SMR.301/ 33

FIRST AUTUMN WORKSHOP ON MATHEMATICAL ECOLOGY

(31 October - 18 November 1988)

REVIEW OF RECENT MODELS OF HIV/AIDS TRANSMISSION

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HIV, the human immunodeficiency virus, is the etiological agent for AIDS (Acquired Immune Deficiency Syndrome). In 1982 Gallo suggested that the cause of AIDS was likely to be a new human retrovirus and, in 1983, researchers at the Pasteur Institute under the direction of Montagnier were able to isolate a new retrovirus from a New York AIDS victim (see Barre-Sinoussi et al. 1983). In 1984, Gallo and his colleagues isolated the same type of retrovirus and proved it to be the etiological agent of AIDS (for more details see Gallo 1986,1987; Wong-Staal and Gallo 1985). This virus has been estimated to kill at least 30% of those infected. By April 1988, about 58,000 individuals have died of AIDS in the United States, and the Coolfont Report (1986) predicts that by 1991 the lower bound for the cumulative number of AIDS cases will be 290,000 individuals in the United States alone. One of the biggest problems associated with HIV is that most infected individuals appear to be asymptomatic and infectious for long periods of time, with an average infectious period of at least 8 years. Furthermore, there is growing evidence that the infectiousness of individuals varies with time since infection; the amount of free virus is relatively high just after infection (Francis et al. 1984; Suluhuddin et al. 1984) , remains low for several years, and climbs again within a year or so of the onset of AIDS (Lange et al. 1986).

Some of the important factors in the dynamics of HIV relate to the heterogeneity of the host population. These considerations include sexual preference (homosexual, bisexual and heterosexual), degree and type of sexual activity (number of partners, length of partnerships, anal sex), age-structure (degree of sexual activity may be a function of age), intravenous drug use (sharing of contaminated needles), socio-economic factors (which affect the level of education and hence the degree of response to education programs, and, in the lower socio-economic classes, a higher incidence of prostitution, shared needles in intravenous drug use, etc.), and cultural factors (different degrees of sexual activity for males and females, acceptability and frequency of use of prostitutes, etc.). In addition, there are epidemiological factors that may be crucial to the dynamics of HIV, including latent periods, long periods of infectivity, variable infectivity, and a high percentage of asymptomatic carriers.

Mathematical models help investigate the relative importance of these factors. If this first step is accomplished with some degree of success, then we can proceed to determine the demographic and economic impact of this epidemic. This process may help us to develop reasonable, scientifically and socially sound intervention plans that are applicable under a variety of circumstances, and to determine the best ways to implement them rapidly. The series of models briefly reviewed in this chapter represent a first step in approaching these objectives, and also provide a complement to the more extensive and complete chapter by May and Anderson reprinted in this volume (or see May and Anderson 1988a, 1988b). While the following exposition suffers from inevitable incompleteness deriving from constraints of space, I hope this discussion of the modelling approaches to the spread of AIDS will attract more investigators into the field of mathematical epidemiology.

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The role of long periods of infectivity

We (Castillo-Chavez et al. 1988a,1988b, 1988c) have developed a series of mathematical models that begin by looking at AIDS as an exclusively sexually-transmitted disease. Our objective has been to evaluate the role of long periods of infectiousness in the dynamics of HIV. These models are natural extensions of those developed by Anderson and May (1987, 1988). Our approach has been to divide the population under discussion into social groups defined by criteria such as sex, sexual behavior, or age, and these groups can be extended to include socioeconomic categories of various types. As is customary in these models, differences among individuals of the same group are ignored but not those among groups; hence we assume a network of interactions of various strengths (see Fig. 1).

For our immediate purposes, only the simplest version of this model - - that of a single group - - is included. We divide this population into five classes: S (susceptible), I (infectious that will go on to develop AIDS); Y (infectious that will not develop full-blown AIDS), Z (former Y that are no longer sexually active), and A (former I that have developed full-blown AIDS) (see Fig. 2). We assume that individuals become infectious immediately, and that individuals who develop full-blown AIDS have no sexual contacts and hence are not responsible for new infections. In order to explore the role played by the long period of asymptomatic infection we assume that the I- and Y-infectious individuals remain infectious for fixed periods of time: ω and τ units of time respectively.

We denote by $I_0(t)$ and $Y_0(t)$ those individuals that were in either class I or Y at time $t = 0$, and are still infectious; $Z_0(t)$, those individuals that were in class Z at time $t = 0$, and are still alive; and $A_0(t)$, those individuals who have

already developed full-blown AIDS at time $t = 0$, and are still alive. Hence it is reasonable to assume that $Z_0(t)$ and $A_0(t)$ vanish for large t. In addition, since ω and τ denote the infectious periods, we assume that $I_i(t) = Y_i(t) = 0$ for $t > \max (\omega, \tau)$.

Λ denotes the "recruitment" rate into the susceptible class (defined as those individuals who become sexually active); μ, the natural mortality rate; d, the disease-induced mortality due to AIDS; p, that fraction of the susceptibles that become I-infectious [and therefore (1 - p) the fraction of the susceptibles that become Y-infectious]. The function H(x) denotes the Heaviside function, defined as being equal to 1 if $x > 0$ and zero otherwise. Following Castillo-Chavez et al. (1988a, 1988b) and Anderson et al. (1988) and using Fig. 2, we arrive at the epidemiological model:

$$\frac{dS(t)}{dt} = \Lambda - \lambda C[T](t) \frac{S(t)W(t)}{T(t)} - \mu S(t) \ ,$$

$$I(t) = I_0(t) + \lambda p \int_{t-\omega}^{t} C[T](x) \frac{S(x)W(x)}{T(x)} H(x) e^{-\mu(t-x)} dx \ ,$$

$$Y(t) = Y_0(t) + \lambda(1 - p) \int_{t-\tau}^{t} C[T](x) \frac{S(x)W(x)}{T(x)} H(x) e^{-\mu(t-x)} dx \ ,$$

$$A(t) = A_0(t) + \lambda p \int_{0}^{t-\omega} C[T](x) \frac{S(x)W(x)}{T(x)} H(x) e^{-\mu(t-x) - d(t-x-\omega)} dx \ ,$$

$$Z(t) = Z_0(t) + \lambda(1 - p) \int_{0}^{t-\tau} C[T](x) \frac{S(x)W(x)}{T(x)} H(x) e^{-\mu(t-x)} dx \ ,$$

where $W(t) = I(t) + Y(t)$, and $T(t) = S(t) + W(t)$.

The function C[T] denotes the mean number of sexual partners of an average individual per unit time, given that the population density is T, and λ (a constant) denotes the transmission probability per partner. More specifically (as in Hyman and Stanley 1988), λ = i φ where i denotes the probability of infection per sexual contact and φ denotes the average number of contacts per sexual partner. Hence λC[T] denotes the probability of transmission per unit time and λC[T] dt denotes the probability that a given sexual partner will transfer the disease to a particular individual in time dt. The factor W/T is the probability that a contact of a susceptible individual with randomly selected individual will be an infectious individual. We (1988a,1988b) have shown analytically that, under appropriate assumptions on C[T], the local dynamics of this system is governed by the reproductive number R, the number of secondary infections produced by a single infected individual in a purely susceptible population. R is given by

R = (prob.of transmission)x

(mean number of sexual partners in a purely susceptible population)X

(the mean infectious period)

or

$$R = \lambda C[\frac{\Delta}{\mu}]\{p\frac{1-e^{-\mu\omega}}{\mu} + (1-p)\frac{1-e^{-\mu\tau}}{\mu}\}.$$

Briefly, the maintenance of the disease in the population at endemic levels can occur only if R > 1. Hence to eliminate the disease we should consider control strategies that could potentially reduce R below this critical value. Approaches of this type have already been used in the development of vaccination strategies for a variety of diseases (see this volume), or in educational programs for reducing transmission.

For AIDS, it is not sufficient to consider homogeneous populations, as the dynamics are affected critically by a variety of factors such as age, sexual behavior, geographical area, or other characteristics. Considering models that incorporate several interacting groups is therefore a priority. In this case, however, the ease of performing analytical computations disappears, and numerical simulations may be the only approach. Numerical computations for intergroup models also show the existence of threshold behaviors, allow estimation of those thresholds, and explore of parameter sensitivity.

Simulations are also useful in one-group models; for example, consider the role of education in the dynamics of HIV. Assuming that education becomes effective and parameters have been changed so that R < 1, then through numerical simulations we see that the time lag in system responsiveness assures a skewed concentration of infected individuals. This delay means that even if the disease eventually is eradicated, the number of infected individuals would continue to increase for a long time--perhaps several times the infectious period. Thus, the effects of education will not produce a decrease in the *total* number of infected individuals for many years. If the rate of decrease in the number of new cases is very slow, and the initial observation is a sharp increase in the number of cases of individuals who develop "full-blown" AIDS, then education could be perceived primarily as a cause of increased promiscuity, rather than as controlling the disease, thus having a serious negative impact on public policy.

Other models that concentrate on the effects of long infectious periods can be found in the works of Anderson and May (1987, 1988), Blythe and Anderson (1988), and Anderson (1988).

Effects of partnership dynamics

Study of the mathematical aspects of partnership models in a demographic context can be found in the works of Kendall (1949), Pollard (1973), and Fredrickson (1971). However, Dietz and Hadeler (1988) were the first to put these demographic models into an epidemiological framework. As Dietz and Hadeler [1988] point out, "The classical models for sexually transmitted infections assume homogeneous mixing either between all males and females or between certain groups of males and females with heterogeneous contact rates. This implies that everybody is all the time at risk of acquiring infection." Therefore, they ignore the periods of 'immunity' due to temporary monogamous partnership among uninfected individuals. These authors raise the question of the potential effects of these temporary periods of 'immunity' in the dynamics of sexually transmitted diseases. A simplified version of the Dietz/Hadeler model forms the background for the discussion that follows.

I will briefly describe this framework for a single homosexual population and expand it to include variable infectivity and variable AIDS-related mortality. This extension is more realistic, as it allows us to see AIDS as a progressive disease. Extensions are then possible to include a variety of sexual tendencies, age structures, multiple groups, and varible infectivity.

At time t we denote by $m(t)$ the number of uninfected single males, $M(t)$ the number of infected single males, Λ the constant "recruitment" rate into the m-category, and $P_{mm}(t)$, $P_{mM}(t)$, $P_{MM}(t)$, the number of m-m, m-M and M-M pairs respectively. Furthermore, we denote by σ the constant break-up rate, μ the constant natural mortality rate for m- individuals, d the constant mortality rate for M-individuals, i the probability of infection per contact, and α the number of contacts per unit time while in a partnership. Since infection only takes place

while in a partnership, we can make use of Fig. 3 to arrive at the following set of ordinary differential equations that describe the dynamics of HIV:

$$\frac{dm}{dt} = \Lambda - \mu m + 2(\sigma+\mu)P_{mm} + (d+\sigma)P_{mM} - 2\phi(m,m) - \phi(m,M) \ ,$$

$$\frac{dM}{dt} = -dM + (\mu+\sigma)P_{mM} + 2(d+\sigma)P_{MM} - \phi(m,M) - 2\phi(M,M) \ ,$$

$$\frac{dP_{mm}}{dt} = \phi(m,m) - (\sigma+2\mu)P_{mm} \ ,$$

$$\frac{dP_{mM}}{dt} = \phi(m,M) - (\mu+\sigma+d)P_{mM} - \beta P_{mM} \ ,$$

$$\frac{dP_{MM}}{dt} = \phi(M,M) - (2d+\sigma)P_{MM} + \beta P_{mM} \ ,$$

$\beta = i\alpha$ and $\phi(x,y)$ is a non-negative nonlinear pair formation function that satisfies the following conditions as specified by Fredrickson (1971):

$\phi(0,y) = 0$ for all $y \geq 0$,

$\phi(x,0) = 0$ for all $x \geq 0$,

$\phi(\delta x,\delta y) = \delta\phi(x,y)$ for all $x, y, \delta \geq 0$,

$\frac{\partial\phi}{\partial x} \geq 0$, $\frac{\partial\phi}{\partial y} \geq 0$,

Following Dietz and Hadeler (1988), we assume symmetry; that is,

$\phi(x,y) = \phi(y,x)$ for all x and y ≥ 0.

For a discussion of several functional forms, see Keyfitz (1972), Kendall (1949), and Dietz and Hadeler (1988); however, the most common are

$\phi(x,y) = \rho\frac{xy}{x+y}$, and

$\phi(x,y) = \rho \min(x,y)$:

the harmonic mean and the minimum function. A partial local stability analysis of a two-sex model that uses both pair-formation functions can be found in

Dietz and Hadeler (1988). Their main conclusion is that endemic equilibria are possible only if the separation rate is large enough to ensure a sufficient supply of sexual partners. This result immediately suggests possible educational strategies to help reduce the incidence of sexually-transmitted diseases. They include the encouragment of longer monogamous partnerships or simply the encouragement of sequential (rather than overlapping) partnerships.

In the case of AIDS, other effects such as variable infectivity may have to be taken into consideration even in the case of a single population. We can formulate an extension of the Dietz and Hadeler's model that considers the now-serious possibility that AIDS is a progressive disease. The variables t and τ denote time and time since infection. The mortality rate for infected individuals $d = d(\tau)$ is a function of τ, $m(t)$ and $P_{mm}(t)$ have the same meaning as before. However, $M(t,\tau)$, $P_{mM}(t,\tau)$, $P_{MM}(t,\tau,\tau')$ now denote densities, so that for example:

$$\Delta t \int_{\tau}^{\tau + \Delta \tau} \int_{\tau'}^{\tau' + \Delta \tau'} P_{MM}(t, \tau, \tau') \, d\tau \, d\tau'$$

denotes the number of M_τ-$M_{\tau'}$ pairs in time interval $[t, t + \Delta t]$. We still assume that μ and σ are constant and denote $\phi(x,y)$ by ϕ_{xy}. Again following Fig. 3, we arrive at the model:

$$\frac{dm}{dt} = \Lambda - \mu m - 2(\sigma + \mu)P_{mm} + \int_0^\infty (d(\tau) + \sigma)P_{mM}(t,\tau) \, d\tau - 2\phi_{mm} - \int_0^\infty \phi_{mM}(t,\tau) \, d\tau ,$$

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial \tau} = -d(\tau)M(t,\tau) + (\sigma + \mu)P_{mM}(t,\tau) +$$

$$2\int_0^\infty (\sigma + d(\tau))P_{MM}(t,\tau,\tau') \, d\tau' - \phi_{mM}(t,\tau) - 2\int_0^\infty \phi_{MM}(t,\tau,\tau') \, d\tau' ,$$

$$\frac{dP_{mm}}{dt} = \phi_{mm}(t) - (\sigma + 2\mu)P_{mm} ,$$

$$\frac{\partial P_{mM}}{\partial t} + \frac{\partial P_{mM}}{\partial \tau} = \phi_{mM}(t,\tau) - (\sigma + \mu + d(\tau))P_{mM} - \beta P_{mM} ,$$

$$\frac{\partial P_{MM}}{\partial t} + \frac{\partial P_{MM}}{\partial \tau} + \frac{\partial P_{MM}}{\partial \tau'} = \phi_{MM}(t,\tau,\tau') - (\sigma + d(\tau) + d(\tau'))P_{MM} ,$$

where $P_{MM}(t,\tau,0) = \beta P_{mM}(t,\tau)$, $P_{MM}(t,\tau,\tau') = P_{MM}(t,\tau',\tau)$ and appropriate initial conditions are prescribed.

To use the harmonic mean to describe the process of pair formation, we set

$$\phi_{mm}(t) = \rho \frac{m(t) \, m(t)}{m(t) + M(t)} ,$$

$$\phi_{mM}(t,\tau) = 2\rho \frac{m(t) \, M(t,\tau)}{m(t) + M(t)} ,$$

$$\phi_{MM}(t,\tau,\tau') = \rho \frac{M(t,\tau) \, M(t,\tau')}{m(t) + M(t)} ,$$

where

$$M(t) = \int_0^\infty M(t,\tau) \, d\tau .$$

Whether or not the introduction of variable infectivity (and hence long periods of infectiousness) will affect Dietz and Hadeler's main conclusion is still an open question.

The effects of multiple sexual partners

Hyman and Stanley (1988) have developed some risk-based models based on the assumption that individuals with multiple sexual partners are usually infected first and tend to become the major source of spread into those

groups with fewer sexual partners. In addition, they have also explored the role of variable infectivity in the context of their model.The simplest version of their model can serve as an example of this approach.

We let t and τ denote time and time since infection, μ denotes the natural mortality rate, $\delta(\tau)$ denotes the death rate τ-units after the onset of AIDS, $\beta(\tau)$ denotes the rate of developing AIDS τ-units after infection, $i(\tau)$ denotes the probability of infection from a contact with a person infected τ-units of time ago, and r denotes the average number of new sexual partners per year. In addition we denote by $S(t,r)$ the density of susceptibles according to their number of partners per year, $I(t,r,\tau)$ the density of infecteds according to the number of partners per year and the time since infection, $c(r,r')$ the number of contacts between people with r and r' partners per year, and $S_0(r)$ the density of people with r new partners per year before the introduction of the AIDS virus. Using this notation, Hyman and Stanley (1988) arrive at the following model:

$$\frac{\partial S(t,r)}{\partial t} = \mu(S_0(r) - S(t,r)) - \lambda(t,r)S(t,r) ,$$

$$I(t,0,r) = \lambda(t,r)S(t,r) ,$$

$$\frac{\partial I(t,\tau,r)}{\partial t} + \frac{\partial I(t,\tau,r)}{\partial \tau} = (\beta(\tau) + \mu)I(t,\tau,r) ,$$

$$A(t,0) = \int_0^\infty \int_0^\infty \beta(\tau) I(t,\tau,r) \, d\tau \, dr ,$$

$$\frac{\partial A(t,\tau)}{\partial t} + \frac{\partial A(t,\tau)}{\partial \tau} = -\delta(\tau) A(t,\tau) ,$$

$$\frac{dA_T}{dt} = \int_0^\infty \int_0^\infty \beta(\tau) I(t,\tau,r) \, d\tau \, dr ,$$

where

$$\lambda(t,r) = \frac{r \int_0^\infty c(r,r') \, r' \int_0^\infty i(\tau) I(t,\tau,r') \, d\tau \, dr'}{\int_0^\infty r'' S(t,r'') \, dr'' + \int_0^\infty r'' I(t,\tau,r'') \, d\tau \, dr''} .$$

Stanley and Hyman observe that if $c(r,r')$ and $i(\tau)$ are constants, then partners are chosen at random from the population. Hence this model reduces to one of Anderson et al. (see May and Anderson's chapter in this volume). Preliminary numerical investigations show that the shape of the distribution of individuals according to risk can have a marked effect on the shape of the epidemic. In addition, the rate at which the susceptible population is infected seems to be very sensitive to small changes in the infectivity profile.

In the population genetics literature (see Crow and Kimura 1970) the effects of different mating systems on gene flow are studied. An alternative approach to modelling the sexual transmission of HIV is through the mixing of the population genetics and epidemiological approaches, superimposing a 'mating' system, such as assortative mating, within the classical epidemiological framework. A starting point towards this approach may be that of Colgate, Hyman, and Stanley (1988). Their recent risk-based model, based on the observed cubic growth of AIDS cases, has built on the assumption that individuals with multiple sexual partners have sexual intercourse mostly with individuals with multiple sexual partners. That is, most contacts take place between individuals in the same risk group. An important question that Colgate et al. (1988) address is that of the speed of propagation of the disease from highly prosmiscuous individuals to those that are less prosmiscuous. Colgate et al. (1988) derive a diffusion equation when mixing is small. Their diffusion

equation model has similarity solutions which are saturating waves moving from large risk groups to low risk groups with decreasing speed.

Conclusions

In this chapter we have introduced several models that begin to address several questions raised by the AIDS epidemic including the role of long periods of infectivity, the effects of temporary immunity due to the formation of sexual partnerships between non-infected individuals, and the overall effects of high risk (multiple sexual partners) behavior. May and Anderson's chapter in this volume adresses (among other issues) the possible demographic consequences of this epidemic.

Although progress has been made, there is still insufficient information to appropriately predict the dynamics of this epidemic. How will the dynamics be affected by education or intervention programs? How can we implement the use of drugs that may be developed to decrease the level of infectiousness and extend the life of HIV carriers? If a vaccine is developed, what is the optimal vaccination program?

Furthermore, we have to be aware that since many symplifying assumptions are made in the construction of these models, including the clumping or aggregation of many important variables and components, the results of these models cannot be used to circumvent the moral and ethical questions raised by this epidemic.

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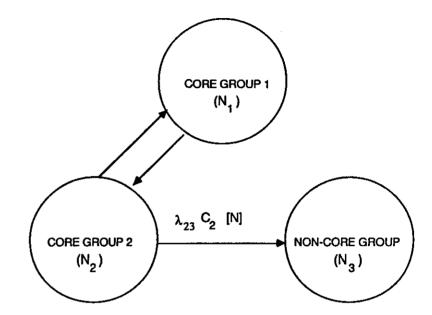
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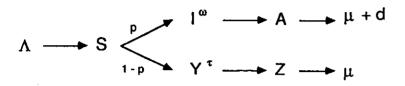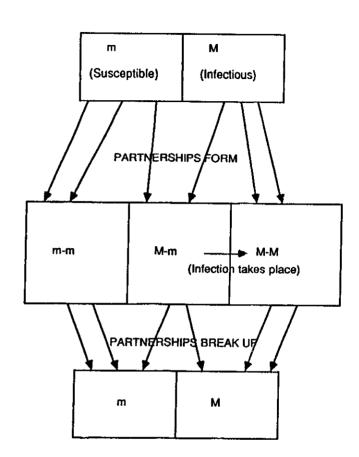
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Legend for figures

Fig. 1: Hypothetical 3 group network, λ_{ij} denotes the probability of transmission per unit time per partner between individuals of group i and j, $C_i[N]$ denotes the mean number of sexual partners that an average individual of group i has given that the population density is $N = N_1 + N_2 + N_3$.

Fig. 2: Single group model; for details see the text.

Fig. 3: Flow diagram for a single group partnership model.

CORE GROUP 1
(N_1)

$\lambda_{23} \ C_2 \ [N]$

CORE GROUP 2
(N_2)

NON-CORE GROUP
(N_3)