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A stochastic model approach to determine the statistical measures for time to seroconversion of HIV infected using exponentiated modified weibull distribution

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Abstract
This paper focuses on the study of a stochastic model for predicting the seroconversion time of HIV transmission using intercontact time between successive contact are poisson random variable. The estimation of excepted time to seroconversion of HIV infected over the time interval (0, t] is an important aspect which helps medical intervention. The purpose of this study to bring out the impact of the intercontact time and also the magnitude of contribution to antigenic diversity in successive contact upon the time to seroconversion. To propose a stochastic model to study the damage process acting on the immune system is non-linear. The mean time to seroconversion and its variance are derived and numerical illustrations are provided.

Keywords: Acquired Immune Deficiency Syndrome, Human Immunodeficiency Virus, Seroconversion, Cumulative Damage Process, Antigenic Diversity Threshold, Poisson Process

1. Introduction
The Human Immunodeficiency Virus (HIV) infection that least Acquire Immune Deficiency Syndrome (AIDS) Epidemiological studies have pointed out that the route of HIV transmission is blood and that the transmission occurs primarily through sexual contacts, sharing of contaminated needles, transfusion of infected blood / blood products, infected mother's breast milk to infants or vertical transmission from mother to fetus in uterus or at delivery. Many authors studied the seroconversion time of HIV transmission by taking sexual contact alone is the only mode of HIV transmission. The sexual contacts are assumed between a seropositive person who is labelled as index case and seronegative counterpart is called as partner. A seroconversion from seronegative to seropositive state takes place after an incubation period due to the contraction of HIV to the partner from the index case by sexual contacts.

The time to seroconversion from the point of infection depends upon what is known as antigenic diversity which acts against the immune ability of an individual. Every individual has a threshold level of antigenic diversity. If the antigenic diversity due to acquiring more and more of HIV infection due to homo or hetero sexual contacts exceeds the threshold level. Then the immune system of the human body is completely suppressed which in turn leads to seroconversion. For a detailed study of antigenic threshold and its estimation one can refer Nowak and May (1991) [4] and Stilianakis *et al*. (1994) [6].

A stochastic model based on the cumulative damage process is derived and using this model it is possible to obtain the expected time to seroconversion and its variance. Sathiyamoorthy and Kannan (2001) [3] and Kannan and Chandrasekar (2015) [5] derived a stochastic model based on the cumulative damage process with the assumption that the antigenic diversity threshold is a random variable and damage process acting on the immune system is assumed to be linear. But as the immune capacities of an individual vary and also have its own system to be 'linear' is not appropriate.

In this paper, we propose a stochastic model for the estimation of expected time to seroconversion is derived under the assumption that the threshold level of antigenic diversity is a random variable which follows exponentiated modified weibull distribution with damage

process acting on the immune system of an infected individual is non-linear and cumulative. In developing such a stochastic model and cumulative damage process discussed by Esary et.al. (1973) [2], is used.

In developing such a model basic assumption made was that the intercontact timing between successive contacts are identically and independently distributed random variable. In this paper stochastic models assume that the intercontact timing between successive contacts are poisson random variable. In developing such a stochastic model a generalized poisson distribution and its applications have been discussed by Anil (2001) [1], is used. In this study the theoretical results while an substantiated using numerical data is simulated.

Assumptions of the model:

- Sexual contact is the only source of HIV transmission.
- An uninfected individual has sexual contacts with a HIV infected partner.
- Damages to individuals are caused by transmission of HIV at each contact and the interarrival time between the contacts are independent identically distributed random variable.
- The damage process acting on the immune systems of an infected individual is non-linear and cumulative.
- The total damage caused exceeds a threshold level Y itself is a random variable, the seroconversion occurs and the person is recognized as seropositive.
- The process that generates the contacts, the sequence of damages and threshold are mutually independent.

Notation

X_i a random variable denoting the increase in the antigenic diversity arising due to the HIV transmitted during the i[th] contact

$X_1, X_2, X_3, ..., X_k$ 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 and follows exponentiated modified Weibull distribution with parameters θ and γ, the p.d.f. being h(.) and c.d.f. H(.).

U_i a continuous random variable denoting the interarrival times between successive contacts with p.d.f. f(.) and c.d.f. F(.).

Z the random variable representing the time between damages.

$g_k(.)$ the p.d.f of random variable $\sum_{i=1}^{k} X_i$.

$F_k(.)$ the k[th] convolution of F(.).

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

a contact rate of the infected partner.

$V_k(.)$ the probability that there are exactly k contacts in (o, t] with intensity represented as a poisson process with parameter 'a'.

$l^*(s)$ is the Laplace stieltje's transform of l(t).

$f^*(s)$ is the Laplace stieltje's transform of f (t).

Result

The probability density function of exponentiated modified Weibull distribution is

$h(y) = \alpha(\theta + \gamma\beta y^{\beta-1}) e^{-(\theta y + \gamma y^{\beta})} [1 - e^{-(\theta y + \gamma y^{\beta})}]^{\alpha-1}$, $y > 0$ and $\theta, \beta, \alpha, \gamma > 0.$

and its distribution function is

$$H(y) = \left[1 - e^{-(\theta y + \gamma y^{\beta})}\right]^{\alpha}, y > 0.$$

then its survival function is

$$\overline{H}(y) = 1 - \left[1 - e^{(\theta y + \gamma y^{\beta})}\right]^{\alpha}$$

Since Y is taken to be exponentiated modified Weibull distribution (θ, γ)

It can be shown that

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

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

Put $\alpha = 2$ and $\beta = 1$ in $\overline{H}(x)$, then it becomes

$$\overline{H}(y) = \left[2e^{-y(\theta+\gamma)} - e^{-2y(\theta+\gamma)}\right] \quad (2)$$

Substituting equation (2) in (1), we get

$$= \left[2g * (\theta + \gamma)\right]^k - \left[g * 2(\theta + \gamma)\right]^k$$ On simplification S(t) = P[T > t]

$$= \sum_{k=0}^{\infty} \Pr\{\text{there are exactly k contacts in } (0, t]\}$$

* Pr{the cumulative total of antigenic diversity < Y}

$$\therefore S(t) = \sum_{K=0}^{\infty} V_k(t) P\left[\sum_{i=1}^{k} X_i < Y\right]$$

$$= \sum_{k=0}^{\infty} \frac{e^{-at}(at)^k}{k!} \left[2g^*(\theta+\gamma)\right]^k - \left[g^*2(\theta+\gamma)\right]^k$$

$$S(t) = 2\, e^{-at}\ e^{at\, g^*(\theta+\gamma)} - e^{-at}\ e^{at\, g^*2(\theta+\gamma)}$$

Let g(.) follows exponential distribution with parameter μ

$$g^*(\theta+\gamma) = \frac{\mu}{\mu+(\theta+\gamma)} \;\&\; g^*(2(\theta+\gamma)) = \frac{\mu}{\mu+2(\theta+\gamma)}$$

Let

L(t) = 1 – S(t)

$$= 1 - \left(2\, e^{-at}\ e^{at\, g^*(\theta+\gamma)} - e^{-at}\ e^{at\, g^*2(\theta+\gamma)}\right)$$

$$= 1 - \left[2e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t} - e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}\right]$$

$$\psi(t) = \frac{d}{dt}[L(t)]$$

$$\psi(t) = 2\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t} - \left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}$$

The expected time to seroconversion is given by

$$E(T) = \int_0^{\infty} t\ \psi(t)\, dt$$

$$E[T] = 2\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)\int_0^{\infty} t\ d\left[\frac{e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t}}{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)}\right] - \left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)\int_0^{\infty} t\ d\left[\frac{e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}}{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)}\right] \quad \text{---------- (3)}$$

Consider

$$I_1 = \int_0^{\infty} t\ d\left[\frac{e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t}}{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)}\right] \qquad \& \qquad I_2 = \int_0^{\infty} t\ d\left[\frac{e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}}{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)}\right]$$

$$I_1 = t\left[\frac{e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t}}{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)}\right]_0^{\infty} - \int_0^{\infty} \frac{e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t}}{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)}\ dt$$

$$= \frac{\mu+(\theta+\gamma)}{a(\theta+\gamma)} \int_0^{\infty} e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t} \; dt$$

$$I_1 = \frac{\left[\mu+(\theta+\gamma)\right]^2}{\left[a(\theta+\gamma)\right]^2} \qquad \text{---------- (4)}$$

$$I_2 = t\left[\frac{e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}}{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)}\right]_0^{\infty} - \int_0^{\infty} \frac{e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}}{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)} \; dt$$

$$= \frac{\mu+2(\theta+\gamma)}{a2(\theta+\gamma)} \int_0^{\infty} e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t} \; dt$$

$$I_2 = \frac{\left[\mu+2(\theta+\gamma)\right]^2}{\left[a2(\theta+\gamma)\right]^2} \qquad \text{---------- (5)}$$

Substituting equations (4) and (5) in (3) we get

$$= \left[2\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right) \times \frac{\left[\mu+(\theta+\gamma)\right]^2}{\left[a(\theta+\gamma)\right]^2}\right] - \left[\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right) \times \frac{\left[\mu+2(\theta+\gamma)\right]^2}{\left[a2(\theta+\gamma)\right]^2}\right]$$

$$= \left[\frac{2\left[\mu+(\theta+\gamma)\right]}{a(\theta+\gamma)}\right] - \left[\frac{\left[\mu+2(\theta+\gamma)\right]}{a2(\theta+\gamma)}\right]$$

$$E(T) = \frac{3\mu+2(\theta+\gamma)}{a2(\theta+\gamma)} \qquad \text{---------- (6)}$$

$$E(T^2) = \int_0^{\infty} t^2 \, \psi(t) \, dt$$

$$E(T^2) = 2\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right) \int_0^{\infty} t^2 \, e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t} \; dt - \left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right) \int_0^{\infty} t^2 e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t} \; dt \qquad \text{------- (7)}$$

Consider

$$I_1 = \int_0^{\infty} t^2 \; e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t} \; dt \qquad \& \qquad I_2 = \int_0^{\infty} t^2 \; e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t} \; dt$$

$$I_1 = t^2 \quad d\left[\frac{e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t}}{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)}\right]$$

$$= \frac{2\left[\mu + (\theta+\gamma)\right]^2}{a^2(\theta+\gamma)^2}\left[\frac{e^{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)t}}{-\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)}\right]_0^{\infty}$$

$$I_1 = \frac{2\left[\mu+(\theta+\gamma)\right]^3}{a^3(\theta+\gamma)^3} \qquad \text{---------- (8)}$$

$$I_2 = t^2 \quad d\left[\frac{e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}}{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)}\right]$$

$$= \frac{2\left[\mu+2(\theta+\gamma)\right]^2}{a^2\left[2(\theta+\gamma)\right]^2}\left[\frac{e^{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)t}}{-\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)}\right]_0^{\infty}$$

$$I_2 = \frac{\left[\mu+2(\theta+\gamma)\right]^3}{a^3 4(\theta+\gamma)^3} \qquad \text{---------- (9)}$$

Substituting equations (8) and (9) in (7) we get

$$E\left[T^2\right] = \left\{2\left(\frac{a(\theta+\gamma)}{\mu+(\theta+\gamma)}\right)\times\frac{2\left[\mu+(\theta+\gamma)\right]^3}{a^3(\theta+\gamma)^3}\right\} - \left\{\left(\frac{a2(\theta+\gamma)}{\mu+2(\theta+\gamma)}\right)\times\frac{\left[\mu+2(\theta+\gamma)\right]^3}{a^3 4(\theta+\gamma)^3}\right\}$$

$$= \frac{8\left[\mu+(\theta+\gamma)\right]^2 - \left[\mu+2(\theta+\gamma)\right]^2}{a^2 2(\theta+\gamma)^2}$$

$$E\left[T^2\right] = \frac{4\gamma^2 + 8\theta\gamma + 12\mu\gamma + 7\mu^2 + 4\theta^2 + 12\mu\theta}{a^2 2(\theta+\gamma)^2}$$

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

$$= \frac{4\gamma^2 + 8\theta\gamma + 12\mu\gamma + 7\mu^2 + 4\theta^2 + 12\mu\theta}{a^2 2(\theta+\gamma)^2} - \left[\frac{3\mu+2(\theta+\gamma)}{a2(\theta+\gamma)}\right]^2$$

$$V[T] = \frac{5\mu^2 + 4(\theta+\gamma)^2 + 12\mu(\theta+\gamma) + 8\theta\gamma}{a^2 4(\theta+\gamma)^2}$$

On simplification

Table 1

	$\gamma = 0.5, \theta = 0.2, \mu = 0.2$ $q = 0.5, \beta = 0.4$	
a	**Mean**	**Variance**
1	1.428571	2.367347
2	0.714286	0.591837
3	0.476190	0.263039
4	0.357143	0.147959
5	0.285714	0.094694
6	0.238095	0.065760
7	0.204082	0.048313
8	0.178571	0.036990
9	0.158730	0.029227
10	0.142857	0.023673

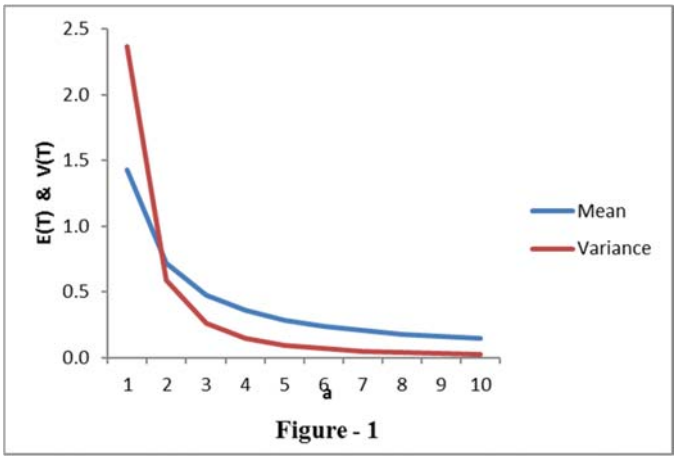

Figure - 1

Numerical Illustrations

Table 2

γ	$\mu = 0.2, \theta = 0.2, a = 2$ $q = 0.5, \beta = 0.4$	
	Mean	**Variance**
0.1	1.000000	1.000000
0.2	0.875000	0.828125
0.3	0.800000	0.720000
0.4	0.750000	0.645833
0.5	0.714286	0.591837
0.6	0.687500	0.550781
0.7	0.666667	0.518519
0.8	0.650000	0.492500
0.9	0.636364	0.471074
1	0.625000	0.453125

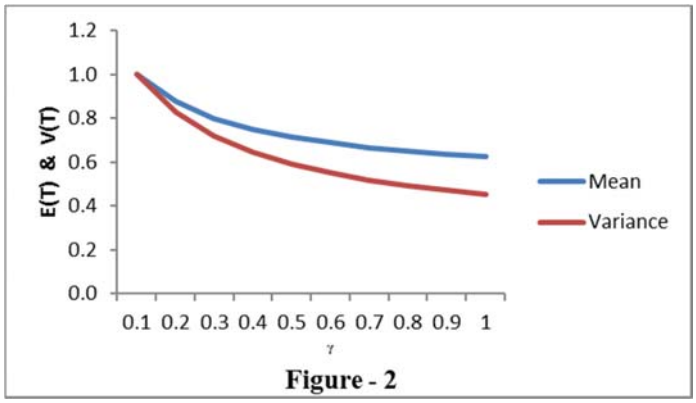

Figure - 2

Table 3

	$\gamma = 0.5, \mu = 0.2, a = 2$ $q = 0.5, \beta = 0.4$	
Θ	Mean	Variance
0.1	0.750000	0.604167
0.2	0.714286	0.591837
0.3	0.687500	0.574219
0.4	0.666667	0.555556
0.5	0.650000	0.537500
0.6	0.636364	0.520661
0.7	0.625000	0.505208
0.8	0.615385	0.491124
0.9	0.607143	0.478316
1	0.600000	0.466667

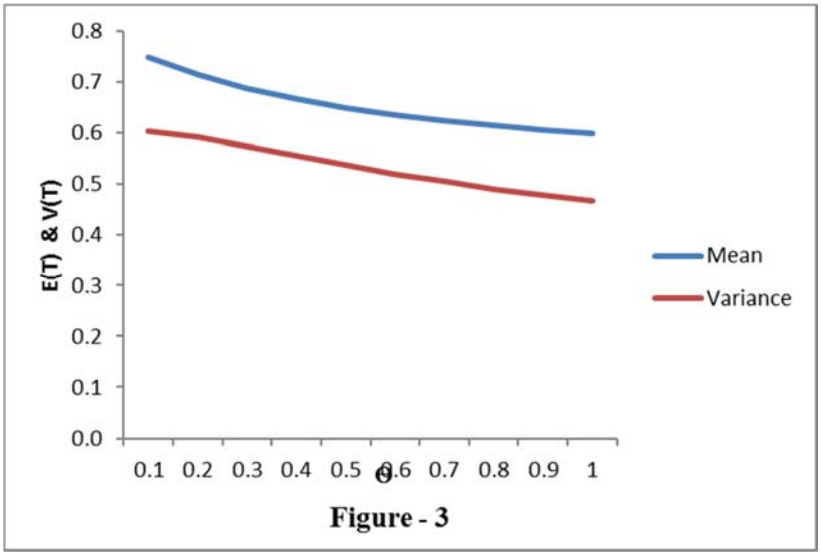

Figure - 3

Conclusion

From the table (1) we observe that for fixed γ, θ and μ when 'a' the contact rate increases, the mean time to seroconversion and its variance decreases. The overall conclusion that could be drawn from the behaviour of mean and variance of time to seroconversion is that number of contact, when increases, tends to shorten the time to seroconversion.

It is observed from the table (2) also the graph as the value of which is the parameter of the exponentiated modified weibull distribution of the threshold increases, the mean time to seroconversion decreases. It is also quite reasonable as regard the variation it could be seen that as the value of 'γ' increases the variance decreases.

From the table (3) we observed that for fixed a, γ and μ when θ is allowed to increases then mean time to seroconversion decreases. The same tendency is also noted on the variance of the seroconversion time.

From the table (4) we observe that for fixed a, γ and θ are fixed 'μ' happened to be the parameter of the random variable defection the amount of antigenic diversity contribution in successive contact. If increases, then both mean time to seroconversion and its variance also increases.

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