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A STOCHASTIC MODEL WITH ANTIGENIC DIVERSITY THRESHOLD OF HIV TRANSMISSION UNDER CORRELATED INTERCONTACT TIMES

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ABSTRACT

This paper focuses on the study of a stochastic model for predicting the time to cross antigenic diversity threshold of HIV transmission under correlated inter contact times. In the estimation of expected time to cross the antigenic diversity threshold of HIV infected, there is an important role for the inter-arrival time between successive contact and it has a significant influence. We propose a stochastic model assuming the inter contact time between successive contact as correlated random variable and threshold distribution is mixed exponential distribution. The expected time to seroconversion and its variance are derived and numerical illustrations are provided.

Key words: *Human Immuno– deficiency Virus, Antigenic diversity threshold, intercontact times, Seroconversion, Acquired Immuno Deficiency syndrome.*

INTRODUCTION:

The use of stochastic model in the study of HIV infection, transmission and the spread of AIDS is quite common. The HIV can be transmitted through a variety of contact mechanisms that include homo or hetro sexual contacts, transfusion of HIV blood products, needle sharing among intravenous drug abuse and mother to fetus. The most common means of spread of this infection is only by sexual contacts. If more and more of HIV are getting transmitted from the infected person to the uninfected, the antigenic variation would be on the increase. If the antigenic diversity crosses a particular level which is known as the antigenic diversity threshold, the immune system collapses and seroconversion takes place. For a detailed study of antigenic diversity threshold and its estimation one can refer to Nowak and May (1991) and Stiliankis et al (1994).

A stochastic model based on the cumulative damage process has been derived by Sathiyamoorthi and Kannan (2001) and using this model it is possible to obtain the expected time to seroconversion and its variance. Every contact is depicted as a shock and in every contact there is some contribution to antigenic diversity which in other words is the damage to the immune capacity of an individual. Cumulative damage process and shock model are widely known in reliability theory. A detailed account of the same could be seen in Esary et al (1973).

In developing such a model the basic assumption made was that the intercontact timings between successive contacts are i.i.d random variables. In this paper a stochastic model assumes that the intercontact timings between successive contacts are correlated random variables. The assumption of correlated intercontact timings seems plausible by the fact that any partner after every contact with an index may have a change physiological obsession and fear of contracting the disease, which may have an impact on intercontact times of contacts such as prolongation of intercontact times. In this model a stochastic model assuming that the intercontact times between sexual contacts as, correlated random variables and the threshold distribution which follows mixed exponential distribution. Shock model with correlated intercontact times has been studied by Sathiyamoorthi (1979). In developing this model the result of Gurland (1955) has been used. Using the same concept, time to seroconversion and its variance are obtained in this paper. In this study the theoretical results are substantiated using numerical data simulated.

ASSUMPTIONS OF THE MODEL:

- Sexual contact is the only source of transmission of HIV.
- An uninfected individual has sexual contact with a HIV infected partner, and a random number of HIV is getting transmitted, at each contact.

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- An individual is exposed to a damage process acting on the immune system and the damage is assumed to be linear and cumulative.
- The intercontact times between successive contacts are not independent but are correlated..
- The total damage caused when exceeds a threshold level Y which itself is a random variable, the seroconversion occurs and a person is recognized as seropositive.
- The process which generates the contacts and the sequence of damages and the threshold 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 , $X_1, X_2, ..., X_n$ 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 which follows mixed exponential distribution with parameter (θ_1, θ_2), the p.d.f. being $h(.)$ and c.d.f. $H(.)$.

U_i a continuous random variable denoting the inter-arrival times 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 $F(.)$.

T a continuous random variable denoting the time to seroconversion with p.d.f. $l(.)$ and c.d.f. $L(.)$.

$V_k(t)$ is the probability of exactly k contacts in (0,t]

$l^*(s)$ is the Laplace transform of $l(t)$.

$f^*(s)$ is the Laplace transform of $f(t)$.

ρ the correlation between X_i and $X_j, i \neq j$

$Z_k \sum_{i=1}^{k} U_i$

RESULTS:

$S(t) = P(T > t)$

= Probability that the seroconversion does not take before t.

$= \sum_{k=1}^{\infty} P$ {no seroconversion before t / exactly k contacts in (0, t]}X P {exactly k contacts in (0, t]}

$= \sum_{k=1}^{\infty} V_k(t) \;\; P\left(\sum_{k=1}^{\infty} X_k < Y \right)$

It can be shown that

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

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

This gives the probability that in k contacts the increase in antigenic diversity does not cross the antigenic threshold level Y.

Let Y ~ mixed exponential (θ_1, θ_2)

$$h(y) = \beta\theta_1 e^{-\theta_1 y} + (1-\beta)\theta_2 e^{-\theta_2 y}$$

$$H(y) = \beta\theta_1 \int_0^y e^{-\theta_1 u}\, du + (1-\beta)\theta_2 \int_0^y e^{-\theta_2 u}\, du$$

$$= \beta\left(1-e^{-\theta_1 y}\right) + (1-\beta)(1-e^{-\theta_2 y})$$

$$\overline{H}(x) = \beta\left(e^{-\theta_1 y} - e^{-\theta_2 y}\right) + e^{-\theta_2 y}$$

$$\mathrm{P}\left[\sum_{i=1}^{k} \mathrm{X}_i < \mathrm{Y}\right] = \beta\, g_k^{*}(\theta_1) + (1-\beta) g_k^{*}(\theta_2)$$

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

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

On simplification

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

Let $U_1, U_2, ..., U_K$ represents the inter - arrival times between Successive contacts which are correlated. Gurland (1955) has derived the cumulative distribution function of the sum, say $Z_k = \sum_{i=1}^{k} U_i$, when $U_i{}'s$ from a sequence of exchangeable constantly correlated random variables each having exponential distribution with p.d.f

$$f(u) = \frac{1}{c} e^{-\frac{x}{c}}, c > 0, 0<\mathrm{X}<\infty. \quad (2)$$

Such that the correlation co-efficient between X_i and $X_j (i \neq j)$ is ρ.

The c.d.f is given by

$$F_k(u) = P[Z_k \leq u]$$

$$= (1-\rho)\sum_{i=0}^{\infty} \frac{(\rho k)^i \eta[k+i, u/b]}{[1-\rho+k\rho]^{i+1}(k+i-1)} \quad (3)$$

Where $b = c(1-\rho)$ and $\eta(k,u) = \int_0^u e^{-\tau}\tau^{k-1} d\tau$

Substitute equation (3) in (1)

$$L(t) = \beta(1-\rho)\left[1 - g^{*}(\theta_1)\right]\sum_{k=1}^{\infty} \left[g^{*}(\theta_1)\right]^{k-1} \sum_{k=1}^{\infty} \frac{(\rho k)^i \eta\left[k+i, \frac{u}{b}\right]}{(1-\rho+k\rho)^{i+1}(k+i-1)}$$

$$+ (1-\beta)(1-\rho)\left[1 - g^{*}(\theta_2)\right]\sum_{k=1}^{\infty} \left[g^{*}(\theta_2)\right]^{k-1} \sum_{k=1}^{\infty} \frac{(\rho k)^i \eta\left[k+i, \frac{u}{b}\right]}{(1-\rho+k\rho)^{i+1}(k+i-1)}$$

The Laplace Stieltje's transform of L (t) is

$$L^*(s) = s\int_0^\infty e^{-st}\beta(1-\rho)\left[1-g^*(\theta_1)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_1)\right]^{k-1}\sum_{k=1}^{\infty}\frac{(\rho k)^i\eta\left[k+i,\frac{u}{b}\right]}{(1-\rho+k\rho)^{i+1}(k+i-1)}dt$$

$$+ s\int_0^\infty e^{-st}(1-\beta)(1-\rho)\left[1-g^*(\theta_2)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_2)\right]^{k-1}\sum_{k=1}^{\infty}\frac{(\rho k)^i\eta\left[k+i,\frac{u}{b}\right]}{(1-\rho+k\rho)^{i+1}(k+i-1)}dt$$

$$L(t) = \beta\left[1-g^*(\theta_1)\right]s\int_0^\infty e^{-st}F_k(t)\sum_{k=1}^{\infty}\left[g^*(\theta_1)\right]^{k-1}dt + (1-\beta)\left[1-g^*(\theta_2)\right]s\int_0^\infty e^{-st}F_k(t)\sum_{k=1}^{\infty}\left[g^*(\theta_2)\right]^{k-1}dt$$

$$L^*(s) = \beta\left[1-g^*(\theta_1)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_1)\right]^{k-1}L_k{}^*(s) + (1-\beta)\left[1-g^*(\theta_2)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_2)\right]^{k-1}L_k{}^*(s)$$

Where $L_k{}^*(s)$ is the Laplace Stieltje's transform of $F_k(t)$

$$L^*(s) = \beta\left[1-g^*(\theta_1)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_1)\right]^{k-1}\frac{1}{(1+\mathrm{bs})^k\left[1+\frac{k\rho bs}{(1-\rho)(1+bs)}\right]}$$

$$+ (1-\beta)\left[1-g^*(\theta_2)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_2)\right]^{k-1}\frac{1}{(1+\mathrm{bs})^k\left[1+\frac{k\rho bs}{(1-\rho)(1+bs)}\right]}$$

$$L^*(s) = \beta\left[1-g^*(\theta_1)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_1)\right]^{k-1}\mathrm{g}^{\mathrm{k}}\left[1+\frac{\mathrm{k}\rho(1-\mathrm{g})}{(1-\rho)}\right]^{-1}$$

$$+ (1-\beta)\left[1-g^*(\theta_2)\right]\sum_{k=1}^{\infty}\left[g^*(\theta_2)\right]^{k-1}\mathrm{g}^{\mathrm{k}}\left[1+\frac{\mathrm{k}\rho(1-\mathrm{g})}{(1-\rho)}\right]^{-1}$$

Where $g = (1+bs)^{-1}$ *and* $g^*(\theta_1) = \frac{\alpha}{\alpha+\theta_1}, g^*(\theta_2) = \frac{\alpha}{\alpha+\theta_2}$

$$E(T) = \mu_1{}' = -\frac{d}{ds}L^*(s)\big/_{s=0}$$

$$= c\left[\frac{\beta(\alpha+\theta_1)}{\theta_1} + \frac{(1-\beta)(\alpha+\theta_2)}{\theta_2}\right] \tag{4}$$

$$E(T^2) = \mu_2{}' = \frac{d^2}{ds^2}L^*(s)\big/_{s=0}$$

$$= 2c^2\left[\frac{\beta(\alpha+\theta_1)}{\theta_1{}^2}\left(\alpha\left(1+\rho^2\right)+\theta_1\right) + \frac{(1-\beta)(\alpha+\theta_2)}{\theta_2{}^2}\left(\alpha\left(1+\rho^2\right)+\theta_2\right)\right]$$

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

$$= 2c^2\left[\frac{\beta(\alpha+\theta_1)}{\theta_1^2}\left(\alpha\left(1+\rho^2\right)+\theta_1\right) + \frac{(1-\beta)(\alpha+\theta_2)}{\theta_2^2}\left(\alpha\left(1+\rho^2\right)+\theta_2\right)\right] - \left\{c\left[\frac{\beta(\alpha+\theta_1)}{\theta_1} + \frac{(1-\beta)(\alpha+\theta_2)}{\theta_2}\right]\right\}^2 \tag{5}$$

It may be observed that the expected time to seroconversion remains unaffected even if the interarrival times are correlated but the variance is a function of ρ. If we put $\rho = 0$ in equation (5) the expression for variance coincides with that of the in uncorrelated case obtained by kannan et al (2011).

Table-1

$\alpha = 0.1, \beta = 0.5, \theta_1 = 1, \theta_2 = 1, \rho = 0.1$		
c	E(T)	V(T)
1	1.1	1.23200
2	2.2	4.92800
3	3.3	11.0880
4	4.4	19.7120
5	5.5	30.8000
6	6.6	44.3520
7	7.7	60.3680
8	8.8	78.8480
9	9.9	99.7920
10	11	123.200

Figure-1

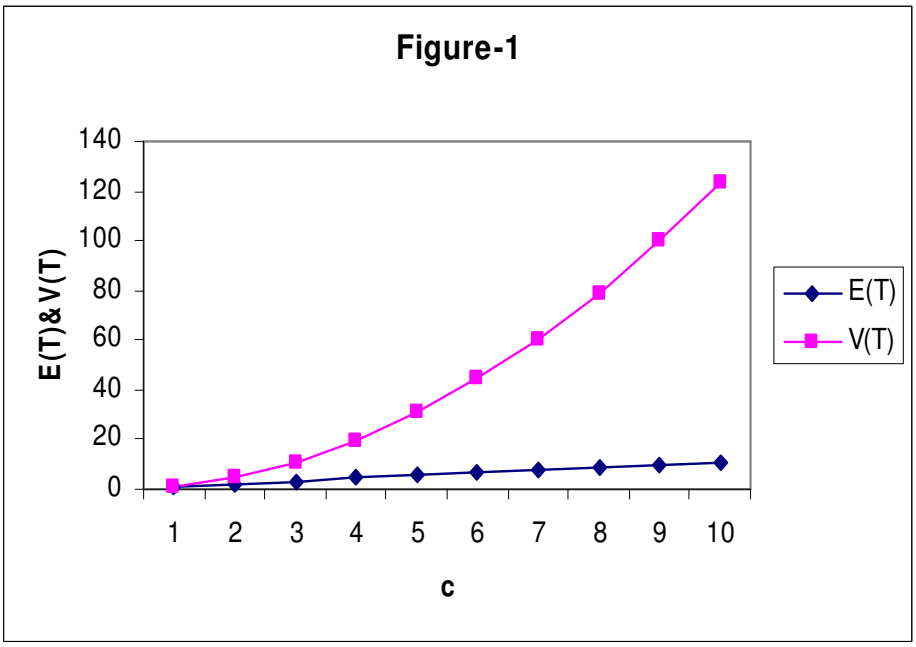


Table-2

$c=1.5, \beta=0.5, \theta_1=1, \theta_2=1, \rho=0.1$		
α	E(T)	V(T)
0.1	1.65	2.772
0.2	1.80	3.348
0.3	1.95	3.978
0.4	2.10	4.662
0.5	2.25	5.400
0.6	2.40	6.192
0.7	2.55	7.038
0.8	2.70	7.938
0.9	2.85	8.892

Figure-2

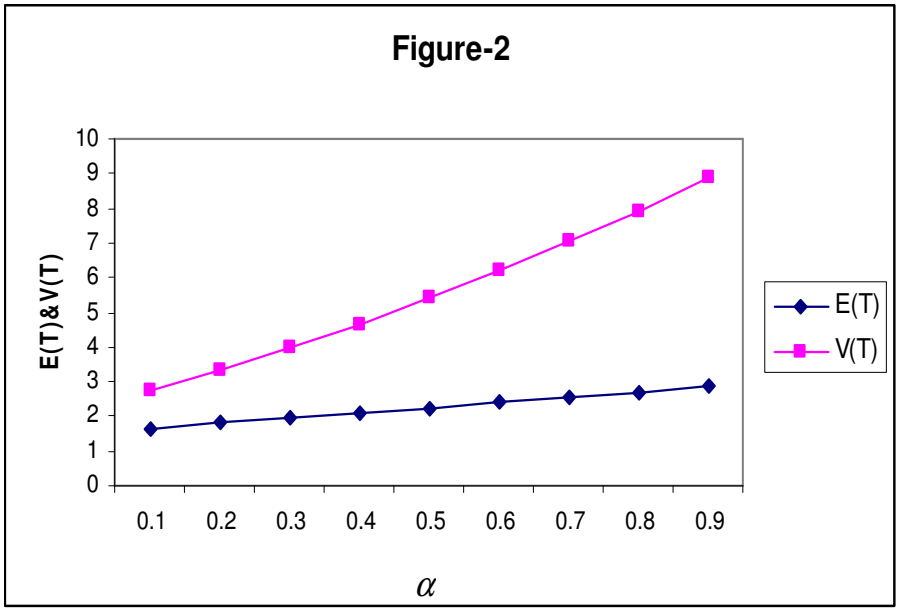


Table-3

$\alpha = 0.1, \beta = 0.5, c = 1.5, \theta_2 = 1, \rho = 0.1$		
θ_1	E(T)	V(T)
0.5	1.725000	3.065625
1	1.650000	2.772000
1.5	1.625000	2.682625
2	1.612500	2.639531
2.5	1.605000	2.614185
3	1.600000	2.597500
3.5	1.596429	2.585686
4	1.593750	2.576883
4.5	1.591667	2.570069
5	1.590000	2.564640

Figure-3

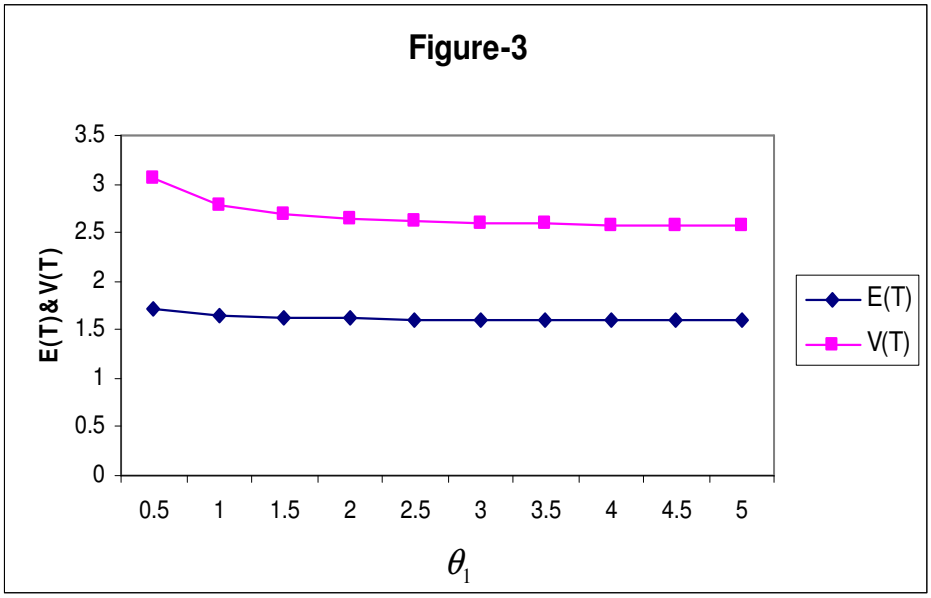


Table-4

$\alpha = 0.1, \beta = 0.5, \theta_1 = 1, c = 1.5, \rho = 0.1$		
θ_2	E(T)	V(T)
1.5	1.625000	2.682625
2.5	1.605000	2.614185
3.5	1.596429	2.585686
4.5	1.591667	2.570069
5.5	1.588636	2.560212
6.5	1.586538	2.553424
7.5	1.585000	2.548465
8.5	1.583824	2.544684
9.5	1.582895	2.541705
10.5	1.582143	2.539298

Figure-4

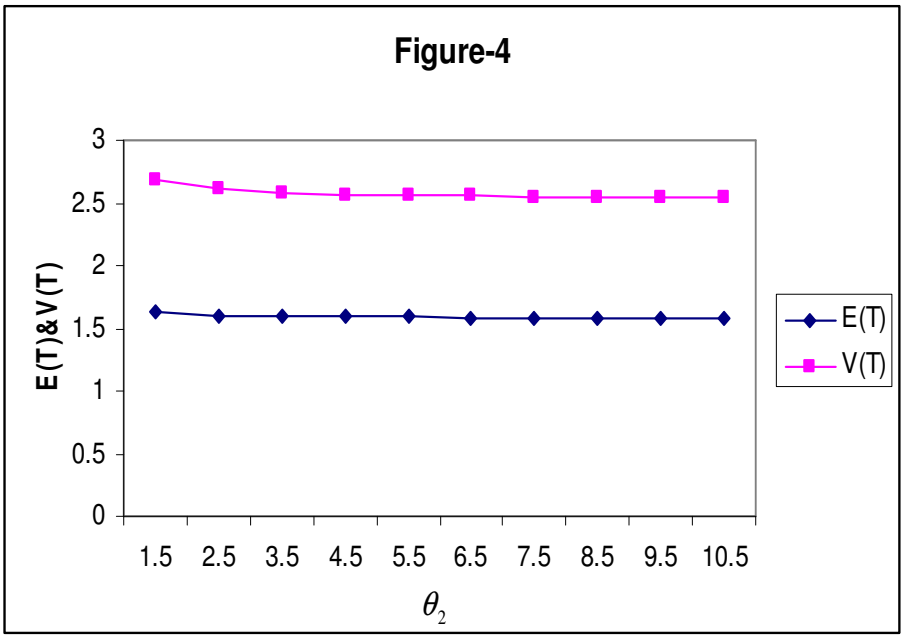
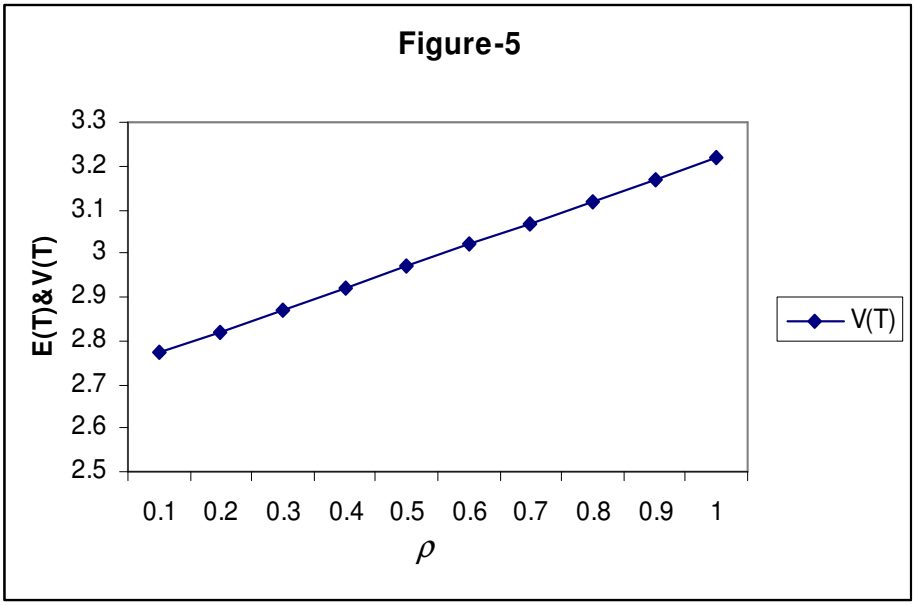


Table-5

$\alpha = 0.1, \beta = 0.5, \theta_1 = 1, \theta_2 = 1, c = 1.5$	
ρ	V(T)
0.1	2.7720
0.2	2.8215
0.3	2.8710
0.4	2.9205
0.5	2.9700
0.6	3.0195
0.7	3.0690
0.8	3.1185
0.9	3.1680
1	3.2175



CONCLUSIONS:

The variation in E(T) and V(T) for fixed value of $\alpha, \beta, \rho, \theta_1 and \theta_2$ when c has variation is given in Table-1 .As the parameter of the threshold distribution c increases the mean time to seroconversion as well as variance time to seroconversion are increases.

In table -2 the variation in E (T) and V (T) are indicated and when the parameter of α which is the parameter of the distribution of the random variable indicating amount of contribution to antigenic diversity increases for fixed value of $c, \beta, \rho, \theta_1 and \theta_2$. It may be observed that E (T) increases as α increases and also
V (T).

This is due to the fact that g (.) ~ Exp (α) so that E(x) = $\frac{1}{\alpha}$ which means that the average contribution to the antigenic diversity is smaller as α increases, so that both E (T) and V (T) are on the increase.

It is observed from the Table-3 also the graph as the value θ_1 which is the parameter of the mixed exponential distribution of the threshold increases the mean time to seroconversion is decreases. It is also quite reasonable as regards the variation it could be seen the value of θ_1 increases the variance decreases.

From the table-4 we observed that for fixed $\alpha, \beta, \rho, c, and \theta_1$ when θ_2 is allowed to increase then mean time to seroconversion decreases. The same tendency is also noted on the variance of the seroconversion time of the HIV transmission.

With regard to variance it can be seen that for fixed $\alpha, \beta, c, \theta_1 and \theta_2$ as ρ Increases the variance of the time to seroconversion increases.

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