} \tag{3.1}$$

Evaluating matrix J at the disease free equilibrium gives

$$J_0 = \begin{pmatrix} -(\mu + u_1) & 0 & (\beta - \alpha \frac{\emptyset}{\mu + u_1}) & 0 \\ 0 & -(\mu + \rho + \delta) & \alpha \frac{\emptyset}{\mu + u_1} & 0 \\ 0 & \rho & -(\mu + \beta + \sigma + \delta + u_2) & 0 \\ u_1 & 0 & \sigma + u_2 & -(\mu + \delta) \end{pmatrix} \tag{3.2}$$

The matrix J_0 has eigenvalues
$$|J_0 - I\lambda| = 0$$

$$\begin{vmatrix} -(\mu + u_1 + \lambda) & 0 & (\beta - \alpha\frac{\phi}{\mu + u_1}) & 0 \\ 0 & -(\mu + \rho + \delta + \lambda) & \alpha\frac{\phi}{\mu + u_1} & 0 \\ 0 & \rho & -(\mu + \beta + \sigma + \delta + u_2 + \lambda) & 0 \\ u_1 & 0 & \sigma + u_2 & -(\mu + \delta + \lambda) \end{vmatrix} = 0 \tag{3.3}$$

$$(\mu + u_1 + \lambda)(\mu + \delta + \lambda)\left((\mu + \rho + \delta + \lambda)(\mu + \beta + \sigma + \delta + u_2 + \lambda) - \rho\alpha\frac{\phi}{\mu + u_1}\right) = 0 \tag{3.4}$$

Then we have,

$$(\mu + u_1 + \lambda) = 0$$
$$(\mu + \delta + \lambda) = 0$$
$$(\mu + \rho + \delta + \lambda)(\mu + \beta + \sigma + \delta + u_2 + \lambda) - \rho\alpha\frac{\phi}{\mu + u_1} = 0$$

which implies that

$$\lambda_1 = -(\mu + u_1) \qquad\qquad (3.5)$$
$$\lambda_2 = -(\mu + \delta) \qquad\qquad (3.6)$$
$$\lambda_{3,4} = \frac{-g \pm \sqrt{g^2 - 4h}}{2e} \qquad\qquad (3.7)$$

Where

$$g = (2\mu + 2\delta + \rho + \sigma + \beta + u_2)$$
$$h = 2\delta\mu + \delta^2 + \mu^2 + \rho\delta + \mu\sigma + \rho\sigma + \delta\sigma + \delta\beta + \rho\beta + \beta\mu + \sigma u_2 + \rho u_2 + \delta u_2 + \mu u_2 - \rho\alpha\frac{\phi}{\mu + u_1}$$

Then the matrix J_0 has the following eigenvalues ;

$$\lambda_1 = -\mu < 0 \,, \lambda_2 = -(\mu + \delta) < 0$$

$$\lambda_{3,4} = \frac{-g \pm \sqrt{g^2 - 4h}}{2e}$$

Thus for local asymptotic stability to hold, we require $\lambda_{3,4} < 0$ (i.e. $g^2 - h < 0$) which is equivalent to

$$\frac{\rho\alpha\phi}{(\mu + u_1)(\mu + \delta + \rho)(\mu + \beta + \sigma + \delta + u_2)} = R_0 < 1$$

Thus, the disease free equilibrium M is locally asymptotically stable if $R_0 < 1$.

Remark 1: The case $R_0 = 1$ is a critical threshold point where the disease free equilibrium M_0 loses its asymptotic stability and simply becomes (neutrally) stable. Moreover, it becomes unstable immediately $R_0 > 1$ and this will lead to the existence of a stable endemic equilibrium M^*. Note that $R_0 = 1$ can literarily be viewed as a transcritical bifurcation point where stability is exchanged between M and M^*

4. Conclusion

In this paper, we studied the mathematical dynamic control of HBV treatment strategies for driving infectious diseases with cure and vaccine towards eradication. We considered an SEIR model with varying size population using vaccination and treatment as control measures. We established the condition for the local stability of the model equilibrium. The existence and stability of the disease-free is analyzed and found that the characteristic roots are all negative, i.e the disease free equilibrium is locally asymptotically stable if $R_0 < 1$

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