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A STOCHASTIC MODEL TO ESTIMATE THE EXPECTED TIME TO SEROCONVERSION – THRESHOLD AS SUM OF TWO COMPONENTS

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Abstract

The spread of the HIV infection has created an pandemic situation all over the world. It has become necessary to have the combined efforts of medical personnel, social workers and mathematicians and statisticians to study the different aspects of this infection and its spread. One of the interesting aspects of study is to estimate the likely time at which an infected person becomes seropositive. It is in this connection the antigenic diversity threshold is considered. The antigenic diversity threshold is a particular level of the antigenic diversity of the invading antigen beyond which the human immune system breaks down and a person becomes seropositive. In this paper the expected time to seroconversion is derived under the assumption that the antigenic diversity threshold comprises of two components namely the natural antigenic diversity threshold level of human immune system and the threshold component due to use of ART. Numerical illustration is also provided.

Key Words: Antigenic Diversity Threshold; Anti Retroviral Therapy (ART); Seroconversion; Expected Time to Seroconversion.

Introduction

In the study of the HIV infection the different modes of transmission of HIV is an interesting concept of study. There are four different modes of transmission and they are:

1. Homo (or) Hetero sexual contacts
2. Sharing unsterile needles
3. Transmission of contaminated blood product
4. From mother to baby in the foetus

Among the four modes of transmission, sexual contact is the most important mode of transmission of HIV.

The HIV infected persons have clinical symptoms of the infection. The progression of HIV to AIDS normally happens in about a period of 10 years. A person who is infected will have the symptoms of HIV and when a person becomes seropositive then symptoms of AIDS will appear slowly. The change over from seronegative to seropositive state is called seroconversion.

The human body has its own immune ability and it would be able to withstand a particular level of antigenic diversity of the invading HIV. Such a level of antigenic diversity is known as the antigenic diversity threshold. If the antigenic diversity of the invading antigen crosses this level then the human immune system collapses. The antigenic diversity threshold is considered to be a random variable since it varies from person to person. In every contact there is a random amount of addition to the antigenic diversity. The expected time to cross the antigenic diversity due to successive contacts during the period (0,t] is estimated using the shock model and cumulative damage process approach by Esary, Marshall and Proschan (1973). Such an approach has been adopted by Sathiyamoorthi and Kannan (1998), Nirmala Ratchager (2003) and others to estimate the expected time to seroconversion.

In a mathematical model developed in this paper, it is assumed that Anti Retroviral Therapy (ART) is given to a person who is identified as HIV infected. Since the ART prolongs the process of seroconversion and the onset of AIDS symptoms, it is assumed that there is an increase in the antigenic diversity threshold. So the antigenic diversity threshold beyond which the human immune system cannot with stand can be represented as sum of

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two random variables. Under this assumption the expected time to seroconversion is derived.

Assumptions

1. A person is exposed to HIV infection. At every epoch of contact with an infected there is some contribution to the antigenic diversity.
2. Anti Retroviral Therapy is administered to the infected.
3. There is a particular level of antigenic diversity of the invading virus, and it is called the antigenic diversity threshold. If antigenic diversity crosses this threshold the seroconversion takes place.
4. The interarrival times between the successive contacts are random variables which are identically independently distributed.

Notations

X_i = A random variable which denotes the magnitude of contribution to antigenic diversity at the i^{th} epoch i = 1,2,…,k.X_i has p.d.f g(x) and c.d.f G(x).

Z_1 = The threshold level of antigenic diversity, which is a random variable Z_1 with p.d.f $m_1(y)$ and c.d.f $M_1(y)$.

Z_2 = A random variable which indicates the additional antigenic diversity level added to the threshold due to ART. It has p.d.f $m_2(y)$ and c.d.f $M_2(y)$.

W = $Z_1 + Z_2$, and W has p.d.f h (w) with c.d.f H(w).

U_i = A random variable U_i denoting the inter-arrival times between successive contacts, i = 1,2,…,k with p.d.f f(.) and c.d.f F(.).

T = A random variable denoting the time to cross the antigenic diversity threshold, with p.d.f l(t) and c.d.f L(t).

Results

There are 'k' contacts during the period (0,t]. On every occasion a random amount of antigens are getting added to the system which inturn adds to the antigenic diversity. As and when the total antigenic diversity crosses the threshold W, the seroconversion takes place. It may be noted that the Anti Retroviral Therapy is started and so the human immune system is able to withstand to a greater extent. This adds to the antigenic diversity threshold. Hence the threshold for the whole process is W= Z_1+Z_2. The seroconversion takes place as and when the total antigenic diversity crosses W.

Hence

$$\Pr\left\{\sum_{i=1}^{k} X_i < W\right\} = (Probability\ that\ the\ antigenic\ diversity\ due\ to\ k\ contacts\ does\ not\ cross\ the\ threshold\ level). \quad \ldots(1)$$

This can be written as,

$$= \int_0^{\infty} g_k(x)\overline{H(x)}dx.$$

Alternatively the expression for (1) can be given as

$$P\left\{\sum_{i=1}^{k} X_i < W\right\} = \int_0^{\infty} G_k(w)h(w)dw \quad \ldots(2)$$

Now the p.d.f of W is given by the convolution of Z_1+Z_2 and we use the convolution formula to determine the p.d.f of W.

Let Z_1~exp (α_1) and Z_2~exp (α_2).

It can be seen that

$$h(w) = \int_0^{w} \alpha_1 e^{-\alpha_1 w}\, \alpha_2 e^{-\alpha_2 (w-m)}\, dw$$

it can be shown by simplification that

$$h(w) = \frac{\alpha_1\alpha_2}{(\alpha_1-\alpha_2)}\left\{e^{-\alpha_2 w} - e^{-\alpha_1 w}\right\} \quad \ldots(3)$$

S(t) = Survivor function = P[T>t]

It gives the probability that the total amount of antigenic diversity in (0,t] has not crossed the threshold Z.

$$P[T>t] = \sum_{k=0}^{\infty} \Pr\left\{\begin{matrix} that\ there\ are\ exactly\ k\ Contact\ in\ (0,t)\ and \\ the\ antigenic\ diversity\ has\ not\ crossed\ W. \end{matrix}\right\}$$

$$= \sum_{k=0}^{\infty} \Pr(exactly\ k\ decision\ epochs\ in\ (0,t)) \times \Pr\left\{\sum_{i=1}^{k} X_i < W\right\}.$$

$$= \sum_{k=0}^{\infty} \left(F_k(t) - F_{k+1}(t)\right)\int_0^{\infty} G_k(w)h(w)dw$$

$$= \sum_{k=0}^{\infty} \left(F_k(t) - F_{k+1}(t)\right)\frac{\alpha_1\alpha_2}{\alpha_1-\alpha_2}\int_0^{\infty} G_k(w)\left(e^{-\alpha_2 w} - e^{-\alpha_1 w}\right)dw$$

Since $\int_0^{\infty} G_k(w)e^{-\alpha_2 w}\,dw = G_k^*(\alpha_2)$ and $\int_0^{\infty} G_k(z)e^{-\alpha_1 w}\,dw = G_k^*(\alpha_1)$

since the random variables X_1 X_2…X_k are i.i.d.,

$$G_k^*(\alpha_2) = \frac{\left(g^*(\alpha_2)\right)^k}{\alpha_2} \text{ and } G_k^*(\alpha_1) = \frac{\left(g^*(\alpha_1)\right)^k}{\alpha_1}$$

Hence

$$S(t) = \frac{\alpha_1\alpha_2}{\alpha_1-\alpha_2}\sum_{k=0}^{\infty} F_k(t) - F_{k+1}(t)\left\{\frac{\left(g^*(\alpha_2)\right)^k}{\alpha_2} - \frac{\left(g^*(\alpha_1)\right)^k}{\alpha_1}\right\} \quad \ldots(4)$$

$$= \frac{\alpha_1\alpha_2}{\alpha_1-\alpha_2}\sum_{k=0}^{\infty} F_k(t) - F_{k+1}(t)\left\{\frac{\alpha_1\left(g^*(\alpha_2)\right)^k - \alpha_2\left(g^*(\alpha_1)\right)^k}{\alpha_1\alpha_2}\right\}$$

$$= \sum_{k=0}^{\infty}\left(F_k(t) - F_{k+1}(t)\right)\left\{\frac{\alpha_1(g^*(\alpha_2))^k - \alpha_2(g^*(\alpha_1))^k}{(\alpha_1-\alpha_2)}\right\}$$

$$S(t) = \frac{\alpha_1}{(\alpha_1-\alpha_2)} - \frac{\alpha_1}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_2))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_2)^{k-1}$$

$$-\frac{\alpha_2}{(\alpha_1-\alpha_2)} + \frac{\alpha_2}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_1))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_1)^{k-1}$$

on simplification

$$= 1 - \frac{\alpha_1}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_2))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_2)^{k-1}$$

$$+\frac{\alpha_2}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_1))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_1)^{k-1} \quad \ldots(5)$$

on simplification

Now $L(t) = 1 - S(t) = P[T \le t]$

$$= \frac{\alpha_1}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_2))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_2)^{k-1}$$

$$-\frac{\alpha_2}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_1))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_1)^{k-1} \quad \ldots(6)$$

Taking Laplace Stieltjes transforms of the above, we get

$$L^*(s) = \frac{\alpha_1}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_2))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_2)^{k-1}$$

$$-\frac{\alpha_2}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_1))\sum_{k=1}^{\infty} F_k(t)g^*(\alpha_1)^{k-1}$$

and

$$l^*(s) = \frac{\alpha_1}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_2))\sum_{k=1}^{\infty} f_k(s)g^*(\alpha_2)^{k-1} - \frac{\alpha_2}{(\alpha_1-\alpha_2)}(1-g^*(\alpha_1))\sum_{k=1}^{\infty} f_k(s)g^*(\alpha_1)^{k-1} \quad \ldots(7)$$

Since the inter-arrival time are i.i.d random variables then

$$f_k^*(s) = [f^*(s)]^k$$

Hence

$$l^*(s) = \frac{\alpha_1}{(\alpha_1-\alpha_2)} f^*(s)(1-g^*(\alpha_2))\sum_{k=1}^{\infty} f_k(s)g^*(\alpha_2)^{k-1} - \frac{\alpha_2}{(\alpha_1-\alpha_2)} f^*(s)(1-g^*(\alpha_1))\sum_{k=1}^{\infty} f_k(s)g^*(\alpha_1)^{k-1} \quad \ldots(8)$$

$$l^*(s) = T_1 - T_2 = \left\{\frac{\alpha_1(1-g^*(\alpha_2))f^*(s)}{(\alpha_1-\alpha_2)\{1-f^*(s)g^*(\alpha_2)\}}\right\} - \left\{\frac{\alpha_2(1-g^*(\alpha_1))f^*(s)}{(\alpha_1-\alpha_2)\{1-f^*(s)g^*(\alpha_1)\}}\right\}$$

on simplification ...(9)

Let f (.) ~ exp (λ) and g (.) ~ exp (θ)

Hence $f^*(s) = \frac{\lambda}{\lambda+s}$, $g^*(\alpha_1) = \frac{\theta}{\theta+\alpha_1}$ $\quad g^*(\alpha_2) = \frac{\theta}{\theta+\alpha_2}$

$$E(T) = -\left.\frac{dl^*(s)}{ds}\right|_{s=0}$$

Now Substituting

$f^*(s),\ g^*(\alpha_1)\ and\ g^*(\alpha_2)\ in\ (9)\ we\ get$

$$= \frac{\lambda\alpha_1\alpha_2}{(\alpha_1-\alpha_2)\{s(\theta+\alpha_2)+\lambda\alpha_2\}} - \frac{\lambda\alpha_1\alpha_2}{(\alpha_1-\alpha_2)\{s(\theta+\alpha_1)\lambda\alpha_1\}} \quad \ldots(10)$$

on simplification

$$E(T) = -\left.\frac{dl^*(s)}{ds}\right|_{s=0}$$

$$E(T) = \frac{\theta(\alpha_1+\alpha_2)+\alpha_1\alpha_2}{\lambda\alpha_1\alpha_2} \quad \text{on simplification} \quad \ldots(11)$$

similarly

$$E(T^2) = \frac{2\lambda\alpha_1\alpha_2}{(\alpha_1-\alpha_2)}\cdot\frac{(\theta+\alpha_2)^2}{(\lambda\alpha_2)^3} - \frac{(\theta+\alpha_1)^2}{(\lambda\alpha_1)^3} \quad \text{on simplification} \quad \ldots(12)$$

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

$$= \frac{2\lambda\alpha_1\alpha_2}{(\alpha_1-\alpha_2)}\left\{\frac{(\theta+\alpha_2)^2}{(\lambda\alpha_2)^3} - \frac{(\theta+\alpha_1)^2}{(\lambda\alpha_1)^3}\right\} - \left[\frac{\theta(\alpha_1+\alpha_2)+\alpha_1\alpha_2}{\lambda\alpha_1\alpha_2}\right]^2$$

$$V(T) = \frac{2\lambda\alpha_1\alpha_2}{(\alpha_1-\alpha_2)}\left\{\frac{(\theta+\alpha_2)^2}{(\lambda\alpha_2)^3} - \frac{(\theta+\alpha_1)^2}{(\lambda\alpha_1)^3}\right\} - \left[\frac{\theta^2(\alpha_1+\alpha_2)^2+\alpha_1^2\alpha_2^2}{\lambda^2\alpha_1^2\alpha_2^2}\right] \quad \ldots(13)$$

Table 1: Variation in E (T) and V (T) θ = 0.5 λ = 1.0 α_2=1.0

α_1	E(T)	V(T)
1.5	1.83	4.69
2.0	1.75	4.31
2.5	1.70	4.09
3.0	1.67	3.94
3.5	1.64	3.84
4.0	1.63	3.77
4.5	1.61	3.70
5.0	1.60	3.66
5.5	1.59	3.62
6.0	1.58	3.59

Fig. 1

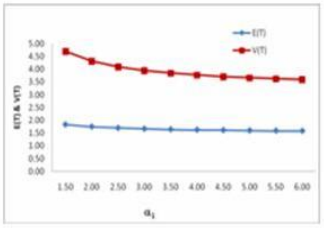


Table 2: Variation in E (T) and V (T) θ = 0.5 λ = 1.0 α_1=2.0

α_2	E(T)	V(T)
0.2	3.75	18.31
0.4	2.50	8.63
0.6	2.08	6.09
0.8	1.88	4.95
1.0	1.75	4.31
1.2	1.67	3.90
1.4	1.61	3.62
1.6	1.57	3.41
1.8	1.53	3.25

Fig. 2

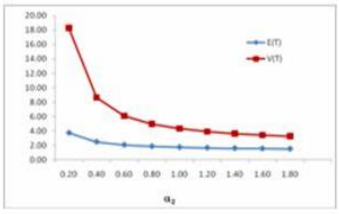


Table 3: Variation in E (T) and V (T) α_1 = 1.0 α_2=1.2 λ = 1.0

θ	E(T)	V(T)
0.4	1.73	4.20
0.8	2.47	7.95
1.2	3.20	12.24
1.6	3.93	17.07
2.0	4.67	22.44
2.4	5.40	28.36
2.8	6.13	34.82
3.2	6.87	41.82
3.6	7.60	49.36
4.0	8.33	57.44

Fig. 3

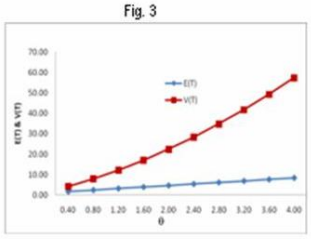
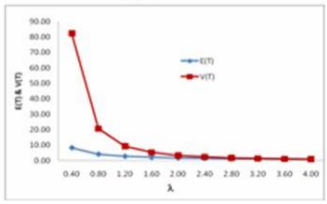


Table 4: Variation in E (T) and V (T) α_1 = 1.0 α_2=1.5 λ = 1.4

λ	E(T)	V(T)
0.4	8.33	82.28
0.8	4.17	20.57
1.2	2.78	9.14
1.6	2.08	5.14
2.0	1.67	3.29
2.4	1.39	2.29
2.8	1.19	1.68
3.2	1.04	1.29
3.6	0.93	1.02
4.0	0.83	0.82

Fig. 4



Conclusion

i) It can be seen that if θ, λ, α_2 are all fixed and α_1 namely the parameter of the exponential distribution representing the first compound Z_1 of the threshold increases, then $E(Z_1)=1/\alpha_1$ decreases. Hence the overall threshold Z_1+Z_2 also decreases. So the expected time to seroconversion decreases, which is given in Table 1 and Fig 1. The variance also decreases but in a slow manner.

ii) If θ, λ and α_1 are all kept fixed and if α_2 is allowed to increase then E(T) decreases. So also is V(T). This is due to the fact that since Z_2 ~ exp(α_2) then $E(Z_2) = 1/\alpha_2$. Hence as α_2 increases E(T) decreases. which implies that the threshold becomes smaller and it takes less time to cross the threshold as indicated in Table 1 and Fig 1.

iii) If θ, namely the parameter of the random variable X which is the magnitude of contribution to antigenic diversity in each contact increases, it can be seen from table 3 that E(T) increases. This due to the fact that since X ~ g(x) which is exp (θ) E(T) = 1/θ. As θ increases then E(X) decreases and so the average contribution to the antigenic diversity in each contact decreases. Hence E(T) increases and V(T) also increases.

iv) If α_1, α_2 and θ are kept fixed and if λ is allowed to increases it is seen from table 3 that E(T) decreases. Also V(T) decreases. This because of the fact that λ is the parameter of the distribution of the random variable U_i, which is the interarrival time between contacts. U_i~ exp(λ). So E(U)=1/λ. As λ increases then E(U) decreases. Hence the interarrival times between contacts

decreases. So there are more number of contacts in (0,t). Hence the contribution to antigenic diversity increases. So it takes less time for seroconversion. Therefore E(T) is decreasesing. So also is V(T) as indicated in Fig 4 and Table 4.

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