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# A THOUSAND AND ONE EPIDEMIC MODELS

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## INTRODUCTION

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Although chronic diseases such as cancer and heart disease receive more attention in developed countries, infectious diseases are the most important causes of suffering and mortality in developing countries. Recently, the human immunodeficiency virus (HIV), which is the etiological agent for acquired immunodeficiency syndrome (AIDS), has become an important sexually-transmitted disease throughout the world. Tuberculosis is again becoming a problem because drug-resistant strains have evolved. Understanding the transmission characteristics of infectious diseases in communities, regions and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are useful in building and testing theories, and in comparing, planning, implementing and evaluating various detection, prevention, therapy and control programs. See Hethcote and Van Ark [30] for a discussion of the purposes and limitations of epidemiological modeling.

The first goal of this paper is to present a building block approach to the construction of deterministic epidemiological models. Each model is built from components such as the epidemiological compartment structure, the form of the incidence, the distributions of waiting times in the compartments, the demographic structure, and the epidemiological-demographic interactions. Because there are many choices for each aspect, the combinatorial possibilities are enormous. The title of this article suggests that the number of possible epidemiological models is very large; indeed, I show that there are more possibilities than 1001.

The second goal of this paper is to convince modelers and mathematicians that it may be inappropriate to analyze the many different possible models one by one in published papers. Only the analyses of models which break new ground or illustrate the importance of some new aspect are of significant interest. Analyses which consider some slight variation of a previous model and which lead to essentially the same solution behavior may not be worth publishing. If the thresholds and behavior of the new model are predictable based on the insight gained from the analysis of previous models, then the analysis of the new model is probably not an important contribution. However, if a change in a model leads to different results such as periodic solutions, multiple thresholds or multiple endemic equilibria, then it is interesting and significant. Papers which analyze entire classes of models are certainly relevant. One purpose of analyzing epidemiological models is to get a clear understanding of the similarities and differences in the behavior of solutions of the models; this understanding leads to rational decisions in

choosing models for applications. Papers modeling specific diseases are very important; indeed, applications of results of epidemic models are significantly behind the mathematical theory. As in any scientific area, good taste and judgment need to be exercised in deciding which results are really new and exciting.

The mathematical analysis of epidemiological models has advanced rapidly in the last twenty years. A tremendous variety of models have been formulated, mathematically analyzed and applied to infectious diseases. These models have involved aspects such as passive immunity, gradual loss of vaccine and disease-acquired immunity, stages of infection, vertical transmission, disease vectors, macroparasitic loads, age structure, spatial spread, vaccination, quarantine, chemotherapy, etc. Special models have been formulated for diseases such as measles, rubella, chickenpox, whooping cough, diphtheria, smallpox, malaria, onchocerciasis, filariasis, rabies, gonorrhea, herpes, syphilis, and HIV/AIDS. Some idea of the scope of epidemic modeling can be gained by looking at the books by Bailey [7], Hethcote and Yorke [32], Castillo-Chavez [16], Becker [8], Anderson and May [4] [5], and Hethcote and Van Ark [30]. Some mathematical aspects of infectious disease models are surveyed in Hethcote *et al.* [27] and Hethcote and Levin [26].

Many of the infectious disease models analyzed mathematically so far have assumed that the total population size remains constant. These models are appropriate when the time period is very short or when the natural births balance the natural deaths or the immigration balances the emigration. However, these constant population size models are not suitable when the disease-related deaths are significant or when the inflow and outflow are not balanced. In these cases the models with a variable total population size are suitable. These models are often more difficult to analyze mathematically because the population size is an additional variable which is governed by a differential equation in a deterministic model.

There are many examples of situations where infectious diseases have caused enough deaths so that the population size has not remained constant or even approximately constant. Indeed, infectious diseases have often had a big impact on population sizes and historical events [43]. The black plague caused 25% population decreases and led to social, economic and religious changes in Europe in the 14th century. Diseases such as smallpox, diphtheria and measles brought by Europeans devastated native populations in the Americas. Even today diseases caused by viruses, bacteria, protozoans, helminths, fungi, and arthropods combined with low nutritional status cause significant early mortality in developing countries. The longer life spans in developed countries seem to be primarily a result of the decline of mortality due to communicable diseases. Infectious diseases which have played a major role in the debilitation and regulation of human populations include plague, measles, scarlet fever, diphtheria, tuberculosis, smallpox, malaria, schistosomiasis, leishmaniasis, trypanosomiasis, filariasis, onchocerciasis, hookworm, the gastroenteritis and the pneumonias. See articles in [4] for further discussion of the effects of diseases on host populations.

Deterministic epidemic models with varying population size have been formulated and analyzed mathematically by Anderson and May [2] [3], Anderson *et al.* [1], Brauer [9] [10] [11], Bremmerman and Thieme [12], Busenberg and van den Driessche [14],

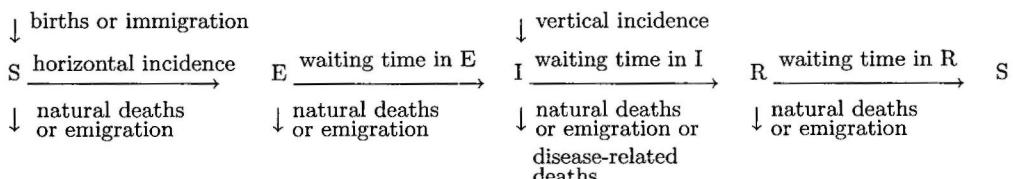
Busenberg and Hadeler [13], Derrick and van den Driessche [18], Gao and Hethcote [19], Greenhalgh [20] [21] [22] 23], May and Anderson [41] [42], Mena and Hethcote [44], Pugliese [45] [46], Swart [47], Zhou [51] and Zhou and Hethcote [52]. Some models of HIV/AIDS with varying population size have been considered by Jacquez *et al.* [34], Castillo-Chavez *et al.* [17], Hyman and Stanley [33], Lin [35] [36], Anderson *et al.* [6], Thieme and Castillo-Chavez [50], and Lin *et al.* [37].

## 2. EPIDEMIOLOGICAL COMPARTMENT STRUCTURES

The notation for the epidemiological classes in an infectious disease model has now become somewhat standard. Let  $S$  be the fraction of the population which is susceptible,  $E$  be the exposed fraction in the latent period,  $I$  be the infectious fraction and  $R$  be the removed fraction which has recovered with temporary or permanent immunity. Using this notation eight possible compartmental models described by their flow patterns are  $SI$ ,  $SIS$ ,  $SEI$ ,  $SEIS$ ,  $SIR$ ,  $SIRS$ ,  $SEIR$ , and  $SEIRS$ . For example, in an  $SEIRS$  model, susceptibles become exposed in the latent period (*i.e.* infected, but not yet infectious), then infectious, then removed with temporary immunity and then susceptible again when the immunity wears off. Sometimes a class  $P$  of passively immune newborns, a class  $A$  of asymptomatic infectives, a class  $C$  of carriers, or a class  $V$  of vaccinated persons is included in a model. For HIV/AIDS the models often include classes corresponding to the stages of HIV infection leading to AIDS. Thus there are at least 10 different models for directly transmitted diseases in a single homogeneous population.

If there is an insect vector for the disease, then the compartment structure of the insect vector could conceivably have at least 10 different formulations so that there could be over 100 different host-vector model formulations. Similarly, there could be over 1000 models for a vector borne disease with two distinct hosts. In heterogeneous populations where there are subgroups with different characteristics, then each subgroup could conceivably have different epidemiological compartment structures so there could be many possible models. For any model it is also possible to incorporate a chronological age structure to get partial differential equations in age and time.

The point of the paragraphs above is that there are lots of possibilities in choosing a compartment structure. Even when this is chosen, there are still many possible forms of the incidence, waiting times in the compartments, demographic structures and epidemiological-demographic interactions. The transfer diagram below indicates possibilities for an  $SEIRS$  model.



### 3. HORIZONTAL INCIDENCES

Horizontal incidence is the flow rate out of the susceptible class into the exposed class or into the infectious class if the latent period is being ignored, as in an SIRS model. If  $X(t)$  is the number of susceptibles at time  $t$ ,  $Y(t)$  is the number of infectives, and  $N(t)$  is the total population size, then  $S(t) = X(t)/N(t)$  and  $I(t) = Y(t)/N(t)$  are the susceptible and infectious fractions, respectively. Most forms of the incidence involve  $X, Y$  and  $N$  so we use  $f(X, Y, N)$  for the incidence. If  $\lambda$  is the average number of adequate contacts (*i.e.* sufficient for transmission) of a person per unit time, then  $\lambda X/N$  is the average number of contacts with susceptibles per unit time of one infective so the standard form of the incidence is

$$f_{\text{standard}}(X, Y, N) = (\lambda X/N)Y = \lambda S(NI).$$

An alternate form of the incidence based on the simple mass action law is

$$f_{\text{mass-action}}(X, Y, N) = \beta XY = \beta NS(NI)$$

where  $\beta$  is a mass action coefficient (which has no direct epidemiological interpretation). For more information about the differences in models using these two forms of the incidence, see Hethcote [24], Hethcote and Van Ark [29] and Mena and Hethcote [44]. Another possible incidence has a density dependent contact rate  $\lambda(N)$  so the form is

$$f_{\text{dens-dep}}(X, Y, N) = \lambda(N)XY/N = \lambda(N)S(NI).$$

Population size dependent contact functions have been considered by Brauer [10] [11], Pugliese [45] [46], Thieme [48] [49], and Zhou [51]. These population size dependent contact rates have also occurred in AIDS models by Castillo-Chavez *et al.* [17] and Thieme and Castillo-Chavez [50].

Various forms of nonlinear incidences have been considered. The saturation incidence

$$f(X, Y, N) = \beta Y(1 - cY)X$$

was used by London and Yorke [40] in their modeling of measles. Another saturation incidence

$$f(X, Y, N) = \frac{\beta Y}{1 + cY}X$$

was used by Capasso and Serio [15] in their modeling of cholera. Liu *et al.* [39] used  $f(X, Y, N) = \beta Y^p X^q$  and Liu *et al.* [38] analyzed models with nonlinear incidence of

the form  $f(S, I, N) = \lambda I^p S^q$ . Hethcote and van den Driessche [31] considered models with  $f(S, I, N) = \lambda g(I)S$  and

$$f(S, I, N) = \frac{\lambda I^p}{1 + \alpha I^q} S.$$

See Derrick and van den Driessche [18] for a discussion of which forms of nonlinear incidence can not lead to periodic solutions. In any of the forms of incidence above, the proportionality constant  $\lambda$  or  $\beta$  could be a periodic function of time  $t$ . See Hethcote and Levin [26] for a survey of periodicity in epidemiological models. In a multigroup model the interactions between groups are specified by a contact or mixing matrix [29]. In an  $n$  group model there are  $n^2$  entries in the matrix so the number of possible contact matrices is enormous [25].

#### 4. WAITING TIMES IN THE $E$ , $I$ AND $R$ COMPARTMENTS

The most common assumption is that the movements out of the  $E$ ,  $I$  and  $R$  compartments and into the next compartment are governed by terms like  $\epsilon E$ ,  $\gamma I$  and  $\delta R$  in an ordinary differential equations model. It has been shown [27] that these terms correspond to exponentially distributed waiting times in the compartments. For example, the transfer rate  $\epsilon E$  corresponds to  $P(t) = e^{-\epsilon t}$  as the probability of still being in the exposed class  $t$  units after entering this class and  $1/\epsilon$  as the mean waiting time.

Another possible assumption is that the probability of still being in the compartment  $t$  units after entering is a nonincreasing, piecewise continuous function  $P(t)$  with  $P(0) = 1$  and  $P(\infty) = 0$ . Then the probability of leaving the compartment at time  $t$  is  $-P'(t)$  so the mean waiting time in the compartment is  $\int_0^\infty t(-P'(t))dt = \int_0^\infty P(t)dt$ . These distributed delays lead to integral or integrodifferential or functional differential equations. If the waiting time distribution is a step function given by

$$P(t) = \begin{cases} 1 & \text{if } 0 \leq t \leq \tau \\ 0 & \text{if } \tau \leq t \end{cases},$$

then the mean waiting time is  $\tau$  and for  $t \geq \tau$  the model reduces to a delay-differential equation [27].

Each waiting time can have a different distribution. Thus, in an *SEIRS* model each of the three waiting time distributions can be chosen in three different ways so there are 27 different possibilities. In a male-female *SEIRS* model for a sexually transmitted disease, there would be  $3^6$  possibilities. Hence, there are many choices in choosing waiting time distributions in models.

## 5. DEMOGRAPHIC STRUCTURES

Many different demographic structures can be applied to an epidemic model. A simple birth-death demographic structure is based on the differential equation

$$\frac{dN}{dt} = bN - dN$$

where  $bN$  represents the births and  $dN$  represents the natural deaths. In an *SEIRS* epidemic model without vaccination where the number of people in the latent period is  $W = EN$ , the newborns would be susceptible and natural deaths would occur in each class so that a simple model would be:

$$\begin{aligned} dX/dt &= bN - dX - f(X, Y, N) + \delta Z \\ dW/dt &= f(X, Y, N) - \epsilon W - dW \\ dY/dt &= \epsilon W - \gamma Y - dY \\ dZ/dt &= \gamma Y - \delta Z - dZ \end{aligned}$$

with  $N = X + W + Y + Z$ . So far no one has proved global stability of the endemic equilibrium for this simple model with the standard incidence and  $b = d$  [28]. Note that a similar model with all deaths occurring in the removed class is ill-posed [24].

If there are no births, deaths or migration, then the above model with  $b = d = 0$  is suitable for describing an epidemic in a short time period less than one year. If  $b = d \neq 0$ , then there is an inflow of newborn susceptibles, but the population size remains constant. This inflow of new susceptibles leads to an endemic or persistent equilibrium above the threshold [24]. If  $r = b - d \neq 0$ , then the population would be naturally exponentially growing or decaying in the absence of the infectious disease. The persistence of the disease and disease-related deaths can affect the demographic behavior and can even reverse exponential growth so there is a stable equilibrium or exponential decay [13] [14] [19] [44].

Another possible demographic model is

$$\frac{dN}{dt} = A - dN$$

where  $A$  represents immigration and  $dN$  represents natural deaths. Without the disease the population size  $N$  approaches  $A/d$ . See [2] [42] [44] for the formulation and analysis of models with this demographic structure. Many of the models of HIV/AIDS referenced in Section 1 have used this structure.

Another reasonably simple demographic structure is based on the logistic equation:

$$\frac{dN}{dt} = r(1 - N/K)N$$

where  $r = b - d$  and  $K$  is the carrying capacity of the environment. Recently, Gao and Hethcote [19] have considered a logistic model written as

$$\frac{dN}{dt} = (b - arN/K)N - [d + (1 - a)rN/K]N$$

with  $0 \leq a \leq 1$ . Here the logistic term  $r(1 - N/K)N$  due to crowding or limited resources is divided into the first term corresponding to a decreasing birth rate and the second term corresponding to an increasing natural death rate. A generalized logistic differential equation would have the form

$$\frac{dN}{dt} = [B(N) - D(N)]N$$

where  $B(N)$  is the density dependent birth rate and  $D(N)$  is the density dependent death rate. Note that all of the above demographic structures are special cases of this general formulation. Epidemic models with logistic or generalized logistic demographic structure have been considered in [1], [9], [10], [11], [12], [45], and [52].

## 6. EPIDEMIOLOGICAL-DEMOGRAPHIC INTERACTIONS

The infectious disease can affect the demographic process through disease-related deaths and reduced fertility of exposed, infectious and removed individuals. The demographics can affect the epidemiological process through vertical transmission. Since each of these aspects of an epidemic model can be left out or included, there are at least 10 different possibilities. All of these interactions are considered below.

If there is an increased death rate (above the natural death rate) due to the infectious disease, then the excess deaths can be modeled by an extra flow term  $\alpha Y$  out of the infectious class. In a birth-death demographic process with birth rate  $B(N)N$  and death rate  $D(N)N$ , the disease-related deaths can affect the population size. In this case the differential equation for  $N$  becomes

$$\frac{dN}{dt} = [B(N) - D(N)]N - \alpha Y$$

where  $Y$  is the number of infectives. Disease-related deaths and persistence of the disease can change a naturally growing population into a stable or decaying population. For examples see [2], [14], [19], [42], [44], [48], [49], [51], [52].

As a consequence of the infectious disease, females in the exposed, infectious and removed class may not have as many children as susceptible females. A typical birth term which includes reduced fecundity or fertility would be  $B(N)(X + \rho_1 W + \rho_2 Y + \rho_3 Z)$  where the last three terms with  $0 \leq \rho_i \leq 1$  are the reduced fertility terms. See Anderson *et al.* [1] for a fox rabies model with reduced fertility of rabid foxes. See Pugliese [45] [46] for analyses of similar models in which reduced fertility leads to periodicity. Determination of precisely how reduced fertility leads to periodicity in epidemic models is an interesting unresolved problem. The models which lead to periodicity seem to be very special; they are of SEI type with logistic demographics and reduced fertility.

Vertical incidence is the flow of newborns infected by their mothers (before, during or just after the birth process) into the infectious class. Vertical incidence can be inserted as shown in the transfer diagram in Section 2; note that an E category of vertically infected babies in a latent period might also be appropriate. Since all vertically infected people are newborns, vertical incidence is most naturally incorporated into an age structured model. A typical vertical incidence term in a deterministic model would be the product of the probability of transmission per birth, the birth rate and the number of infected women.

## 7. EPILOGUE

I have achieved my goal of presenting a tremendous number of models by enumerating the components used in model construction. In each of the five previous sections, I outline at least 10 different choices so the number of possible epidemic models exceeds  $10^5$ . In the book, *A Thousand and One Nights*, Scheherezade had to entertain King Shahriyar with a new story each evening in order to avoid being killed. If they were mathematical biologists and she had only to present one new epidemiological model each night to entertain him, then she could have survived each night for at least 270 years. Of course, the King would probably have become disenchanted by the "new" models if they were only very slight variations on previous models and would have killed Scheherezade. Similarly, referees (the Kings) might become disenchanted if the papers which they receive contain models which are only slight variations on previous models. Thus I suggest that we as modelers and mathematicians should be cautious and not assume that every mathematical analysis of a slightly different model is interesting.

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