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AN APPLICATION OF GEOMETRIC PROCESS IN THE STUDY OF HIV INFECTION

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Abstract

In the study of HIV infection the expected time to cross the antigenic diversity threshold which means the manifestation of AIDS, the interarrival times between successive sexual contacts play a vital role. The use of the shock models and cumulative damage process is a viable method in this context. Under the assumption that the sequence of interarrival times forms a geometric process the expected time to cross the antigenic diversity threshold and its variance are obtained. Numerical examples using Monte-Carlo simulation study are furnished to substantiate the theoretical results derived in this paper.

Key Words: Antigenic Diversity Threshold; Interarrival Time; Shock Model; Cumulative Damage Process.

1. Introduction

In the study of HIV infection the Antigenic diversity which implies the viral genetic diversity is an important contributory factor for the disease progression. Every individual has an innate immune ability, which sustains the immune system against the antigens. Successive contacts with infectious partners add to the antigenic diversity. As and when the antigenic diversity crosses the threshold level the indication of AIDS prevalence takes place. The concept of shock models and cumulative damage processes is used in estimating the expected time to cross the Antigenic diversity threshold (CADT).

For a detailed study of shock models and cumulative damage process one can refer to Esary, Marshall and Proshan (1973). Sathiyamoorthy and Kannan (1998) have obtained the impact of the interarrival times on the expected time to CADT assuming the same as random variables. In this paper to find the expected time to CADT is obtained under the assumption that the intercontact times form a geometric process. Shiboski and Jewell (1992) discussed the time dependence of HIV infectivity based on partner study data. The Mathematical biology of HIV infections: antigenic variation and diversity threshold discussed by Nowak and May (1991). Taylor et al., (1990) works on estimating the distribution of times from HIV seroconversion to AIDS using multiple impution.

2. Definition of a Geometric Process

Suppose that $\{\xi(t),\ t\geq 0\}$ is a counting process and $\{U_n,\ n=1,2....\}$ is a sequence of non-negative independent random variables and the distribution function of U_n is $F(a^{n-1}t),\ n=1,2.....$, where a is positive constant. If $T_n=\sum_{i=1}^{n} U_i,\ n\geq 1$ and $\{\xi(t)\geq n\}=\{T_n\leq t\},\ (t\geq 0,\ n=1,2.....)$ then the counting process $\{\xi(t),\ t\geq 0\}$ is a geometric process. Here T_n is called the n^{th} change time, and U_n is called the n^{th} change inter arrival time.

Obviously, if $a>1$, then $\{U_n,\ n=1,2.....\}$ is stochastically decreasing i.e. $U_n >_{st} U_{n+1},\ n=1,2.....$ If $0<a<1$, then $\{U_n,\ n=1,2..\}$ forms stochastically increasing sequence of random variables. If $a=1$, then $\{U_n,\ n=1,2...\}$ is a sequence of independent random variables with common distribution. Therefore the geometric process $\{\xi)t),\ t\geq 0\}$ will become a renewal process.

The assumption of a geometric process for the inter arrival times between successive contacts can be justified by the following.

It is known that the sharing of unstreile needles for drug abuse is a potential source of HIV transmission. Usually, it can be observed that the time intervals between successive occasions of needle sharing forms a decreasing sequence of random variables since the person will get more addiction towards drugs and the frequency of occasions of sharing the needles will be more and more and hence it can be considered as a geometric process.

The same model, when applied to the case that a person who is exposed to a contact / transmission, becomes mentally alert and postpones the next contact. After the second contact the fear is still increased and the time interval between the second and third contact is further elongated and so on. Therefore the successive time intervals U_1, U_2….. will form a geometric process.

3. Assumptions of the model

i. A person is exposed to the transmission of HIV and the mode of transmission is only through sexual contacts.

ii. The sequence of random variables which represent the inter occurrence times between successive contacts forms a geometric process.

iii. The sequence of contacts, the threshold level is independent.

4. Notations

U_I - a random variable representing the inter arrival times between successive contacts with p.d.f $h_I(.)$

$W_i(.)$ - c.d.f. of U_i

T - a random variable representing the time to CADT with c.d.f. $L(t)$ and p.d.f $l(t)$

Y - a random variable representing the antigenic diversity threshold level, which is assumed to follow exponential distribution with parameter μ

X_I - amount of damage caused to the immune system due to i^{th} sexual contact and X_i's are assumed to i.i.d random variables

$f_n(.)$ - p.d.f of $\sum_{i=1}^{n} X_I$

ψ - $P(X_i<Y)$, since X_i's are i.i.d and Y is exponential we can write $\psi^k = P(\sum_{i=1}^{k} X_i < Y)$

5. Results

Since U_i's form a geometric process, we can write the c.d.f. U_n as

$$H_n(u) = W(a^{n-1}u)$$

The probability that there are exactly k contacts in the interval (0,t] and the total damage does not cross the threshold level is given by

$$S(t) = P(T>t) = \sum_{k=0}^{\infty} [W_k(t) - W_{k-1}(t)]\, P[\sum_{i=1}^{k} X_i < Y] \quad (1)$$

Since X_i's are i.i.d and Y is assumed to follow exponential distribution with parameter μ we have

$$P(\sum_{i=1}^{k} X_i < Y) = \int_0^{\infty} f_k(x)\, e^{-\mu x}\, dx = [f^*(\mu)]^k = \Psi^k \text{ (say)} \quad (2)$$

As the inter arrival times forms a geometric process,

$$W_2(t) = P(U_1 + U_2 \le t)$$

$$= \int_0^t w(u)\, H_2(t-u)\, du$$

and $w_2(t) = \int_0^t w(u)\, h_2(t-u)\, du$ where $h_2(u) = a.w(au)$

i.e. $w_2(t) = \int_0^t w(u)\, w[a(t-u)]\, du$

Taking Laplace transform we have $w^*_2(s)=aw^*(s)$.

But the Laplace transform of $w(at) = (1/a)\, w^*(s/a)$.

$$\therefore \quad w_2^*(s) = w^*(s)\, w^*(s/a)$$

Proceeding in this manner, we can get

$$w_n^*(s) = \prod_{k=1}^{n} w^*(s/a^{k-1}) \quad (3)$$

Now using (2) we have

$$L(t) = \sum_{k=1}^{\infty} [W_k(t) - W_{k-1}(t)]\, \Psi^k$$

$$= (1-\Psi) \sum_{k=1}^{\infty} W_k(t)\, \Psi^{k-1}$$

Now using (2) we have

$$L(t) = \sum_{k=1}^{\infty} [W_k(t) - W_{k+1}(t)]\, \Psi^k$$

$$= (1-\Psi) \sum_{k=1}^{\infty} W_k(t)\, \Psi^{k-1}$$

The p.d.f of T is

$$l(t) = (1-\Psi) \sum_{k=1}^{\infty} w_k(t)\, \Psi^{k-1} \quad (4)$$

Taking Laplace transform we have,

$$l^*(s) = (1-\Psi) \sum_{n=1}^{\infty} \Psi^{n-1} \sum_{k=1}^{n} w^*[s/a^{k-1}]$$

The expected time to CADT is

$$E(T) = \frac{d}{ds}[l^*(s)]\Big|_{s=0} = -(1-\Psi) \sum_{n=1}^{\infty} \Psi^{n-1} \frac{d}{ds}\left[\prod_{k=1}^{n} w^*[s/a^{k-1}]\right]\Big|_{s=0} \quad (5)$$

Now

$$\frac{d}{ds}\left(\prod_{k=1}^{n} w(s/a^{k-1})\right)\Big|_{s=0} = w^{*\prime}(0)\, [1 + (1/a) + (1/a^2) + \ldots + 1/a^{n-1})$$

$$= w^{*\prime}(0)\left(\frac{a^n - 1}{a^{n-1}(a-1)}\right)$$

Using the above in equation (5), we have

$$E(T) = -(1-\Psi)\sum_{n=1}^{\infty}\Psi^{n-1}\, w^{*\prime}(0)\left(\frac{a^n - 1}{a^{n-1}(a-1)}\right)$$

$$= \frac{-a\, w^{*\prime}(0)}{(a-\Psi)}$$

$$\therefore E(T) = E(U_1)\,\frac{a}{(a-\Psi)}$$

Now

$$E(T^2) = \frac{d^2}{ds^2}[l^*(s)]\Big|_{s=0} = (1-\Psi)\,\Psi^{n-1}\,\frac{d^2}{ds^2}\left[\, w^*[s/a^{k-1}]\right]\Big|_{s=0} \quad (6)$$

We have

$$\frac{d^2}{ds^2}\prod_{k=1}^{n} w^*(s/a^{k-1})\Big|_{s=0} = \{w^{*\prime\prime}(0) - [w^{*\prime\prime}(0)]^2\}\left(\frac{a^{2n}-1}{(a^2-1)a^{2(n-2)}}\right)$$

$$+ [w^{*\prime}(0)]^2\left(\frac{a^{2n} - 2a^{n+1}}{(a-1)^2\, a^{2(n-1)}}\right)$$

Therefore

$$E(T^2) = \frac{a^2}{(a-1)^2}\,E(U_1)^2\left(\frac{(a^2-\Psi)(a-\Psi) - 2(1-\Psi)(a^2-\Psi) + (1-\Psi)(a-\Psi)}{(a-\Psi)(a^2-\Psi)}\right)$$

$$+ \frac{a^2\, V(U_1)}{(a^2-\Psi)}$$

Then, the variance of the time to CADT can be derived as

$$V(T) = \frac{a^2\, V(U_1)}{(a^2-\Psi)} + \left(\frac{E(U_1)^2\, a^2\,(a^2-\Psi-a+a\Psi)}{(a-1)(a-\Psi)(a^2-\Psi)} - \frac{E(U_1)^2\, a^2}{(a-\Psi)^2}\right)$$

$$= \frac{a^2\, V(U_1)}{(a^2-\Psi)} + \left(\frac{E(U_1)^2\, a^2\,\Psi(1-\Psi)}{(a-\Psi)^2\,(a^2-\Psi)}\right)$$

Table 1. Mean Time to CADT ($\beta = 0.07$, $\mu = 1.00$)

Contact Rate (λ)	$a = 0.5$	$A = 1$	$a = 1.5$
1	1.15054	1.07397	1.05281
2	0.57527	0.53897	0.52097
3	0.38351	0.36443	0.35369
4	0.28763	0.26731	0.26498
5	0.23011	0.21496	0.21450
6	0.19176	0.17901	0.17355
7	0.16439	0.14962	0.14825
8	0.14382	0.13127	0.12891
9	0.12784	0.11969	0.11638
10	0.11505	0.10647	0.10460

Table 2. Variance of Time to CADT ($\beta = 0.07$, $\mu = 1.00$)

Contact Rate (λ)	$a = 0.5$	$a = 1$	$a = 1.5$
1	1.78929	1.15341	1.07567
2	0.43545	0.29049	0.26323
3	0.19443	0.13281	0.12134
4	0.11617	0.07145	0.06813
5	0.07362	0.04621	0.04464
6	0.04919	0.03204	0.02922
7	0.03543	0.02238	0.02131
8	0.02899	0.01723	0.01613
9	0.02170	0.01433	0.01314
10	0.01802	0.01134	0.01062

It may be noted that in the case where $a<1$ the mean and variance exits only when the difference $(a-\Psi) > 0$.

A Monte-Carlo simulation study for the estimation of mean time to CADT and its variance under this model has been done with the assumption that the distribution of damage is exponential with parameter β and the distribution of U_1 is exponential with parameter λ. Since generation of random numbers for time to CADT using the probability distribution given in (4) is not possible, a simulation is performed as follows:

First the random numbers of sizes n from the distributions of the threshold, inter arrival time and the damage have been generated and the estimates for μ, λ and β have been obtained. The estimates for $E(T)$ and $V(T)$ under these models are obtained by substituting estimated values for the corresponding parameters, which are ML estimates. This procedure has been repeated for ten thousand times and the averages based on these ten thousand observations are calculated for various values of a. The behaviour of E(T) and V(T) for different values of a, β and μ is furnished with the following tables with corresponding of graphs.

Figure 1. Mean Time to CADT (β= 0.07, μ= 1.00)

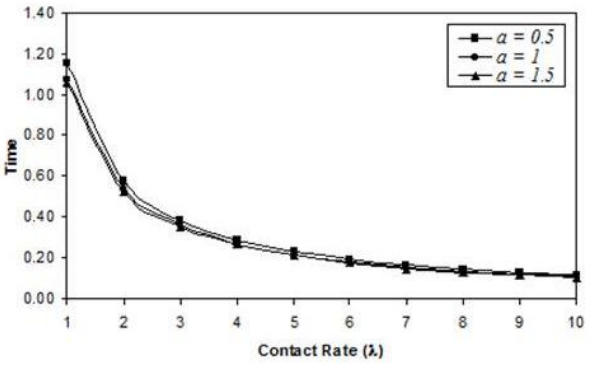
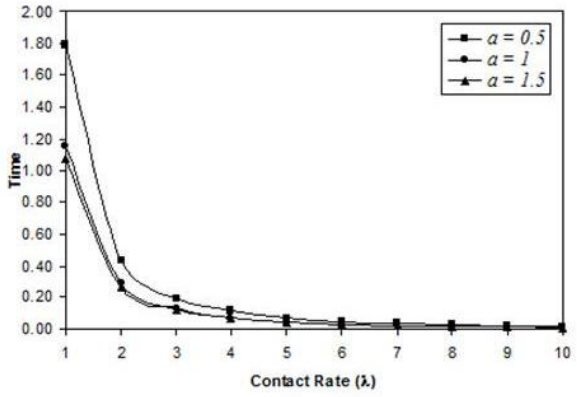


Figure 2. Variance of Time to CADT (β = 0.07, μ = 1.00)



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