Ultra Scientist Vol. 24(2)A, 311-318 (2012).

A stochastic model with variable threshold in HIV infection

S. VIJAYA

Department of Mathematics, Annamalai University (INDIA)

(Acceptance Date 15th May, 2012)

Abstract

In the study of HIV infection the progression of the disease takes place with the passage of time. This is due to the increasing the antigenic diversity level of the Retrovirus. As and when the total antigenic diversity crosses a threshold level, the sero conversion takes place. The threshold itself is considered to be a random variable. In this paper assuming that the antigenic diversity threshold satisfies the property known as Setting the Clock Back to Zero (SCBZ) property, the expected time to sero conversion and its variance are derived. The results are augumented with suitable numerical illustrations.

Notations

X_i - A random variable representing the increase in the antigenic diversity due to the HIV transmitted during the i^{th} contact $X_i's$ are i.i.d with p.d.f. g(x) and distribution function G(x).

Y - A random variable representing the antigenic diversity threshold with p.d.f. h(y) and distribution function H(y)

U_i - A random variable representing the interarrival times between successive contacts i = 1,2, …k with p.d.f. f (u) and distribution F(u)

$g_k(.)$- The p.d.f of the random variable $\sum X_i$, i=1,2,……..k

F_k (.)- The k convolution of F(.)

T - The continuous random variable denoting the time to sero conversion with p.d.f. l(t) and distribution function L (t)

l * (s), L* (s) - Laplace transform of l (t) and L(t) respectively

Introduction

In the study of HIV infection, the estimation of expected time to sero conversion and its variance arc considered to be indicative of the disease progression. There are many factors which contribute to the disease progression and collapse of the immune system. Nowak and May[2] have obtained the expression for the antigenic diversity threshold which is defined to be the maximum possible level of antigenic diversity which the immune system of the human body is able to withstand. The antigenic diversity is due to the genetic variability of the

HIV which promotes the withstanding ability of HIV against the anti bodies which are generated in the human body to fight against the virus[1].

A person is exposed to HIV infection at random time points and it is due to the homo (or) hetero sexual contacts which a person has with an infected partner at random time intervals. The immune ability of an individual is also a random variable and it is mainly responsible for containing the disease progression. As and when the total anligenic diversity crosses the level called the threshold, the sero conversion takes place. Under these assumptions Sathyamoorthi and Kannan[4] have developed a mathematical model in which the expected time to scroconversion and its variance are obtained by using the shock model and cumulative damage process by Esary, Proschan and Marshall[1]. In doing so, they have assumed that the threshold whieli is a random variable is distributed as exponential.

A random variable Y has a distribution which satisfies the SCBZ property, if

$\frac{S(y+y_0,\theta^*)}{S(y_0,\theta)} = S(y, \theta_0)$ where $\theta^* = \theta^*(y_o,\theta)$

$\in \Omega$ where Ω is the parameter space

where $S(y, \theta_0)$ = the survivor function

$= P_r(Y > y)$

and y_0 is called the truncation point. Where y_0 is taken to be a random variable

Assumptions of the model :

We have made the following assumptions to develop our model.

(i) A person is exposed to HIV infection on successive occasions with random time intervals in between.

(ii) At every occasion of exposure a random amount of HIV are added to the system, so that they contribute to the antigenic diversity which inturn damages the immune ability of an individual

(iii) The damages on successive occasions are linear and cumulative and the amount of damage caused and the threshold are statistically independent[3].

The model :

In this paper it is assumed that the threshold distribution satisfies the so called Setting the Clock Back to Zero property (SCBZ). According to this properly the threshold distribution has a parametric change after a particular value of the random variable which is called the truncation point. For a detailed study of SCBZ property one can refer to Raja Rao and Talwaker[3]. The assumption of the SCBZ property for the threshold distribution is justified by the fact that the threshold undergoes a change with the passage of time due to the progression of the infection after the initial exposure.

we consider the case where the truncation point y_0 is a random variable then

$$h(y) = \begin{cases} \theta_1 e^{-\theta_1 y}; & y \le y_0 \\ \theta_2 e^{-\theta_2 y} e^{\tau_0(\theta_2-\theta_1)}; & y > y_0 \end{cases}$$

Assume $y_0 \sim \exp(\lambda)$

The survivor function of y_0 $(y_0 \ge y)$ is $e^{-\lambda y}$

The distribution function of y_0 $(y_0 < y)$ is

$$\int_0^y \lambda e^{-\lambda y_0} dy_0$$

When y_0 is a random variable

Then $h(y) = \theta_1 e^{-\theta_1 y} e^{-\lambda y} + \theta_2 e^{-\theta_2 y} \int_0^y e^{y_0(\theta_2-\theta_1)} \lambda e^{-\lambda y_0} dy_0$

$= \theta_1 e^{-(\theta_1+\lambda)y} + \theta_2 e^{-\theta_2 y} \lambda \int_0^y e^{-y_0(\theta_1-\theta_2+\lambda)} dy_0$

$= \theta_1 e^{-(\theta_1+\lambda)y} + \lambda\theta_2 e^{-\theta_2 y} \left[\frac{1}{\theta_1-\theta_2+\lambda} - \frac{e^{-y(\theta_1-\theta_2+\lambda)}}{\theta_1-\theta_2+\lambda} \right]$

$= \theta_1 e^{-y(\lambda+\theta_1)} + \frac{\lambda\theta_2 e^{-\theta_2 y}}{\theta_1-\theta_2+\lambda} - \frac{\lambda\theta_2 e^{-y(\theta_1+\lambda)}}{\theta_1-\theta_2+\lambda}$

$= e^{-(\theta_1+\lambda)y} \left[\theta_1 - \frac{\lambda\theta_2}{\theta_1-\theta_2+\lambda} \right] + \frac{\lambda\theta_2 e^{-\theta_2 y}}{\theta_1-\theta_2+\lambda}$

$= \frac{(\theta_1-\theta_2)(\lambda+\theta_1)}{\theta_1-\theta_2+\lambda} e^{-(\theta_1+\lambda)y} + \frac{\lambda\theta_2}{\theta_1-\theta_2+\lambda} e^{-\theta_2 y}$

$\therefore H(y) = \frac{(\theta_1-\theta_2)(\lambda+\theta_1)}{\theta_1-\theta_2+\lambda} \int_0^y e^{-(\theta_1+\lambda)t} dt + \frac{\lambda\theta_2}{\theta_1-\theta_2+\lambda} \int_0^y e^{-\theta_2 t} dt$

$= \frac{\theta_1-\theta_2}{\theta_1-\theta_2+\lambda} - \frac{\theta_1-\theta_2}{\theta_1-\theta_2+\lambda} e^{-(\theta_1+\lambda)y} + \frac{\lambda}{\theta_1-\theta_2+\lambda} - \frac{\lambda e^{-\theta_2 y}}{\theta_1-\theta_2+\lambda}$

$\therefore \overline{H}(y) = \frac{\theta_1-\theta_2}{\theta_1-\theta_2+\lambda} - e^{-(\theta_1+\lambda)y} + \frac{\lambda}{\theta_1-\theta_2+\lambda} e^{-\theta_2 y}$

Now, $P[T > t] = \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \int_0^{\infty} g_k(x) \overline{H}(x) dx$

$\therefore P[T > t] = \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \int_0^{\infty} g_k(x) \left[\frac{(\theta_1-\theta_2) e^{-(\theta_1+\lambda)y} + \lambda_2 e^{-\theta_2 y}}{\theta_1-\theta_2+\lambda} \right]$

$= \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \frac{1}{\theta_1-\theta_2+\lambda} \left[(\theta_1-\theta_2) \int_0^{\infty} g_k(x) e^{-(\theta_1+\lambda)y} dy + \lambda \int_0^{\infty} g_k(x) e^{-\theta_2 y} dy \right]$

$= \frac{1}{\theta_1-\theta_2+\lambda} \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \left\{ (\theta_1-\theta_2) g_k^*(\theta_1+\lambda) + \lambda g_k^*(\theta_2) \right\}$

$= p \left\{ 1 - (1 - g^*(\theta_1+\lambda)) \sum_{k=1}^{\infty} F_k(t) [g^*(\theta_1+\lambda)]^{k-1} \right\}$

$+ q \left\{ 1 - (1 - g^*(\theta_2)) \sum_{k=1}^{\infty} F_k(t) [g^*(\theta_2)]^{k-1} \right\}$

$$= 1 - p\left(1 - g^*(\theta_1 + \lambda)\right) \sum_{k=1}^{\infty} F_k(t)\left[g^*(\theta_1 + \lambda)\right]^{k-1} - q\left(1 - g^*(\theta_2)\right) \sum_{k=1}^{\infty} F_k(t)\left[g^*(\theta_2)\right]^{k-1}$$

Here p+q =1, $p = \dfrac{\theta_1 - \theta_2}{\lambda + \theta_1 - \theta_2}$, $q = \dfrac{\lambda}{\lambda + \theta_1 - \theta_2}$

Now,

L(t) = P[T < t] = 1- p[T ≥ t]

$$= p\left(1 - g^*(\theta_1 + \lambda)\right) \sum_{k=1}^{\infty} F_k(t)\left[g^*(\theta_1 + \lambda)\right]^{k-1} + q\left(1 - g^*(\theta_2)\right) \sum_{k=1}^{\infty} F_k(t)\left[g^*(\theta_2)\right]^{k-1} \quad (1)$$

Taking Laplace transform

$$\begin{aligned} l^*(s) &= p\left(1 - g^*(\theta_1 + \lambda)\right) \sum_{k=1}^{\infty} \left[f^*(s)\right]^k \left[g^*(\theta_1 + \lambda)\right]^{k-1} \Bigg\} \\ &\quad + q\left(1 - g^*(\theta_2)\right) \sum_{k=1}^{\infty} \left[f^*(s)\right]^k \left[g^*(\theta_2)\right]^{k-1} \Bigg\} \\ &= p\left[1 - \frac{g^*(\theta_1 + \lambda) f^*(s)}{1 - f^*(s) g^*(\theta_1 + \lambda)}\right] + q\left[1 - \frac{g^*(\theta_2) f^*(s)}{1 - f^*(s) g^*(\theta_2)}\right] \\ &= l^*(s_1) + l^*(s_2) \end{aligned} \quad (2)$$

Now,

$$l^*(s_1) = p\left(1 - \frac{g^*(\theta_1 + \lambda) f^*(s)}{1 - f^*(s) g^*(\theta_1 + \lambda)}\right)$$

If g(·)~exp c; f(·)~exp α

$$\therefore\ l^*(s_1) = p\left(\frac{\alpha(\theta_1 + \lambda)}{(\theta_1 + \lambda) + s(\theta_1 + \lambda + c)}\right)$$

$$\therefore \frac{d}{ds}(l^*(s_1)) = p\left\{\frac{-\alpha(\theta_1 + \lambda)(\theta_1 + \lambda + c)}{[(\alpha(\theta_1 + \lambda) + s(\theta_1 + \lambda + c)]^2}\right.$$

$$\therefore -\frac{d}{ds} l^*(s_1)\Big|_{s=0} = p\left\{\frac{\theta_1 + \lambda + c}{\alpha(\theta_1 + \lambda)}\right\}$$

$$\frac{d^2}{ds^2}\left(l^*(s_1)\right)\Big|_{s=0} = 2p\left(\frac{\theta_1 + \lambda + c}{\alpha(\theta_1 + \lambda)}\right)^2$$

Similarly

$$l^*(s_2) = q\frac{\left(1 - g^*(\theta_2)\right) f^*(s)}{1 - g^*(\theta_2) f^*(s)}$$

$$= q\left\{\frac{\alpha\theta_2}{\alpha\theta_2 + s(c + \theta_2)}\right\}$$

$$\therefore \frac{d}{ds^2} l^*(s_2)\Big|_{s=0} = q\left(\frac{c + \theta_2}{\theta_2 \alpha}\right)$$

$$\left.\frac{d^2\mathbf{I}^*(s_2)}{ds^2}\right|_{s=0} = q\left\{2\left(\frac{c+\theta_2}{\theta_2\alpha}\right)^2\right\} - p^2\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right)^2 - q^2\left(\frac{c+\theta_2}{\theta_2\alpha}\right)^2 - 2pq\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right)\left(\frac{c+\theta_2}{\theta_2\alpha}\right)$$

Therefore

$$E(T)\big|_{s=0} = p\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right) + q\left(\frac{c+\theta_2}{\theta_2\alpha}\right) \quad (3)$$

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

$$= 2p\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right)^2 + 2q\left(\frac{c+\theta_2}{\theta_2\alpha}\right)^2 - p^2\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right)^2 - q^2\left(\frac{c+\theta_2}{\theta_2\alpha}\right)^2 - 2pq\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right)\left(\frac{c+\theta_2}{\theta_2\alpha}\right)$$

$$= p(2-p)\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right)^2 + q(2-q)\left(\frac{c+\theta_2}{\theta_2\alpha}\right)^2 - 2pq\left(\frac{\theta_1+\lambda+c}{\alpha(\theta_1+\lambda)}\right)\left(\frac{c+\theta_2}{\theta_2\alpha}\right) \quad (4)$$

Numerical illustration :

Table 5.1

α	λ = 1.0, c = 1.5, θ1 = 0.5, θ2 = 1.0		λ = 2.0, c = 2.5, θ1 = 0.5, θ2 = 1.0		λ = 3.0, c = 3.5, θ1 = 0.5, θ2 = 1.0	
	E (T)	V(T)	E (T)	V(T)	E (T)	V(T)
1	3.26	2.27	4.76	6.25	6.3	11.75
2	1.63	0.90	2.38	1.52	3.14	3.05
3	1.08	0.26	1.59	0.68	2.01	1.73
4	0.81	0.14	1.2	0.36	1.57	0.75

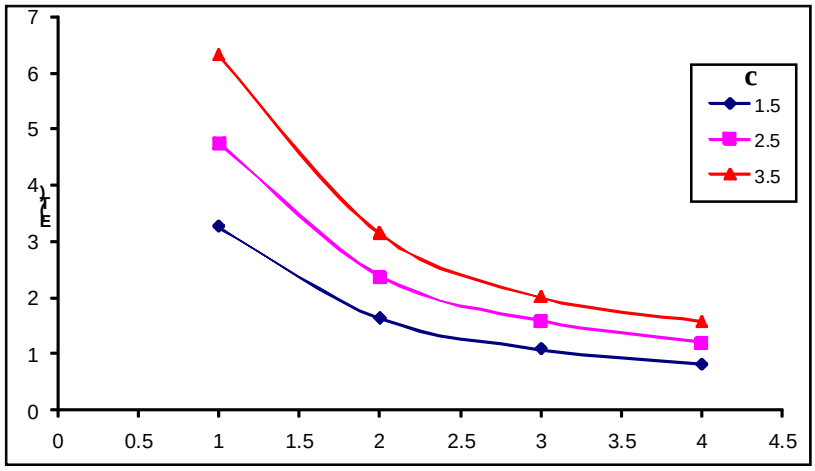

Figure 5.1 Variation of α with E(T)

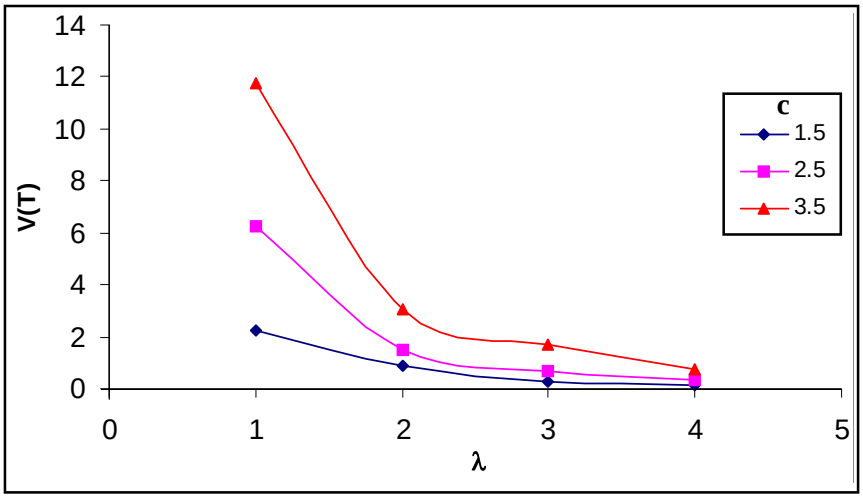

Figure 5.2

Table 5.2

Table 5.6α	λ = 1.0, c = 1.5, q_1 = 0.5, θ_2 = 1.0		λ = 2.0, c = 2.5, θ_1 = 0.5, θ_2 = 1.0		λ = 3.0, c = 1.5, θ_1 = 0.5, θ_2 = 1.0	
	E (T)	V(T)	E (T)	V(T)	E (T)	V(T)
1	3.26	2.27	3.5	2.06	3.6	1.91
2	1.63	0.90	1.75	0.86	1.82	0.38
3	1.08	0.26	1.16	0.25	1.2	0.22
4	0.81	0.14	0.88	0.13	0.91	0.1

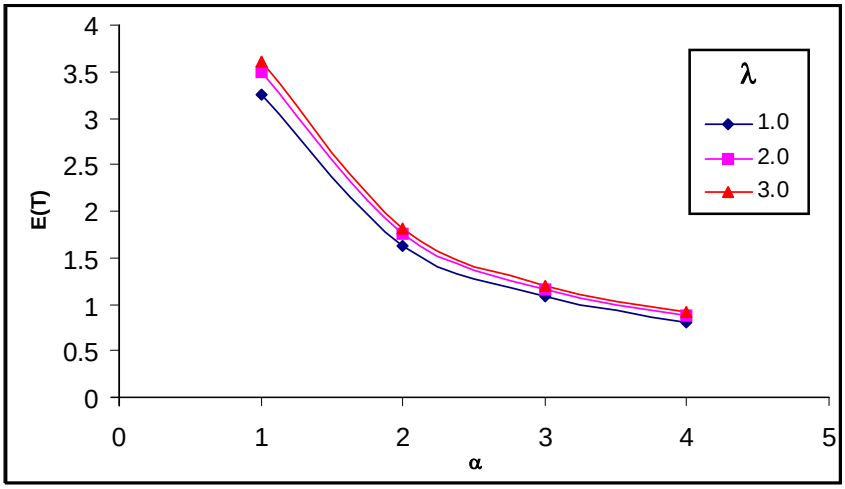

Figure 5.3 Variation of α with E(T)

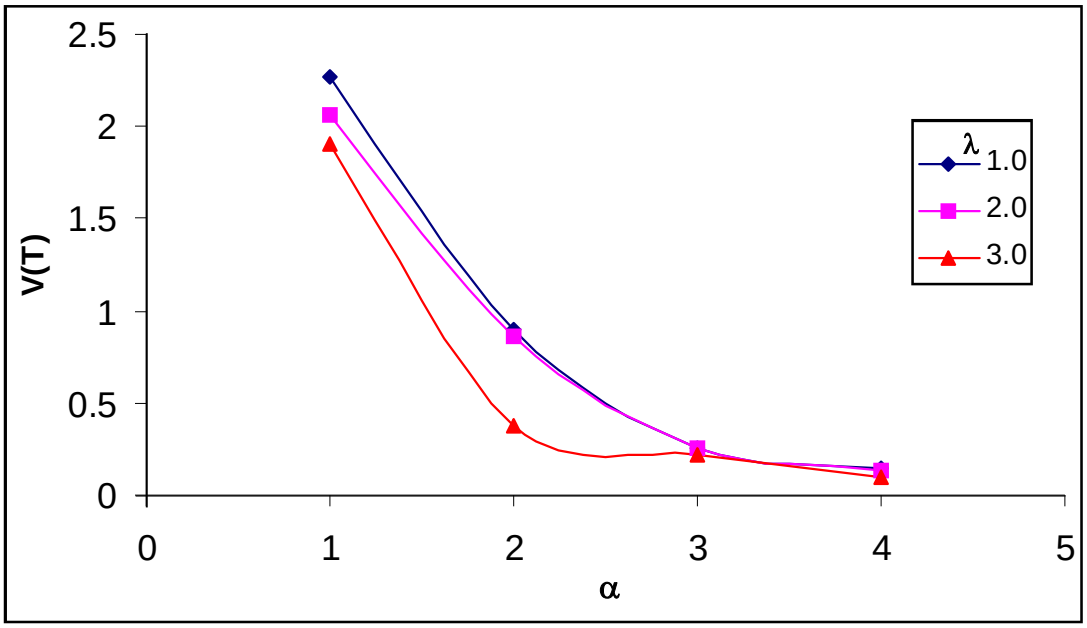

Figure 5.4 Variation of α with V(T)

Conclusion

In Table 5.1 the changes of E(T) and V(T) consequent to the increase the values of α, namely the parameter of the distribution of the interarrival times in considered three different cases namely c = 1.5, c = 2.5 and c = 3.5 are compared where λ is the parameter of the change point. For c =1.5, it may be noted that expectation of T and variance both decreases as α increases. This is due to the fact that $\theta_1<\theta_2$, c is the parameter of the random variable X_i denoting the contribution to antigenic diversity is more and so the expected time to cross the threshold namely E(T) and its variance decreases.

In Table 5.2. the changes of E(T) and V(T) consequent to the increase the values of α namely the parameter of the distribution of the interarrival times is considered three different cases namely λ=1.0, λ=2.0, and λ=3.0 are compared, where λ is the parameter of change point. For λ=1.0, it may be noted that expectation of T and V(T) both decreases as α increases. This is due to the fact that E(U) = 1/α which is the average interarrival time. So as α increases 1/α decreases which implies decrease in interarrival times. These results in more frequent contacts and more contribution to antigenic diversity and so E(T) decreases. As the value of the parameter λ namely the parameter of the random variable denoting the change point, the value of E(T) decreases in relation to the λ=1.0 case when λ=3.0 the changes in E(T) and V(T) in relation to the case λ =2.0 is only marginal.

References

1. Esary, J. D., Marshall, A. W. and Proschan, I'., Shock models and wear processes. Ann. Probability, 627-649 (1973).
2. Martin Nowak, A. and Robert May, M., Mathematical Biology of HIV infections. Antigenic Variation and Diversity Threshold. *Mathematical Biosciencsl06,* 1-21 (1991).
3. Raja Rao, B., Life Expectancy for a Class of Life Distributions having the "Setting the Clock Back to Zero" property, *Mathematical Biosciences 98,* 251-271 (1990).
4. Sathiyamoorlhi, R. and Kannan, R., Stochastic model for the time to scro-conversion of HIV transmission. *Journal of Kerala Statistical Association* Vol. *12,* 23-28 Dec. (2001).