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Estimation of Expected Time for Antigenic Diversity to Cross the Threshold in HIV Infection

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Abstract

Antigenic diversity is an important aspect in the progression of HIV infection. Several authors have studied the antigenic diversity in HIV infected. Nowak and May (1991) have studied the mathematical biology of HIV infection with particular reference to antigenic diversity. Nowak et al., (1991) have studied the impact of antigenic diversity threshold in the progression of AIDS. As and when the total antigenic diversity crosses the so called threshold level, the seroconversion takes place. The estimation of time to cross the antigenic diversity threshold is very useful in the prediction of the expected time to seroconversion. In this paper the expected time to seroconversion is estimated by using the shock model approach. The Shock model approach and cumulative damage process have been studied by Esary et al., (1973). In estimating the time for the antigenic diversity to cross the threshold, it is assumed that the threshold follows the first order statistic. Numerical illustration is also provided.

Keywords: Shock model Approach, Cumulative damage process, Antigenic Diversity

Introduction

Research studies relating to HIV infection, its progression and AIDS are considered to be very important now-a-days due to the fact that the spread of HIV is terribly on the increase all over the world. The cure for this pandemic is not yet available. Research is going on in different aspects of this problem. Medical research is not only on finding the cure of the epidemic but also to arrest the progression of the same. Mathematicians and statisticians focus their attention on different aspects such as the rate of growth of the infected over time, and on the rate of progression of this epidemic over an infected person. It may be observed that the antigenic diversity of

the invading antigens namely HIV is a matter of great interest. Several authors have studied the different aspects of antigenic diversity. Nowak and May (1991) have discussed the effect of antigenic variation in the HIV infection and spread. Stilianakis et al., (1994) have discussed a model related to antigenic diversity threshold. Krischner et al., (2000) have discussed the cell population dynamics which changes due to what is called the 'homing process' and apoptosis of the CD4 cell in the human system.

The cumulative contribution to the antigenic diversity of the invading antigen in successive contacts if exceeds a particular level called the antigenic diversity threshold, then the human immune system is unable to with stand and also unable to fight against the antigens. In this paper the expected time for the antigenic diversity to cross the threshold is found out. The variance for the same is also obtained. In doing so, it is assumed that the antigenic diversity threshold is a random variable which follows the distribution of the first order statistic. Similarly it follows the n^{th} order statistic also. During the expression for the expected time to cross the threshold, the concept of shock model and cumulative damage process by Esary et al., (1973) is used. Numerical illustration is used to study the behavior of the expected time and its variance.

Assumptions of the model

The following are the assumptions used in this model

1. There is a random amount of contribution to the antigenic diversity due to successive sexual contacts
2. Sexual contacts are the only source of infection.
3. There is a particular level of antigenic diversity called the threshold level. If the total contribution to antigenic diversity, due to successive contacts, exceeds the threshold level, then the seroconversion takes place.
4. The interarrival times between successive contacts are i.i.d. random variables.
5. The threshold and the contribution to antigenic diversity at random epochs due to sexual contacts are mutually independent.

Notations

X_i	a random variable denoting the increase in the antigenic diversity arising due to the HIV transmitted during the i^{th} contact.X_1, X_2, X_3...,X_k are continuous i.i.d random variables, with p.d.f g(.) and c.d.f.G(.).
Y	a random variable representing antigenic diversity threshold with p.d.f. h(.)
U_i	a continuous random variable denoting the interarrival time between successive contacts with p.d.f.f(.) and c.d. f. F(.)
g_k (.)	the p.d.f of random variable $\sum_{i=1}^{k} X_i$
F_k (.)	the k convolution of F(.)
l^*(s)	is the Laplace transform of l (t)
f^{**}(s)	is the Laplace transform of f *(t)*

Results

It can be shown that

$$P\left[\sum_{i=1}^{k} X_i < Y\right] = \int_0^{\infty} g_k(x)\overline{H(x)}dx$$

Where $\overline{H}$(x) = 1-H(x)

If the random variable Y follows exponential distribution with parameter θ

Then $h(t) = \theta e^{-t\theta}$ and $H(t) = 1 - e^{t\theta}$

Let Y_1, Y_2, $Y_{3\ldots}$, Y_n be a random sample of observations on Y. Arranging the values in increasing order of magnitude we get

$$Y_{(1)} \leq Y_{(2)} \leq \ldots, \leq Y_{(n)}$$

The p.d.f of the first order statistics $Y_{(1)}$ is

$$h_{(1)}(t) = n[1 - H(t)^{n-1}h(t) = n\theta\left[e^{-t\theta}\right]^n$$

$$P[\sum xi \leq y] = \int_0^{\infty} g_k(x)\overline{H(x)}dy$$

$if\ X_i$~exp (λ) Then $X_{(1)} + X_{(2)} + \cdots X_{(k)}$ is $gamma(k, \lambda)$

Now the threshold random variable Y follows first order statistics

$$h_{(1)}(t) = n\theta\left[e^{-t\theta}\right]^n$$

$$H_{(1)}(x) = \int_0^{x} n\theta\left[e^{-t\theta}\right]^n dt = 1 - e^{-nx\theta}$$

$$\therefore\ \overline{H_{(1)}(x)} = e^{-nx\theta}$$

$$P\left[\sum X_i < Y\right] = \int_0^{\infty} g_k(x)\overline{H_{(1)}(x)}$$

$$= \int_0^{\infty} g_k(x)e^{-n\theta x}dx = [g^*(n\theta)]^k$$

And since X_i, i=1,2…K are i.i.d.

$$S(t) = \sum_{k=0}^{\infty}[F_k(t) - F_{k+1}(t)]P\left[\sum_{i=1}^{k} X_i < Y\right] = \sum_{k=0}^{\infty}[F_k(t) - F_{k+1}(t)]\,[g^*(n\theta)]^k$$

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

$$L(t) = 1 - \sum_{k=0}^{\infty}[F_k(t) - F_{k+1}(t)]\,[g^*(n\theta)]^k$$

$$= [1 - g^*(n\theta)]\sum_{k=1}^{\infty} F_k(t)[g^*(n\theta)]^{k-1}\ on\ \text{Simplification}$$

$$l^*(s) = [1 - g^*(n\theta)] \sum_{k=1}^{\infty} {F_k}^*(s)[g^*(n\theta)]^{k-1}$$

$= \frac{[1-g^*(n\theta)]\, f^*(s)}{[1-f^*(s)g^*(n\theta)]}$ On Simplification (1)

Since g(.) ~ exp(λ) $g^*(n\theta) = \frac{\lambda}{n\theta+\lambda}$

$let\ f(.)$ ~exp (μ) $f^*(s) = \frac{\mu}{\mu + s}$

Subsisting in (1) we get

$$l^*(s) = \frac{\left[1 - \frac{\lambda}{\lambda + n\theta}\right]\left(\frac{\mu}{\mu + s}\right)}{\left[1 - \frac{\mu}{\mu + s}\ \frac{\lambda}{\lambda + n\theta}\right]}$$

$$l^*(s) = \left[1 + \frac{s(\lambda + n\theta)}{n\mu\theta}\right]^{-1}$$

Now, $E(T) = \frac{-dl^*(s)}{ds}\Big|_{s=0}$

$= \left(\frac{\lambda + n\theta}{n\mu\theta}\right)$

$$E(T^2) = \frac{2(\lambda + n\theta)^2}{(n\mu\theta)^2}$$

Hence, V (T) = E (T^2) – [E (T)] ^{2}

$$V(T) = \frac{2(\lambda + n\theta)^2}{(n\mu\theta)^2} - \left(\frac{\lambda + n\theta}{n\mu\theta}\right)^2 \ \therefore V(T) = \left(\frac{\lambda + n\theta}{n\mu\theta}\right)^2$$

Numerical Illustration

Following numerical illustrations are taken up to study the changes in E (T) and V (T). The behavior of the values of E (T) and V (T) are observed by the variations in the different parameters of the distributions of the random variables involved in this model.

Conclusion

If the value of μ increases, when all the other parameters kept fixed it is seen that E (T) and also V (T) both decrease and it is due to the fact that the inter-arrival times between successive contacts follow exponential distribution with parameter 'μ' Therefore E (U) = 1/μ hence if 'μ' increases E (U) decreases which means that the inter-arrival times are shorter, Therefore, more number of contacts are possible and hence there is a good deal of contribution to antigenic diversity. Therefore E (T)

decreases which means that the antigenic diversity threshold will be crossed earlier, which is shown in figure (1).

If 'λ' which is the parameter of the exponential distribution of random variable 'X' which denotes that the magnitude contribution to antigenic diversity in the successive contacts increases then E (U) = 1/λ decreases. Therefore it takes more time to cross the threshold and it has been indicated in the corresponding figure (2)

If 'θ' which is the parameter of the threshold Y increases, then $E(U) = 1/\theta$ decreases. Therefore the threshold becomes smaller and, E (T) decreases. A similar behavior is noted for V (T) also and it has been indicated in figure (3).

If the value of 'n' which denotes the number of observations in the sample increases, then the value of $Y_{(n)}$ also increases. Therefore it implies the increase in the threshold value. Therefore E (T) the time to cross threshold shows a decrease. Similarly V (T) also decreases but the decrease in both E (T) and V (T) is only marginal. This has been indicated in the corresponding figure (4).

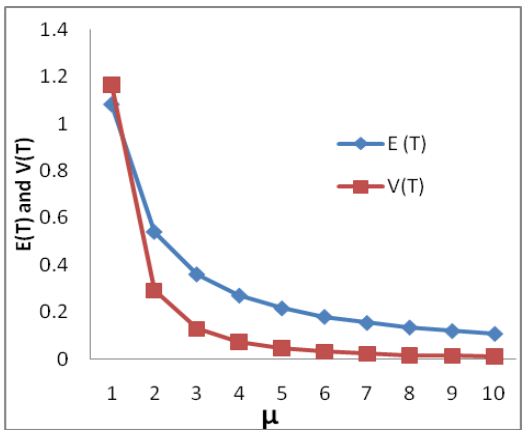

Figure 1

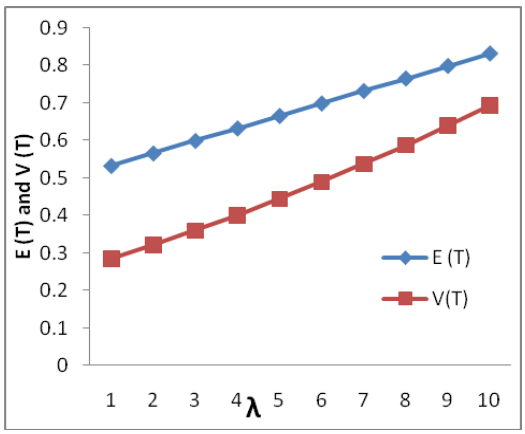

Figure 2

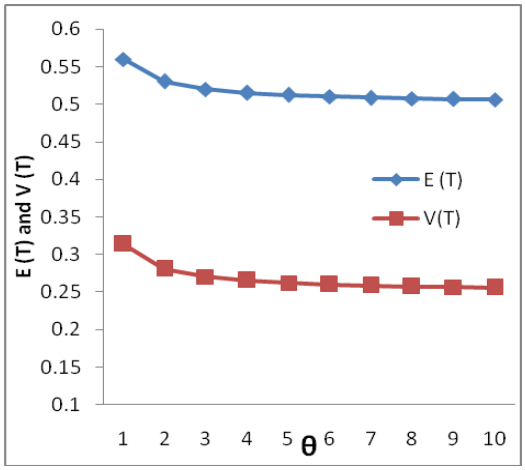

Figure 3

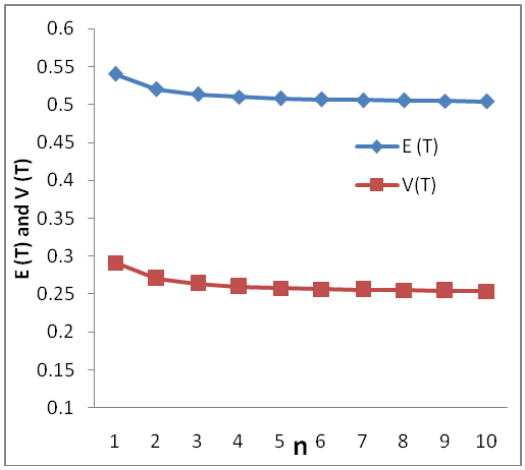

Figure 4

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