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A Stochastic Model for Hepatitis B Patients Using Two Sources of Transmission

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Abstract

The Hepatitis B (HBV) infection has led to a global pandemic. Addressing this issue requires the collaborative efforts of medical professionals, social workers, mathematicians, and statisticians to analyse various facets of the infection and its transmission. A particularly intriguing aspect of this research is estimating when an infected individual becomes seropositive. This brings us to the concept of the antigenic diversity threshold. This threshold refers to a specific level of antigenic diversity in the invading pathogen, beyond which the human immune system fails, resulting in seropositivity. In this paper, we derive the expected time to seroconversion by considering the antigenic diversity threshold comprising two elements: the natural threshold level of the human immune system and the threshold associated with antiretroviral therapy (ART). Additionally, numerical examples are provided.Keywords: Skin Lesion, Deep Learning, Ceroscopy, Classification, Neural Network, Melanoma.

Keywords: Hepatitis B virus (HBV), Antigenic Diversity Threshold, Anti-Retroviral Therapy (ART), Seroconversion, Expected Time to Seroconversion.

Introduction

Hepatitis B virus (HBV) significantly contributes to chronic liver diseases, hepatocellular carcinoma, and liver failure. Despite the availability of vaccines and antiviral therapies, HBV continues to spread in inadequate and/or unsanitary healthcare environments. Its transmission routes are like those of HIV, including unprotected sexual contact (both homosexual and heterosexual), blood exposure, use of unsterilized needles, and perinatal transmission. In the U.S., about 5 to 15% of individuals diagnosed with HIV also report HBV infection (1-3). The progression to chronic cirrhosis happens more easily for individuals coinfected with both HIV and HBV than for those with HBV alone (4). Conversely, chronic HBV does not significantly alter the progression of HIV infection, nor does it affect HIV suppression or CD4 T lymphocyte responses when initiating antiretroviral therapy (ART) (5,6). Post-initiation, numerous liver-related complications may arise due to immune modification (7,8). There is also a risk of HBV reactivation after discontinuing antiretroviral (ARV) treatments for both HIV and HBV (9-14). Consequently, a mathematical understanding of HBV is crucial for creating effective control strategies.

The human body possesses intrinsic immune capabilities, enabling it to endure a certain degree of antigenic diversity presented by the invading Hepatitis B virus (HBV). This specific degree of antigenic diversity is called the antigenic diversity threshold. When the antigenic diversity of an invading antigen exceeds this threshold, the human immune system fails. This antigenic diversity threshold is a variable that differs for everyone. In each interaction, a stochastic augmentation of the antigenic diversity exists. The anticipated duration required to navigate through the antigenic diversity, resulting from successive interactions within the time frame [0,t], is assessed utilizing the shock model and cumulative damage process methodology as articulated by Esary, Marshall, and Proschan (1973) (15). Sathiyamoorthi and Kannan (1998), Nirmala Ratchager (2003), and others have utilized this approach to estimate the anticipated time for seroconversion (16, 17).

This paper presents a mathematical model that assumes Anti-Retroviral Therapy (ART) is administered to individuals identified as HBV positive. Given that Antiretroviral Therapy (ART) extends the duration of seroconversion and the manifestation of Hepatitis B Virus (HBV) symptoms, it is suggested that there is an elevation in the antigenic diversity threshold. Consequently, the threshold of antigenic diversity, beyond which the human immune system cannot withstand, can be characterized as the sum of two random variables. Based on this premise, the anticipated time to seroconversion is deduced. This new family of distribution functions is always positively skewed, and the skewness decreases as both the shape parameters increase to infinity. Interestingly, the new three-parameter generalized exponential distribution has increasing; decreasing, Uni-modal and bathtub shaped Hazard Functions. One can see for more detail in Sathiyamoorthy (1980), Pandiyan *et.al.,* (2010), Subramanian *et.al.,* (2011), Pandiyan *et.al.,* (2012) about the expected time to cross the threshold level of the seroconversion.

2. ASSUMPTIONS OF THE MODEL

- Hepatitis B infections are caused by sharing needles and sexual risk.
- The threshold of any individual is a random variable.
- Seroconversion happens and a person is identified as infected if the total harm surpasses a threshold level Y, which is a random variable in and of itself.
- The inter-arrival times between successive contacts, the sequence of damage and the threshold are mutually independent.

3. NOTATIONS

X_i : A continuous random variable denoting the amount of contribution to the antigenic diversity due to the Hepatitis B virus transmitted in the ith contact, in other words the damage caused to the immune system in the ith contact, with p.d.f $g(.)$ and c.d.f $F(.)$.

Y_1, Y_2 : A continuous random variable denoting the threshold for two components which follows three parameter generalized exponential distribution

$g(.)$: The probability density functions of X_i

$g^*(.)$: Laplace transform of g (.)

$g_k(.)$: The k- fold convolution of g (.) i.e., p.d.f. of $\sum_{j=1}^{k} X_i$

$g_k^*(.)$: Laplace transform of $g_k(.)$.

U_i : A random variable denoting the inter-arrival times between contact with c.d.f. $F_i(.)$, $i = 1,2\ 3 \ldots k$.

$f(.)$: p.d.f. of random variable denoting between successive contacts with the corresponding c.d.f. $F(.)$

$F_k(.)$: The k-fold convolution functions of F (.)

$S(.)$: The survivor function, i.e. $P\ [T > t]$

$L(t)$: 1 - S (t)

$V_k(t)$: Probability that there are exactly k contacts.

4. MODEL DESCRIPTION

$$\bar{H}(x) = \left\{e^{-(\lambda_2 x - \lambda_2\theta_2)} + e^{-\lambda_1(x-\theta_1)} - e^{-\lambda_1(x-\theta_1)-\lambda_2(x-\theta_2)}\right\} \quad \ldots (1)$$

It can also be proved that

$$P(X_i < Y) = \int_0^\infty g_k(x)\bar{H}(x)dx$$

$$= \left\{\left[g^*[\lambda_2(1-\theta_2)]\right]^k + \left[g^*[\lambda_1(1-\theta_1)]\right]^k - \left[g^*[\lambda_1(1-\theta_1)] + [\lambda_2(1-\theta_2)]\right]^k\right\} \quad \ldots (2)$$

$P(T > t) =$ Probability that exactly k contact in (0,t] and the combined threshold level is not crossed

$$P(T > t) = \sum_{k=0}^{\infty} V_k(t)P(X_i < Y) \quad \ldots (3)$$

Therefore on simplification it can be shown that

$$L(t) = 1 - S(t)$$

Using convolution theorem for Laplace transforms, $F_0(t) = 1$ and on simplification, it can shown that, $L(T) = 1 - S(t)$

Taking Laplace transformation $L(T)$, we get

$$L(t) = 1 - \left\{ \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \left[g^*[\lambda_2(1-\theta_2)] \right]^k \right.$$
$$+ \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \left[g^*[\lambda_1(1-\theta_1)] \right]^k$$
$$\left. - \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \left[g^*\left[\lambda_1(1-\theta_1)[\lambda_2(1-\theta_2)]\right] \right]^k \right\}$$

$$L(t) = 1 - \{T_1 + T_2 - T_3\}$$

Then

$$T_1 = 1 - [1 - g^*\lambda_2(1-\theta_2)] \sum_{k=1}^{\infty} F_k(t) \left[g^*[\lambda_2(1-\theta_2)] \right]^{k-1} \quad \ldots (4)$$

Similarly

$$T_2 = 1 - [1 - g^*\lambda_1(1-\theta_1)] \sum_{k=1}^{\infty} F_k(t) \left[g^*[\lambda_1(1-\theta_1)] \right]^{k-1} \quad \ldots (5)$$

$$T_3 = 1 - [1 - g^*\lambda_1(1-\theta_1) + \lambda_2(1-\theta_2)] \sum_{K=1}^{\infty} F_k(t) [g^*\lambda_1(1-\theta_1) + \lambda_2(1-\theta_2)]^{k-1} \quad \ldots (6)$$

$$L(t) = 1 - \left\{ \left[1 - g^*[\lambda_2(1-\theta_2)]\right] \sum_{K=1}^{\infty} F_k(t) \left[g^*[\lambda_2(1-\theta_2)] \right]^{k-1} + 1 \right.$$
$$- \left[1 - g^*[\lambda_1(1-\theta_1)]\right] \sum_{K=1}^{\infty} \left[g^*[\lambda_1(1-\theta_1)] \right]^{k-1} - 1$$
$$+ [1 - g^*\lambda_1(1-\theta_1)$$
$$\left. + \lambda_2(1-\theta_2)] \sum_{K=1}^{\infty} F_k(t) [g^*\lambda_1(1-\theta_1) + \lambda_2(1-\theta_2)]^{k-1} \right\}$$

By taking Laplace-Stieltjes transform, it can be shown that

$$l^*(s) = \frac{[1 - g^*\lambda_2(1-\theta_2)]\ f^*(s)}{[1 - g^*\lambda_2(1-\theta_2)\ f^*(s)]} + \frac{[1 - g^*\lambda_1(1-\theta_1)]\ f^*(s)}{[1 - g^*\lambda_1(1-\theta_1)\ f^*(s)]}$$
$$- \frac{[1 - g^*\lambda_1(1-\theta_1) + \lambda_2(1-\theta_2)]\ f^*(s)}{[1 - g^*\lambda_1(1-\theta_1) + \lambda_2(1-\theta_2)\ f^*(s)]} \quad \ldots (7)$$

Let the random variable U denoting inter arrival time which follows exponential with parameter c. Now $f^*(s) = \left(\frac{c}{c+s}\right)$, substituting in the (7.7) equation we get

$$l^*(s) = \frac{[1-g^*\lambda_2(1-\theta_2)]\left(\frac{c}{c+s}\right)}{\left[1-g^*\lambda_2(1-\theta_2)\left(\frac{c}{c+s}\right)\right]} + \frac{[1-g^*\lambda_1(1-\theta_1)]\left(\frac{c}{c+s}\right)}{\left[1-g^*\lambda_1(1-\theta_1)\left(\frac{c}{c+s}\right)\right]} - \frac{[1-g^*\lambda_1(1-\theta_1)+\lambda_2(1-\theta_2)]\left(\frac{c}{c+s}\right)}{\left[1-g^*\lambda_1(1-\theta_1)+\lambda_2(1-\theta_2)\left(\frac{c}{c+s}\right)\right]}$$

$$= \frac{[1-g^*\lambda_2(1-\theta_2)]c}{[c+s-g^*\lambda_2(1-\theta_2)c]} + \frac{[1-g^*\lambda_1(1-\theta_1)]c}{[c+s-g^*\lambda_1(1-\theta_1)c]} - \frac{[1-g^*\lambda_1(1-\theta_1)+\lambda_2(1-\theta_2)]c}{[c+s-g^*\lambda_1(1-\theta_1)+\lambda_2(1-\theta_2)\,c]} \quad \ldots (8)$$

$$E(T) = -\frac{d}{ds}l^*(s) \text{ given } s = 0$$

$$= \frac{c[1-g^*\lambda_2(1-\theta_2)]}{c^2[1-g^*\lambda_2(1-\theta_2)]^2} + \frac{c[1-g^*\lambda_1(1-\theta_1)]}{c^2[1-g^*\lambda_1(1-\theta_1)]^2} - \frac{c[1-g^*\lambda_1(1-\theta_1)+\lambda_2(1-\theta_2)]}{c^2[1-g^*\lambda_1(1-\theta_1)+\lambda_2(1-\theta_2)\,c]^2}$$

$$= \frac{1}{c[1-g^*(\lambda_2-\lambda_2\theta_2)]} + \frac{1}{c[1-g^*(\lambda_1-\lambda_1\theta_1)]} - \frac{1}{c\,[1-g^*(\lambda_2-\lambda_2\theta_2+\lambda_1-\lambda_1\theta_1)\,]} \quad \ldots (9)$$

$$E(T^2) = \frac{d^2}{ds^2}l^*(s) \text{ given } s = 0$$

We know that

$$= \frac{2}{c^2[1-g^*\lambda_2(1-\theta_2)]^2} + \frac{2}{c^2[1-g^*\lambda_1(1-\theta_1)]^2} - \frac{2}{c^2[1-g^*\lambda_1(1-\theta_1)+\lambda_2(1-\theta_2)]^2} \quad \ldots (10)$$

Now, $g^*(.) \sim \exp(\mu)$, $g^*(\lambda) \sim \exp\left(\frac{\mu}{\mu+\lambda}\right)$, $g^*(\lambda\theta) \sim \exp\left(\frac{\mu}{\mu+\lambda\theta}\right)$,

$$E(T) = \frac{1}{c\left[1-\left(\frac{\mu}{\mu+\lambda_2}-\frac{\mu}{\mu+\lambda_2\theta_2}\right)\right]} + \frac{1}{c\left[1-\left(\frac{\mu}{\mu+\lambda_1}-\frac{\mu}{\mu+\lambda_1\theta_1}\right)\right]} - \frac{1}{c\left[1-\left(\frac{\mu}{\mu+\lambda_2}-\frac{\mu}{\mu+\lambda_2\theta_2}+\frac{\mu}{\mu+\lambda_1}-\frac{\mu}{\mu+\lambda_1\theta_1}\right)\right]}$$

On simplification we get,

$$E(T) = \frac{\mu^2+\lambda_2\mu\,\theta_2+\lambda_2\mu+\lambda_2^2\theta_2}{c\,[\mu^2+2\,\lambda_2\mu+\lambda_2^2\theta_2]} + \frac{\mu^2+\lambda_1\mu\,\theta_1+\lambda_1\mu+\lambda_1^2\theta_1}{c\,[\mu^2+\,2\lambda_1\mu+\lambda_1^2\theta_1]}$$

$$-\frac{(\mu^2+\lambda_2\mu\,\theta_2+\lambda_2\mu+\lambda_2^2\theta_2)(\mu^2+\lambda_1\mu\theta_1+\lambda_1\mu+\lambda_1^2\theta_1)}{c[\mu^4+2\mu^3\lambda_1+\mu^2\lambda_1^2\theta_1+2\mu^3\lambda_2+\lambda_1\lambda_2\mu^2\theta_1+3\lambda_1\lambda_2\mu^2+\lambda_2^2\theta_2\mu^2+2\lambda_1\lambda_2^2\,\mu\,\theta_2+\lambda_1^2\lambda_2^2\theta_1\theta_2+\lambda_1\lambda_2\mu^2\theta_2]}$$

$V(T)=E(T^2)-[E(T)]^2$ On simplification

$$V(T)=\left(\frac{\mu^2+\lambda_2\mu\,\theta_2+\lambda_2\mu+\lambda_2^2\theta_2}{c\,[\mu^2+2\,\lambda_2\mu+\lambda_2^2\theta_2]}\right)^2+\left(\frac{\mu^2+\lambda_1\mu\,\theta_1+\lambda_1\mu+\lambda_1^2\theta_1}{c\,[\mu^2+\,2\lambda_1\mu+\lambda_1^2\theta_1]}\right)^2$$

$$-\left(\frac{(\mu^2+\lambda_2\mu\,\theta_2+\lambda_2\mu+\lambda_2^2\theta_2)(\mu^2+\lambda_1\mu\theta_1+\lambda_1\mu+\lambda_1^2\theta_1)}{c[\mu^4+2\mu^3\lambda_1+\mu^2\lambda_1^2\theta_1+2\mu^3\lambda_2+\lambda_1\lambda_2\mu^2\theta_1+3\lambda_1\lambda_2\mu^2+\lambda_2^2\theta_2\mu^2+2\lambda_1\lambda_2^2\,\mu\,\theta_2+\lambda_1^2\lambda_2^2\theta_1\theta_2+\lambda_1\lambda_2\mu^2\theta_2]}\right)^2$$

$$-2\left(\frac{\mu^2+\lambda_2\mu\,\theta_2+\lambda_2\mu+\lambda_2^2\theta_2}{c\,[\mu^2+2\,\lambda_2\mu+\lambda_2^2\theta_2]}\right)\left(\frac{\mu^2+\lambda_1\mu\,\theta_1+\lambda_1\mu+\lambda_1^2\theta_1}{c\,[\mu^2+\,2\lambda_1\mu+\lambda_1^2\theta_1]}\right)+2\left(\frac{\mu^2+\lambda_1\mu\,\theta_1+\lambda_1\mu+\lambda_1^2\theta_1}{c\,[\mu^2+\,2\lambda_1\mu+\lambda_1^2\theta_1]}\right)$$

$$\left(\frac{(\mu^2+\lambda_2\mu\,\theta_2+\lambda_2\mu+\lambda_2^2\theta_2)(\mu^2+\lambda_1\mu\theta_1+\lambda_1\mu+\lambda_1^2\theta_1)}{c[\mu^4+2\mu^3\lambda_1+\mu^2\lambda_1^2\theta_1+2\mu^3\lambda_2+\lambda_1\lambda_2\mu^2\theta_1+3\lambda_1\lambda_2\mu^2+\lambda_2^2\theta_2\mu^2+2\lambda_1\lambda_2^2\,\mu\,\theta_2+\lambda_1^2\lambda_2^2\theta_1\theta_2+\lambda_1\lambda_2\mu^2\theta_2]}\right)$$

$$+2\left(\frac{\mu^2+\lambda_1\mu\,\theta_1+\lambda_1\mu+\lambda_1^2\theta_1}{c\,[\mu^2+\,2\lambda_1\mu+\lambda_1^2\theta_1]}\right)$$

$$\left(\frac{(\mu^2+\lambda_2\mu\,\theta_2+\lambda_2\mu+\lambda_2^2\theta_2)(\mu^2+\lambda_1\mu\theta_1+\lambda_1\mu+\lambda_1^2\theta_1)}{c[\mu^4+2\mu^3\lambda_1+\mu^2\lambda_1^2\theta_1+2\mu^3\lambda_2+\lambda_1\lambda_2\mu^2\theta_1+3\lambda_1\lambda_2\mu^2+\lambda_2^2\theta_2\mu^2+2\lambda_1\lambda_2^2\,\mu\,\theta_2+\lambda_1^2\lambda_2^2\theta_1\theta_2+\lambda_1\lambda_2\mu^2\theta_2]}\right)$$

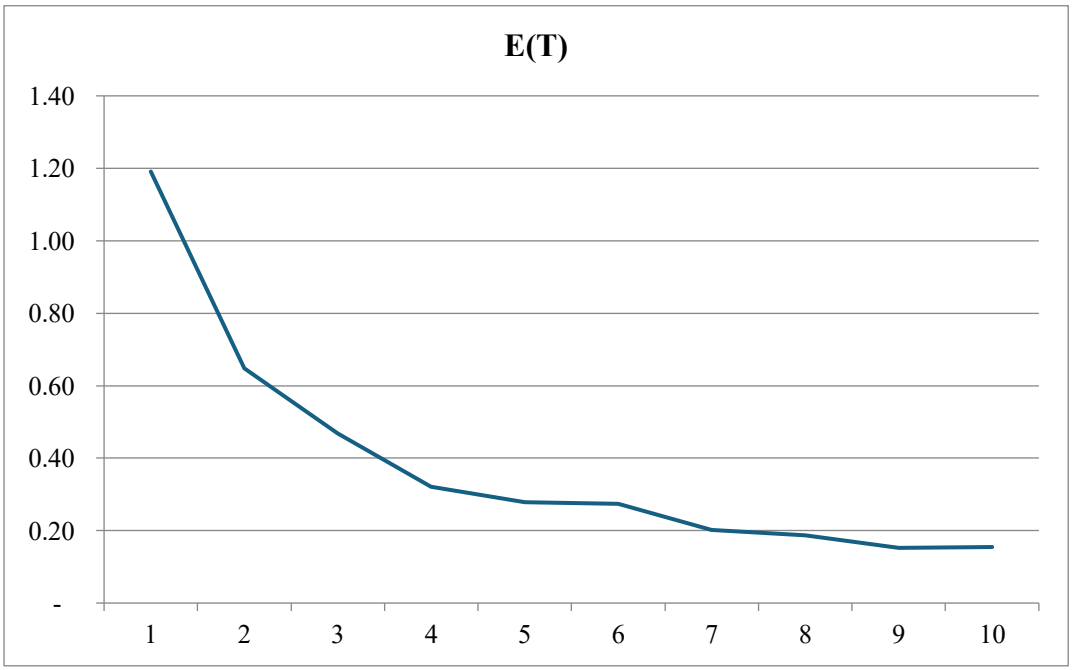

Figure – 1: The Chart for infected person's Expected time

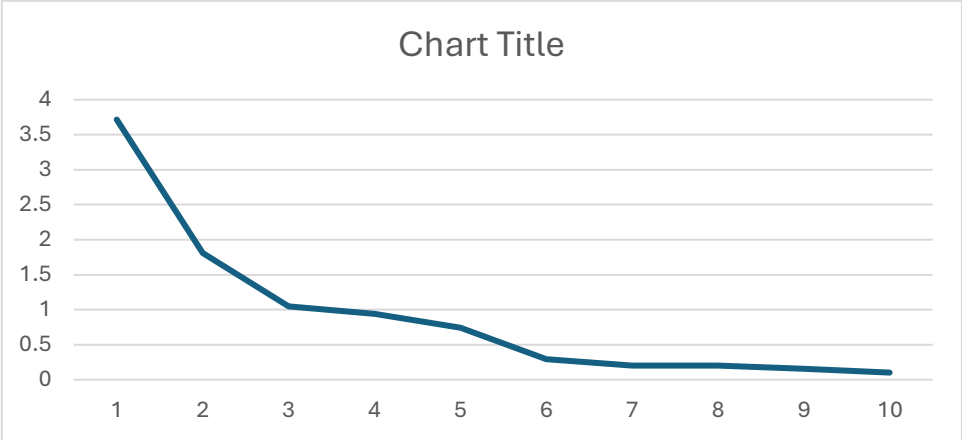

Figure – 2: The Chart for infected person's Variance time

5. CONCLUSIONS

When μ is kept fixed with other parameters $\lambda_1, \lambda_2, \theta_1$ and θ_2 the inter-arrival time $'c'$, which follows Exponential distribution, is an increasing parameter. Therefore, the value of the expected time $E(T)$ to cross the threshold of seroconversion is decreasing, for all cases of the parameter value μ. when the value of the parameter μ increases, the expected time is also found increasing, this is observed in Figure a and the same case is found in variance $V(T)$ which is observed in Figure 2. Mathematical models have significantly advanced our understanding of HBV epidemiology and played a vital role in public health decision-making. By informing the design and implementation of effective control and prevention strategies, these models have helped shape responses to HBV at both national and global levels. As we continue to refine these models with new data and insights, we move closer to the goal of reducing the global burden of HBV infection, as well as its associated morbidity and mortality. Continued investment in research and surveillance is essential to deepen our understanding of HBV transmission dynamics and to optimize intervention strategies aimed at mitigating this persistent public health threat.

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