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MATHEMATICAL ANALYSIS OF A BASIC VIRUS INFECTION MODEL WITH APPLICATION TO HBV INFECTION

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ABSTRACT. The basic virus infection model (BVIM) is widely used in the studies of hepatitis B virus (HBV) infection dynamics. This model assumes that the infection process follows a mass action law. The basic infection reproductive number of the model is proportional to the number of all cells of the host's organa prior to the infection. This suggests that the BVIM may not be a reasonable model for describing the HBV virus infection since it implies that an individual with a smaller liver may be more resistent to virus infections than an individual with a larger one. In this paper, we formulate a standard incidence based model that amends the BVIM (we shall call it ABVIM below) which will correct this mass action induced model artifact. If its basic infection reproductive number is less than 1, then every positive solution will converge to the infection-free steady state. We also present an application of ABVIM to some clinic HBV infection data.

1. Introduction. Hepatitis B is one of the major diseases in the world. The WHO has reported that over one-third of the world's population (more than 2 billion people) has been or is actively infected by HBV, more than 350 million have chronic (lifelong) infections [**12**], 25-40 percent of these chronic infection carriers will die from liver cirrhosis or primary hepatocellular carcinoma [**10**]. The HBV carrier rate varies from 0.1 percent to 20 percent in different areas of the world [**4**]. Chronic HBV infection is often the result of exposure early in life, leading to viral persistence in the absence of strong antibody or cellular immune responses [**9**].

The study of anti-HBV infection treatment may benefit from the use of mathematical modeling. Several models have been introduced for

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understanding HBV dynamics [**1, 3, 6, 7, 8, 10, 13, 14**]. Among those models, the basic virus infection model (BVIM) introduced by Zeuzem et al. [**14**] and Nowak et al. [**10**] is widely used in the studies of virus infection dynamics. The BVIM with three variables takes the form of

$$\begin{cases} \dot{x} = \lambda - dx - \beta vx \\ \dot{y} = \beta vx - ay \\ \dot{v} = ky - \mu v \end{cases} \tag{1}$$

where x, y and v are numbers of uninfected (susceptible) cells, infected cells and free virus, respectively. Uninfected cells are assumed to be produced at the constant rate λ. Uninfected cells are assumed to die at the rate of dx and become infected at the rate of βvx, where β is a (questionable) rate constant describing the infection process. Infected cells are thus produced at the rate of βvx and are assumed to die at the rate ay. Free virions are assumed to be produced from infected cells at the rate of ky and are removed at the rate of μv. This model can describe some aspects of the viral dynamics in HBV infection.

Clearly, BVIM has a basic infection reproductive number of

$$R_0^* = \frac{\lambda \beta k}{ad\mu}. \tag{2}$$

If $R_0^* > 1$, then the BVIM has two steady states, the infection free steady state E_f and the endemic steady state E^*:

$$E_f = \left(\frac{\lambda}{d}, 0, 0\right), \tag{3}$$

$$E^* = \left(\frac{au}{\beta k}, \frac{\lambda}{a}\left(1 - \frac{1}{R_0^*}\right), \frac{d}{\beta}(R_0^* - 1)\right). \tag{4}$$

It is known that if a basic reproduction number R_0^* is less than 1, then E_f is locally asymptotically stable and E^* does not exist. The global attractive properties of these steady states are studied by Leenheer and Smith [**5**] recently.

Observe that the basic infection reproductive number R_0^* is proportional to λ/d which represents the number of total cells of the liver. This suggests that the BVIM may not be a reasonable model for describing HBV virus infection since it implies that an individual with

a smaller liver may be more resistent to the virus infection than an individual with a larger one. Therefore, the practical meaning of R_0^* is biologically questionable at the best.

A typical chronically infected HBV patient has a total serum daily production rate of about 2×10^{11} to 3×10^{12} virions [**3**]. An average human liver consists of billions of liver cells. These large numbers suggest that a more plausible HBV model should employ a standard incidence function, instead of the mass action incidence used in BVIM. Therefore, we propose the following amended basic HBV virus model (to be referred to as ABVIM)

$$\dot{x} = \lambda - dx - \frac{\beta v x}{x+y} \tag{5a}$$

$$\dot{y} = \frac{\beta v x}{x+y} - ay \tag{5b}$$

$$\dot{v} = ky - \mu v \tag{5c}$$

where the meanings of the variables x, y, v and the parameters λ, d, a, k and μ are the same as those of the BVIM. However, here β has a clear biological meaning which is the maximum infection rate of a virus. An extension of this model with a time delay in infection is presented and studied in Gourley et al. [**1**].

For (5), if $y(0) = v(0) = 0$, then we see that $y(t) = v(t) = 0$ for $t > 0$. It is easy to show that the solution with initial condition $x(0) > 0$, $y(0) > 0$ and $v(0) \geq 0$ or $x(0) > 0$, $v(0) > 0$ and $y(0) \geq 0$ will have all its component positive for $t > 0$. *Hence, we will assume below that* $x(0) > 0$, $y(0) = 0$ *and* $v(0) > 0$. Notice that the ABVIM has a basic infection reproductive number of

$$R_0 = \frac{\beta k}{a\mu} \tag{6}$$

that is independent of the questionable factor λ/d.

If $R_0 > 1$, then the ABVIM also has two steady states

$$E^* = \left(\frac{\lambda}{d + a(R_0 - 1)}, \frac{\lambda(R_0 - 1)}{d + a(R_0 - 1)}, \frac{\lambda k (R_0 - 1)}{\mu[d + a(R_0 - 1)]} \right), \tag{7}$$

representing the disease free steady-state and the endemic steady state, respectively. Observe that a biologically meaningful E^* (meaning its

component must be nonnegative) does not exist if $R_0 < 1$, and it becomes E_f when $R_0 = 1$.

Let $z = x + y$; then we have

$$\dot{z} \leq \lambda - \min\{a, d\}z.$$

A simple comparison argument shows that

$$\limsup_{t\to\infty} (x(t) + y(t)) \leq \lambda / \min\{a, d\}.$$

Which shows that the x and y components of the solution are eventually uniformly bounded by $\lambda/\min\{a, d\}$. Indeed, we can show the x component of the solution is eventually uniformly bounded by λ/d. The v equation implies that the v component of the solution is eventually uniformly bounded by $k\lambda/\mu \min\{a, d\}$.

It is clear that if $0 < x(0) < \lambda/d$, $v(0) > 0$ and $y(0) \geq 0$, then $0 < x(t) < \lambda/d$ for $t > 0$.

2. Dynamics of ABVIM. We consider first the local stability of the steady state E_f. The Jacobian matrix of the vector field corresponding to ABVIM (5) is

$$J = \begin{pmatrix} -d - \dfrac{\beta v y}{(x+y)^2} & \dfrac{\beta v x}{(x+y)^2} & -\dfrac{\beta x}{x+y} \\ \dfrac{\beta v y}{(x+y)^2} & -\dfrac{\beta v x}{(x+y)^2} - a & \dfrac{\beta x}{x+y} \\ 0 & k & -\mu \end{pmatrix}. \tag{8}$$

The Jacobian matrix, evaluated at E_f, is

$$J_{Q_1} = \begin{pmatrix} -d & 0 & -\beta \\ 0 & -a & \beta \\ 0 & k & -\mu \end{pmatrix}. \tag{9}$$

The three eigenvalues of the matrix J_{Q_1} are

$$\lambda_1 = -d \tag{10}$$

$$\lambda_2 = \frac{-(a+\mu) + \sqrt{(a+\mu)^2 - 4(a\mu - \beta k)}}{2} \tag{11}$$

$$\lambda_3 = \frac{-(a+\mu) - \sqrt{(a+\mu)^2 - 4(a\mu - \beta k)}}{2}. \tag{12}$$

It follows that if $R_0 = (\beta k/a\mu) < 1$, then E_f is locally asymptotically stable. If $R_0 > 1$, then E_f is unstable.

We now consider the local stability of steady state E^*. We assume in the rest of this section that $R_0 > 1$. The Jacobian matrix at E^* is

$$J_{E^*} = \begin{pmatrix} -d - \dfrac{a^2\mu(R_0-1)^2}{\beta k} & \dfrac{a^2\mu(R_0-1)}{\beta k} & -\dfrac{a\mu}{k} \\ \dfrac{a^2\mu(R_0-1)^2}{\beta k} & -\dfrac{a^2\mu(R_0-1)}{\beta k} - a & \dfrac{a\mu}{k} \\ 0 & k & -\mu \end{pmatrix} \tag{13}$$

$$\triangleq \begin{pmatrix} -d - C_1 & C_2 & -C_3 \\ C_1 & -C_2 - a & C_3 \\ 0 & k & -\mu \end{pmatrix}.$$

Notice that $kC_3 = a\mu$. The characteristic equation associated with J_{E^*} is given by

$$l^3 + (\mu + d + a + C_1 + C_2)l^2 + (\mu C_2 + dC_2 + C_1\mu + ad + d\mu + C_1 a)l + dC_2\mu + C_1 a\mu = 0. \tag{14}$$

For convenience, we denote the above equation by

$$l^3 + a_2 l^2 + a_1 l + a_0 = 0. \tag{15}$$

Observe that

$$a_0 = \frac{a^2\mu^2(R_0-1)[d + a(R_0-1)]}{\beta k} > 0.$$

Clearly, a_1, a_2 are both lager than zero and

$$a_1 a_2 > d\mu C_2 + a\mu C_1 + ad\mu > a_0.$$

By the Routh-Hurwitz criterion, we see that E^* is locally asymptotically stable whenever $R_0 > 1$.

Therefore, we have proven the following theorem for model (5).

Theorem 2.1. *If $R_0 < 1$, then E_f is locally asymptotically stable and E^* does not exist. If $R_0 > 1$, then E_f is unstable and E^* is locally asymptotically stable.*

The global stability of E_f is implied by the more general result of Gourley et al. [**1**]. Their proof employed the more advanced monotone dynamical system theory. For convenience, we provide a similar but much more straightforward proof. In addition, we explicitly describe an initial condition determined positive invariant region that confines the solution.

Theorem 2.2. *If the basic reproduced number* $R_0 = (\beta k/a\mu) < 1$, *then solutions initiated in the domain*

(16)
$$\mathcal{D} = \left\{(x, y, v) \mid x \in \left[0, \frac{\lambda}{d}\right],\ y \geq 0,\ v \geq 0,\ y + \frac{av}{k} \leq y(0) + \frac{av(0)}{k}\right\}$$

stay in it and tend to E_f.

Proof. Assume that $R_0 = (\beta k/a\mu) < 1$. It is easy to see that the solutions initiated in the domain $\mathcal{D}$ satisfy $x(t) \in [0, (\lambda/d)]$. Let $z = y + (av/k)$. Then

$$\dot{z} \leq \beta v - \frac{a\mu v}{k} = \beta\left(1 - \frac{1}{R_0}\right)v \leq 0. \tag{17}$$

This shows that solutions initiated in $\mathcal{D}$ stay in it. If $v(0) = y(0) = 0$, then clearly $v(t) = y(t) = 0$ and $x(t)$ tend to λ/d. In the case of $y(0) = 0$ and $v(0) > 0$, we see that $v(t)$ tends to zero which in turn forces that $y(t)$ tends to zero. In all these cases, we see that, as a result, we must have $x(t)$ tends to λ/d. □

While we know that E^* is locally stable when it exists and numerically E^* appears to be globally stable, the mathematical proof of it remains open.

3. An application to HBV infection dynamics. In the study [**2**], one group of HBeAg-Positive chronic hepatitis B patients received 100 mg of lamivudine once daily. The study comprised 48 weeks of

TABLE 1. Rapid decline in plasma virus: mean HBV DNA levels (log copies/ml) in response to the therapy, and the virus level returning rapidly after the treatment was stopped.

Week	0	1	2	4	6	8	12	18
Patient Nos.	272	272	272	267	267	267	267	267
Virus load	9.8	7.8	6.6	5.6	5.1	4.8	4.4	4.3
Simulation EQ.5	9.8	7.77	6.18	5.91	5.83	5.76	5.61	5.37
Simulation EQ.1	9.8	7.77	6.18	5.92	5.85	5.77	5.62	5.40
Week	24	30	36	42	48	52	60	72
Patients Nos.	263	263	259	260	249	248	228	241
Virus load	4.2	4.0	4.15	4.2	4.5	7.0	8.0	8.20
Simulation EQ.5	5.14	4.90	4.67	4.44	4.20	7.98	8.08	8.22
Simulation EQ.1	5.17	4.95	4.72	4.50	4.27	8.03	8.11	8.22

treatment and a 24 week treatment free follow-up. While the onset of therapy and viral levels decline rapidly, the virus returns as soon as the drug is withdrawn (see Table 1). In the following subsections, we shall simulate such phenomena with both ABVIM and BVIM models.

3.1. ABVIM-based dynamic simulation. We shall use this set of clinical data to formulate an anti-HBV infection therapy model. Assume that, during the lamivudine drug treatment, the dynamic model of the patients with the mean load HBV DNA is described by the following amended ABVIM

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - (1-m)\frac{\beta v x}{x+y}, \\ \frac{dy}{dt} &= (1-m)\frac{\beta v x}{x+y} - ay, \\ \frac{dv}{dt} &= (1-n)ky - \mu v. \end{aligned} \tag{18}$$

Before the drug therapy, assume $m = n = 0$ and that the patients are in the stable state E^*. Therefore,

$$k = \frac{\mu v(0)[d + a(R_0 - 1)]}{\lambda(R_0 - 1)}, \qquad \beta = \frac{a\mu R_0}{k}. \tag{19}$$

The following are the detailed steps involved in the estimation of model parameters.

1) A human liver contains approximately 2×10^{11} hepatocytes [**10**]. A patient has a total of about 3000 ml plasma. Usually, tested virus qualities are in copies/ml. Consequently, we can assume that

$$\lambda/d \approx 2 \times 10^{11}/3000. \tag{20}$$

2) Since the half-life of a hepatocyte is about half a year [**11**], we can assume that

$$d = -\ln(0.5)/183 \approx 0.00379. \tag{21}$$

3) We select that $\mu = 0.67$ [**10**], which is equivalent to assuming that the half life of a virus is about one day.

4) Assume that, before the lamivudine treatment, the patients are in the stable virus persist infection state, that is,

$$(\bar{x}, \bar{y}, \bar{v}) = E^* = \left(\frac{\lambda}{d + a(R_0 - 1)}, \frac{\lambda(R_0 - 1)}{d + a(R_0 - 1)}, \frac{\lambda k(R_0 - 1)}{\mu[d + a(R_0 - 1)]} \right).$$

It follows that

$$\frac{\bar{y}}{\bar{x} + \bar{y}} = \frac{R_0 - 1}{R_0}.$$

In a chronic HBV infection between 5 percent $\sim$ 40 percent of all hepatocytes can be infected [**10**]. Consequently, we can choose $R_0 = 1.33$.

5) Based on the clinical data and numerical simulation, we can select the parameters as follows.

$$\{d, a, \mu, R_0, m, n\} = \{3.7877 \times 10^{-3}, 3.38d, 0.67, 1.33, 0, 0.99982\}. \tag{22}$$

Here we take the restraining rate $m = 0$ because even though we choose $m = 1$, there are no obvious affections on our numerical simulation results for both the therapy period and the treatment-free follow-up. The basic reproduction number $R_0 = 1.33$ is the one before the therapy, i.e., $m = n = 0$. R_0 will be reduced to 2.394×10^{-4} during the

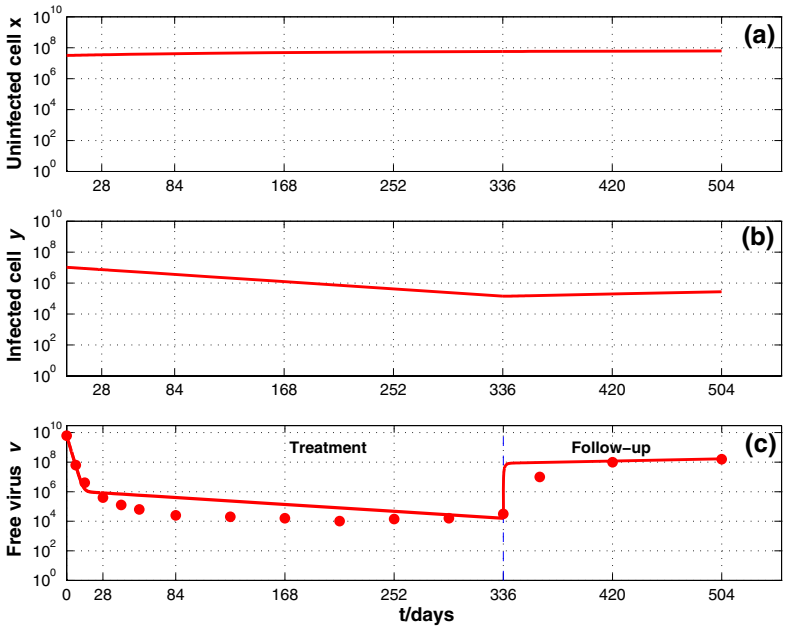

FIGURE 1. The dynamic simulation (solid lines) of the treatment model (18). (a) uninfected cells x; (b) infected cells y; (c) virus declines in response to drug treatment and virus resurges as soon as the drug is withdrawn in which the clinical data are marked by dots.

treatment. After the lamivudine treatment, the patients are assumed to return to the state before the therapy, that is, $m = n = 0$.

Taking the endemic steady state (7) as the initial condition, the numerical simulation is shown in Figure 1. The simulated data are given in the fourth and eighth rows in Table 1. As can be seen from Figure 1 (c), after the onset of therapy viral levels decline rapidly, but as soon as the drug is withdrawn, virus level returns rapidly. Figure 1 (c) indicates that the model simulation agrees well with the clinical data reported [**3**].

3.2. BVIM-based dynamic simulation. Now let us substitute the term $(\beta vx)/(x + y)$ of equation (18) by βvx. Then we obtain an anti-HBV infection therapy model based on the basic virus dynamic equation (1). In this case the parameters k and β formulated by (19)

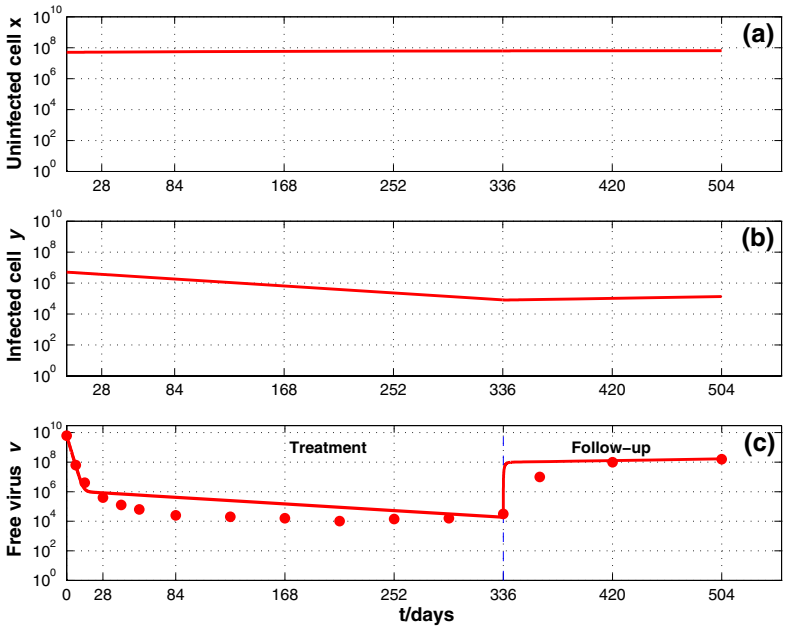

FIGURE 2. The dynamic simulation (solid lines) of the treatment model based on (1). (a) uninfected cells x; (b) infected cells y; (c) virus declines in response to drug treatment and virus resurges as soon as the drug is withdrawn in which the clinical data are marked by dots.

have the form

$$k = \frac{\mu v(0) a R_0^*}{\lambda(R_0^* - 1)}, \ \beta = \frac{\lambda a \mu R_0^*}{dk}. \tag{23}$$

The other parameters are the same as those given in (22) except taking $a = 3.259d$ to replace $a = 3.38d$. Otherwise, simulation data will deviate more from the clinical ones.

Taking the endemic steady state (4) as the initial condition, the numerical simulation is shown in Figure 2. The simulated data are given in the fifth and tenth rows in Table 1.

3.3. Discussion. From Table 1 and Figures 1 and 2, it can been seen that the simulation results of the BVIM (1) and the ABVIM (18)

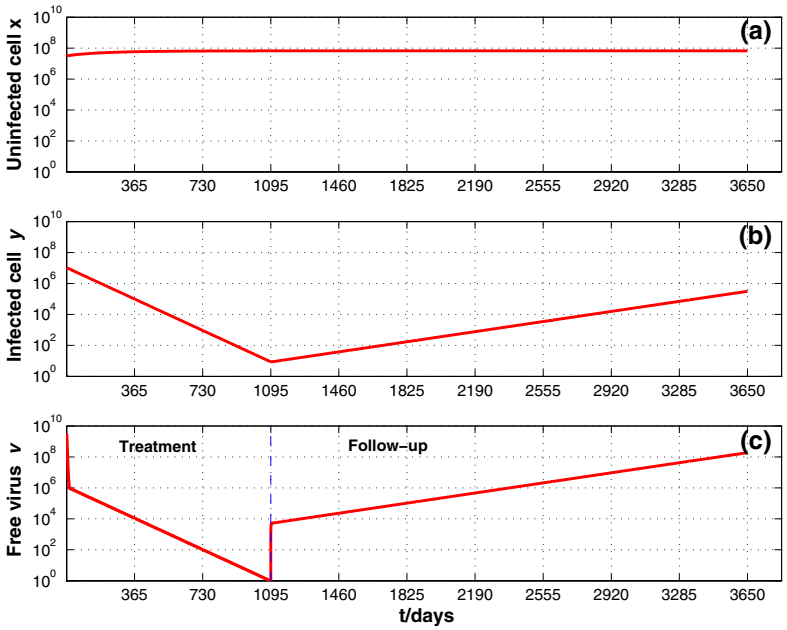

FIGURE 3. The simulation (solid lines) of the solution of the treatment model (18) for a prolonged treatment lasting 3.44 years. (a) uninfected cells x; (b) infected cells y; (c) viruses decline in response to drug treatment and viruses rebound as soon as the drug is withdrawn.

are similar. However, the ABVIM can interpret the clinical data better in biological terms since it does not imply the absurd statement that an individual with a smaller liver may be more resistant to virus infections than an individual with a larger one.

If we prolong the drug treatment to three years and then follow up in seven years, the corresponding simulation results of equation (18) are shown in Figure 3. It can be seen that, even though the HBV DNA load of the patient is reduced to about 1 cppies/ml at the end point of the three years' treatment, the HBV DNA load can still relapse to about 5×10^3 log copies/mL soon after stopping treatment for 10 days, and then gradually increases to 1.8×10^8 copies/ml after the treatment is withdrawn in about seven years (see Figure 3).

Only after delaying the therapy to about 4.8 years, all infected cells can be replaced by uninfected ones (HBV DNA load less than 1/3000

copies/ml), so that the treatment benefit can be kept. A similar case appears in the simulation of the BVIM (1). However, treatment only needs to be prolonged to 3.56 years to delete all HBV in vivo. Clinical trials demonstrate that it is too short to cure HBV infection with the drug lamivudine for most patients.

4. Concluding remarks. The widely used BVIM has been examined. It has been found that its basic infection reproductive number R_0^* is questionable. The ABVIM has been introduced whose basic infection reproductive number denoted by R_0 seems to be reasonable. The possible relationships of the BVIM and the ABVIM parameters are discussed, and other free model parameters are determined based upon the clinical data [**2**]. The simulation results of the ABVIM appear more close to the clinical trial. The predictions of the treatment endpoint with the drug lamivudine are given, which are longer than 3.5 years for patients with mean plasma HBV DNA levels.

To the best of our knowledge, no other researchers have set up mathematical models for interpreting clinical trial data both for drug treatments and treatment free follow-up. The quantitative understanding of the HBV dynamic will make it possible to devise optimal treatment strategies for individual patients. More detailed assay data are needed for modeling. Further research for HBV dynamics is promising [**11**].

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