St. Joseph's Journal of Humanities and Science
ISSN: 2347 - 5331
http://sjctnc.edu.in/6107-2/

ESTIMATION OF EXPECTED TIME TO SEROCONVERSION WHEN BOTH ANTIGENIC DIVERSITY THRESHOLD AND VIRULENCE THRESHOLD FOLLOWS ORDER STATISTIC

- R. Ramajayam *
- R. Lakshmijayam **
- Mercy Anthony ***

ABSTRACT

The incidence and spread of Human Immune Deficiency Virus (HIV) and the consequent Acquired Immune Deficiency Syndrome (AIDS) is really a matter of great concern in many of the countries. The spread of HIV is at an alarming rate and the complete cure from the same is not yet available. The people in the field of medicine strive hard and do research to find a medicine to cure the disease. The use of mathematical namely stochastic models to describe the rate of spread of epidemic, to determine the likely time at which a person becomes seropositive and also the likely time at which a person becomes an AIDS case are all areas of interest in medical research. In this paper, a stochastic model to derive the expected time to seroconversion under the assumption that both the antigenic diversity threshold and the virulence threshold are such that they are random variables distributed as the nth order statistic. In doing so it assumed that the occurrence of the seroconversion takes place if either the cumulative antigenic diversity of the invading antigens crosses the so called antigenic diversity threshold or the cumulative level of virulence crosses the virulence threshold level. In doing so the shock model and cumulative damage process due to Eassary et.al (1973) has been applied. Numerical illustrations have also been provided.

Key words: antigenic diversity threshold, virulence threshold, seroconversion, nth order statistic.

INTRODUCTION

The progression of HIV to Acquired Immune Deficiency Syndrome (AIDS) is a matter of concern due to the fact that the affected person suffers both physical and mental torture. The governments in administration suffer a great burden both financially and social. Many authors have used Mathematical and Stochastic models to depict the progression of this infection among the affected. Nowak and May (1991) have identified the antigenic diversity as the main cause for the progression of the infection. They also describe a particular level of antigenic diversity as antigenic diversity threshold. It is observed that not only the antigenic diversity of an

*, *** Assistant Professor, Department of Statistics, St. Joseph's College of Arts and Science (Autonomous), Cuddalore, Tamil Nadu, India, Mobile:- +91 9943228183. Email: ramajayam82@yahoo.com

** Research Scholar, Annaalai University, Annamalai Nagar. Tamil Nadu, India.

invading antigen plays a vital role in the progression of the infection but also the virulence of the antigens. May and Anderson (1983) have given an interpretation of virulence and its impact. The concept of virulence threshold in AIDS has been discussed by Boer et.al. (1994). Bull (1994) has discussed about the virulence of the invading antigens and its perspective. In this paper the expected time to seroconversion of the infected is derived under the assumption that both the antigenic diversity threshold and virulence threshold are such that they are random variables distributed as the nth order statistic. Numerical illustrations have also been provided.

ASSUMPTIONS

1. A person is exposed to sexual contacts with an infected partner and on each occasion of contact the transmission of HIV takes place.
2. The mode of transmission of HIV on successive occasions results in the contribution to the antigenic diversity of the invading antigens. Also there is increase in the virulence of the invading antigens.
3. As and when the total antigenic diversity crosses a particular level called the antigenic diversity threshold, then the seroconversion takes place. Similarly if the total virulence of the invading antigens crosses the virulence threshold, then the seroconversion will occur.
4. The crossing of both antigenic diversity threshold and virulence threshold simultaneously is considered to be an impossible event.
5. The two thresholds are random variables and are mutually independent.

NOTATIONS

X_i : a random variable denoting the contribution to antigenic diversity on the th contact and with probability density function g(.) with cumulative distribution function G(.)

Y_i : the increase in the virulence due to the th contact with probability density function q (.) and cumulative distribution function Q(.)

Z_1 : a random variable denoting antigenic diversity threshold. It follows the order statistic and has probability density function and cumulative distribution function

Z_2 : a random variable denoting the virulence threshold. It follows the order statistic and has probability density function and cumulative distribution function

U_i : a random variable denoting the inter arrival times between contacts with probability density function of f (.) and cumulative distribution function F(.)

$l^*_{(s)}$: Laplace transform of l(t)

T : time to seroconversion

MODEL DESCRIPTIONS AND RESULTS

The survivor function is given by

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

= P [The total antigenic diversity due to 'k' contacts does not cross the threshold level and total vinllince developed due to k contacts does not cross the vinulence threshold]

$$S(t) = P\left[\sum_{i=1}^{k} x_i < Z_1 \cap \sum_{i=1}^{k} y_i < Z_2\right] = P\left[\sum_{i=1}^{k} x_i < Z_1 P \sum_{i=1}^{k} x_i < Z_2\right]$$

= P_r [That there are K contacts in (0, t) and the antigenic diversity does not cross threshold and the vinllence does not cross the threshold]

$$S(t) = \sum_{k=0}^{\infty} [F_k(t) - F_{k+1}(t)] \left[\int_0^{\infty} g_k(x)\,\overline{H(x)}\,dx\right] \left[\int_0^{\infty} g_k(y)\,\overline{M(y)}\,dy\right]$$

Let Z_1 follows n^{th} order Statistic

$\therefore h_{(n)}(Z_1) = n\,[H(Z_1)]^{n-1} h(Z_1)$

And Let

$$Z_1 \sim \exp(\theta) = n\theta[1 - e^{-Z_1\theta}]^{n-1} e^{-Z_1\theta}$$

$$\text{Now } H_n(x) = \int_0^x h_{(n)}(Z_1)\,dy$$

$$\overline{H_n(x)} = 1 - [1 - e^{-x\theta}]^n$$

Let Z_2 follows n^{th} order Statistic

$\therefore m_{(n)}(Z_2) = n\,[M(Z_2)]^{n-1} m(Z_2)$

And Let

$$Z_2 \sim \exp(\lambda) = n\lambda[1 - e^{-Z_2\lambda}]^{n-1} e^{-Z_2\lambda}$$

Now $M_n(y) = \int_0^y m_{(n)}(Z_2)\,dx$

$\overline{M_n(y)} = 1-[1-e^{-y\lambda}]^n$

Hence, $S(t) = \sum_{k=0}^{\infty}[F_k(t) - F_{k+1}(t)]$

$$\left[\int_0^\infty g_k(x)[1-(1-e^{-x\theta})^n]dx\right]\left[\int_0^\infty q_k(y)[1-(1-e^{-y\lambda})^n]dy\right]$$

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

$$\left[\int_0^\infty g_k(x)\,ne^{-x\theta}dx - nc_2\int_0^\infty g_k(x)\,e^{-2x\theta}dx + ...\right.$$

$$\left.(-1^n)\int_0^\infty g_k(x)\,e^{-nx\theta}dx + ...\right]$$

$$\left[\int_0^\infty g_k(y)\,ne^{-y\lambda}dy - nc_2\int_0^\infty q_k(y)\,e^{-2y\lambda}dy + ...\right.$$

$$\left.(-1^n)\int_0^\infty q_k(y)\,e^{-ny\lambda}dy\right]$$

$$= \sum_{k=0}^{\infty}[F_k(t)-F_{k+1}(t)]\left[[ng^*_k(\theta)]\right] - \left[[nc_2g^*_k(2\theta)]\right]....$$

$$\left[[(-1)^n g^*_k(n\theta)]\right] + \left[[nq^*_k(\lambda)]\right]$$

$$-\left[[nc_2q^*_k(2\lambda)]\right]....\left[[(-1)^n q^*_k(n\lambda)]\right]$$

where $F_k(t) - F_{k+1}(t)$

denotes the probability of exactly k contacts during (o, t) by renewal theory.

$$= n[1-g^*(\theta)]\sum_{k=1}^{\infty}F_k(t)[g^*(\theta)]^{k-1} - nc_2[1-g^*(2\theta)]$$

$$\sum_{k=1}^{\infty}F_k(t)[g^*(2\theta)]^{k-1}....(-1)^n[1-g^*(n\theta)]$$

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

$$n[1-q^*(\lambda)]\sum_{k=1}^{\infty}F_k(t)\,[q^*(\lambda)]^{k-1} - nc_2[1-q^*(2\lambda)]$$

$$\sum_{k=1}^{\infty}F_k(t)[q^*(2\lambda)]^{k-1}.....(-1)^n[1-q^*(n\lambda)]$$

$$\sum_{k=1}^{\infty}F_k(t)[q^*(n\lambda)]^{k-1}$$

(On simplification)

$L(t) = P[T < t] = 1 - s(t)$

Taking the Laplace trance form of L(t) we have L*(S) and then using the relationship

$$L^*(S) = \frac{1}{s}l^*(S) \text{ and } F_k{}^*(s) = \frac{[f^*(s)]^k}{s}$$

We have

Now,

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

$$-nc_2[1-g^*(2\theta)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[g^*(2\theta)]^{k-1}$$

$$+nc_3[1-g^*(3\theta)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[g^*(3\theta)]^{k-1}$$

$$-nc_4[1-g^*(4\theta)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[g^*(4\theta)]^{k-1}$$

$$+nc_5[1-g^*(5\theta)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[g^*(5\theta)]^{k-1}$$

....

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

$$+n[1-q^*(\lambda)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[q^*(\lambda)]^{k-1}$$

$$+nc_2[1-q^*(2\lambda)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[q^*(2\lambda)]^{k-1}$$

$$+nc_3[1-q^*(3\lambda)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[q^*(3\lambda)]^{k-1}$$

$$+nc_4[1-q^*(4\lambda)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[q^*(4\lambda)]^{k-1}$$

$$+nc_5[1-q^*(5\lambda)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[q^*(5\lambda)]^{k-1}$$

....

$$+(-1)^n[1-q^*(n\lambda)]f^*(s)^{k-1}\sum_{k=1}^{\infty}f^*(s)\,[q^*(n\lambda)]^{k-1}$$

$$= \frac{n[1-g^*(\theta)f^*(s)}{[1-g^*(\theta)f^*(s)]} - \frac{nc_2[1-g^*(2\theta)]f^*(s)}{[1-g^*(2\theta)f^*(s)]}$$

$$+\frac{nc_3[1-g^*(3\theta)]f^*(s)}{[1-g^*(3\theta)f^*(s)]} - \frac{nc_4[1-g^*(4\theta)]f^*(s)}{[1-g^*(4\theta)f^*(s)]}$$

$$+\frac{nc_5[1-g^*(5\theta)]f^*(s)}{[1-g^*(5\theta)f^*(s)]}.....\frac{(-1)^n[1-g^*(n\theta)]f^*(s)}{[1-g^*(n\theta)f^*(s)]}$$

$$= \frac{n[1-q^*(\lambda)f^*(s)}{[1-q^*(\lambda)f^*(s)]} - \frac{nc_2[1-q^*(2\lambda)]f^*(s)}{[1-q^*(2\lambda)f^*(s)]}$$

$$+\frac{nc_3[1-q^*(3\lambda)]f^*(s)}{[1-q^*(3\lambda)f^*(s)]} - \frac{nc_4[1-q^*(4\lambda)]f^*(s)}{[1-q^*(4\lambda)f^*(s)]}$$

$$+\frac{nc_5[1-q^*(5\lambda)]f^*(s)}{[1-q^*(5\lambda)f^*(s)]}.....\frac{(-1)^n[1-q^*(n\lambda)]f^*(s)}{[1-q^*(n\lambda)f^*(s)]}$$

(On simplification)

Then,

$$T_1 = \frac{n[1-g^*(\theta)]f^*(S)}{[1-g^*(\theta)f^*(S)]}$$

$$T_2 = \frac{nc_2[1-g^*(2\theta)]f^*(S)}{[1-g^*(2\theta)f^*(S)]}$$

$$T_3 = \frac{nc_3[1-g^*(3\theta)]f^*(S)}{[1-g^*(3\theta)f^*(S)]}$$

$$T_4 = \frac{nc_4[1-g^*(4\theta)]f^*(S)}{[1-g^*(4\theta)f^*(S)]}$$

$$T_5 = \frac{nc_5[1-g^*(5\theta)]f^*(S)}{[1-g^*(5\theta)f^*(S)]}$$

.....

$$T_n = \frac{-1^n[1-g^*(n\theta)]f^*(S)}{[1-g^*(n\theta)f^*(S)]}$$

Now,

$$S_1 = \frac{n[1-g^*(\lambda)]f^*(S)}{[1-g^*(\lambda)f^*(S)]}$$

$$S_2 = \frac{nc_2[1-g^*(2\lambda)]f^*(S)}{[1-g^*(2\lambda)f^*(S)]}$$

$$S_3 = \frac{nc_3[1-g^*(3\lambda)]f^*(S)}{[1-g^*(3\lambda)f^*(S)]}$$

$$S_4 = \frac{nc_4[1-g^*(4\lambda)]f^*(S)}{[1-g^*(4\lambda)f^*(S)]}$$

$$S_5 = \frac{nc_5[1-g^*(5\lambda)]f^*(S)}{[1-g^*(5\lambda)f^*(S)]}$$

.....

$$S_n = \frac{-1^n[1-g^*(n\lambda)]f^*(S)}{[1-g^*(n\lambda)f^*(S)]}$$

When $E(T) = \frac{-d}{ds}l^*(s) \quad / s = 0$

We assuming that $f(\cdot) \sim \exp(\eta)$ and $f^*(S) = \frac{n}{n+s}$

$g(\cdot) \sim \exp(\beta)$ and $g^*(\theta) = \beta/\beta+\theta$

$g(\cdot) \sim \exp(\mu)$ and $g^*(\lambda) = \mu/\mu+\lambda$

$$E(T) = \frac{n(\beta+\theta)}{\eta\theta} - \frac{nc_2(\beta+2\theta)}{2\eta\theta} + \frac{nc_3(\beta+3\theta)}{3\eta\theta}$$
$$- \frac{nc_4(\beta+4\theta)}{4\eta\theta} + \frac{nc_5(\beta+5\theta)}{5\eta\theta} ..... \frac{(-1)^{n+1}(\beta+n\theta)}{n\eta\theta}$$
$$+ \frac{n(\mu+\lambda)}{\eta\lambda} - \frac{nc_2(\mu+2\lambda)}{2\eta\lambda} + \frac{nc_3(\mu+3\lambda)}{3\eta\lambda}$$
$$- \frac{nc_4(\mu+2\lambda)}{4\eta\lambda} + \frac{nc_5(\mu+5\lambda)}{5\eta\lambda} ..... \frac{(-1)^{n+1}(\mu+n\lambda)}{n\eta\lambda}$$

Now to find $E(T^2)$ we have

$$E(T^2) = \frac{d^2 l^*(s)}{ds^2} / s = 0$$

$$E(T^2) = \frac{2n(\beta+\theta)^2}{(n\theta)^2} - \frac{2nc_2(\beta+2\theta)^2}{(2n\theta)^2} + \frac{2nc_3(\beta+3\theta)^2}{(3n\theta)^2}$$
$$- \frac{2nc_4(\beta+4\theta)^2}{(4n\theta)^2} + \frac{2nc_5(\beta+5\theta)^2}{(5n\theta)^2} ....(-1)^{n+1}\frac{2(\beta+n\varphi)^2}{(n\eta\varphi)^2}$$
$$+ \frac{2n(\mu+\lambda)^2}{(n\lambda)^2} - \frac{2nc_2(\mu+2\lambda)^2}{(2n\lambda)^2} + \frac{2nc_3(\mu+3\lambda)^2}{(3n\lambda)^2}$$
$$- \frac{2nc_4(\mu+4\lambda)^2}{(4n\lambda)^2} + \frac{2nc_5(\mu+5\lambda)^2}{(5n\lambda)^2} ....(-1)^{n+1}\frac{2(\mu+n\lambda)^2}{(n\eta\lambda)^2}$$

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

From (5) and (6) the expression for V(T) can be obtained.

$$V(T) = \left[\frac{2n(\beta+\theta)^2}{(n\theta)^2} - \frac{2nc_2(\beta+2\theta)^2}{(2n\theta)^2} + \frac{2nc_3(\beta+3\theta)^2}{(3n\theta)^2}\right.$$
$$- \frac{2nc_4(\beta+4\theta)^2}{(4n\theta)^2} + \frac{2nc_5(\beta+5\theta)^2}{(5n\theta)^2} ....(-1)^{n+1}\frac{2(\beta+n\theta)^2}{(n\eta\theta)^2}$$
$$+ \frac{2n(\mu+\lambda)^2}{(n\lambda)^2} - \frac{2nc_2(\mu+2\lambda)^2}{(2n\lambda)^2} + \frac{2nc_3(\mu+3\lambda)^2}{(3n\lambda)^2}$$
$$\left. - \frac{2nc_4(\mu+4\lambda)^2}{(4n\lambda)^2} + \frac{2nc_5(\mu+5\lambda)^2}{(5n\lambda)^2} ....., (-1)^{n+1}\frac{2(\mu+n\lambda)^2}{(n\eta\lambda)^2}\right]$$
$$- \left[\frac{n(\beta+\theta)}{n\theta} - \frac{nc_2(\beta+2\theta)}{2n\theta} + \frac{nc_3(\beta+3\theta)}{3n\theta}\right.$$
$$- \frac{nc_4(\beta+4\theta)}{4n\theta} + \frac{nc_5(\beta+5\theta)}{5n\theta} .... \frac{(-1)^{n+1}(\beta+n\theta)}{n\eta\theta}$$
$$+ \frac{n(\mu+\lambda)}{n\lambda} - \frac{nc_2(\mu+2\lambda)}{2n\lambda} + \frac{nc_3(\mu+3\lambda)}{3n\lambda}$$
$$\left. - \frac{nc_4(\mu+4\lambda)}{4n\lambda} + \frac{nc_5(\mu+5\lambda)}{5n\lambda} ... \frac{(-1)^{n+1}(\mu+n\lambda)}{n\eta\lambda}\right]^2$$

NUMERICAL ILLUSTRATION

The behaviour of and due to the changes in the different parameters associated with the distribution of the random variables in the model is explained by taking a numerical example.

Table 1:

Changes of Є (T) and V (T) due to the variations in

2.0, θ = 1.5, λ = 1.2, n = 10, β = 0.5

μ	E (T)	V (T)
1	0.5332	0.2212
2	0.5843	0.2847
3	0.6256	0.3267
4	0.6643	0.3689
5	0.6903	0.4023
6	0.7463	0.4271
7	0.7823	0.4821
8	0.8231	0.5129
9	0.8637	0.5432
10	0.8847	0.5723

Fig. 1:

Changes of Є (T) and V (T) due to the variations in λ

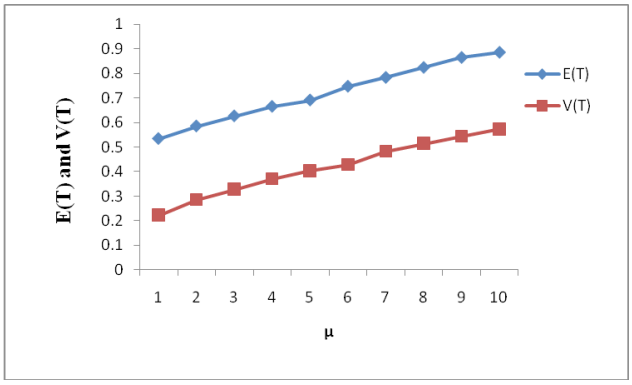


Table 2:

Changes of Є (T) and V (T) due to the variations in

2.0, θ = 1.5, λ = 1.2, n = 1.0, β = 0.5

μ	E (T)	V (T)
1	2.9731	2.9813
2	1.8935	1.0281
3	1.2814	0.6152
4	0.9445	0.5219
5	0.8321	0.4120
6	0.7845	0.2642
7	0.7060	0.2113
8	0.4919	0.1823
9	0.3214	0.1029
10	0.2026	0.0934

Fig.2: Changes of Є (T) and V (T) due to the variations in λ

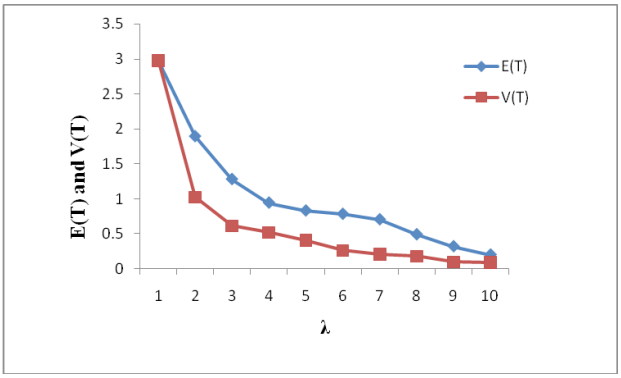


Table 3:

Changes of Є (T) and V (T) due to the variations in

2.0, λ = 1.5, μ = 1.2, n = 10, β = 0.5

θ	E (T)	V (T)
1	0.9546	0.5273
2	0.9345	0.5083
3	0.9050	0.4822
4	0.8803	0.4723
5	0.8734	0.4625
6	0.8635	0.4329
7	0.8532	0.4211
8	0.8421	0.3902
9	0.8345	0.3821
10	0.8212	0.3756

Fig.3:

Changes of Є (T) and V (T) due to the variations in

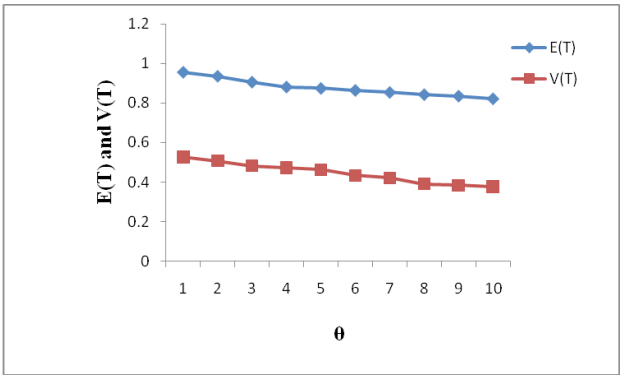


Table 4:

Changes of Є (T) and V (T) due to the variations in η

η	E (T)	V (T)
1	1.9241	1.9812
2	1.6712	1.0714
3	1.4042	0.8734
4	1.3061	0.7123
5	1.1989	0.6145
6	0.9800	0.4287
7	0.8245	0.3451
8	0.7312	0.2230
9	0.7165	0.2140
10	0.7053	0.1032

Fig 4: Changes of Є (T) and V (T) due to the variations in η

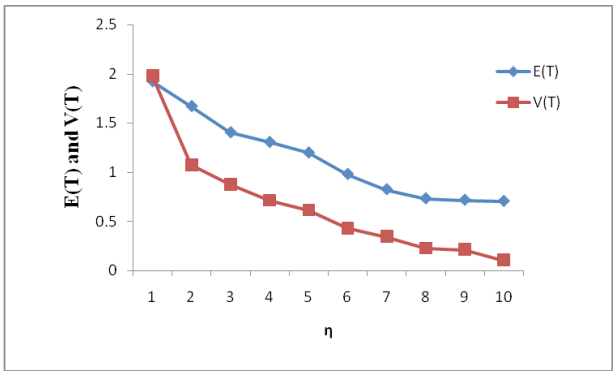


Table 5:

Changes of Є (T) and V (T) due to the variations in β

= 1.5, λ = 1.2, μ = 1.0, n = 10, η = 2.0

β	E (T)	V (T)
1	0.8245	0.4623
2	0.8311	0.4745
3	0.8464	0.4821
4	0.8522	0.4980
5	0.8619	0.5023
6	0.8721	0.5120
7	0.8823	0.5234
8	0.8898	0.5406
9	0.8923	0.5532
10	0.9067	0.5686

Fig.5:

Changes of Є (T) and V (T) due to the variations in β

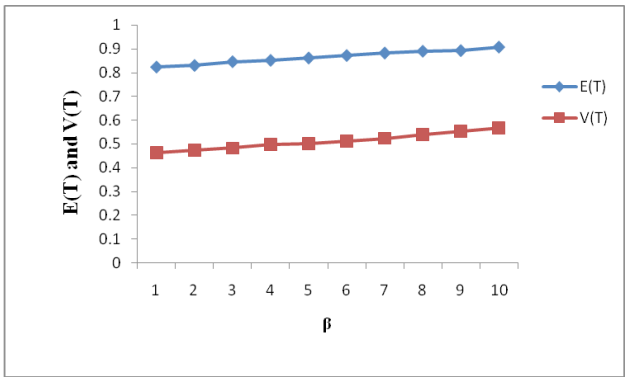


Table 6:

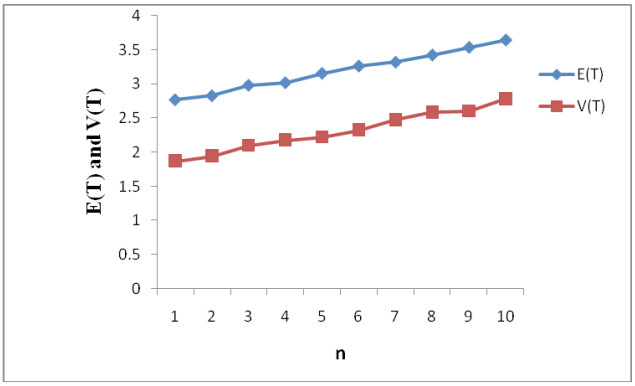
Changes of Є (T) and V (T) due to the variations in

= 1.5, λ = 1.2, μ = 1.0, n = 10, η = 2.0

n	E (T)	V (T)
1	2.7682	1.8652
2	2.8274	1.9420
3	2.9801	2.0952
4	3.0174	2.1752
5	3.1542	2.2210
6	3.2600	2.3218
7	3.3164	2.4721
8	3.4217	2.5820
9	3.5321	2.6002
10	3.6401	2.7812

Fig.6:

Changes of Є (T) and V (T) due to the variations in



CONCLUSION

1. When μ which is the parameter of the random variable Y_i denoting the magnitude of contribution to virulence threshold is on the increase, it is seen that E(T) increases. This is due to the fact that follows exponential distribution and so $(Y_i) = \frac{1}{\mu}$. As increases then, $\frac{1}{\mu}$ this is the contribution to virulence decreases. Hence it takes more time to cross the threshold. This is true when Z_2 follows n^{th} order statistic also. This has been shown in table .1 and figure. 1.
2. The threshold is a random variable which is the n^{th} order statistic. Now the virulence threshold Z_2 follows exponential with parameter λ. Hence $E(Z_2) = \frac{1}{\lambda}$ and it decreases as λ increases. Hence the threshold is smaller as λ increases. So as λ increases, it takes less time to cross the threshold as indicated in table. 2 and figure.2.
3. The threshold is a random variable which is the n^{th} order statistic. Now the antigenic diversity threshold Z_1 follows exponential with parameter θ. Hence $E(Z_1) = \frac{1}{\theta}$ and it decreases as θ increases. Hence the threshold is smaller as θ increases. So as θ increases, it takes less time to cross the threshold as indicated in table. 3 and figure.3.
4. The inter arrival times between successive contacts distributed as exponential with parameter η. As η increases, then E(U) = 1/ η decreases. Hence, the contacts will be more frequent and a greater contribution to the antigenic diversity and virulence. So, it takes less time to cross the threshold. Hence E(T) becomes smaller. This has been indicated in table. 4 and figure. 4.
5. When β which is the parameter of the random variable X_i denoting the magnitude of contribution to antigenic diversity threshold is on the increase, it is seen that E(T) increases. This is due to the fact that X_i follows exponential distribution and so $E(X_i) = \frac{1}{\beta}$. As β increases then, $\frac{1}{\beta}$ this is the contribution to antigenic diversity decreases. Hence it takes more time to cross the threshold. This is true when Z_1 follows n^{th} order statistic also. This has been shown in table .1 and figure. 1.
6. As 'n' increases, then the n^{th} order also increases. This would mean that the magnitude of the n^{th} order statistic will be greater. Hence, the threshold is higher and so it takes more time to cross the threshold and so E(T) is on the increase. This has been indicated in table.4 and figure. 4.

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