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Seroconversion of HIV infected with correlated intercontact times and antigenic diversity threshold with scbz property

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Abstract
The incidence and spread of HIV and consequently the incidence of AIDS are on the increase all over the world. The antigenic diversity of the invading antigens creates innumerable problems for the medical research persons who attempt to find a cure for this infection. The expected time to seroconversion of the infected is an important aspect of consideration. Several results have been obtained in this direction. In this paper the expression for expected time to seroconverion is derived under the assumptions that the interarrival times between sexual contacts are constantly correlated and the antigenic diversity threshold of the infected is a random variable satisfying the Setting the Clock Back to Zero (SCBZ) property. Numerical illustrations are also provided.

Keywords: Human Immuno – deficiency Virus, Antigenic diversity threshold, Acquired Immuno Deficiency syndrome, Seroconversion. SCBZ Property.

1. Introduction
The incidence and spread of Acquired Immuno Deficiency Syndrome (AIDS) as a consequence of Human Immuno deficiency Virus (HIV) infection is on the increase in many countries of the world. It has created rather a pandemic situation. Not only the infected suffer but also the government of those countries face a critical situation due to the huge expenditure involved to contain the epidemic and to provide rehabilitative measures for those who are infected. Biological aspects of this infection create numerous problems for the medical research persons also.

One of the modes of transmission of HIV from the infected to any other person is by sexual contacts. The transmission of HIV from the infected to the other leads to the contribution of antigenic diversity of the antigen which inturn increases the survival of the antigens. The antibodies developed by the human immune system are unable to suppress invading antigens. Ultimately by there is damage of CD4 lymphocytes which results in the downfall of the human immune mechanism. Hence the seroconversion of the HIV infected occurs and the person infected becomes seropositive. Every person possesses the immune ability which is of random nature and changes from one to another. This level of immune ability of the infected person can be represented as the antigenic diversity threshold. If the total antigenic diversity of the invading antigens crosses this threshold the person becomes seropositive. Several authors have discussed stochastic models for the estimation of expected time to seroconversion. [1] have derived the expected time to seroconversion, under the assumption that the antigenic diversity is the total of three segments. [2] have obtained the expected time to seroconversion assuming that the antigenic diversity threshold is distributed as first order statistic. [3] have obtained the expression for the determination of antigenic diversity threshold. The distribution of sum of correlated random variables has been discussed by [4]. [5] have discussed the concept of Setting the Clock Back to Zero Property (SCBZ) Using these concepts the expected time to seroconversion of HIV infected is derived in this paper. The following are the assumptions which are made in deriving the results.

1. Assumptions

1. On every occasion of sexual contacts between the infected and the uninfected, there is transmission of HIV and it contributes a random amount of antigenic diversity in the uninfected.
2. The time interval between successive contacts are random variables which are constantly correlated exchangeable and with exponential distribution.
3. If the antigenic diversity crosses a particular level called the threshold the seroconversion takes place.
4. The process which generates the contacts, the sequence of damages and the threshold are independent.

2. Notations

Xi = a random variable which indicates the amount of contribution to antigenic diversity during the i^{th} contact, i = 1, 2, 3…, k, and has p.d.f g (.) and c.d.f G (.)

Y = a random variable denoting the antigenic diversity threshold and it satisfies the SCBZ property. Y has p.d.f h(.) and c.d.f H(.)

U_i = a random variable denoting the interarrival times between successive contacts and U_i, i = 1,2,3,.., k are constantly correlated exchangeable exponential random variables with p.d.f f(.) and c.d.f F(.).

T = a random variable denoting the time to serconversion and has p.d.f l(t) and c.d.f L(t)

*l** (s) = Laplace transform of l(t) and L(t) respectively.

3. Results

A person has k contacts during (0, t). Let Xi, i = 1, 2,3,…, k, be the amount of contribution to the antigenic diversity and so $\sum_{i=0}^{K} X_i$ is the total manganitute of contribution to antigenic diversity.

Let Y be the antigenic diversity threshold which is a random variable. Y satisfies the SCBZ property, due to Raja Rao and Talwalker (1990). This is justified by the fact that when a person is exposed to HIV infection and when the person is getting aged, the immune capacity of the individual undergoes a change. This inurn has its impact on the antigenic diversity threshold of the individual.

The p.d.f of Y satisfies the SCBZ property so that the p.d.f of Y undergoes a parametric change after a truncation point denoted as y_0

$$h\,(y) = \theta_1{}^{-\theta_1 y}\; if\; y \le y_0.$$
$$= \theta_2{}^{-\theta_2 y}\, e^{y_0(\theta_2 - \theta_1)}\; if\; y > y_0 \qquad (1)$$

It can be shown that $\int_0^{\infty} h(y)dy = 1$

Here y_0 is the truncation point which itself is a random variable following exponential distribution parameter λ

y_0 has p.d.f $\lambda\, e^{-\lambda y_0}$

The c.d.f of y_0 is F(y) = P [$y_0 \le$ y]

$= 1 - e^{-\lambda y}$

P [$y_0 >$ y] = $e^{-\lambda y}$

Now,

$$h(y) = \theta_1 e^{-\theta_1 y}\, \mathrm{P}[y \le y_0] + \theta_2 e^{-\theta_2 y_0(\theta_2 - \theta_1)}\mathrm{P}[y_0 > y]$$
$$= e^{-y(\theta_1+\lambda)}\frac{(\theta_1-\theta_2)(\lambda+\theta_1)}{(\lambda+\theta_1-\theta_2)} + \frac{\lambda\theta_2 e^{-\theta_2 y}}{\theta_1+\lambda-\theta_2}\, on\ simplification \qquad (2)$$

Now,

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

$$= 1 - \frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}\,e^{-(\lambda+\theta_1)y} - \frac{\lambda}{(\lambda+\theta_1-\theta_2)}\,e^{-\theta_2 y} \qquad (3)$$

$$\therefore\ \overline{H\,(y)} = 1 - H\,(y)$$

$$\frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}e^{-(\lambda+\theta_1)y} + \frac{\lambda}{(\lambda+\theta_1-\theta_2)}\,e^{-\theta_2 y}\quad on\ simplification \qquad (4)$$

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

$$= \frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}\int_0^{\infty} g_k(x)\,e^{-(\lambda+\theta_1)x}dx + \frac{\lambda}{(\lambda+\theta_1-\theta_2)}\int_0^{\infty} g_k(x)\,e^{-\theta_2 x}dx$$

$$= \frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}g_k{}^*(\lambda+\theta_1) + \frac{\lambda}{(\lambda+\theta_1-\theta_2)}g_k{}^*(\theta_2) \qquad (5)$$

S (t) = pr [there are exactly k contacts in (0,t) and the total antigenic diversity does not exceed the threshold level]

$$= \sum_{k=0}^{\infty}[F_k(t) - F_{k+1}(t)]\ \mathrm{P}\left[\sum_{i=1}^{k} x_i < Y\right]$$

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

$= T_1 + T_2$

$$T_1 = \sum_{k=0}^{\infty}[F_k(t) - F_{k+1}(t)]\left\{\left(\frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}\right)g_k{}^*(\lambda + \theta_1)\right\} \qquad (6)$$

$$T_2 = \sum_{k=0}^{\infty}[F_k(t) - F_{k+1}(t)]\frac{\lambda}{(\lambda+\theta_1-\theta_2)}g_k{}^*(\theta_2) \qquad (7)$$

we have,

$$T_1 = \left(\frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}\right)\sum_{k=0}^{\infty}[F_k(t)-F_{k+1}(t)]g_k{}^*(\lambda+\theta_1)$$

Consider

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

$$= 1-[1-g^*(\lambda+\theta_1)]\sum_{k=1}^{\infty}F_k(t)\,[g^*(\lambda+\theta_1)]^{k-1}\ on\ \ simplfication$$

$$T_1 = \frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)} - \frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)}[1-g^*(\lambda+\theta_1)]\sum_{k=1}^{\infty}F_k(t)\,[g^*(\lambda+\theta_1)]^{k-1} \quad (8)$$

Now,

$$T_2 = \frac{\lambda}{(\lambda+\theta_1-\theta_2)} - \frac{\lambda}{(\lambda+\theta_1-\theta_2)}[1-g^*(\theta_2)]^{k-1}$$

L (t) = 1- S (t)

$$= 1-\left[\frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)}+\frac{\lambda}{(\lambda+\theta_1-\theta_2)}\right] + \frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)}[1-g^*(\lambda+\theta_1)]\sum_{k=1}^{\infty}F_k(t)\,[g^*(\lambda+\theta_1)]^{k-1} + \frac{\lambda}{(\lambda+\theta_1-\theta_2)}[1-g^*(\theta_2)]\sum_{k=1}^{\infty}F_k(t)\,[1-g^*(\theta_2)]^{k-1} \quad (9)$$

Taking Laplace transform of L (t), we have

$$L^*(\mathrm{s}) = \frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)}\,[1-g^*(\lambda+\theta_1)]\sum_{k=1}^{\infty}F^*{}_k(s)\,[g^*(\lambda+\theta_1)]^{k-1} + \frac{\lambda}{(\lambda+\theta_1-\theta_2)}\,[1-g^*(\theta_2)]\sum_{k=1}^{\infty}F^*{}_k(s)\,[1-g^*(\theta_2)]^{k-1} \quad (10)$$

Since the interarrival times between successive contacts U_i, i= 1,2,3, …,k are constantly correlated and exchangeable exponential random variables with parameter 'a' we have from Gurland (1955).

$$f_k{}^*(s) = \frac{1}{(1+bs)\left[1+\frac{kRbs}{(1-R)(1+bs)}\right]} \quad (11)$$

Where $f_k{}^*(s)$ is the Laplace transform of f_k (x); b = a (1-R) and R is the constant correlation coefficient

$$since\ F_k{}^*(s) = \frac{f_k{}^*(s)}{s}\ and\quad L^*\,(s) = \frac{l^*\,(s)}{s}, we\ have$$

$$l^*\,(s) = \frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\lambda+\theta_1)]}{g^*(\lambda+\theta_1)}\sum_{k=1}^{\infty}f_k{}^*(s)\,[g^*(\lambda+\theta_1)]^k + \frac{\lambda}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\theta_2)]}{g^*(\theta_2}\sum_{k=1}^{\infty}f_k{}^*(s)\,[1-g^*(\theta_2)]^k \quad (12)$$

$$l^*(s) = \frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\lambda+\theta_1)]}{g^*(\lambda+\theta_1)}(1-R)\sum_{k=1}^{\infty}(1-R+bs-Rbs+kRbs)^{-1}\,[g^*(\lambda+\theta_1)]^k$$

$$\therefore A = \frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\lambda+\theta_1)]}{g^*(\lambda+\theta_1)}\,(1-R)\sum_{k=1}^{\infty}(1-R)[1-R+bs-Rbs+kRbs]^{-1}\,[g^*(\lambda+\theta_1)]^k$$

$$\therefore B = \frac{\lambda}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\theta_2)]}{g^*(\theta_2)}\sum_{k=1}^{\infty}\frac{(1-R)g^*(\theta_2)^k}{[1-R+bs-Rbs+kRbs]}$$

$$Now\ \left.\frac{dl^*(s)}{ds}\right|_{s=0} = \left.\frac{dA}{ds}\right|_{s=0}+\left.\frac{dB}{ds}\right|_{s=0}$$

$$= \frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\lambda+\theta_1)]}{g^*(\lambda+\theta_1)}\,(1-R)\sum_{k=1}^{\infty}(-1)(1-R+bs-Rbs+kRbs)^{-1}\,[g^*(\lambda+\theta_1)]^{-2}(b-Rb+kRb)\,[g^*(\lambda+\theta_1)]^k + \frac{\lambda}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\theta_2)]}{g^*(\theta_2)}\frac{b}{(1-R)}\sum_{k=1}^{\infty}g^*(\theta_2)^k\,[1-R+kR]$$

$$\therefore \left.\frac{dA}{ds}\right|_{s=0} = \frac{\theta_1-\theta_2}{(\lambda+\theta_1-\theta_2)}\frac{[1-g^*(\lambda+\theta_1)]}{g^*(\lambda+\theta_1)}(b)\frac{1}{(1-R)}\sum_{k=1}^{\infty}(1-R+kR)g^*(\lambda+\theta_1)^k \quad (13)$$

$$if\ X\sim\exp(\alpha)\ \ then\ g^*(\lambda+\theta_1) = \frac{\alpha}{(\alpha+\lambda+\theta_1)}$$

$$= \frac{(\theta_1-\theta_2)(\lambda+\theta_1)^2\alpha(1-R)}{(\alpha+\lambda+\theta_1)^2(\lambda+\theta_1-\theta_2)} + \frac{\alpha^2(\theta_1-\theta_2)(\lambda+\theta_1)R}{(\alpha+\lambda+\theta_1)^2(\lambda+\theta_1-\theta_2)} \text{ on simplication}$$

$$\frac{-dB}{ds}\Big|_{s=0} = \frac{\lambda}{(\lambda+\theta_1+\theta_2)} \frac{[1-g^*(\theta_2)]}{g^*(\theta_2)} \sum_{k=1}^{\infty}(1-R)\, g^*(\theta_2)^k(-1)\,[1-R+bs-Rbs+kRbs]^{-2}[b-Rb+kRb] \quad (14)$$

Since g(.) ~ exp (α) we have $g^*(\theta_2)\ \frac{\alpha}{\alpha+\theta_2}$

$$= \frac{b\lambda(\alpha+\theta_2)}{(\lambda+\theta_1-\theta_2)}\left[1+\frac{R(\alpha+\theta_2)}{\theta_2}\right]$$

$$= \frac{b\lambda(\alpha+\theta_2)}{(\lambda+\theta_1-\theta_2)}\left[\frac{\theta_2+R\alpha+R\theta_2}{\theta_2}\right] \text{ on simplification}$$

$$\therefore E(T) = \frac{-dA}{ds}\Big|_{s=0} + \frac{-dB}{ds}\Big|_{s=0}$$

$$E(T) = \frac{a(1-R)\,\lambda(\alpha+\theta_2)}{(\lambda+\theta_1-\theta_2)} \frac{\theta_2+R\alpha+R\theta_2}{\theta_2} \text{ on simplification} \quad (15)$$

Now

$$\frac{dA}{ds} = \frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)} \frac{[1-g^*(\lambda+\theta_1)]}{g^*(\lambda+\theta_1)}(1-R)\sum_{k=1}^{\infty}(-1)\,[1-R+bs-Rbs+kRbs]^{-2}[b-Rb+kRb][g^*(\lambda+\theta_1)^k]$$

$$= \frac{(\theta_1-\theta_2)}{(\lambda+\theta_1-\theta_2)} \frac{[1-g^*(\lambda+\theta_1)]}{g^*(\lambda+\theta_1)} \frac{2b^2}{(1-R)^2}\sum_{k=1}^{\infty}(1-R+kR)^2[g^*(\lambda+\theta_1)]^k \quad (16)$$

$$\frac{d^2B}{ds^2}\Big|_{s=0} = \frac{\lambda}{(\lambda+\theta_1+\theta_2)} \frac{[1-g^*(\theta_2)]}{g^*(\theta_2)}(1-R)2b^2\sum_{k=1}^{\infty}[g^*(\theta_2)]^k(1-R)^{-3}[1-R+kR]^{-2} \quad (17)$$

$$g^*(\lambda+\theta_1) = \frac{\alpha}{\alpha+\lambda+\theta_1} \text{ and } g^*(\theta_2) = \frac{\alpha}{\alpha+\theta_2}$$

We have

$$\text{Now, } E(T^2) = \frac{d^2A}{ds^2}\Big|_{s=0} + \frac{d^2B}{ds^2}\Big|_{s=0}$$

$$= \frac{2(\theta_1-\theta_2)a^2}{(\lambda+\theta_1-\theta_2)^{\alpha}}\left[1+\frac{2R(1-R)}{(\lambda+\theta_1)}+\frac{2R^2}{(\lambda+\theta_1)^2}+\frac{R}{(\lambda-\theta_1)}\right] + \frac{2\lambda a^2(1-R)^2\alpha}{(\lambda+\theta_1-\theta_2)}\left[1+\frac{2R(\alpha+\theta_2)}{\theta_2}+\frac{R^2}{(1-R)}\frac{2(\alpha+\theta_2)}{{\theta_2}^2} + \frac{2R^2}{(1-R)^2}\frac{(\alpha+\theta_2)}{\theta_2}\frac{1}{\alpha}\right] \quad (1$$

Using $E(T^2)$ and E (T) we can find V (T)

$$V(T) = \frac{2(\theta_1-\theta_2)a^2(1-R)}{(\lambda+\theta_1-\theta_2)\alpha^2}\left[(1-R)\alpha+\frac{2R\alpha(\alpha+\lambda+\theta_1)}{(\lambda+\theta_1)} + \frac{R^2}{(1-R)}\frac{2\alpha^2(\alpha+\lambda+\theta_1)}{(\lambda+\theta_1)^2}+\frac{R^2}{(1-R)}\frac{\alpha(\alpha+\lambda+\theta_1)}{(\lambda+\theta_1)}\right] + \frac{2\lambda a^2(1-R)}{(\lambda+\theta_1-\theta_2)}\left[(1-R)\alpha+\frac{2R\alpha(\alpha+\theta_2)}{\theta_2} + \frac{R^2}{(1-R)}\frac{2\alpha^2(\alpha+\theta_2)}{\theta_2}+\frac{R^2}{(1-R)}\frac{2(\alpha+\theta_2)}{\theta_1}\right] - \left[\frac{\alpha(1-R)\lambda(\alpha+\theta_2)}{(\lambda+\theta_1-\theta_2)}\frac{\theta_2-R\theta_2}{\theta_2}\right]^2 \quad (19)$$

4. Numerical illustration

Using the expressions for E (T) and V (T), the variation in the same are found out due to the changes that occur in the different parameter involved in E(T)and V(T).

Table 1

$\theta_1 = 1$ $\theta_2 = 1.5$	$\lambda = 1.5$	$R = 0.8$ $\alpha = 1.4$
a	E(T)	V(T)
1.2	0.548	0.635
1.4	0.696	0.754
1.6	0.86	0.965
1.8	1.04	1.345
2	1.236	2.396

Fig 1

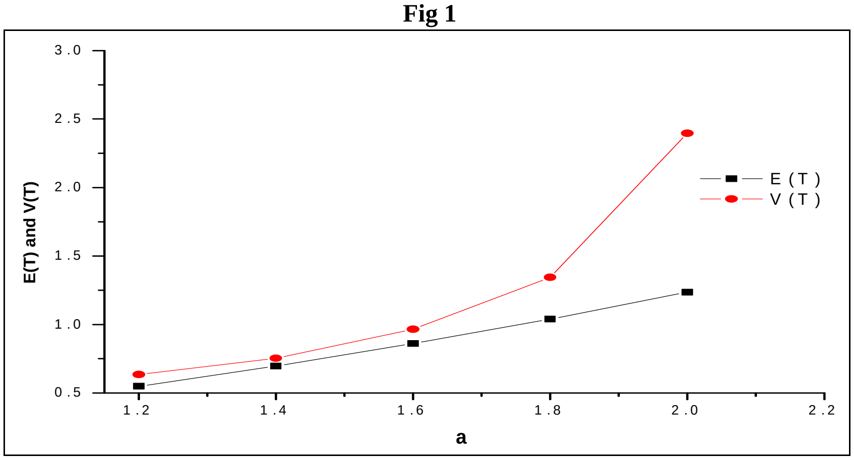


Table 2

$a = 1.2 \quad \theta_2 = 1.5 \quad \lambda = 1.5 \quad R = 0.8 \quad \alpha = 1.4$		
θ_1	E(T)	V(T)
1	0.548	0.487
1.2	0.602	0.509
1.4	0.643	0.545
1.6	0.675	0.598
1.8	0.7	0.675

Fig 2

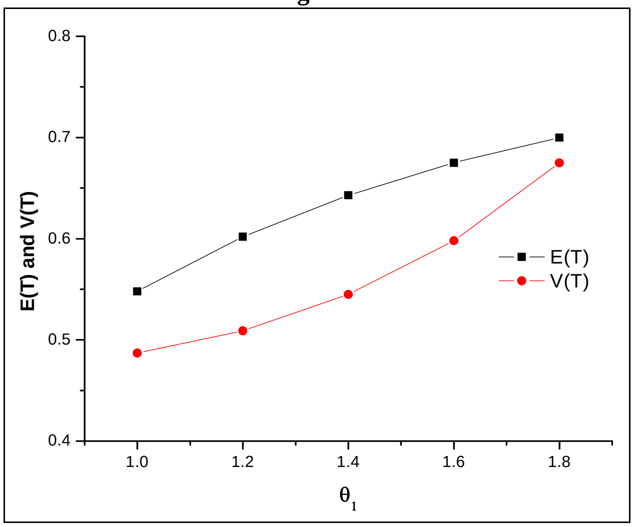


Table 3

$\theta_1 = 1 \quad a = 1.2 \quad \lambda = 1.5 \quad R = 0.8 \quad \alpha = 1.4$		
θ_2	E(T)	V(T)
1.5	0.548	0.782
1.7	0.439	0.645
1.9	0.345	0.598
2.1	0.263	0.412
2.3	0.19	0.375

Fig 3

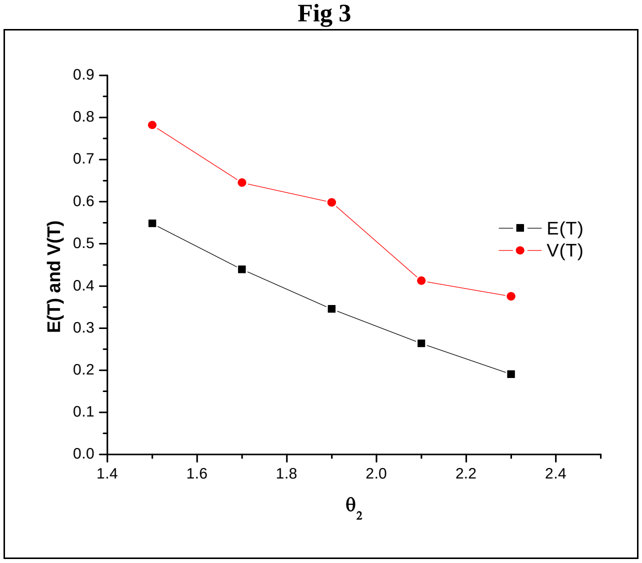


Table 4

$\theta_1 = 1 \quad \theta_2 = 1.5 \quad a = 1.2 \quad R = 0.8 \quad \alpha = 1.4$		
λ	E(T)	V(T)
1.5	0.548	0.782
1.7	0.623	0.872
1.9	0.687	0.899
2.1	0.744	0.982
2.3	0.795	1.025

Fig 4

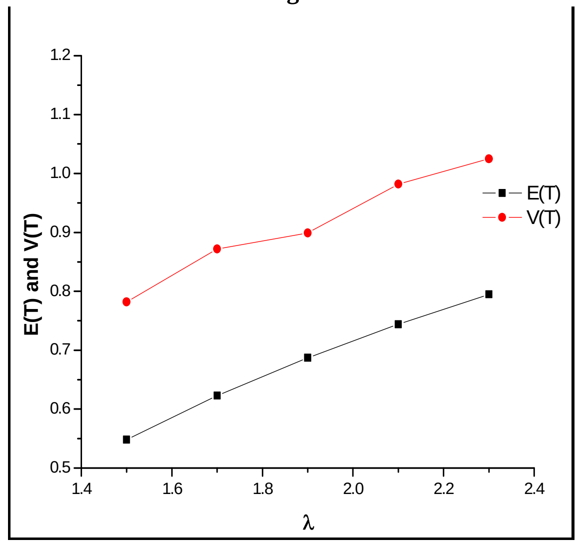


Table 5

$\theta_1 = 1 \quad \theta_2 = 1.5 \quad a = 1.2 \quad \lambda = 1.5 \quad \alpha = 1.4$		
R	E(T)	V(T)
0.2	1.578	0.988
0.4	1.485	0.912
0.6	1.142	0.899
0.8	0.548	0.796
1	0.296	0.584

Fig 5

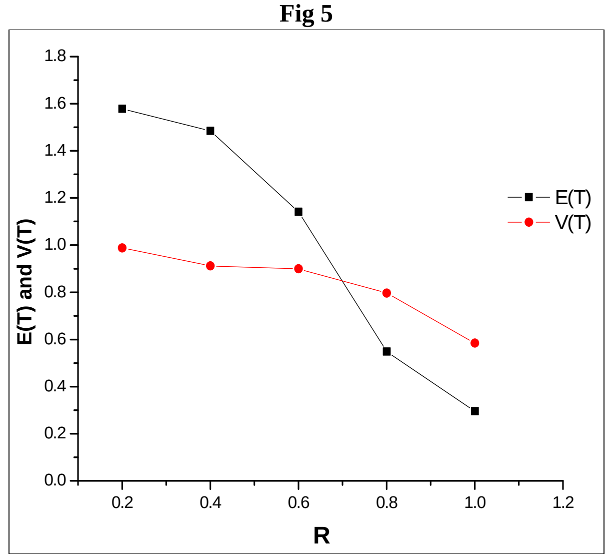
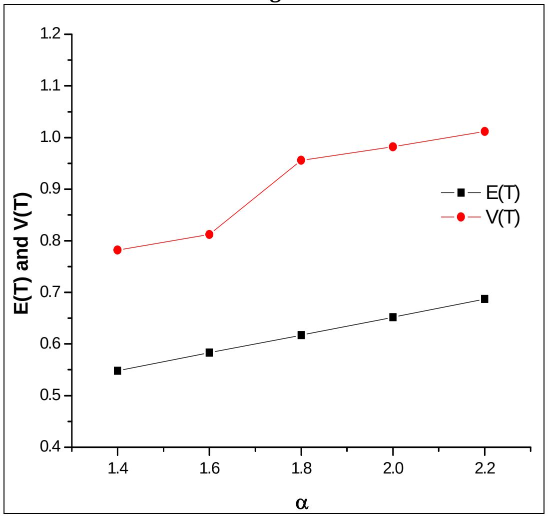


Table 6

$\theta_1 = 1 \quad \theta_2 = 1.5 \quad a = 1.2 \quad \lambda = 1.5 \quad R = 0.8$		
α	E(T)	V(T)
1.4	0.548	0.782
1.6	0.583	0.812
1.8	0.617	0.956
2	0.652	0.982
2.2	0.687	1.012

Fig 6



6. Conclusion

One the basis of the numerical illustration worked out for this model, the following conclusions could be drawn

1) If the value of 'a' which is the parameter of the exponetional distribution of the correlated exchangeable random variables X_i indicating the interarrival times between sexual contacts increases then E (T) increases. This is due to the fact that as 'a' increases E (U_i) increases and so the interarrival times are large. So E (T) increases. V (T) also increases. This is given in table (1) and figure (1).
2) If θ_1 which is the parameter of the random variable Y indicating the antigenic diversity threshold before the truncation point increases E(T) and V(T) both increase, as indicated in table (2) and figure (2).
3) If θ_2 which is the parameter of Y after the truncation point increases then E (T) decreases. This is due to the fact that E (Y) $=\frac{1}{\theta_2}$ and it decreases as θ_2 increases. Hence it takes less time to cross the threshold. It is given in table (3) and figure (3). V (T) also decreases.
4) If λ which is the parameter of y_0 the random variable which indicates the truncation point of Y increases then E $(y_0) = \frac{1}{\lambda}$ decreases. Then the truncation would at a lower value of Y. Hence E (T) increases, as indicated in table (4) and figure (4).this is also the case with V (T).
5) If 'R' which is coefficient of correlation between successive U_i values, then E(T) and V(T) decrease as in indicated in Table (5) and Figure (5).
6) If 'α' which is the parameter of X_i, indicating the contribution to antigenic diversity increases then $E(X_i) = \frac{1}{\alpha}$ decreases. This means that the average contribution to antigenic diversity decreases and E (T) increases, as indicated in Table (6) Figure (6). The same is true for V (T).

7. Reference

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