# ON THE MODELLING OF EPIDEMICS

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## ABSTRACT

A discussion of Cornell's epidemiology group work on the mathematical modelling of (1) the myxoma-rabbit system in Australia and Europe, (2) the interaction of multiple strains of influenza in an age-structured population, and (3) the interaction of human immunodeficiency virus with specific human populations is presented. The role of supercomputers with vector and parallel processing capabilities in the analysis of these models is also discussed. It is argued that "the increased availability of a data base for infectious diseases, the new theoretical advances in dynamical systems theory, the power of supercomputers, and the ethical considerations regarding experimentation with human subjects have made the use of numerical simulations--when guided by careful mathematical analyses--an essential component in the study of disease dynamics." This paper will be presented on March 24, 1989 at the European Symposium on High Performance Computing, to be held in Montpellier, France

# On the Modelling of Epidemics

by

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## Introduction:

In 1760, physician and mathematician Daniel Bernoulli presented to the Royal Academy of Sciences in Paris a simple mathematical model to demonstrate the increased life expectancy of those individuals innoculated against smallpox. After this early beginning, the theory of mathematical models of infectious diseases made no significant advances until one hundred years ago with the work of the Russian physician P. D. En'ko in 1889 (see Dietz 1988). En'ko constructed the first chain binomial model (wrongly attributed to Frost), and used it while at the St. Petersburg Alexander Institute to fit several observed epidemics there. These so-called Reed-Frost models still play a very important role in theoretical and applied epidemiology.

However, the key concepts in the development of a mathematical theory derive from the English physician Sir Ronald Ross (1911), although partial credit should be given to Brownlee (1907) and McKendrick (1912). Ross introduced the assumption--historically and overgenerously attributed by Soper to Hamer (see the discussion in Volume 92 of the Journal of the Royal Statistical Society, 1929)-- that the rate of new infections is proportional both to the number of susceptibles and to the number of infectious individuals. Ross also developed the first mathematical model for the spread of a vector-transmitted disease (malaria), and later concluded that to eradicate malaria it was sufficient to bring the vector population below a threshold level. This theoretical result, the first threshold theorem, implied that a succesful control program did not require the elimination of the whole mosquito population. McKendrick, another english physician, extended this result after being drawn into the field of mathematical epidemiology under Ross's encouragement and influence (Dietz pers. comm.). In 1927, he co-authored his celebrated paper with Kermack establishing that 'standard' mathematical epidemiological models imply that a threshold number of susceptible individuals must be available if an epidemic is to take place. This key idea has provided the theoretical justification for the implementation of vaccination programs. Soper's 1929 study of the causes of periodic disease outbreaks represents the next important breakthrough, opening up what is still a very active and important area of research (see Hethcote and Levin, 1989).

Ross was keenly aware of the necessity of considering the effects of nonhomogeneous mixing, demography, seasonality, geographical distribution, and the

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genetic variability of hosts and pathogens in order to increase the predictive and explanatory power of mathematical models in epidemiology as well as to increase their value in the development of control measures. This level of detail, however, could only be introduced by the stratification of populations into subpopulations according to specified criteria, and by a detailed description of the interactions of individuals within and between subpopulations. The numerical study of hierarchically-constructed models of this type will be greatly enhanced by the systematic use of supercomputers because their sophisticated vector and parallel processing capabilities are well suited to numerical simulation of models of this type.

What follows will briefly outline our investigations into two viral diseases--myxomatosis and influenza--as well as our current work on the retroviral disease AIDS, and will illustrate some important theoretical questions in this area. Our work is both analytical and numerical, and has made use of the Cornell National Supercomputer Facility (CNSF).

## I. Myxomatosis

By the middle of this century, the devasting effects of a burgeoning introduced rabbit population, on the natural vegetation of Australia were readely apparent. Clearly, the European rabbit, Oryctolagus cuniculus, was destroying the fragile ecological balance of the continent. In the early 1950s, the myxoma virus, the etiological agent of the often-fatal disease myxomatosis, was introduced in Australia, with mosquitos as mechanical vectors. The first epidemic outbreaks brought the rabbit population under control. Shortly thereafter, similar introductions in England and France led to huge reductions in rabbit populations in those countries as well. The introduction of the myxoma virus became a textbook success story of biological control.

However, the early successes dissipated within a few years as evolutionary changes took place. The most virulent grade of the myxoma virus can kill more than 99% of infected and non-immune rabbits within two weeks. However, over the last 38 years, rabbits have evolved resistance to the virus, and the virus itself has generated less virulent forms. A key theoretical issue in this coevolutionary process is whether or not a balance will be reached between host resistance and the virulence of the infecting agent; a key practical question for the myxoma-rabbit system is whether or not the virus can remain an effective control agent.

Fenner and Ratcliffe (1965) have used the case mortality of rabbits injected with one specific strain of myxoma (KM 13) to measure the resistance of rabbits from different field populations. In addition, Fenner has worked with other colleagues (see Fenner and Ratcliffe 1965) to develop a set of categories to track grades of virulence. The most virulent strains--those causing 99% mortality of infected laboratory rabbits--constitute grade I, while those causing 50% mortality under the same conditions were placed in grade V. Since as early as 1952, most field isolates of the virus have been graded as having a virulence level of III (subdivided into IIIA and IIIB) and IV. In addition, the case mortality of rabbits to KM 13 has declined from about 90% after the first outbreak in 1950-

51, to less than 30% only eight years later, after about seven outbreaks (Marshall and Douglas 1961).

Levin and Pimentel (1981) and Anderson and May (1982) developed simple mathematical models to show how natural selection can favor the intermediate or less virulent grades of the myxoma virus over the more extreme categories. Recently, Dwyer, Levin, and Buttel (1989) have built a data-based model that is both more mechanistic and more biologically sound. Their model includes differences in infectiousness as a function of time since infection, differences in efficiency of vector(s), and differences in grade-induced disease mortality. In addition, the host's age structure has been incorporated through the use of juvenile (non-reproductive) and adult classifications, and through the recognition of a seasonally varying birth rate that exhibits a strong peak in the spring and a lesser peak in the fall (data from Gilbert et al. 1987). However, the model assumes an exponentially growing rabbit population in the absence of disease, and initially ignores the host's genetic variability.

Single grade computer simulations for this model are initiated by specifying a reproductive data set, a natural mortality rate, and an age at first reproduction. Results of a set of simulations for strain IIIB can be found in Dwyer et al. (1989) for the reproductive data set determined at the Texas station in Queensland (see Marshall et al. 1957) and an age at first reproduction of 150 days. As the natural mortality $\mu$ is increased to .004, the disease controls the rabbit population; for $\mu$ = .005 the population enters a cycle with a period of two years, for $\mu$ =.0065 and $\mu$ =.007 the rabbit population, though still controlled by the disease, enters a cycle with a very long, or perhaps aperiodically fluctuating period (see Fig , taken from Dwyer et al. 1989). Figure 1 shows the output for a single strain (IIIB) model (the population dynamics for total rabbit population form 20 to 40 years).

When $\mu$ =.0085, the virus fades out of the population and the rabbit population goes extinct as $\mu$ exceeds the birth rate. Extensive simulations with a variety of grades lead Dwyer et al. (1989) to the conclusion that small changes in either virus virulence or natural mortality lead to very distinct population dynamics. In particular, for fixed reproductive parameters and fixed age of first reproduction, an increase in the natural mortality leads to an increased period of oscillation. The smallest value of $\mu$ capable of controlling the rabbit population is a function of the virus grade, and it decreases as the age at first reproduction increases. Finally, in the absence of evolved host resistance, Dwyer et al.'s simulations show that when six grades (I, II, IIIA, IIIB, IV, V) are put into competition, grade IV is the most successful. The model of Dwyer et al. (1989) is given by a set of difference equations; the host population is divided into two classes (juveniles and adults); the juveniles are divided into 90-150 age classes (the length of an age class is one day); the adults (reproductive stage) are all clumped together; and reproduction is allowed to vary with season (the scarcity of susceptible rabbits between breeding seasons may have a significant effect upon virus availability and hence on virus survival, Fenner and Ratcliffe 1965). In addition, each class is divided into epidemiological subclasses: susceptibles, infected by grade (multiple-grade infections are not allowed), and recovered (total cross-immunity to other strains is assumed, see Marshall and Fenner 1957). The average period of infectiousnes varies from 11 to 118 days depending on the grade, and infected rabbits do not participate in the reproduction process (kittens born to infected rabbits usually die, Parer 1977). Our simulations consisted of the iteration of the model equations with a time step of one day for a period of 40 years. It is clear from the model description that age-structured models are well suited to exploit the parallel and

vector capabilities of supercomputers, as age and age since infection provide natural settings for code vectorization. Furthermore, epidemiological subclassifications may allow for the efficient use of parallel processors, and the speed at which these simulations can be executed, allows for an extenisive sensitivity analysis to model parameters. For a detailed description, a throrough discussion of the model results, and its computer implementation and simulation, see Dwyer et al. (1989).

## 2. Influenza

There are several types of the influenza virus as well, and two major types, called A and B, are endemic in human populations. Our studies (Levin and Andreasen 1986, Castillo-Chavez et al. 1988, 1989, Andreasen 1988, 1989) have concentrated on the dynamics of influenza A. The type-A virus is capable of rapid genetic change, and major shifts have produced three distinct subtypes: H1N1, H2N2, and H3N2; minor genetic changes in surface antigens (or "drifts") continually generate a great variety of strains for these subtypes. Our research has concentrated on understanding the reasons behind the observed periodic recurrences of different subtypes and the recently documented co-circulation of viral strains (see Couch and Kassell 1982, Thacker 1986). To study these questions, we have extended the classical epidemiological models to take into consideration the existence of multiple infective and resistance classes, age-specific contact rates, and seasonality in transmission (i.e. epidemics usually start in the fall, when there is an abrupt change in contact rates among school-age children).

In order to describe our model briefly, we let $x(a,t)$, $y_i(a,t)$, $z_i(a,t)$, $v_i(a,t)$, and $w(a,t)$, denote the age-specific densities of individuals in the susceptible, infected by strain or subtype i, recovered from strain or subtype i, infected by strain or subtype i (once recovered from strain or subtype $j \neq i$), and recovered from both strains or subtypes, respectively. In addition, $b(a)$ represents the age-specific contact rate, $\lambda(t)$ denotes the instantaneous force of infection, $\beta_i$ denotes the transmission scaling factor, $\mu(a)$ is the age-specific mortality rate, and $\gamma_i$ denotes the (constant) recovery rate. The susceptibility coefficients $\sigma_1$ and $\sigma_2$ denote different degrees of cross-immunity associated with the interaction of two strains or two subtypes. Individuals are assumed to have gained permanent immunity once recovered from a specific strain and we further assume that individuals cannot be infected by two infections simultaneously (this is a reasonable simplification as the infectious period for influenza is of between 3-6 days).

The "force" of infection is described by the use of the proportionate mixing assumption (see Barbour, 1978; Nold, 1980; Hethcote and Yorke, 1984; Dietz and Schenzle, 1985). Therefore, the contact rate between susceptible persons of age a and infected ones of age a' is assumed to be proportional to $b(a)b(a')$. If we now follow the Transfer Diagram 1 and assume a bilinear (Ross's) incidence rate, we arrive at the following initial boundary value problem:

$$\frac{\partial x(a,t)}{\partial a} + \frac{\partial x(a,t)}{\partial t} = -(\lambda_1(t)\, b(a) + \lambda_2(t)\, b(a) + \mu(a))\, x(a,t),$$

$$\frac{\partial y_i(a,t)}{\partial a} + \frac{\partial y_i(a,t)}{\partial t} = \lambda_i(t)\, b(a)\, x(a,t) - (\gamma_i + \mu(a))\, y_i(a,t), \quad i = 1, 2$$

$$\frac{\partial z_i(a,t)}{\partial a} + \frac{\partial z_i(a,t)}{\partial t} = \gamma_i y_i\,(a,t) - \sigma_j \lambda_j(t)\, b(a)\, z_i(a,t) - \mu(a)\, z_i(a,t), \quad i = 1, 2$$

$$\frac{\partial v_i(a,t)}{\partial a} + \frac{\partial v_i(a,t)}{\partial t} = \sigma_i \lambda_i(t)\, b(a)\, z_j(a,t) - (\gamma_i + \mu(a))\, v_i(a,t), \quad i = 1, 2$$

$$\frac{\partial w(a,t)}{\partial a} + \frac{\partial w(a,t)}{\partial t} = (\gamma_1 + \gamma_2 - \mu(a))\, w(a,t),$$

$$\lambda_i\,(t) = \beta_i \int_0^\infty b(a')\, [y_i(a',t) + v_i(a',t)]\, da',$$

$$x(0,t) = \rho,\ y_i(0,t) = 0,\ z_i(0,t) = 0,\ v_i(0,t) = 0,\ w(0,t) = 0,$$

$$x(a,0) = x_0(a),\ y_i(a,0) = y_{0i}(a),\ z_i(a,0) = z_{0i}(a),\ v_i(a,0) = v_{0i}(a),\ w(0,t) = w_0(a),$$

$$\rho = \left[ \int_0^\infty e^{-M(a)}\, da \right]^{-1} \quad \text{where} \quad M(a) = \int_0^a \mu(\alpha)\, d\alpha\,.$$

Our analyses, both theoretical and on the CNSF show that weakly damped oscillations can result from the effects of age structure alone or due to shifts among co-circulating strains that have been incorporated at the population level through the coefficient of cross-immunity. When both mechanisms are present, the two damped oscillations are capable of exciting each other to generate sustained periodic dynamics. The inclusion of seasonality in the transmission rates leads to aperiodic and possibly chaotic behavior. The study of the effects of seasonal transmission rates has been facilitated by the construction of portraits in which a particular variable is plotted against lagged representations of its own dynamics. Poincaré sections through these representations (Fig. 2) reduce the dimensionality and allow for the construction of return maps that help us understand the effects of seasonality.

An specific discretization of the above model was simulated in the following fashion: the population was divided into 80 one-year (360 day) age classes, births and deaths were balanced to hold population size constant. Since no disease induced mortality was incorporated, we started with a population that had already reached its stationary age

distribution and hence a fixed fraction of the population of each age class was assumed. The daily contact rate of an infective in age class I with an infective in age class k was assumed constant and proportionate to the product of the activity level of both age groups (proportionate mixing). We used a time step of three days, as dictated by the dynamics of influenza (i.e., the infectious period is of the order of 3-6 days); and since the transmission of influenza depends strongly on the age structure of the population, our population was aggregated into five activity levels: preschool (ages 1 to 5), elementary school (ages 6 to 12), secondary school age (ages 13 to 18), adults (ages 19 to 60) and senior citizens (ages 61 to 80). The 640 compartments were updated after every iteration of the model, that is, at every time step for a period of 2000 years. Sensitivity analysis to the coefficients of cross-immunity and to the transmission coefficients (including seasonality) were performed (see Castillo-Chavez et al. 1988 and 1989). Furthermore, the extensive sensitivity analysis performed on this model lead Andreasen (1988, 1989a) to the analytical clarification of the role of cross-immunity in the period of the oscillation. Again, the age structure of the population and its epidemiological classification make these models well suited for supercomputers with vector and parallel processing capabilities. We hope that the description of our simple, although not optimal (for supercomputers) approaches to the numerical simulation of these models attract the interest of those experts on numerical algorithms also interested in biological applications.

## 3. Acquired Immunodeficiency Syndrome (AIDS)

The Human Immunodeficiency Virus (HIV) is the etiological agent for AIDS. In the United States, this retrovirus has killed over 50% of the 85,000 individuals that have developed "full-blown" AIDS. Study of the virus has been complicated for many reasons. Most infected individuals are asymptomatic for several years, and infectiousness varies with time since infection. There are several known routes of transmission, including anal intercourse, blood transfusions, and the sharing of contaminated needles. It has now become evident that an increased quantitative and qualitative understanding of the mixing structure of the host population is crucial both to achieve a reasonable scientific understanding of disease dynamics and to develop socially-sound intervention strategies (see Castillo-Chavez et al. 1987, Castillo-Chavez et al. 1989a, b, c).

We (Castillo-Chavez, Cooke, Huang, and Levin) have developed a series of models that look at AIDS as an exclusively sexually-transmitted disease. In this note, we describe the simplest version of this model, which considers a homogeneously mixed population and assumes that all individuals are equally infectious. Further extensions and elaborations of these models can be found in Castillo-Chavez e t al. 1989a,b,c,d and Huang et al. 1989a,b.

The population under consideration is divided into three classes: S (susceptible), I (HIV carriers), and A (full-blown AIDS). We assume that A-individuals are sexually inactive and, hence, do not contribute to the dynamics of AIDS. $\Lambda$ denotes the "recruitment" rate into S; $\mu$, the natural mortality rate; d, the AIDS-induced mortality; and $\lambda$, the transmission rate per infectious partner. C(T) denotes the mean number of sexual

partners an average individual has per unit time, given that the sexually active population is T (i.e. S + I). In general, C(T) will increase linearly for small T and saturate for large T; we assume only that C(T) is a nondecreasing function of T. The factor I/T denotes the probability that a randomly-selected individual will be infectious. The incidence rate (i.e. the number of new cases per unit time) is therefore given by $\lambda C(T)SI/T$. We now let P(s) represent the conditional probability that an individual, if still alive, will be infectious s time units after infection. P(s) is non-negative and non-increasing; furthermore, P(0) =1, and

we assume that $\int_0^\infty P(s)\,ds < \infty$ . Note that $-P'(x)$ denotes the rate of removal of individuals from group I into group A, x time units after infection. Finally, using the Transfer Diagram 2, we arrive at the following distributed delay model for the sexual spread of HIV/AIDS:

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

$$I(t) = I_0(t) + \int_0^t \lambda C(T(x))S(x)\frac{I(x)}{T(x)}\, e^{-\mu(t-x)} P(t-x)\,dx,$$

$$A(t) = A_0(t) + A_1 e^{-(\mu+d)t} + \int_0^t \left\{ \int_0^\tau \lambda C(T(x))S(x)\frac{I(x)}{T(x)}\, e^{-\mu(\tau-x)} [-P'(\tau-x)e^{-(\mu+d)(t-\tau)}]dx \right\} d\tau,$$

where the functions (with compact support) $I_0(t)$, $A_0(t)$, and the constant $A_1$, take care of the initial conditions.

This model generalizes and extends those of Anderson et al. (1986), Anderson and May (1987). Our analytical results for this model generalize and confirm the local results and numerical simulations done by Blythe and Anderson (1988) for specific forms of P(s) and constant C(T(t)). This model has two attracting states, the infection-free state and the endemic state. For $P(s) = e^{-\alpha s}$ we (Castillo-Chavez et al. 1989b,c) have shown that:

the disease-free state $(\frac{\Lambda}{\mu},0)$ is a globally asymptotically stable equilibrium if and only if the reproductive number $R \equiv \lambda C(\frac{\Lambda}{\mu})\frac{1}{\mu+\alpha} \leq 1$. If $R > 1$, then there is a unique endemic state, which is a global attractor for all positive solutions. Hence we note that R plays a fundamental role in the dynamics of the disease, determining whether or not the disease can be maintained.

We can generalize for an arbitrary P(s) as follows: the infection-free state is a global attractor whenever the reproductive number $R = \lambda C(\frac{\Lambda}{\mu}) \int_0^\infty e^{-\mu s} P(s) ds \leq 1$. If $R > 1$, then the limiting system

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

$$I(t) = \int_{-\infty}^{t} \lambda C(T(x)) S(x) \frac{W(x)}{T(x)} e^{-\mu (t-x)} P_I(t-x) \, dx ,$$

has a unique endemic state, which is locally asymptotically stable.

Briefly, the maintenance of the disease in the population at endemic levels can occur only if R>l, and hence one considers control strategies that can reduce R below its critical value. (For an extension of these results using variable infectivity see Castillo-Chavez et al. l989d).

For AIDS, it is not sufficient to consider homogeneous populations, as the dynamics may be critically affected by the fact that different groups have different behavior patterns. As we have shown that our single group models are robust, we have began using them to construct multiple group models. The simplest way to proceed is to divide our population into n groups and then assume that the mixing is homogeneous within each group while the mixing between groups is proportionate to their sexual activity (this is called proportionate mixing). We have shown that the simplest model of this type has multiple endemic equilibria (Castillo-Chavez et al. 1989e, Huang et al. l989a,b). However, even in this simple situation, the ease of performing analytical computations disappears, and numerical studies become indispensable, if we wish to obtain further understanding of the dynamics of this "simple" model.

The situation becomes even more complex when we take into account the fact that proportionate mixing has been shown to be an inadequate assumption for modelling AIDS, and that new social /sexual mixing structures need to be developed and incorporated into dynamic models of disease transmission. A preliminary theory of mixing has been initiated by Blythe and Castillo-Chavez (l989a, b). In addition, we (see Huang et al. 1989b) have developed a dynamic model for an arbitrary number of groups that can incorporate any mixing structure. We intend to perform sensitivity studies on this framework to these mixing structures to increase our understanding of their role in disease dynamics. We believe that this understanding is crucial in the development of any potential control measures. Supercomputers will play a key role in this process.

## Conclusions

It is abundantly clear that the availability of supercomputers with vector and parallel processing capabilities will change fundamentally the way we study the population dynamics of infectious diseases. The increased availability of a data base for infectious diseases, the new theoretical advances in dynamical systems theory, the power of supercomputers, and the ethical considerations regarding experimentation with human subjects have made the use of numerical simulations--when guided by careful mathematical analyses--an essential component in the study of disease dynamics.

The level of uncertainty in the formulation of public policy in relation to the critical environmental and public health challenges posed by infectious diseases will be significantly reduced through the analysis of more realistic mathematical models. This analysis has been now greatly facilitated by the expanded capabilities of supercomper as well as by their increased availability to researchers in the biological sciences.

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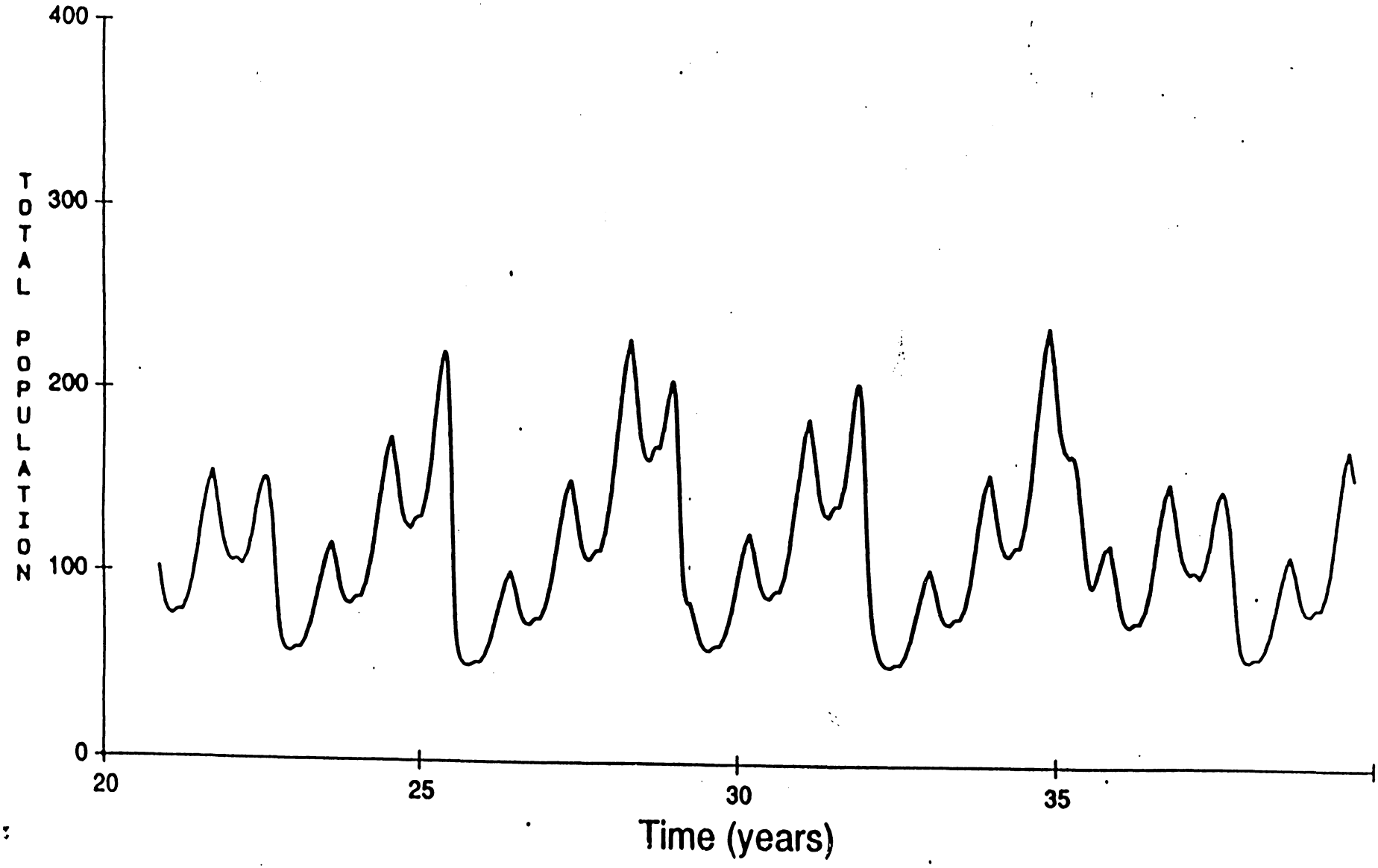
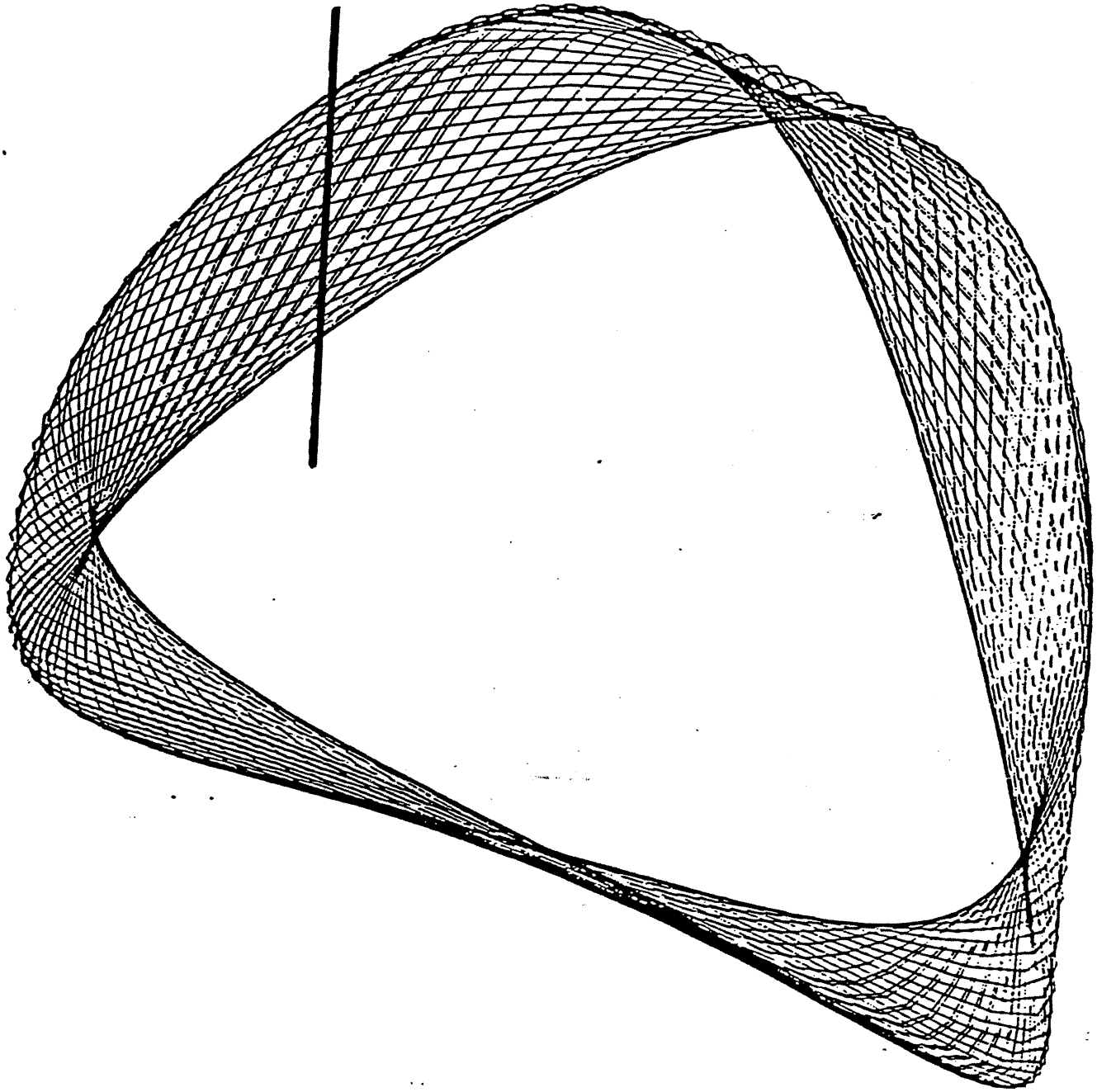
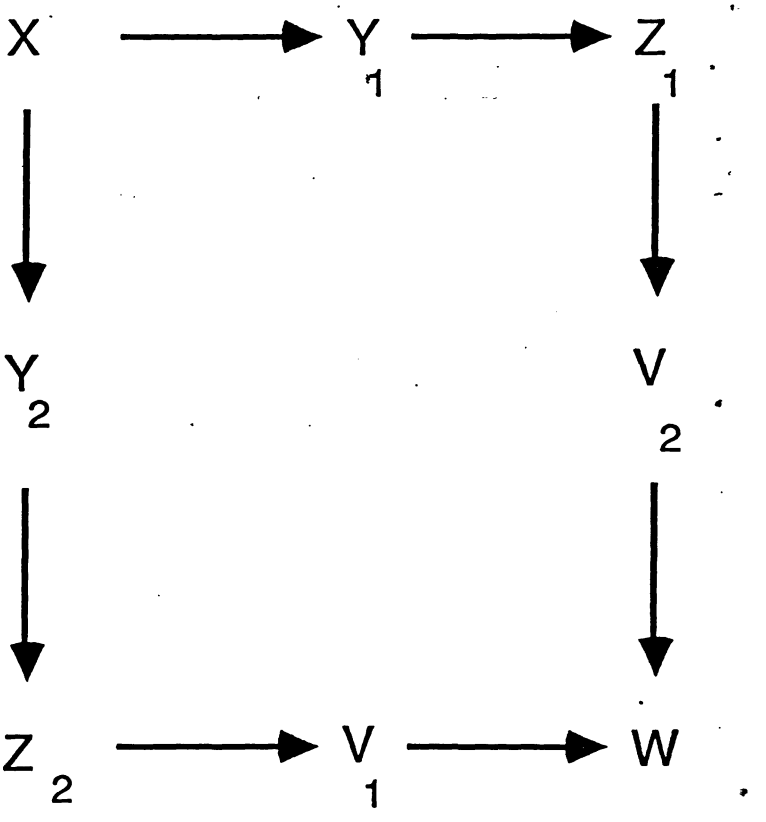
Strain IIIB. Natural mortality = 0.007/day





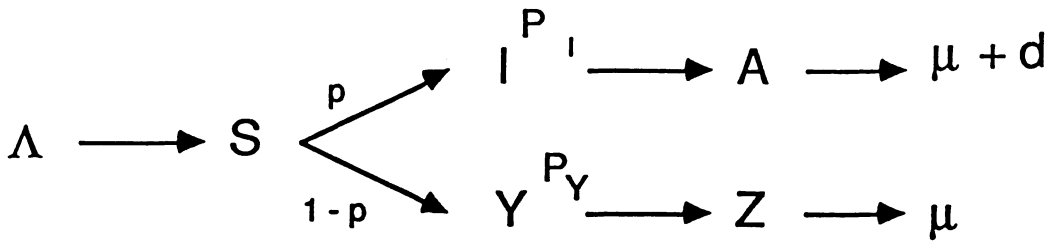
Influenza model. Lagged phase portrait
[ I(t), I(t+10), I(t+20) ] Definition of Poincaré section

## TRANSFER DIAGRAM 1




X SUSCEPTIBLE INDIVIDUALS, $Y_i$ INDIVIDUALS INFECTED STRAIN I.
$Z_i$ INDIVIDUALS RECOVERED FROM STRAIN I BUT SUSCEPTIBLE TO THE OTHER STRAIN.
$V_i$ INDIVIDUALS INFECTED WITHSTRAIN I BUT RECOVERED FROM THE OTHER STRAIN.
W INDIVIDUALS RECOVERED FROM BOTH STRAINS.

## TRANSFER DIAGRAM 2




Flow diagram for a single group model with distributed periods of infectiousness.