This is to certify that the

thesis entitled

SYSTEMS MODELLING, ANALYSIS
AND SIMULATION OF
TYPE A INFLUENZA EPIDEMICS

presented by

Roy Gardner

has been accepted towards fulfillment
of the requirements for

Ph. D. degree in Systems Science

Robert O. Barr, Jr.
Major professor

Date February 19, 1980

OVERDUE FINES ARE 25¢ PER DAY
PER ITEM

Return to book drop to remove
this checkout from your record.

SYSTEMS MODELLING, ANALYSIS AND SIMULATION OF TYPE A INFLUENZA EPIDEMICS

By

Roy Gardner

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Electrical Engineering
and Systems Science

1980

ABSTRACT

SYSTEMS MODELLING, ANALYSIS AND SIMULATION OF TYPE A INFLUENZA EPIDEMICS

By

Roy Gardner

A pandemic results from the emergence of a new subtype of type A influenza virus. Following the pandemic, epidemics occur in two to three year cycles due to the structural change of the same subtype virus. The graphic representation of disease incidence from one pandemic to the next resembles underdamped oscillation. A review of the literature reveals no existing dynamic model of influenza epidemics which depicts the behavior of the virus and its interaction with the population. This paper develops a model for such a system using systems theory and application.

As a basis for describing the dynamic behavior, three epidemic models are analyzed in the context of systems analysis and simulated. All simulations in this research are performed using DYNAMO. Variables which are of interest to epidemiologists, such as the peaks and the durations of epidemics, are defined, and the formulas for computing these variables are derived. The numerical values obtained from analysis are compared with the simulation results.

The influenza epidemic model developed using the basic

epidemic models is a nonlinear system with four state variables, one of which is the structural state of the virus. The virus was modelled using the idea of a logistic curve, the asymptote of which is the immunity level of the population. The linearized model was used to analyze system behavior. With a proper choice of the parameter associated with the virus, the system provides an epidemic curve which resembles underdamped oscillation. A range of the parameter required for this underdamped oscillation was computed using a sufficient condition, expressed in terms of the coefficients of the characteristic equation, for the third order linear system to be stable, oscillatory, and underdamped. This sufficient condition was derived based on the relationship between the roots location and the coefficients of a cubic equation.

Simulation results of the system for four test cases are presented and compared. With this model three epidemics can be shown. The attempt to fit the model outputs with the historical data on the mortality rate of three selected epidemics of recent times was carried out as model validation. The model was modified to include the population growth and the seasonal variation of influenza outbreaks. Simulation results show a reasonable fit, considering the complexity of the real world system.

To minimize the severity of the epidemic, an immunization model was developed as a subsystem of a control system. This model consists of the vaccinated population as the state

variable. The state equation was constructed using the idea of a goal seeking curve. A comparison of simulation outputs of the system without immunization and with immunization is given. Simulation shows that, with this control system, instead of the expected epidemic, an endemic state results. This control system, however, is an idealized system where only individuals in the susceptible population are immunized, and it does not consider the efficacy of the vaccine. To interpret the simulation results more realistically, a simple formula is given to compute the percentage of the total population that requires immunization to prevent the epidemic. This percentage varies depending on the efficacy of the vaccine.

To Martha and Kenzo.

ACKNOWLEDGMENTS

This work is a result of the culmination of knowledge I have acquired from each member of my guidance committee:

I would like to thank Dr. Robert Barr, my chairman and thesis advisor, for his direction and for his excellent teaching.

A special thanks is due to Dr. Robert Moon, Department of Microbiology and Public Health, for patiently teaching me about the fascinating subjects of viruses and epidemics.

I wish to thank Dr. Gerald Park for guiding me toward a more interdisciplinary approach to this dissertation.

I also wish to express my gratitude to Dr. Connie Shapiro, Department of Statistics, for her constant concern and encouragement.

Finally, I want to thank my wife Martha for editing my manuscript and coming up with suitable sentences at times when nothing seemed to come out of my head.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1.1 Statement of the Problem

In 1979 smallpox was declared eradicated from the face of the earth. Once-devastating infectious diseases such as cholera, typhoid fever, and yellow fever are now under control through improved sanitation, vaccination, and quarantine. Yet, control of influenza epidemics and pandemics (world wide epidemics) is not in sight. This is because the infectious agent, a virus, is constantly changing with the resultant consequence of invading a population which has little or no immunity for the changed agent. This dissertation concerns the development, analysis, and simulation of models of influenza epidemics.

Influenza can be just as devastating as cholera. It is estimated that the pandemic of 1918 killed 20 million people world wide and over 500,000 in the United States in a period of just a few weeks. The occurrence of pandemics and major epidemics in recent times (Kilbourne, 1975, p.494) is as given in Table 1.1.

Table 1.1. Major epidemic and pandemic years and their intervals.

	Pandemic	Pandemic Interval	Major Epidemic Interval
1889	+		
1900			11
1918	+	29	18
1929			11
1946	+	28	17
1957	+	11	11
1968	+	11	11

+ indicates occurrence of an unquestioned pandemic.

It is interesting to note the recurrence of the 11 year intervals in the above table. The exact reasons for the cyclical properties of the epidemics are not known, but the relationship between the immunity level of the population and the occurrence of an epidemic is an important factor to be considered.

Another interesting theory of the cyclical nature of pandemics is the return of the same virus subtype every sixty years. The pandemic of 1918 is believed to have been caused by the "swine flu" virus. Isolation of the swine flu virus from soldiers at Fort Dix, New Jersey, in 1976 prompted a national immunization program in anticipation of another pandemic. The fact that the pandemic did not materialize points out the need for a model to more accurately forecast future influenza epidemics. Such a model requires an extensive knowledge of the basic three elements in the system -- the virus, the host, and the environment -- and the complex interactions among them. In many socio-economic and ecological systems, the degree of

uncertainty, in essence, determines the validity and hence the usefulness of the model. In the case of the influenza epidemic system, this uncertainty is compounded by the limited knowledge of the virus itself. As the secrets of the virus are unraveled, prediction and control of epidemics may become reality.

1.2 Description of the Influenza Epidemic System

To build a realistic system dynamics model of any phenomena, it is fundamental to have a good understanding of the real world system the model is to represent. The following is a brief but essential description of the various elements and interactions involved in influenza epidemics as they are understood today.

Influenza is an infectious disease caused by a class of viruses called myxoviruses, or interchageably known as influenza viruses. There are three types of influenza viruses, types A, B, C, which are classified according to the immunity each produces by infection. Type A has subtypes, and each subtype has variants. Type B has no subtype, but has variants. Type C virus is uncommon and does not cause epidemics. Type A is the only type found in animals and birds as well as humans. Epidemics of type A occur every two to three years, and epidemics of type B occur every four to six years.

Appearance of a new subtype of type A can result in a pandemic. In fact, one author defines an influenza

pandemic as an emergence of a new subtype (Beveridge, 1977). A remarkable fact about the subtypes of type A virus is that when a new subtype appears, the old subtype rapidly disappears. Hence, only one subtype of type A predominates at any given time. However, the type B virus can coexist with type A virus. The table below (Volk, 1978, p. 542) lists the subtypes of human viruses isolated up to the present time:

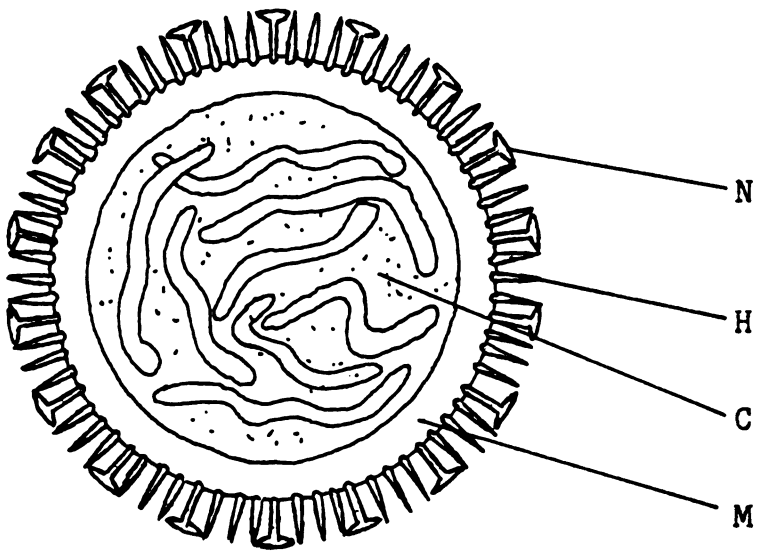
Table 1.2. Subtypes of human influenza A viruses and the year isolated.

Year Isolated	Subtype
1934	H_0N_1
1947	H_1N_1
1957	H_2N_2
1968	H_3N_2

In immunological terms, the change in subtype is called antigenic shift. In simple terms, antigenic shift is a major change in the type A virus which may lead to a pandemic, while antigenic drift reflects minor changes in the type A or B virus which may cause more localized epidemics.

Understanding the structure of the virus makes it possible to understand shifts and drifts: The virus is 80-100nm in diameter and is roughly spherical in shape. It consists of a helical symmetric core which contains the genetic material of the virus called ribonucleic acid (RNA) and two types of spikes, hemagglutinin and

neuraminidase. The RNA is in eight separate pieces, each being a single genetic unit. The spikes are attached to the membrane which encloses the core (Beveridge, 1977, p. 69).



N = Neuraminidase
H = Hemagglutinin
C = Core
M = Membrane

Figure 1.1. Diagram of influenza virus section.

When the virus attacks a person, it first must attach to host cells. This attachment is facilitated by the H and N spikes and is necessary for the virus to penetrate the host cells. Once inside the cell, multiplication of the virus takes place through the process of translation and transcription of the genetic codes.

An antigen is defined to be any substance which causes the body to produce antibodies. There are four antigens in the influenza virus: the two spikes H and N,

the core, and the membrane. Antibodies produced in response to the core antigen and the membrane antigen are not protective and do not prevent infection. The core antigen is significant, however, because the types A, B, and C are classified according to the differences in the antibodies induced by the core antigen. Antibodies induced by the N spike are not protective, either, but they may play some role in reducing the spread of infection, since they interfere with the release of the virus from the infected cell. Antibodies induced by the H spike are protective and neutralize infectivity of the virus by coating the surface of the cell so that the H spikes cannot be attached (Volk, 1978, p. 540).

Basically, the coating of the surface of the cell by the antibodies results in immunity to the specific virus. However, if the chemical composition, and hence the antigenicity, of the H or N spikes change, the body does not recognize the change, and the person can be infected again. Slight changes may occur by mutation during the multiplication process, and these changes in the spikes are called antigenic drift. If there is a major change so that there is negligible immunity in the population, then the change is called antigenic shift.

Antigenic shifts are believed to result from the creation of a hybrid between human and animal influenza viruses. This is the recombination theory which states that a human influenza virus may infect lower animals or

birds and then be recombined with an animal virus present in the animal host to produce a new subtype of the human influenza (Laver, 1979).

The recombination theory plays a significant role in the control of influenza epidemics. First, it implies that future pandemics will be difficult to control since vaccines cannot be prepared by simply manipulating the human influenza viruses. Second, it widens the whole dimension of the influenza epidemic system by involving the ecology of animals and birds.

Early identification of a new variant or subtype is crucial for the preparation of a proper vaccine to immunize against a possible epidemic. The World Health Organization maintains a world-wide network for surveillance of influenza viruses. At present, early detection and vaccination seem to be the only effective tools against influenza epidemics.

1.3 Purpose, Background and Methodology of Research

The purpose of this research is to build a large-scale, or aggregated, model of an influenza epidemic system using systems theoretic concepts which shows the relationship between the dynamics of the epidemic and the changing structural state of the influenza virus. In the systems approach, the identification of the virus and vaccination are controllable inputs to the influenza epidemic, while shifts and drifts are uncontrollable inputs. Exogeneous

inputs include seasons, susceptibility due to genetic factors and standard of living, and general health and ages which affect morbidity and mortality rates. Populations with different immunity levels and the number of susceptibles and the number of immunes may be considered design parameters. Desirable outputs are a high level of immunity in populations and low morbidity and mortality rates. Complications such as Guillain-Barre syndrome and high economic costs are undesirable outputs.

In reality many of the variables identified above are probabilistic or stochastic in nature. For instance, not all individuals who have contact with an infective person come down with the disease. The complexity of the human body and its interaction with the invading virus can never be adequately described by mathematical expressions. In a stochastic approach, disease incidence at any given time period is associated with a probability. Stochastic models are more appropriate if one is investigating the system behavior in which the statistical fluctuation is significant, such as in infectious outbreaks involving a few individuals. In a large-scale model this statistical fluctuation averages out and becomes less significant. Deterministic models are adequate for describing epidemics involving a large number of people and will be used in this research.

Epidemic models using "system dynamics" techniques have been found only as examples and illustrations in the texts of Goodman (1974, pp. 85-88, 365-375) and Sage (1977,

pp. 212-213). No influenza epidemic models were found in any of the systems and simulations literature. Bailey (1975) presents an extensive literature review of mathematical models of epidemics from the beginnings of research in that area up to and including recent developments.

Elveback, Fox, Ackerman (1975) use a stochastic discrete time model to simulate an influenza epidemic in a community of one thousand people and deduce an optimal strategy for vaccination.

Several Russian researchers (Baroyan, 1971) constructed a computer simulation model to forecast the outbreak of influenza epidemics in forty-three cities in the U.S.S.R. This model is based on a migration model and uses transportation data as one of the parameters.

Using the parameter estimation technique developed by the above Russian researchers, Spicer (1979) shows that a stochastic discrete time model conforms to the historical data on influenza deaths in the United Kingdom from the years 1952 to 1973.

Kilbourne (1975, p. 496) gives a graphic representation of the pattern of pandemics in recent years, depicting the relationship between the immunity level of the population and the drifts and the shifts of the virus as shown in Figure 1.2. This graph resembles underdamped oscillation and gives some insight into the structure of the influenza epidemic model which is the subject of this research.

Three basic models of epidemics described in Bailey

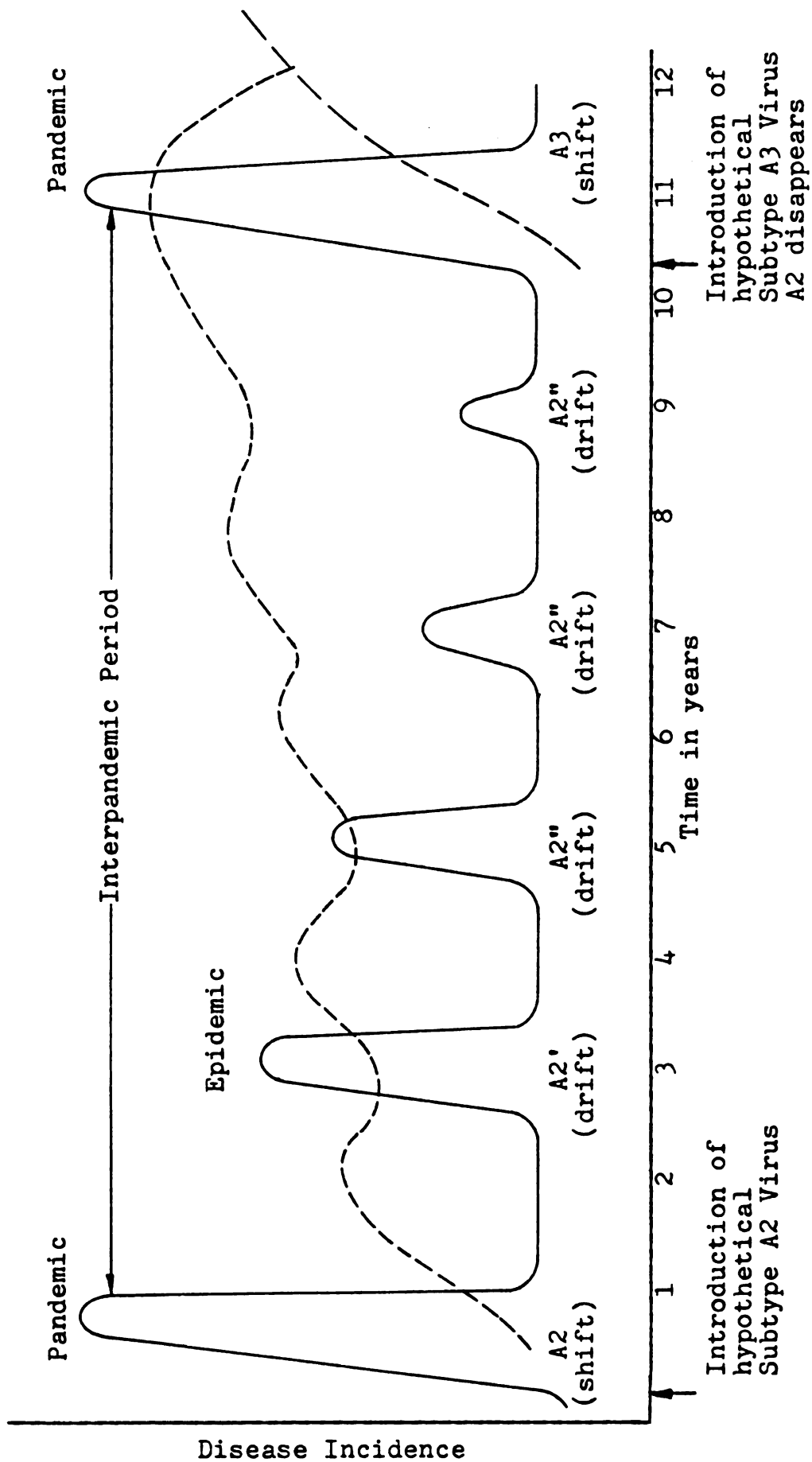


Figure 1.2. The pattern of influenza pandemics.

(1975) will be discussed in Chapter 2. These models lead to an influenza epidemic model developed in Chapter 3 which includes the structural state of the virus as one of the state variables. The model will be simulated, and the results compared to historical data provided by the Center for Disease Control in Chapter 4. Finally, in Chapter 5, an immunization model will be developed as a subsystem of a control system, and the percentage of the population required to be immunized to prevent epidemics will be determined.

All models will be discussed in the context of systems analysis, focussing on such topics as stability, linearization, phase portrait, and transient response. A qualitative modeling approach, namely causal loop diagrams, will show the relationship among the various variables. Normally, the causal loop diagram does not show the mathematical processes relating variables. However, to make the description more precise, in the simple models such definitions taken from the state model will be included alongside each variable defined.

Block diagrams as well as DYNAMO flow diagrams will be used to show the parameters, the flow of quantities, and the rate and level variables. All simulations will be done by DYNAMO, a well-accepted dynamic systems simulation program. DYNAMO was chosen because of its versatile capabilities of plotting and its ease of programming.

CHAPTER 2

BASIC EPIDEMIC MODELS

Before one attempts to build a large-scale socio-economic or biological model, it is useful to learn the in-depth behavior of the simple model which may be used as a basis of a more complex one. The dynamic model of the basic system should contain a minimum number of the state variables, or levels, which provide outputs that represent a reasonable similarity to the real world situation. In the case of epidemic models, the system usually consists of three state variables: (1) the size of the susceptible population (population capable of contracting the disease); (2) the size of the infective population (population capable of transmitting the disease); and (3) the size of the removed population (either immune, recovered, or dead, and hence no longer infectious).

In this chapter, three basic epidemic models which were presented by Bailey (1975) have been arranged from simplistic to more realistic and will be discussed in the context of systems analysis and the system dynamics approach. Discussion of each model will be organized as follows: First, the state model (a set of differential equations) and the assumptions made in formulating the model will be

presented. From these assumptions the causal loop diagram will be constructed. A brief interpretation of feedback loops will be given. Next, the block diagrams, DYNAMO flow diagrams and typical DYNAMO simulation outputs will be shown. Analysis will follow. The variables which are of particular interest to epidemiologists will be examined. These variables are defined as follows:

(1) Epidemic curve E(t) = the curve representing disease incidence versus time.

(2) The peak of the epidemic E_{max} = the maximum disease incidence.

(3) The peak time t_{max} = the time at which the disease incidence is maximum.

(4) The duration of the epidemic t_d = the time at which the epidemic curve falls below the initial value in the first two models discussed; in the third model, which is oscillatory, t_d is taken as the two percent settling time.

We will make one assumption common to all three models. This assumption is that the total population, the sum of the susceptible, the infective, and the removed populations, is constant.

2.1 Simple Epidemics Model

The first epidemic model, called the simple epidemics model, consists only of the size of the susceptible population and the size of the infective population as the state

variables. Yet, the model provides interesting results about the epidemic curve which are similar to the real world behavior of epidemics in general.

Basically, we assume that the disease is transmitted through contact between an infective and a susceptible individual. No allowance for incubation period is made in the model. The rate of infection is then assumed to be proportional to the product of the susceptible and the infective populations. Once infected, the infected individual remains infective until all the susceptible individuals are exhausted. We further assume that the susceptible population is homogeneous in the sense that every one has an equal chance of contracting the disease from the infective population.

We let

x_1 = size of susceptible population,

x_2 = size of infective population,

b = infective (or contact) rate,

N = total population.

Then, these assumptions may be formulated into the state model:

$$\begin{aligned} \dot{x}_1 &= -b\, x_1\, x_2 \\ \dot{x}_2 &= b\, x_1\, x_2 \end{aligned} \qquad (2.1)$$

with the initial conditions $x_1(0) = c_1$, $x_2(0) = c_2$, and the boundary conditions $x_1 + x_2 = N$, $0 \le x_1$, $0 \le x_2$.

The causal loop diagram is shown in Figure 2.1.

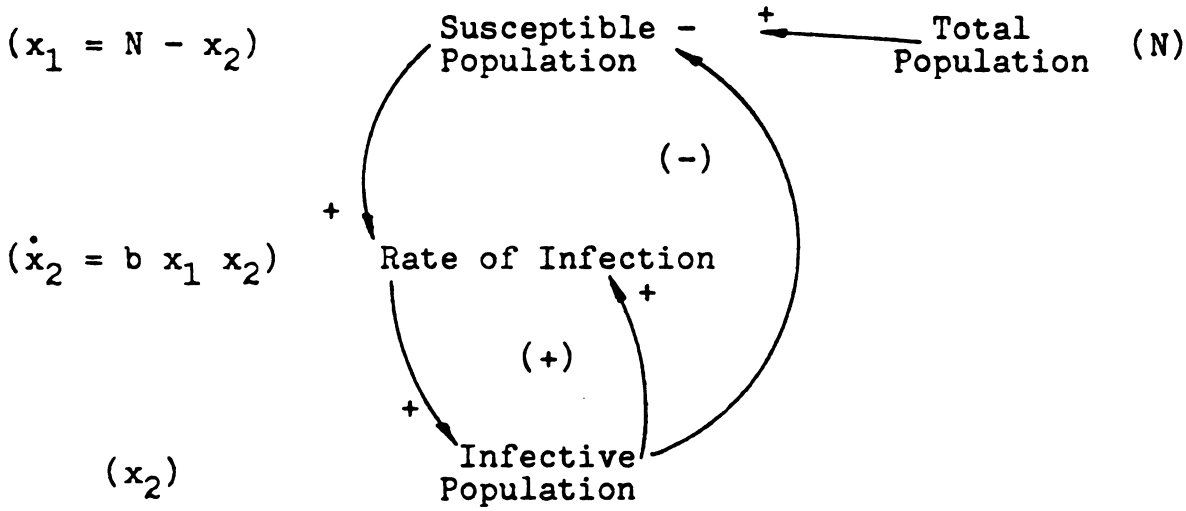


Figure 2.1. Causal loop diagram of simple epidemics.

An epidemic curve is a graphic representation of disease incidence (the rate of disease occurrence per unit of time). In this case we will assume disease incidence; that is, the epidemic curve, to be the rate of infection.

$$E(t) = \dot{x}_2(t)$$

In the causal loop diagram, the rise of the epidemic curve is represented as the positive feedback loop imbedded in the negative feedback loop, which is the fall of the epidemic curve.

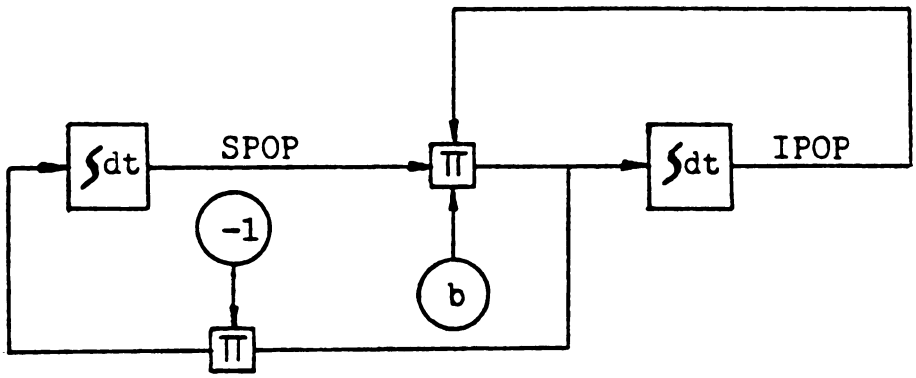
The block diagram and the flow diagram are shown in Figure 2.2 and Figure 2.3. DYNAMO simulation output for the following test case is given in Figure 2.4:

$N = 1000$

$c_1 = 950$ $\qquad$ $b = .002$

$c_2 = 50$

Goodman (1974, pp. 85-88), in the discussion of an epidemic growth model, gives DYNAMO simulation output similar to

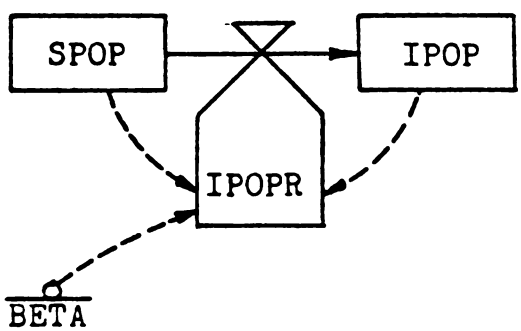


SPOP = Susceptible Population (x_1)

IPOP = Infective Population (x_2)

b = Infective Rate (Contact Rate)

Figure 2.2. Block diagram of simple epidemics.



SPOP = Susceptible Population

IPOP = Infective Population

IPOPR = Disease Incidence

BETA = Infective Rate (Contact Rate)

Figure 2.3. Flow diagram of simple epidemics.

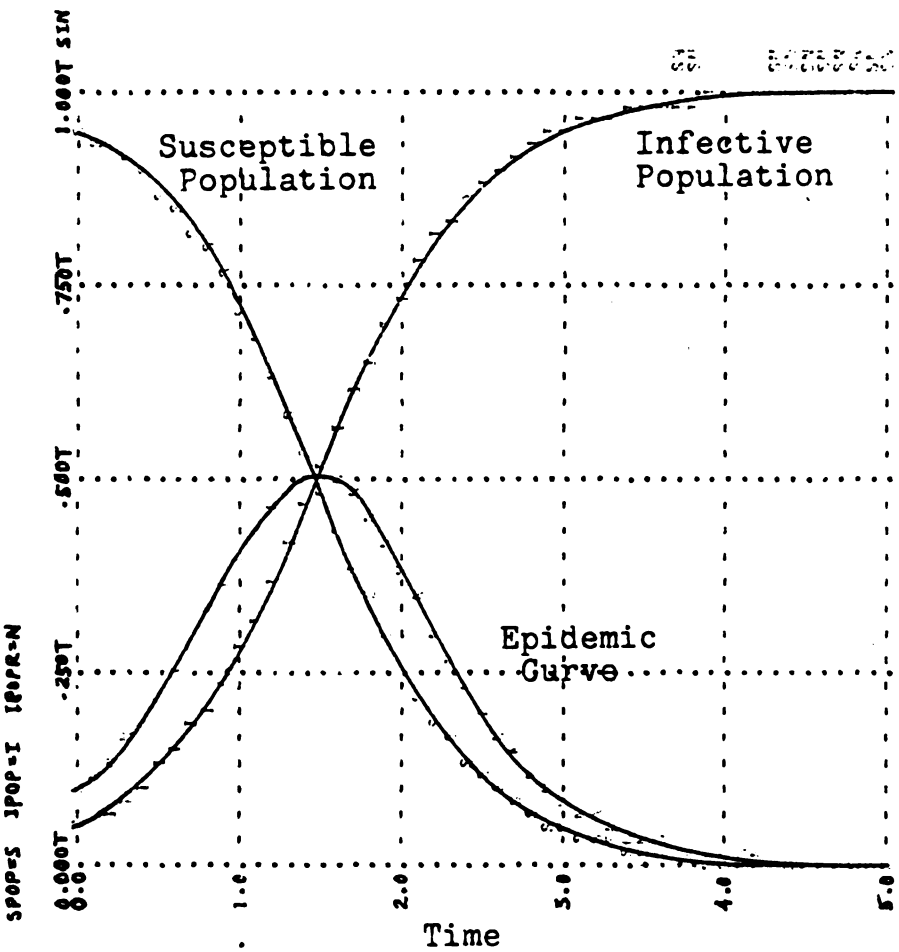


Figure 2.4. Simple epidemics model.

Figure 2.4.

DYNAMO uses the Euler integration method to approximate numerical solutions of differential equations. The choice of the size of DT, the time increment, is an important step in simulation. The wrong choice of DT may cause instability of the system arising from the simulation, rather than the model. Also the size of DT must be small enough to maintain the bounds of each variable; in this case $0 \leq x_1(t) \leq N$, $0 \leq x_2(t) \leq N$.

There is no precise formula for determining DT other than the rule of thumb given in the DYNAMO User's Manual (Pugh, 1976, p. 44), which is to take one half the smallest first order delay in the model. In the test case cited above, when DT was set equal to .1 and again set equal to .01, the graphs produced by simulation were close to the one plotted from the analytical solution; however, the tabulated results showed inaccuracies between the peak and the end of the epidemic curve. When DT = .001, the tabulated result was almost exactly the analytical solution.

Since the simple epidemics model is a conservative system; that is, no quantities are lost through dissipation, and the sum of the state variables is constant, the dimension of the system can be reduced by one by writing one variable as a function of the other. Hence, consider the single state model reduced from the state model (2.1) by eliminating x_1.

$$\dot{x}_2 = b(N - x_2)x_2$$

with the initial condition $x_2(0) = c_2$.

Separating variables and integrating, we have

$$\int \frac{dx_2}{b(N - x_2)x_2} = \int dt.$$

The left hand side of the equation can be integrated using the partial fraction decomposition.

$$\frac{1}{(N - x_2)x_2} = \frac{1}{N}\left(\frac{1}{x_2} + \frac{1}{N - x_2}\right).$$

Integration yields

$$t = \frac{1}{bN}\left[\log x_2 - \log (N - x_2)\right] + \text{constant}.$$

Applying the initial condition and noting $N - c_2 = c_1$ we obtain the solution

$$x_2(t) = \frac{N}{1 + \frac{c_1}{c_2} e^{-bNt}}.$$

From the relation $x_1 = N - x_2$ we have

$$x_1(t) = \frac{N}{1 + \frac{c_2}{c_1} e^{bNt}}.$$

The epidemic curve $E(t)$ which we defined to be the rate of infection is given by

$$E(t) = b\, x_1(t)\, x_2(t)$$

$$= \frac{bN^2}{\left(1 + \frac{c_1}{c_2} e^{-bNt}\right)\left(1 + \frac{c_2}{c_1} e^{bNt}\right)}.$$

This symmetric property of the epidemic curve can be shown by verifying the equality

$$E(t_{max} + t) = E(t_{max} - t).$$

We now calculate the peak of the epidemic E_{max}, the peak time t_{max}, and the duration of the epidemic t_d. The initial value of the epidemic curve is given by

$$E(0) = \frac{bN^2}{(1 + \frac{c_1}{c_2})(1 + \frac{c_2}{c_1})}$$

$$= b\, c_1\, c_2 \quad (\text{since } c_1 + c_2 = N).$$

Computation of $\dot{E}(t)$ is easier if we use the substitution

$$x = \frac{c_2}{c_1} e^{bNt}$$

then

$$E(t) = \frac{bN^2}{(1 + \frac{1}{x})(1 + x)} .$$

Differentiating the above expression with respect to t using the chain rule, we obtain

$$\dot{E}(t) = \frac{(1 - x)\,\dot{x}}{(1 + x)^3} bN^2.$$

Setting $\dot{E}(t) = 0$ gives the solution $x = 1$, and hence

$$t_{max} = \frac{\log \frac{c_1}{c_2}}{bN} ,$$

and

$$E_{max} = E(t_{max}) = \frac{bN^2}{4} .$$

Using the symmetric property of the epidemic curve, the duration of the epidemic is given by

$$t_d = 2\, t_{max}$$

$$= \frac{2 \log \frac{c_1}{c_2}}{bN} .$$

From the equations for t_{max} and E_{max}, we note that the larger the infective rate, the shorter the peak time and the higher the peak. Therefore, we can say the epidemic is more intense and of shorter duration if the infective (or contact) rate is large. We also note that the peak of the epidemic is independent of the initial conditions c_1 and c_2, which is somewhat unrealistic. However, the peak time depends on the initial conditions as well as the infective rate and the total population. If the ratio of the initial susceptible population to the initial infective population is large, the peak time is longer and hence the duration of the epidemic is longer.

The comparison of the analytical calculation and the DYNAMO output for the peak of the epidemic, the peak time, and the duration of the epidemic for the test case is as follows:

	Analytic	DYNAMO
E_{max}	500.00	499.64
t_{max}	1.4722	1.5
t_d	2.9444	3.0

2.2 General Epidemics Model

The second model takes the more realistic view that after a certain period of time, the infective population are removed from circulation and become inactive throughout the rest of the epidemic period. In the case of influenza,

most of the infected people will recover and become immune hence the term immune will be used in place of removed as usually denoted in the literature. Let x_3 be the third state variable, namely, the size of the immune population. Then we have the following state model:

$$\begin{aligned} \dot{x}_1 &= -b\, x_1\, x_2 \\ \dot{x}_2 &= b\, x_1\, x_2 - r x_2 \\ \dot{x}_3 &= r x_2 \end{aligned} \qquad (2.2)$$

with the initial conditions

$$x_1(0) = c_1, \quad x_2(0) = c_2, \quad x_3(0) = c_3,$$

and the boundary conditions

$$x_1 + x_2 + x_3 = N, \quad 0 \le x_1, \quad 0 \le x_2, \quad 0 \le x_3.$$

An additional assumption made in this model is that the infective population decreases at the rate of r, which is called the removal rate. We note that the infective population increases only when $\dot{x}_2 > 0$; that is,

$$\dot{x}_2 = (bx_1 - r)x_2 > 0$$

equivalently,

$$x_1 > \frac{r}{b} = p.$$

p is called the relative removal rate. This means that the epidemic occurs only when the initial size of the susceptible population is greater than p. This phenomenon is referred to as the threshold phenomenon. Thus, if we know the threshold of a particular epidemic disease to which everyone is susceptible, we only need to vaccinate up to the threshold level to prevent an outbreak of the

epidemic.

In the simple epidemic model we considered $\dot{x}_2$ to be the epidemic curve. However, in reality, it is difficult to know the instant when an individual becomes infected. It is more convenient to equate the rate of immunity $\dot{x}_3$ with the disease incidence, because the disease incidence is normally associated with the number of individuals entering a hospital or seeing a doctor in a given time period, and that quantity is more readily observable. Hence, we define the epidemic curve to be

$$E(t) = \dot{x}_3 = rx_2.$$

The causal loop diagram is shown in Figure 2.5.

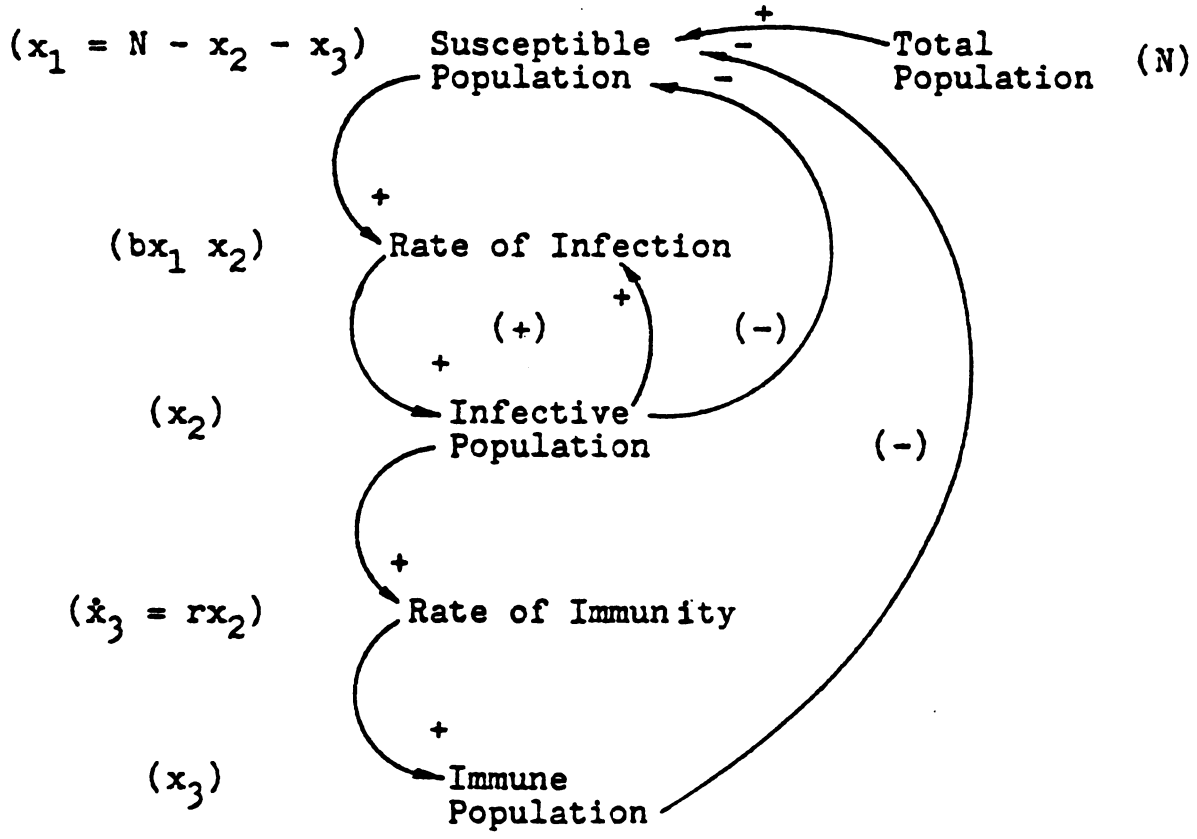


Figure 2.5. Causal loop diagram of general epidemics.

In this model the positive feedback of the infectious cycle is now imbedded in two negative feedback loops; hence, the epidemic is slowed down by the removal rate r.

The block diagram and the flow diagram are shown in Figure 2.6 and Figure 2.7. The output from the simulation for the following test case is given in Figure 2.8(a):

$N = 1000$ $\quad b = .002$

$c_1 = 950$ $\quad r = .8$

$c_2 = 50$ $\quad p = 400$

$c_3 = 0$

In the case where the initial susceptible population is below the threshold level p, the initial infective population steadily decreases to zero; hence, the epidemic does not occur. The output from the simulation of this case is shown in Figure 2.8(b).

We now consider the reduced state model by eliminating x_3 from the state model (2.2).

$$\dot{x}_1 = -b\, x_1\, x_2$$

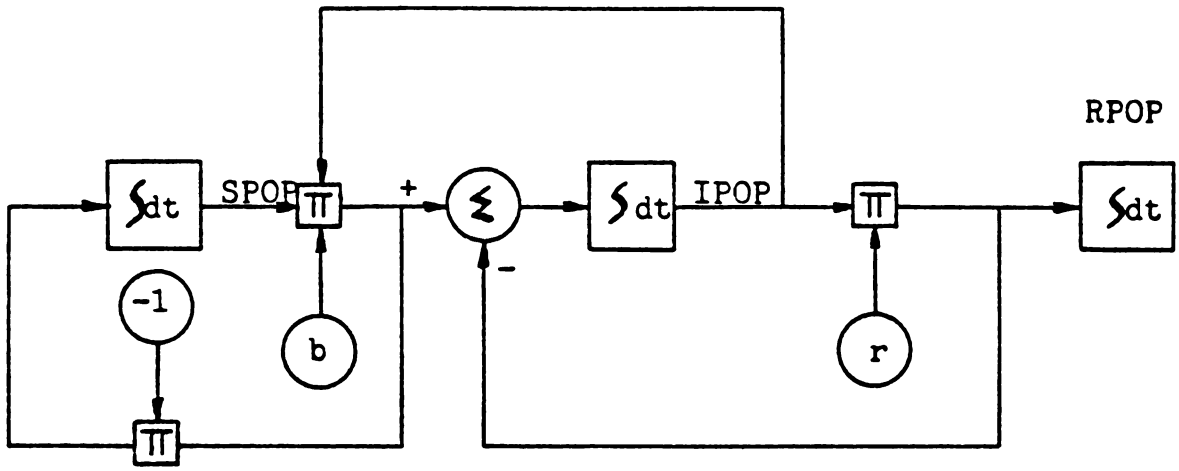
$$\dot{x}_2 = b\, x_1\, x_2 - r x_2$$

with the initial conditions $x_1(0) = c_1$, $x_2(0) = c_2$. We will analyze this system by the isocline and the phase portrait technique (Olinick, 1978).

The isocline is

$$s = \frac{\dot{x}_2}{\dot{x}_1} = \frac{b x_1\, x_2 - r x_2}{-b\, x_1\, x_2}$$

$$= -1 + p\,\frac{1}{x_1}.$$



SPOP = Susceptible Population

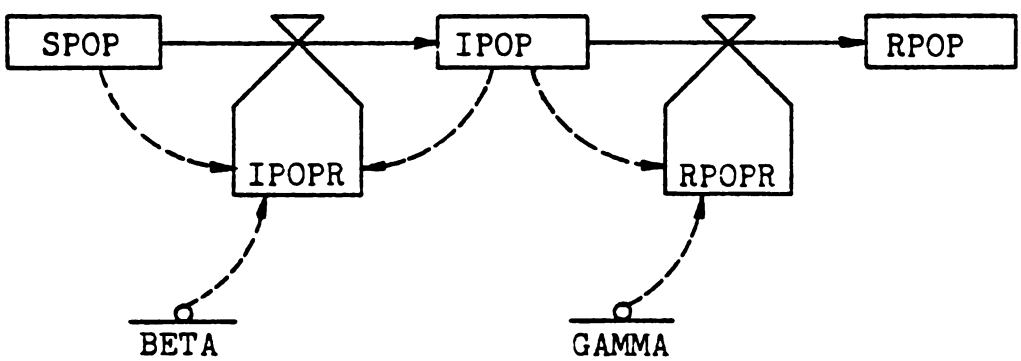
IPOP = Infective Population

RPOP = Immune Population

b = Infective Rate (Contact Rate)

r = Removal Rate

Figure 2.6. Block diagram of general epidemics.



SPOP = Susceptible Population
IPOP = Infective Population
IPOPR = Rate of Infection
RPOP = Immune Population
RPOPR = Rate of Immune (Disease Incidence)
BETA = Infective Rate (Contact Rate)
GAMMA = Removal Rate

Figure 2.7. Flow diagram of general epidemics.

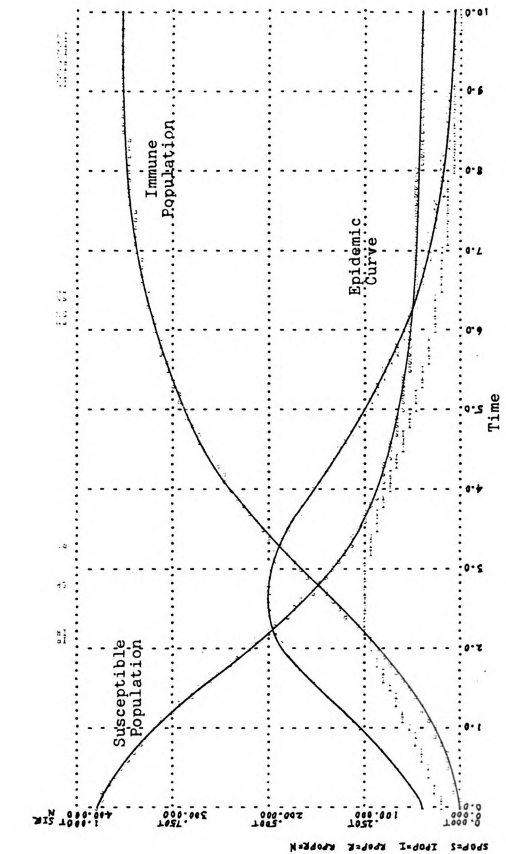


Figure 2.8(a). General epidemic model: $p = 400$, $c_1 = 950$.

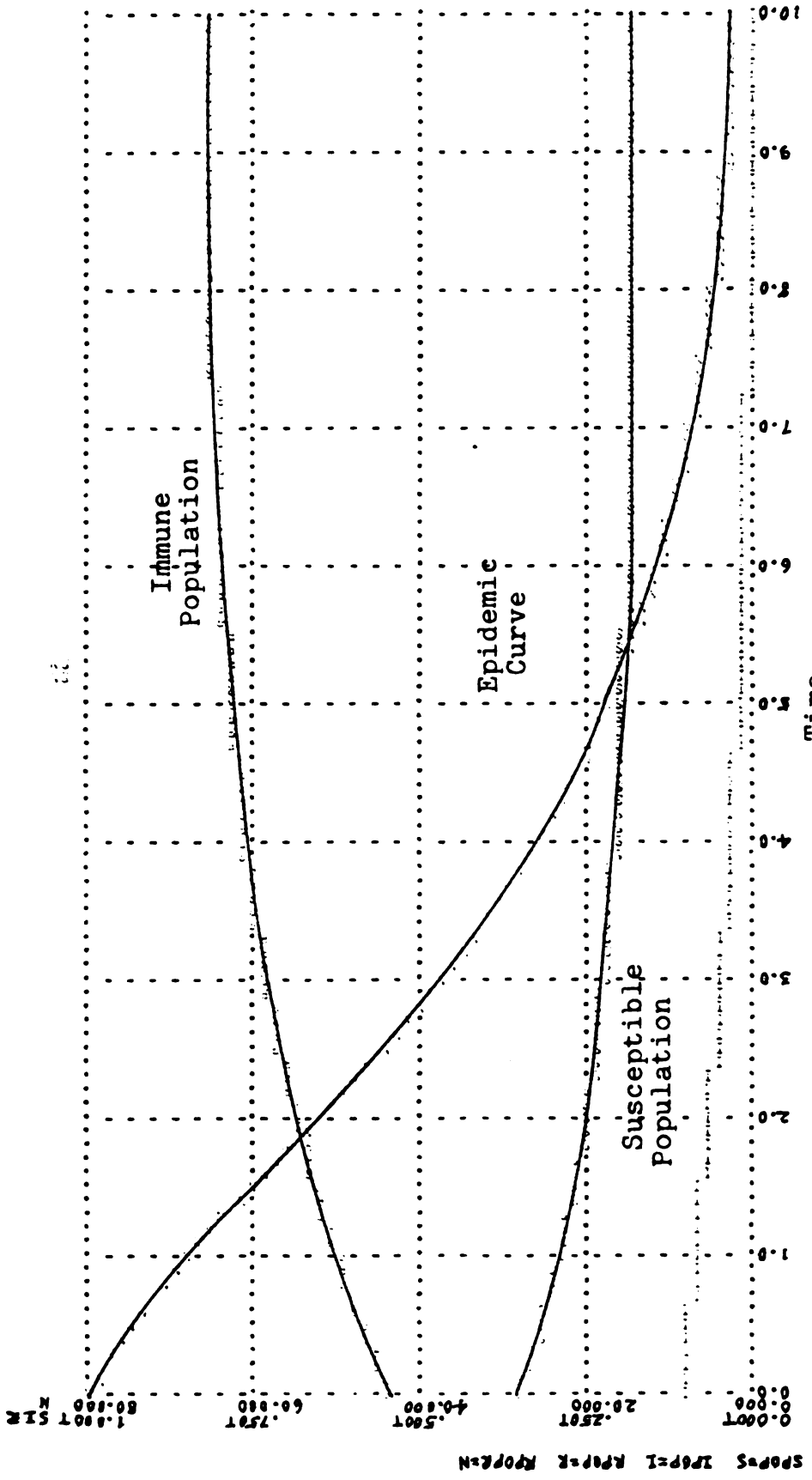


Figure 2.8(b). General epidemic model: p = 400, c_1 = 350.

In this case, by separating variables, we can integrate and solve for x_2 in terms of x_1:

$$\int dx_2 = \int (-1 + p \frac{1}{x_1}) dx_1$$

which gives

$$x_2 = -x_1 + p \log x_1 + \text{constant}.$$

From the initial conditions, we obtain

$$x_2 = c_1 + c_2 - x_1 + p \log \frac{x_1}{c_1}. \qquad (2.3)$$

The trajectory of the test case, $c_1 = 950$, $c_2 = 50$, $c_3 = 0$, $p = 400$, is shown in Figure 2.9. Note that the trajectory moves in the plane bounded by $x_1 + x_2 = N$, $x_1 = 0$ and $x_2 = 0$. When $x_1 = p$, x_2 attains maximum since the isocline at that point is horizontal.

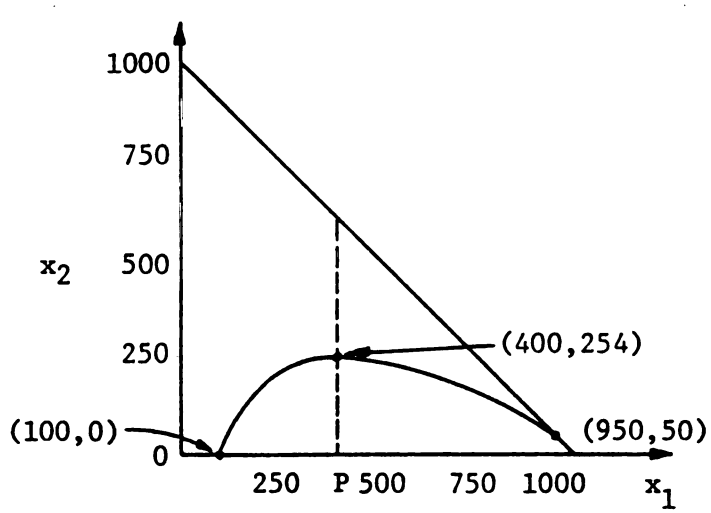


Figure 2.9. Phase portrait of general epidemics model.

The steady state for x_1, denoted by S, can be found by setting $x_2 = 0$ in Equation (2.3) and solving for x_1:

$$0 = c_1 + c_2 - x_1 + p \log \frac{x_1}{c_1} .$$

Equivalently, S is the root of the equation

$$c_1 e^{-\frac{1}{p}(c_1 + c_2 - x)} - x = 0. \qquad (2.4)$$

The root can be approximated by Newton's method. From the relation $x_1 + x_2 + x_3 = N$, the steady state for x_3, denoted by R, is then

$$R = N - S.$$

A non-zero steady state for x_1 means that there is always a portion of the susceptible population which escapes being infected during the epidemic.

We define the immunity level of the population A(t) to be the ratio of the immune population to the total population:

$$A(t) = \frac{x_3}{N} .$$

The steady state of the immunity level, denoted by I, is then

$$I = \frac{R}{N} .$$

This ratio can also be considered the attack rate of the epidemic referred to in the literature. Hence, if we are given the attack rate, we can calculate the steady state for x_3 and consequently the steady state for x_1. From this information, together with the initial conditions, the relative removal rate p can be computed from Equation (2.4) and the general epidemics model which satisfies the steady

state can be constructed.

The explicit time solution for the epidemic curve E(t) cannot be obtained, although the parametric form of the exact solution was worked out by Kendall (1956). An approximate form of the epidemic curve, in the case $c_3 = 0$, is given by Bailey (1975). To show this, we need to express x_1 in terms of x_3. This expression can be obtained from Equation (2.3). We rewrite Equation (2.3) as

$$x_1 + x_2 = c_1 + c_2 + p \log \frac{x_1}{c_1} .$$

Since $x_3 = N - (x_1 + x_2)$ and $c_3 = N - (c_1 + c_2)$, we have

$$x_3 = c_3 - p \log \frac{x_1}{c_1} .$$

Therefore, we can write x_1 in terms of x_3:

$$x_1 = c_1 \, e^{-\frac{1}{p}(x_3 - c_3)} .$$

If we assume the initial condition $c_3 = 0$, then

$$x_1 = c_1 \, e^{-\frac{1}{p} x_3} .$$

The epidemic curve, then, can be written as

$$\begin{aligned} E(t) = \dot{x}_3 &= r x_2 \\ &= r(N - x_1 - x_3) \\ &= r(N - x_3 - c_1 \, e^{-\frac{1}{p} x_3}) . \end{aligned}$$

We now approximate the exponential term by Taylor expansion to the third term:

$$e^{-\frac{1}{p}x_3} = 1 - \frac{x_3}{p} + \frac{x_3^2}{2p^2}.$$

Hence, we obtain the state equation for x_3 in terms of the quadratic expression of x_3 given by

$$\dot{x}_3 = r[N - c_1 + (\frac{c_1}{p} - 1)x_3 - \frac{c_1}{2p^2} x_3^2].$$

Separating variables and integrating, we have

$$\frac{1}{r} \int \frac{dx_3}{[N - c_1 + (\frac{c_1}{p} - 1)x_3 - \frac{c_1}{2p^2} x_3^2]} = \int dt.$$

The left hand side of the equation can be integrated using a table of integrals. Because the algebraic manipulation is tedious, we give the final expression without stating the intermediate steps.

$$x_3(t) = \frac{p^2}{c_1} \left\{ \frac{c_1}{p} - 1 + \alpha \tanh(\tfrac{1}{2} \alpha rt - \phi) \right\}$$

where

$$\alpha = \left\{ (\frac{c_1}{p} - 1)^2 + \frac{2c_1 c_2}{p^2} \right\}^{\frac{1}{2}}$$

$$\phi = \tanh^{-1} \frac{1}{\alpha} (\frac{c_1}{p} - 1).$$

Differentiating $x_3(t)$ with respect to time, we obtain the epidemic curve

$$E(t) = \frac{r\alpha^2 p^2}{2c_1} \operatorname{sech}^2 (\tfrac{1}{2} \alpha rt - \phi). \quad (2.5)$$

t_{max}, E_{max}, t_d can be calculated from Equation (2.5). The curve $y = \operatorname{sech}^2 x$ is symmetric with respect to the Y

axis and attains maximum at the origin, and $y_{max} = y(0) = 1$. Hence, setting $\frac{1}{2}\alpha rt - \phi = 0$ in Equation (2.5) and solving for t, we obtain

$$t_{max} = \frac{2\phi}{\alpha r}.$$

And, therefore,

$$E_{max} = E(t_{max}) = \frac{r\alpha^2 p^2}{2c_1},$$

and

$$t_d = 2\, t_{max}.$$

However, the exact value of E_{max} can be obtained from Equation (2.3).

$$E_{max} = rx_{2max} = r(c_1 + c_2 - p + p \log \frac{p}{c_1}).$$

Another approximate time solution, t in terms of x_1, can be derived by the use of the quadratic approximation of Equation (2.3). We take three points on the curve in the phase portrait, (c_1, c_2), (p, x_{2max}), $(S, 0)$, and determine the coefficients of the parabola $x_2 = a_2 x_1^2 + a_1 x_1 + a_0$ by solving three simultaneous linear equations. We, then, substitute the parabolic equation into the state equation and obtain

$$\dot{x}_1 = -b\, x_1\, x_2$$

$$\dot{x}_1 = -b\, x_1(a_2 x_1^2 + a_1 x_1 + a_0).$$

Separating variables and integrating, we have

$$-\frac{1}{b}\int \frac{dx_1}{x_1(a_2 x_1^2 + a_1 x_1 + a_0)} = \int dt.$$

The left hand side of the equation can be integrated using a table of integrals. Integration yields

$$t = -\frac{1}{b}\left[\frac{1}{2a_0}\log\frac{x_1^2}{x_2} + \frac{a_1}{a_0\sqrt{q}}\tanh^{-1}\left(\frac{2a_2 x_1 + a_1}{\sqrt{q}}\right)\right] + C, \quad (2.6)$$

where $q = a_1^2 - 4a_2 a_0$.

From the initial condition $t = 0$, $x_1 = c_1$ we determine the constant C.

$$C = \frac{1}{b}\left[\frac{1}{2a_0}\log\frac{c_1^2}{c_2} + \frac{a_1}{a_0\sqrt{q}}\tanh^{-1}\left(\frac{2a_2 c_1 + a_1}{\sqrt{q}}\right)\right].$$

At the peak time, t_{max}, the infective population x_2 is maximum and the susceptible population x_1 is p, and at the duration time t_d, by definition the infective population is equal to its initial value. To compute t_{max}, we substitute x_{2max} and p into x_2 and x_1, respectively, in Equation (2.6). To compute t_d, we substitute c_2 and h, which is the susceptible population corresponding to c_2, into x_2 and x_1, respectively.

Then,

$$t_{max} = -\frac{1}{b}\left[\frac{1}{2a_0}\log\frac{p^2}{x_{2max}} + \frac{a_1}{a_0\sqrt{q}}\tanh^{-1}\left(\frac{2a_2 p + a_1}{\sqrt{q}}\right)\right] + C$$

$$t_d = -\frac{1}{b}\left[\frac{1}{2a_0}\log\frac{h^2}{c_2} + \frac{a_1}{a_0\sqrt{q}}\tanh^{-1}\left(\frac{2a_2 h + a_1}{\sqrt{q}}\right)\right] + C$$

where h is the smaller root of the equation

$$a_2x^2 + a_1x + a_0 = c_2.$$

The comparison of the two analytical approximations and the results obtained from the simulation for the test case shown in Figure 2.8 with respect to the peak of the epidemic, the peak time, and the duration of the epidemic is as follows:

	Taylor Expansion	Quadratic	Simulation
E_{max}	167.37	203.20	203.18
t_{max}	2.1299	2.0872	2.7
t_d	4.2578	6.3177	6.3

The quadradic approximation and the simulation reflect the skewness of the epidemic curve with respect to peak time, which is descriptive of many actual epidemic curves.

2.3 Endemic Model

In the first two models discussed, the epidemic curve asymptotically approaches zero. The third model, which is more reflective of influenza epidemics, results in an endemic state (the state at which the disease incidence is constant) after an epidemic.

Suppose we consider that a certain portion of the immune population is put back into the susceptible pool at a constant rate e. The cause of such a transfer is not specified in this model. One example for this transfer to take place is the loss of immunity in infants. A newborn baby has acquired from her mother immunity against many diseases (this type of immunity is referred to as passive immunity)

and loses it within six months to a year. Another example which gives the same effect as the transfer is the migration of the susceptible individuals into the system and at the same time the migration of immune individuals out of the system in such a way that the total population remains constant. A specific cause of the transfer; that is, once immune individuals becoming susceptible because of the changes in the virus, will be discussed in the next chapter.

Using the above assumption of the constant transfer from the immune population to the susceptible population, we formulate the following state model:

$$\begin{aligned} \dot{x}_1 &= -b\, x_1\, x_2 + e \\ \dot{x}_2 &= b\, x_1\, x_2 - r x_2 \\ \dot{x}_3 &= r x_2 - e \end{aligned} \tag{2.7}$$

with the initial conditions

$$x_1(0) = c_1, \quad x_2(0) = c_2, \quad x_3(0) = c_3,$$

and the boundary conditions

$$x_1 + x_2 + x_3 = N, \quad 0 \le x_1, \quad 0 \le x_2, \quad 0 \le x_3.$$

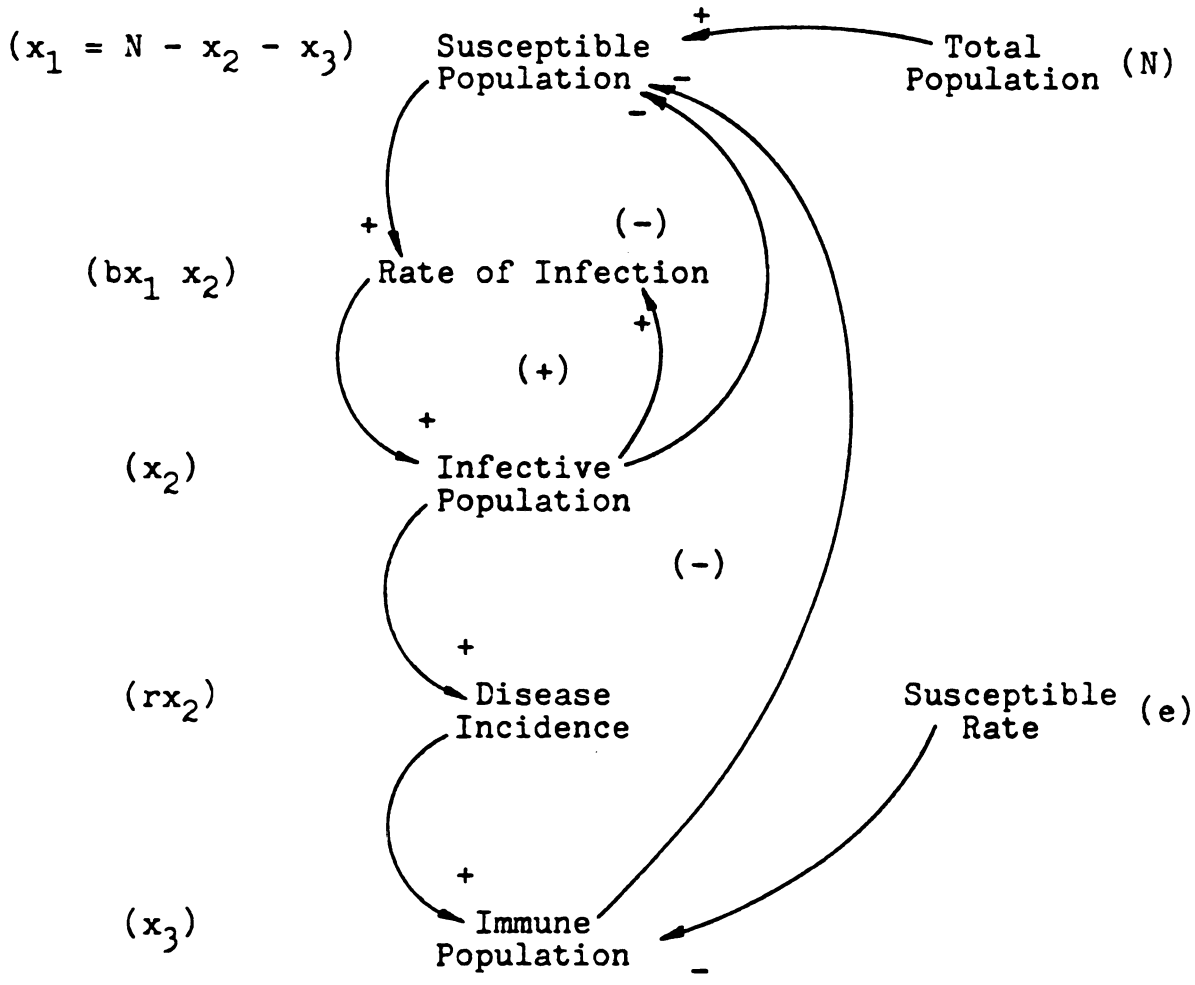


Figure 2.10. Causal loop diagram of endemic model.

The causal loop diagram, Figure 2.10, is the same as that of the general epidemics model with the addition of the susceptible rate e. The increase in the susceptible rate causes the susceptible population to build up through the decrease of the immune population. When the susceptible population crosses the threshold, we can expect another epidemic to occur. Hence, this causal loop diagram suggests that oscillation may occur.

The block diagram and the flow diagram are shown in Figure 2.11 and Figure 2.12. The DYNAMO output for the test

case:

$N = 1000$	$b = .001$	$p_1 = 800$
$c_1 = 900$	$r = .8$	$p_2 = 62.5$
$c_2 = 50$	$e = 50$	
$c_3 = 50$		

is given in Figure 2.13, and for the test case:

$N = 1000$	$b = .002$	$p_1 = 400$
$c_1 = 950$	$r = .8$	$p_2 = 12.5$
$c_2 = 50$	$e = 10$	
$c_3 = 0$		

is given in Figure 2.14.

We now consider the nonlinear autonomous state model $\dot{X} = F(X)$ reduced from the state model (2.7) by eliminating x_3:

$$\dot{x}_1 = -b\, x_1\, x_2 + e$$
$$\dot{x}_2 = b\, x_1\, x_2 - r x_2$$

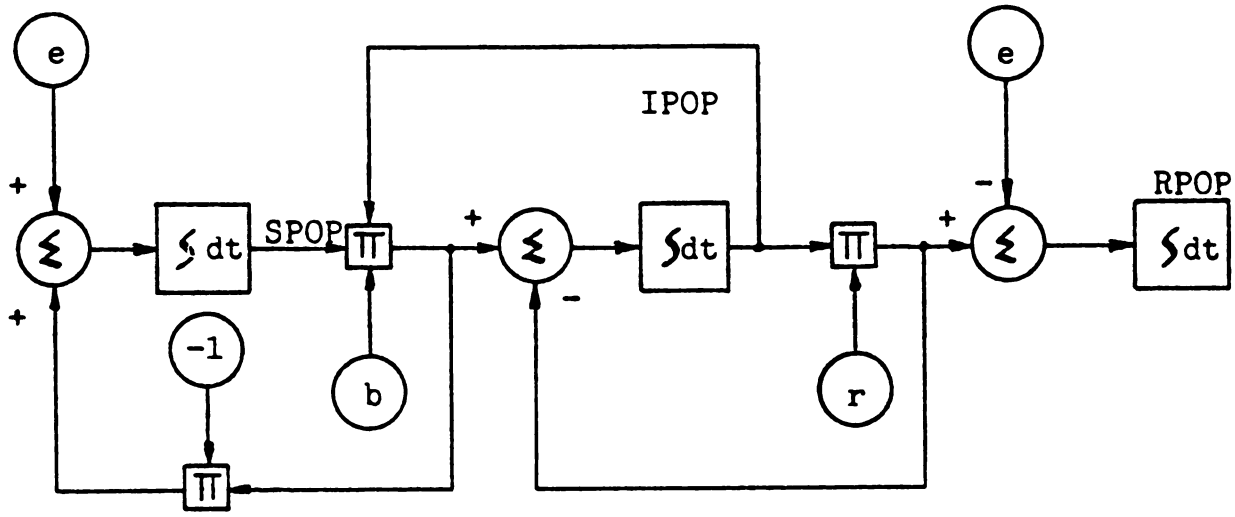
with the initial conditions

$$x_1(0) = c_1, \quad x_2(0) = c_2.$$

This model has a unique equilibrium point given by

$$X_e = \begin{bmatrix} \frac{r}{b} \\ \frac{e}{r} \end{bmatrix}$$

We will analyze this system using the linearization technique. If the system is structurally stable, then the behavior of the nonlinear system in the vicinity of the equilibrium point is similar to that of the linearized system (Aggarway, 1972).



SPOP = Susceptible Population

IPOP = Infective Population

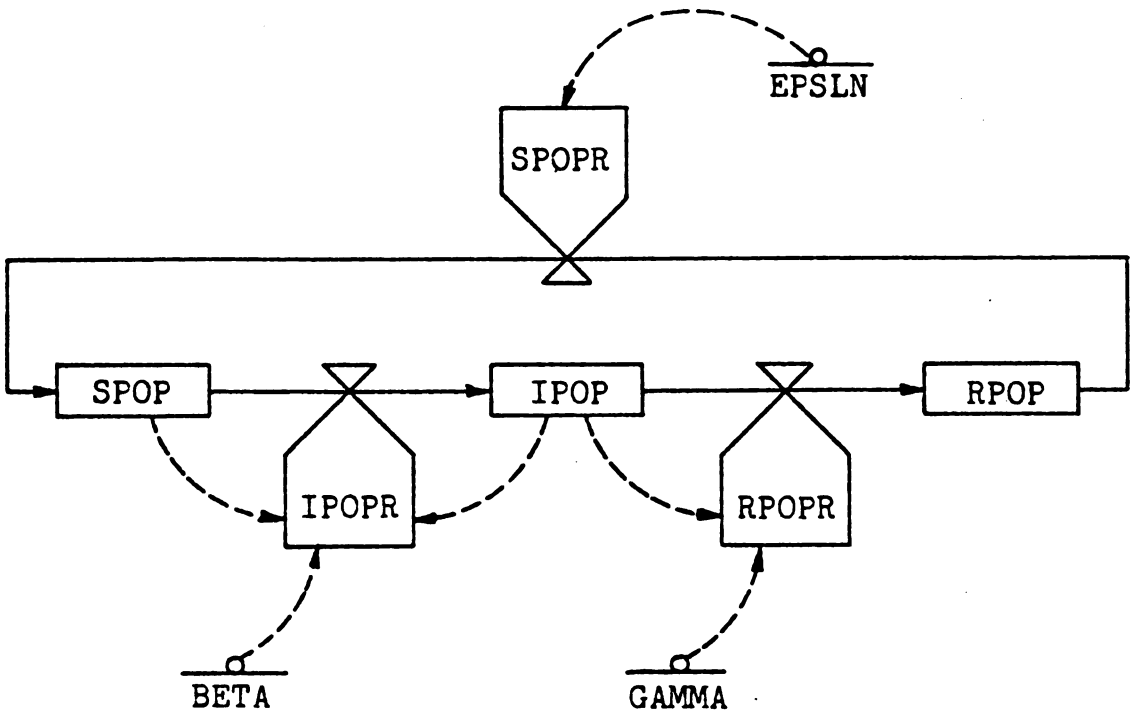
RPOP = Immune Population

b = Infective Rate (Contact Rate)

r = Removal Rate

e = Susceptible Rate

Figure 2.11. Block diagram of endemic model.



SPOP = Susceptible Population

IPOP = Infective Population

RPOP = Immune Population

SPOPR = Rate of Transfer

IPOPR = Rate of Infection

RPOPR = Disease Incidence

BETA = Infective Rate (Contact Rate)

GAMMA = Removal Rate

EPSLN = Susceptible Rate

Figure 2.12. Flow diagram of the endemic model.

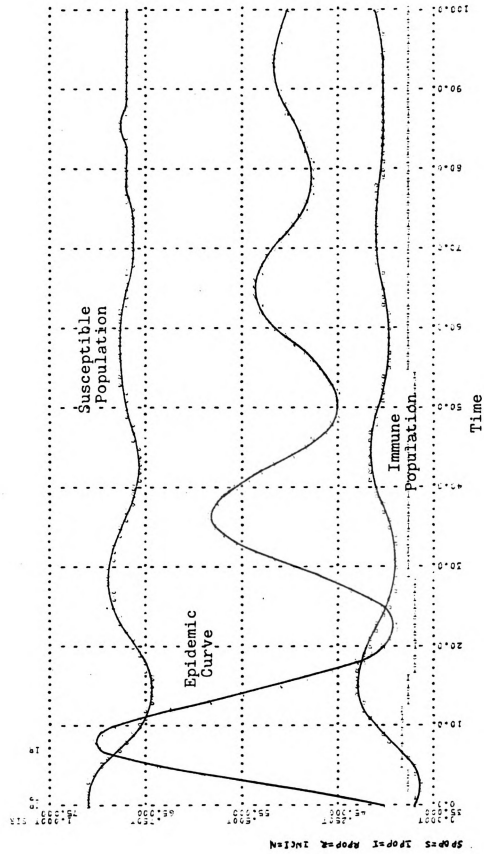


Figure 2.13. Endemic model: $p_1 = 800$, $p_2 = 62.5$.

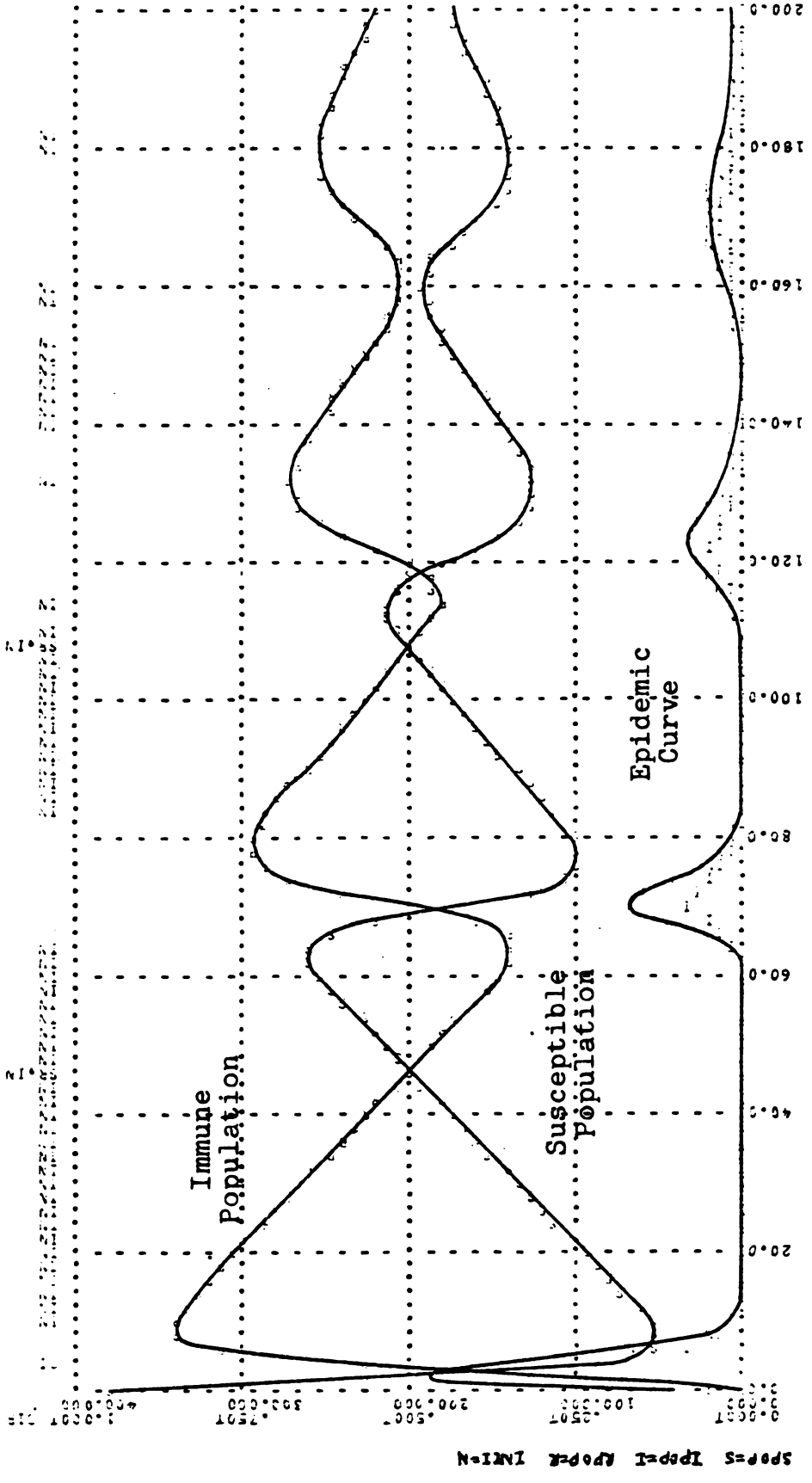


Figure 2.14. Endemic model: $p_1 = 400$, $p_2 = 12.5$.

Matrix A of the linearized system $\dot{X} = AX$ is the Jacobian matrix evaluated at X_e:

$$A = \frac{\partial F}{\partial x_i}\Bigg|_{X_e} = \begin{bmatrix} \frac{-be}{r} & -r \\ \frac{be}{r} & 0 \end{bmatrix}.$$

The characteristic equation and the eigenvalues are

$$s^2 + \frac{be}{r}\, s + be = 0$$

$$s_{1,2} = \frac{\frac{-be}{r} \pm \sqrt{(\frac{be}{r})^2 - 4be}}{2}. \qquad (2.8)$$

Since parameters b, r, e are positive, the real part of the eigenvalues are negative in all cases, and, hence, the linearized system is stable in the sense of Liapunov. Oscillation occurs when the eigenvalues are complex; that is, when the discriminant of the characteristic equation is negative:

$$(\frac{be}{r})^2 - 4be < 0,$$

or equivalently,

$$\frac{e}{r} < 4\,\frac{r}{b}.$$

If as before, we let $p_1 = \frac{r}{b}$ be the relative removal rate, and define $p_2 = \frac{e}{r}$ to be the relative immune rate, the result shows that oscillation occurs when the relative immune rate is less than four times the relative removal rate:

$p_2 < 4\, p_1$.

An interesting oscillation occurs when the susceptible rate e is small. The epidemic curve E(t) dies down and stays close to zero until the pool of susceptibles is built up to

a point above the threshold. It takes a long time to build up the susceptible population; hence, the curve does not resemble damped oscillation. By adjusting the susceptible rate e, one can obtain damped oscillation, or recurrences of epidemics that follow periods relatively free from the incidence of disease, as illustrated in Figure 2.13 and Figure 2.14.

We will derive E_{max}, t_{max}, t_d by first finding the time solution for the linearized system $\dot{X} = AX$. This solution is given by

$$X(t) = e^{At} X(0)$$

where e^{At} is the fundamental matrix. If the eigenvalues are complex,

$$s_{1,2} = u \pm jv,$$

then it can be shown (see Appendix A) that the fundamental matrix is given by

$$e^{At} = e^{ut} [(\cos vt)I + (\tfrac{1}{v} \sin vt)(A - uI)] \qquad (2.9)$$

where I is the identity matrix.

If the eigenvalues given by Equation (2.8) are complex, the real part u and the imaginary part v are

$$u = -\frac{be}{2r}, \qquad v = \tfrac{1}{2}\sqrt{4be - (\frac{be}{r})^2} \ .$$

Then, the A matrix can be written as

$$A = \begin{bmatrix} 2u & -r \\ -2u & 0 \end{bmatrix}.$$

From Equation (2.9), we obtain the fundamental matrix for this system:

$$e^{At} = e^{ut} \begin{bmatrix} \cos vt + \frac{u}{v} \sin vt & -\frac{r}{v} \sin vt \\ -\frac{2u}{v} \sin vt & \cos vt - \frac{u}{v} \sin vt \end{bmatrix} .$$

In particular, we can find the explicit time solution for the epidemic curve $E(t) = rx_2$:

$$E(t) = re^{ut} [c_2 \cos vt - (2c_1 + c_2)\frac{u}{v} \sin vt]$$

$$= ke^{ut} \sin (vt + \phi)$$

where $k = r\sqrt{c_2^2 + [(2c_1 + c_2)\frac{u}{v}]^2}$,

and $\phi = \tan^{-1} \left[- \frac{c_2 v}{(2c_1 + c_2)u} \right]$.

t_{max} is obtained by setting $\dot{E}(t) = 0$ and solving for t, and E_{max} is obtained by evaluating the epidemic curve E(t) at t_{max}:

$$\dot{E}(t) = KHe^{ut} \sin (vt + \phi + \psi)$$

where $H = \sqrt{u^2 + v^2}$, and $\psi = \tan^{-1} \frac{v}{u}$.

Therefore,

$$t_{max} = - \frac{(\phi + \psi)}{v} ,$$

and,

$$E_{max} = E(t_{max})$$

$$= Ke^{ut_{max}} \sin (- \psi).$$

t_d is the 2 percent settling time in this model, as defined earlier, and is given by

$$t_d = \frac{4}{|u|} .$$

To apply the linearized system for computation of E_{max}, t_{max} and t_d, one must first transfer the coordinate of x_1, x_2 plane so that the origin (the equilibrium point of the linearized system) corresponds to the equilibrium point of the nonlinear system; in this case $(\frac{r}{b}, \frac{e}{r})$. Hence, for the new coordinate system

$$x_1 = x_1 - \frac{r}{b}, \qquad x_2 = x_2 - \frac{e}{r}.$$

In particular,

$$c_1 = c_1 - \frac{r}{b}, \qquad c_2 = c_2 - \frac{e}{r}$$

$$\begin{aligned} E_{max} &= rx_2 \\ &= r(x_2 - \tfrac{e}{r}) \\ &= rx_2 - e \\ &= E_{max} - e. \end{aligned}$$

Comparison of the computation from the analytical results of the linearized system and the tabulated results from the simulation in the first test case (Figure 2.13) is as follows:

	Linearized Model	Simulation
E_{max}	67.8013	70.34
t_{max}	8.4542	8.00
t_d	128	129

CHAPTER 3

INFLUENZA EPIDEMIC MODEL

The underdamped oscillation exhibited by the endemic model in Chapter 2 can be used to illustrate Kilbourne's concept of the cyclical nature of influenza epidemics (Figure 1.2) when that model includes the agent; that is, the virus, and its interactions with the population dynamics. Using the endemic model as a basis, we will now develop an influenza epidemic model and analyze it as in Chapter 2.

3.1 Formulation of the State Model

In the endemic model discussed in Chapter 2, the oscillation and the endemic state result from the fact that some individuals are transferred from the immune population into the pool of the susceptible population. The influenza epidemic model described in this chapter specifies the cause of that transfer to be the structural change of the virus. Individuals who have been infected by the virus have gained immunity against that specific strain. As the virus changes due to mutation (drift), a certain percentage of the immune population becomes susceptible to that changed virus.

To construct a state equation for the virus strain, we consider the relationship between the immunity level of the

population and the virus strain. Kilbourne (1979, p. 496) and more recently Pereira (1979, p. 10) state that antigenic drift is the result of the selection process in which the virus mutates in order to overcome a high immunity level of the population built up through a series of epidemics. Pereira further reports that the occurrence of antigenic drift has been demonstrated in the laboratory by growing the virus in the presence of a specific antibody.

In addition to the three state variables in the endemic model we now introduce the fourth state variable and let

$$x_4 = \text{the virus strain.}$$

The virus strain x_4 is defined to be a qualitative measurement of the structural state of the virus. A numerical value of x_4 may be a measurement of a chemical composition of the virus structure which indicates a degree of mutation; that is, the higher the number, the greater the degree of mutation resulting in a higher susceptibility level, or equivalently, a lower immunity level of the population.

The above description of drift suggests that the immunity level is the constraint (or the boundary) toward which the virus structure changes to overcome that constraint. We therefore assume that the numerical value of the structural state of the virus x_4 changes in such a way as to approach asymptotically to the immunity level. Such a process may be described by a state equation which produces a logistic curve.

In Chapter 2 we defined the immunity level of the population:

$$A(t) = \frac{x_3}{N} .$$

If the immunity level is constant, $A(t) = A$, then the state equation

$$\dot{x}_4 = d(A - x_4)x_4 \tag{3.1}$$

with the initial condition $x_4(0) = c_4$ gives a solution

$$x_4 = \frac{A}{1 + \frac{A - c_4}{c_4} e^{-Adt}} .$$

The graph of the solution is a logistic curve where x_4 is asymptotically approaching A as shown in Figure 3.1. Based on equation (3.1), we construct the state equation for the virus strain to be

$$\begin{aligned} \dot{x}_4 &= d(A(t) - x_4)x_4 \\ &= d(\frac{x_3}{N} - x_4)x_4, \end{aligned}$$

where the constant d is called the drift rate.

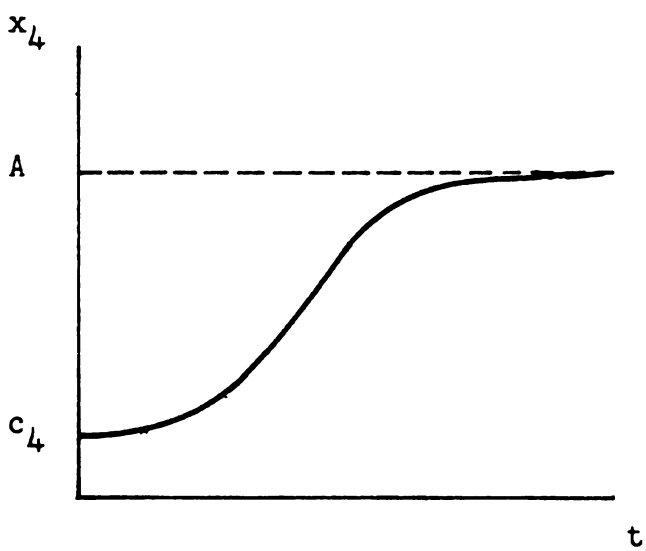


Figure 3.1. Logistic curve of the virus strain.

We also assume that the rate of the transfer of

individuals from the immune to the susceptible population is proportional to the product of the immune population and the virus strain. That is, infection resulting from contact between an individual in the immune population and the new strain of virus indicates susceptibility to that virus as well as the occurrence of drift. Hence, the state equation for the immune population is given by

$$\dot{x}_3 = rx_2 - ex_3 x_4.$$

The constant e is called the susceptible rate.

The transfer of a certain portion of the immune population to the susceptible population now takes place with the introduction of the drift rate d. Individuals who are now susceptible to the changed virus are still immune to the original strain. Therefore, the susceptible population is now a mixture of those who are susceptible to a new strain of the virus as well as those who are susceptible to both new and old strains. Thus, we can speak of the susceptible population collectively as having different levels of susceptibility at different times.

Let S(t) be the susceptible level of the population and define

$$S(t) = 1 - A(t).$$

We then assume that the infective rate $\dot{x}_2$ is proportional to the product of the susceptible and the infective populations and the susceptible level. In effect we have replaced the constant infective rate b in the endemic model with the time varying infective rate bS(t). Then the state equations for

the susceptible population and the infective population are given by

$$\dot{x}_1 = -bS(t)\, x_1\, x_2 + ex_3\, x_4$$

$$= -b(1 - \frac{x_3}{N})\, x_1\, x_2 + ex_3\, x_4$$

$$\dot{x}_2 = b(1 - \frac{x_3}{N})\, x_1\, x_2 - rx_2.$$

Now we write the state model of the influenza epidemic system:

$$\dot{x}_1 = -b(1 - \frac{x_3}{N})\, x_1\, x_2 + ex_3\, x_4$$

$$\dot{x}_2 = b(1 - \frac{x_3}{N})\, x_1\, x_2 - rx_2$$

$$\dot{x}_3 = rx_2 - ex_3\, x_4$$

$$\dot{x}_4 = d(\frac{x_3}{N} - x_4)x_4 \qquad (3.2)$$

with the initial conditions

$$x_1(0) = c_1, \quad x_2(0) = c_2, \quad x_3(0) = c_3, \quad x_4(0) = c_4,$$

and the boundary conditions

$$x_1 + x_2 + x_3 = N, \quad 0 \le x_1, \quad 0 \le x_2, \quad 0 \le x_3.$$

3.2 Causal Loop Analysis

The detailed causal loop diagram is shown in Figure 3.2. To show more clearly the relationship between the virus strain and the population, a simplified causal loop diagram, Figure 3.3, is obtained by leaving only the level variables and the two auxiliary variables, the immunity level A(t) and the

susceptibility level S(t). This diagram shows that the virus strain is the direct cause of the changes in the immune population. The appearance of a drift reduces the size of the immune population which in turn increases the size of the susceptible population. When the size of the susceptible population exceeds the threshold, an epidemic occurs. The size of the epidemic is now dependent not only on the contact rate b, but also on the susceptibility level S(t) which is a function of the virus strain as seen in the causal loop diagram. The increase in the size of the immune population, as a consequence of the epidemic, causes the higher immunity level of the population. In order for the virus to survive, the structure of the virus changes in response to the high level of immunity in the population, which causes another drift, and the epidemic cycle begins again.

3.3 System Analysis

The influenza epidemic system described by the state model (3.2) is classified as a nonlinear autonomous system $\dot{X} = F(X)$ with the dimension 4. This system can be analyzed by linearization about its equilibrium point provided the linearized system is stable in the sense of Liapunov. With the proper choice of the drift rate d, the linearized system of the influenza epidemic model satisfies the stability condition; therefore, the linearized technique will be used for this analysis.

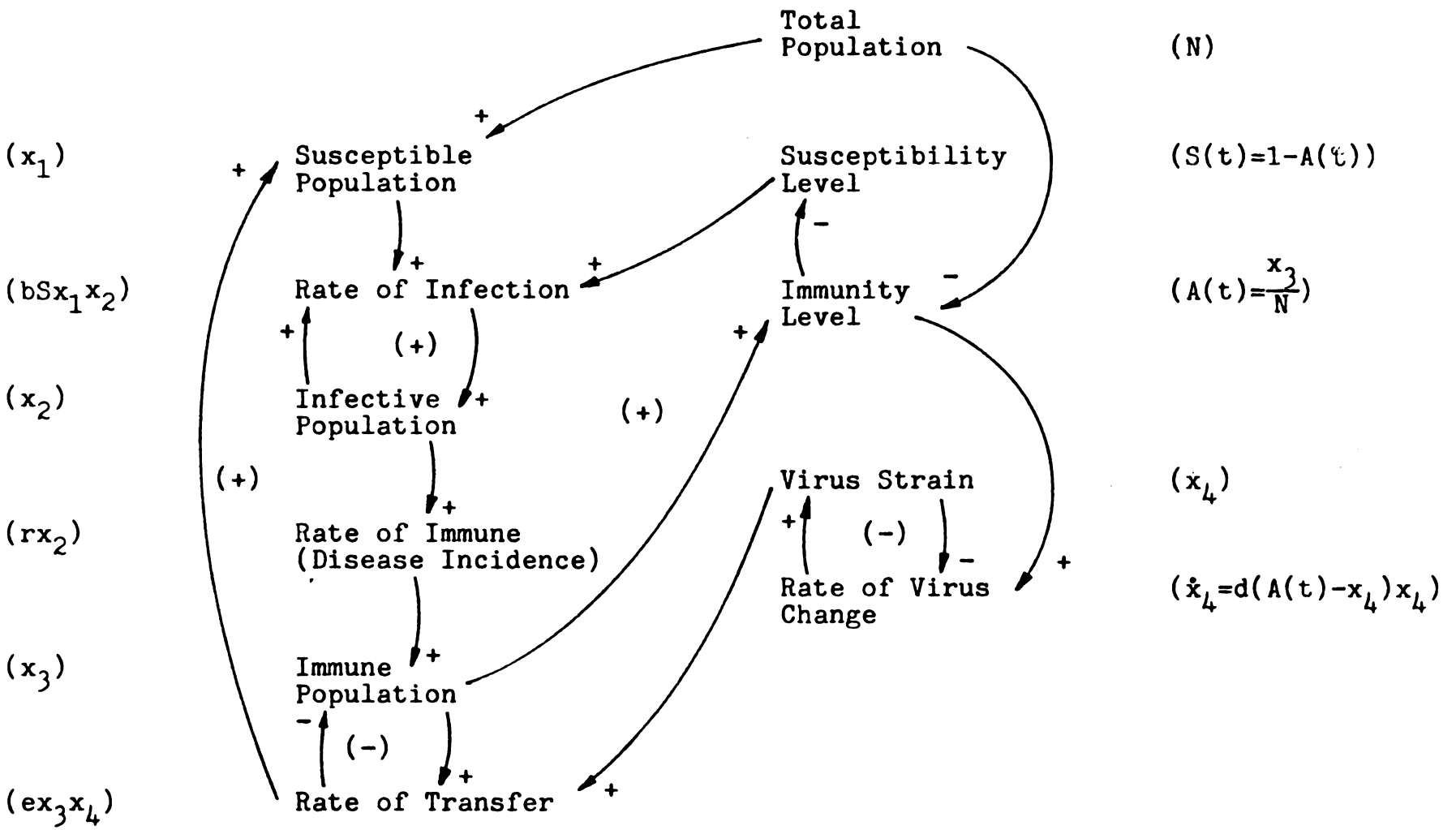


Figure 3.2. Causal loop diagram of influenza epidemic model.

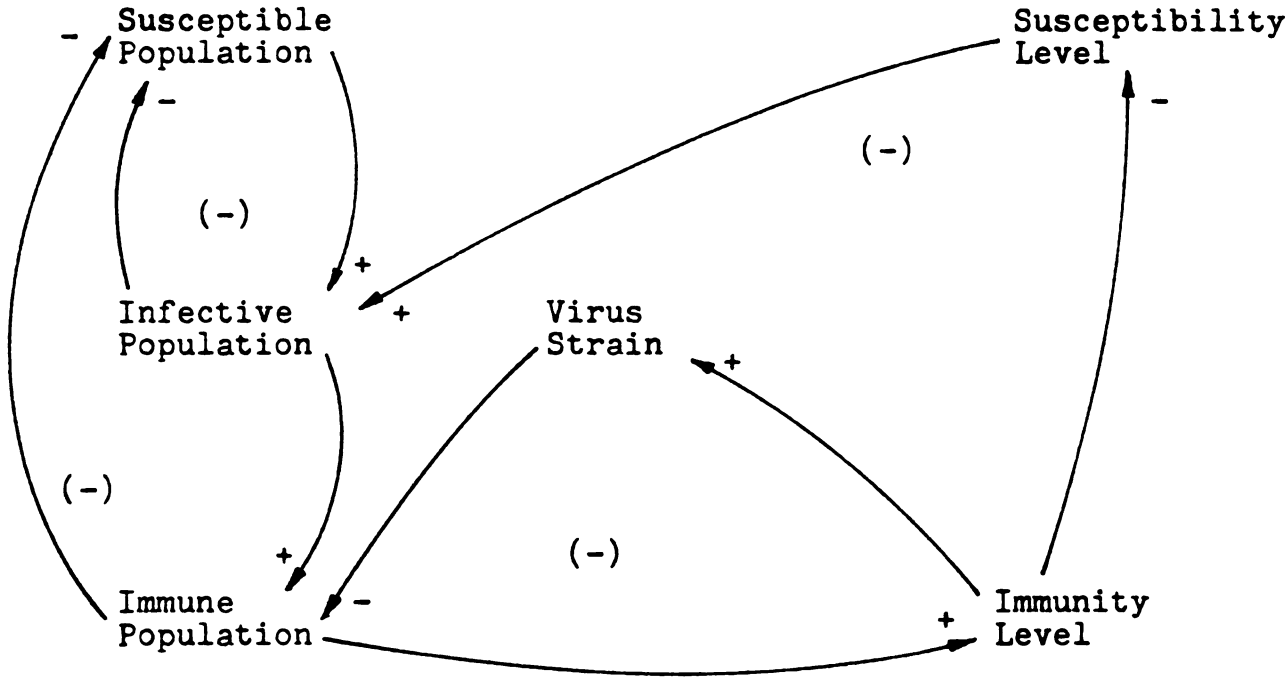
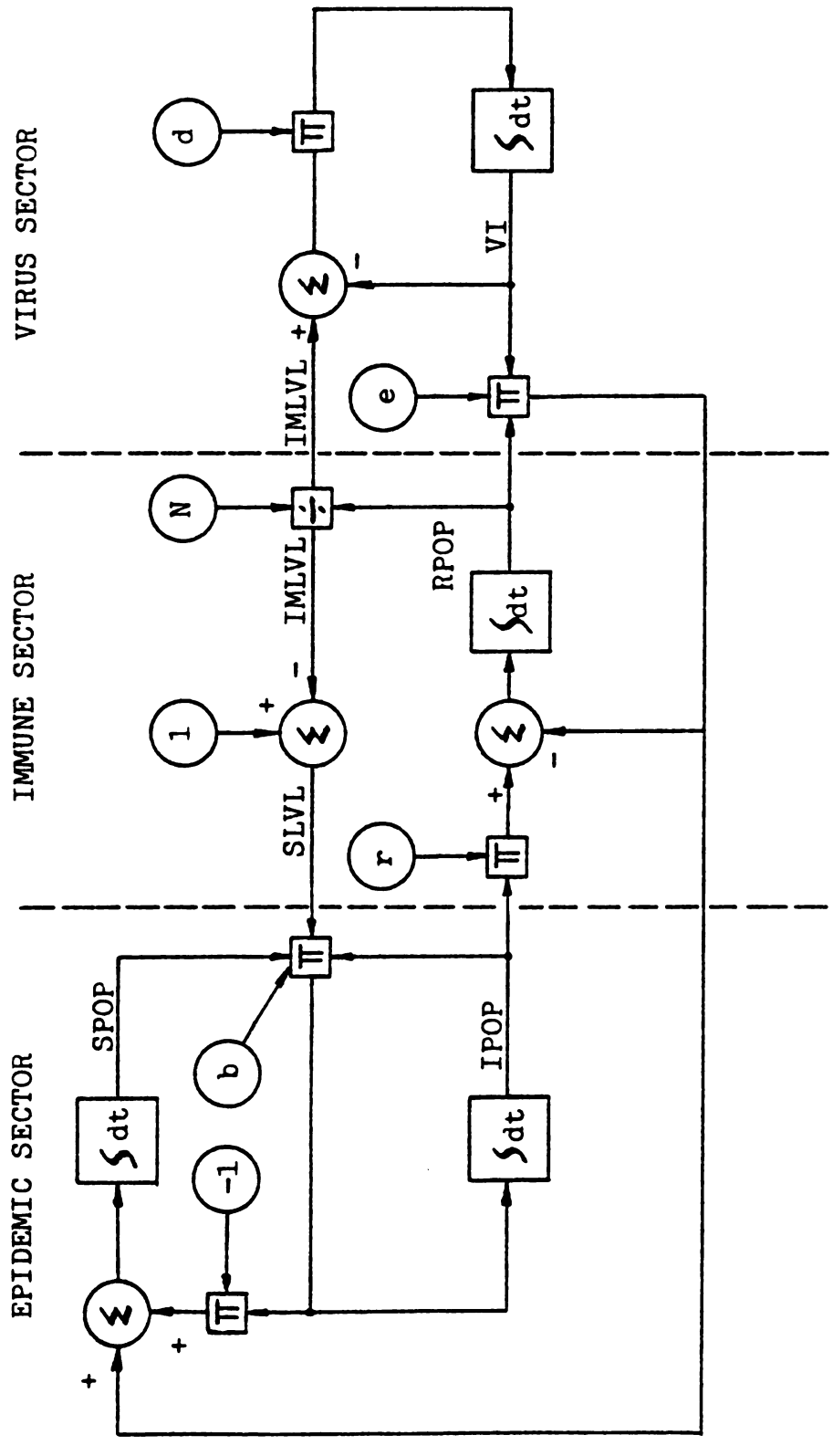


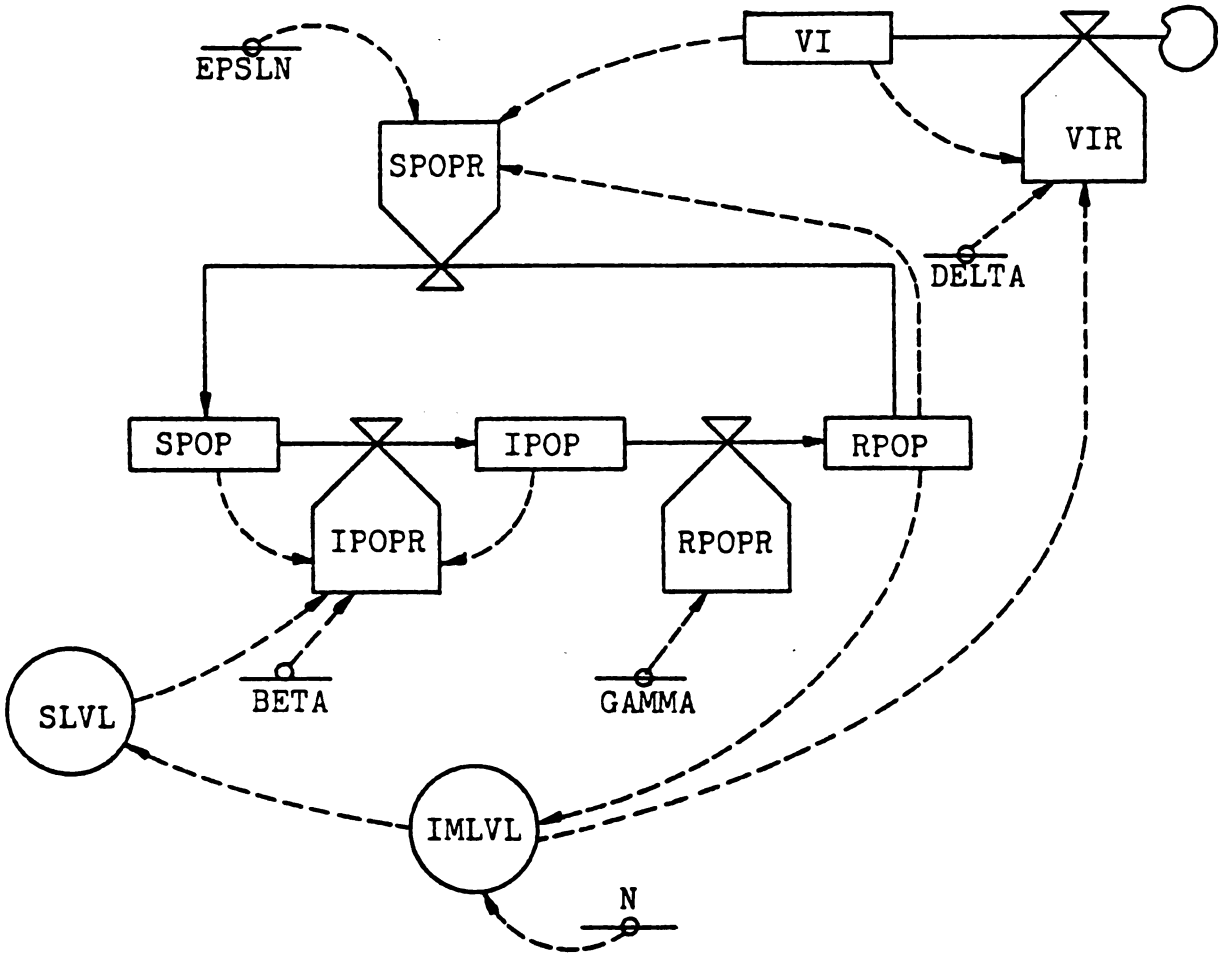
Figure 3.3. Simplified causal loop diagram of the influenza epidemic model.



SPOP = Susceptible Population
IPOP = Infective Population
RPOP = Immune Population
SLVL = Susceptible Level
IMLVL = Immunity Level
VI = Virus Strain

b = Infective Rate (Contact Rate)
r = Removal Rate
e = Susceptible Rate
d = Drift Rate

Figure 3.4. Block diagram of influenza epidemic model.



SPOP = Susceptible Population

IPOP = Infective Population

RPOP = Immune Population

SPOPR = Rate of Transfer

IPOPR = Rate of Infection

RPOPR = Disease Incidence

VIR = Rate of Virus Strain

SLVL = Susceptible Level of Population

IMLVL = Immunity Level of Population

BETA = Infective Rate (Contact Rate)

GAMMA = Removal Rate

EPSLN = Susceptible Rate

DELTA = Drift Rate

Figure 3.5. Flow diagram of influenza epidemic model.

3.3.1 Equilibrium Points Analysis

The equilibrium points for the system are solved by setting each state equation in the state model (3.2) equal to zero; that is, $F(X) = 0$. They are given by

$$X_e^1 = \begin{bmatrix} \frac{r}{b(1-c)} \\ \frac{e}{r} Nc^2 \\ Nc \\ c \end{bmatrix}, \quad X_e^2 = \begin{bmatrix} N-c \\ 0 \\ c \\ 0 \end{bmatrix} \qquad (3.3)$$

where c is some constant. Since we are concerned with a system which produces an endemic state; that is, the steady state of the infective population is non zero, this analysis considers the linearization about the first equilibrium point X_e^1. Moreover, the second equilibrium point X_e^2 can be shown to be structurally unstable for all values of c.

The constant c must be such that the boundary conditions are met; that is:

$$x_{e1} + x_{e2} + x_{e3} = N$$

and

$$0 \le x_{e1} \le N, \quad 0 \le x_{e2} \le N, \quad 0 \le x_{e3} \le N.$$

Hence we have the relations:

$$\frac{r}{b(1-c)} + \frac{e}{r} Nc^2 + Nc = N$$

and

$$0 < c < 1.$$

As before, let $p_1 = \frac{r}{b}$ be the relative removal rate and $p_2 = \frac{e}{r}$ be the relative immune rate. Then we have

$$\frac{p_1}{1-c} + p_2 Nc^2 + Nc = N.$$

The above expression can be written as

$$c^3 - \frac{p_2 - 1}{p_2} c^2 - \frac{2}{p_2} c + \frac{N - p_1}{p_2 N} = 0. \qquad (3.4)$$

Therefore, c is the real root of the cubic equation which lies between 0 and 1. The existence of such c is shown by the intermediate value theorem of calculus. We let

$$f(x) = x^3 - \frac{p_2 - 1}{p_2} x^2 - \frac{2}{p_2} x + \frac{N - p_1}{p_2 N} .$$

Then,

$$f(0) = \frac{N - p_1}{p_2 N} > 0 \quad (\text{since } N > p_1),$$

and

$$f(1) = - \frac{2N + p_1}{p_2 N} < 0.$$

Since the sign of f(x) at x = 0 and x = 1 are opposite, and f(x) is a continuous function, the graph of f(x) must cross the X axis between x = 0 and x = 1.

From the above analysis, given p_1, p_2, there exists an equilibrium point given by (3.3) where the constant c is the real root of the cubic equation (3.4). In most cases this equilibrium point is unique because a chance of having three real roots being in the interval x = 0 to x = 1 is relatively small.

Since the virus strain is bounded by 0 and 1, the structural change of the virus (drift) resulting from one epidemic

to the next may be measured in terms of percentage differences. Suppose that the state of the virus strain causing the initial epidemic were .1 and at the beginning of the next epidemic had changed to .3. Then we would say that the drift was 20 percent, the quantitative measurement of the structural change of the virus. (A more precise definition of drift will be given in Chapter 4.) As a series of epidemics occurs, the virus strain changes in such a way as to approach the immunity level of the population A(t) provided the system is stable. Let I be the steady state of the immunity level of the population as defined before. Then

$$I = \lim_{t \to \infty} A(t) = \lim_{t \to \infty} \frac{x(t)}{N}$$

$$= \frac{Nc}{N} = c.$$

Hence, the steady state of the virus strain is equal to the steady state of the immunity level, and the reciprocal of the drift rate d is analogous to a delay constant in an exponential growth curve.

3.3.2 Linearized Model

The relations $x_1 + x_2 + x_3 = N$ enables one to reduce the dimension of the state model (3.2) by one because any one of the variables can be expressed as a function of the other. We let $x_3 = f(x_1\ x_2)$. Then, we can eliminate the state equation for x_3 from the state model (3.2) and obtain the following reduced state model $\dot{X} = F(X)$:

$$\dot{x}_1 = -b\,(1 - \frac{x_3}{N})\,x_1\,x_2 + ex_3\,x_4$$

$$\dot{x}_2 = b\,(1 - \frac{x_3}{N})\,x_1\,x_2 - rx_2$$

$$\dot{x}_4 = d\,(\frac{x_3}{N} - x_4)\,x_4 \qquad (3.5)$$

with the initial conditions

$$x_1(0) = c_1, \quad x_2(0) = c_2, \quad x_4(0) = c_4.$$

Note x_3 is now a function of x_1 and x_2. The Jacobian matrix $\frac{\partial F}{\partial x_i}$ for the state model (3.5) is given by

$$\begin{bmatrix} -b[(1-\frac{x_3}{N})x_2+\frac{x_1x_2}{N}]-ex_4 & -b[(1-\frac{x_3}{N})x_1+\frac{x_1x_2}{N}]-ex_4 & ex_4 \\ b[(1-\frac{x_3}{N})x_2+\frac{x_1x_2}{N}] & b[(1-\frac{x_3}{N})x_1+\frac{x_1x_2}{N}]-r & 0 \\ -\frac{d}{N}x_4 & -\frac{d}{N}x_4 & -2dx_4 \end{bmatrix}$$

The A matrix of the linearized model $\dot{X} = AX$ is obtained by evaluating the Jacobian matrix at the equilibrium point

$$X_e = \begin{bmatrix} \frac{p_1}{1-c} \\ p_2Nc^2 \\ Nc \\ c \end{bmatrix}$$

and has the form

$$A = \begin{bmatrix} U - ec & V - ec & Nec \\ -U & -(V+r) & 0 \\ -\frac{d}{N}c & -\frac{d}{N}c & -2dc \end{bmatrix} \qquad (3.6)$$

where

$$U = -bc^2 \left[(1 - c)\, p_2 N + \frac{p_1 p_2}{1-c}\right]$$

$$V = -b \left(p_1 + \frac{p_1 p_2\, c^2}{1-c}\right). \qquad (3.7)$$

We now derive a formula which directly gives the coefficients of the characteristic equation of the A matrix without having to compute det(sI - A) = 0 each time as is the normal procedure for obtaining the characteristic equation. The computational advantage of using such a formula becomes quite clear when one is comparing the behavior of the linearized system for a number of different sets of parameters.

The inverse of the matrix A (3.6) is calculated as

$$A^{-1} = \frac{\text{Adj } A}{\det A}$$

$$= \frac{1}{\det A} \begin{bmatrix} 2dc(V+r) & dc(2V-3ec) & Nec(V+r) \\ -2dcU & -dc(2U-3ec) & -NecU \\ \frac{d}{N}c[U-(V+r)] & \frac{d}{N}c(U-V) & U(V-ec)-(V+r)(U-ec) \end{bmatrix}$$

where

$$\det A = -dc[U(2V - 3ec) - (V + r)(2U - 3ec)].$$

In the case of a three by three matrix A, it can be shown that the characteristic equation is given by (Wilkinson, 1965)

$$s^3 - (\text{tr } A)s^2 + (\text{tr Adj } A)s - \det A = 0 \qquad (3.8)$$

where

tr A = trace of matrix A

tr Adj A = trace of the adjoint matrix A.

From the equation (3.8) we obtain the coefficients of the characteristic equation of the matrix A (3.6),

$$s^3 + a_2 s^2 + a_1 s + a_0 = 0,$$

given by

$$a_2 = 2dc - (U - ec) + (V + r)$$

$$a_1 = dc\,[2(V + r) - (2U - 3ec)] + U(V - ec) - (V+r)(U-ec)$$

$$a_0 = dc\,[U(2V - 3ec) - (V + r)(2U - 3ec)]. \qquad (3.9)$$

Note that if we are given p_1, p_2, then the coefficients of the characteristic equation are expressed as functions of d:

$$s^3 + f_1(d)\, s^2 + f_2(d)\, s + f_3(d) = 0.$$

In a linear system, the location of the roots of the characteristic equation determines the system response. Kilbourne's observation of the influenza epidemic cycles (see Figure 1.2.) suggests that the system response for the type A virus epidemic system is stable and underdamped oscillation. The drift rate constant d can be chosen in such a way as to determine the desired response described above.

We will consider first the choice of d required for stability, then for oscillation, and finally, for underdamped oscillation. A linear system is stable in the sense of Liapunov if all the roots of the characteristic equation lie in the left half plane. The Routh stability criterion gives the condition for which the linear system is stable (Saucedo, 1968). The Routh array for the characteristic equation is formed as follows:

s^3	1	a_1
s^2	a_2	a_0
s^1	$a_1 - \frac{a_0}{a_2}$	0
s^0	a_0	0

The Routh criterion states that the number of roots with positive real parts is equal to the number of sign changes in the first column of the Routh array. In this case each element of the first column must be positive for all three roots to lie in the left half plane. Also, from the theory of equations, all coefficients must be positive. Hence, the system is stable if the coefficients of the characteristic equation satisfy the inequalities

$$a_i > 0, \quad i = 0,1,2; \text{ and } a_1 > \frac{a_0}{a_2} .$$

In an oscillatory system one of the roots of the characteristic equation has to be real and the other two complex. From the theory of equations, the necessary and sufficient condition for the cubic equation

$$x^3 + a_2 x^2 + a_1 x + a_0 = 0$$

to have one real root and two complex roots is that the discriminant

$$\Delta = 18\, a_2 a_1 a_0 - 4\, a_2^3 a_0 + a_2^2 a_1^2 - 4\, a_1^3 - 27\, a_0^2$$

is negative. Here we have the characteristic equation whose coefficients are functions of the drift rate d. To find the range of d which gives a set of coefficients satisfying the above condition is computationally impractical. Therefore, we now seek a simpler sufficient condition for the system to be oscillatory.

Consider the characteristic polynomial

$$f(s) = s^3 + a_2 s^2 + a_1 s + a_0.$$

The graph of the cubic polynomial crosses the real axis only once if there is no relative minimum or relative maximum, or if the critical point is the point of inflection. The critical points of f(s) are solved by taking the derivative and setting $f'(s) = 0$. Hence, the critical points are the roots of the quadratic equation $3s^2 + 2a_2 s + a_1 = 0$ and are given by

$$s_{1,2} = \frac{-2a_2 \pm \sqrt{4a_2^2 - 12a_1}}{6}. \qquad (3.10)$$

If the discriminant is non positive; i.e.,

$$4a_2^2 - 12a_1 \leq 0$$

or equivalently

$$a_1 \geq \frac{a_2^2}{3}, \qquad (3.11)$$

then the roots are either complex or multiple roots. If the roots are complex, the cubic polynomial has no critical point; and if the roots are multiple, the critical point is the

point of inflection. Therefore, a sufficient condition for the system to be oscillatory is that the coefficients of the characteristic polynomial satisfy inequality (3.11).

The system is both stable and oscillatory if the coefficients of the characteristic equation satisfy the inequality

$$a_1 > \max\left\{ \frac{a_0}{a_2}, \frac{a_2^2}{3} \right\}. \qquad (3.12)$$

Although such a choice of coefficients guarantees the oscillatory, stable system, the real root of the characteristic equation may lie to the right of the real part of the complex roots. In order to have underdamped oscillation, we require that the real root be on the left side of the real part of the complex roots, preferably as far to the left as possible. (The influence of the real root is negligible if it lies six times as far to the left as the real part of the complex roots.) Figure 3.1 shows the location of the roots and the system response for the third order linear system.

We now derive a sufficient condition for the system to be underdamped. This condition will be such that the widest range of d can be easily obtained. The coefficients of the characteristic equation

$$s^3 + a_2 s^2 + a_1 s + a_0 = 0$$

with the roots s_1, $s_{2,3} = u \pm jv$ have the following relationships:

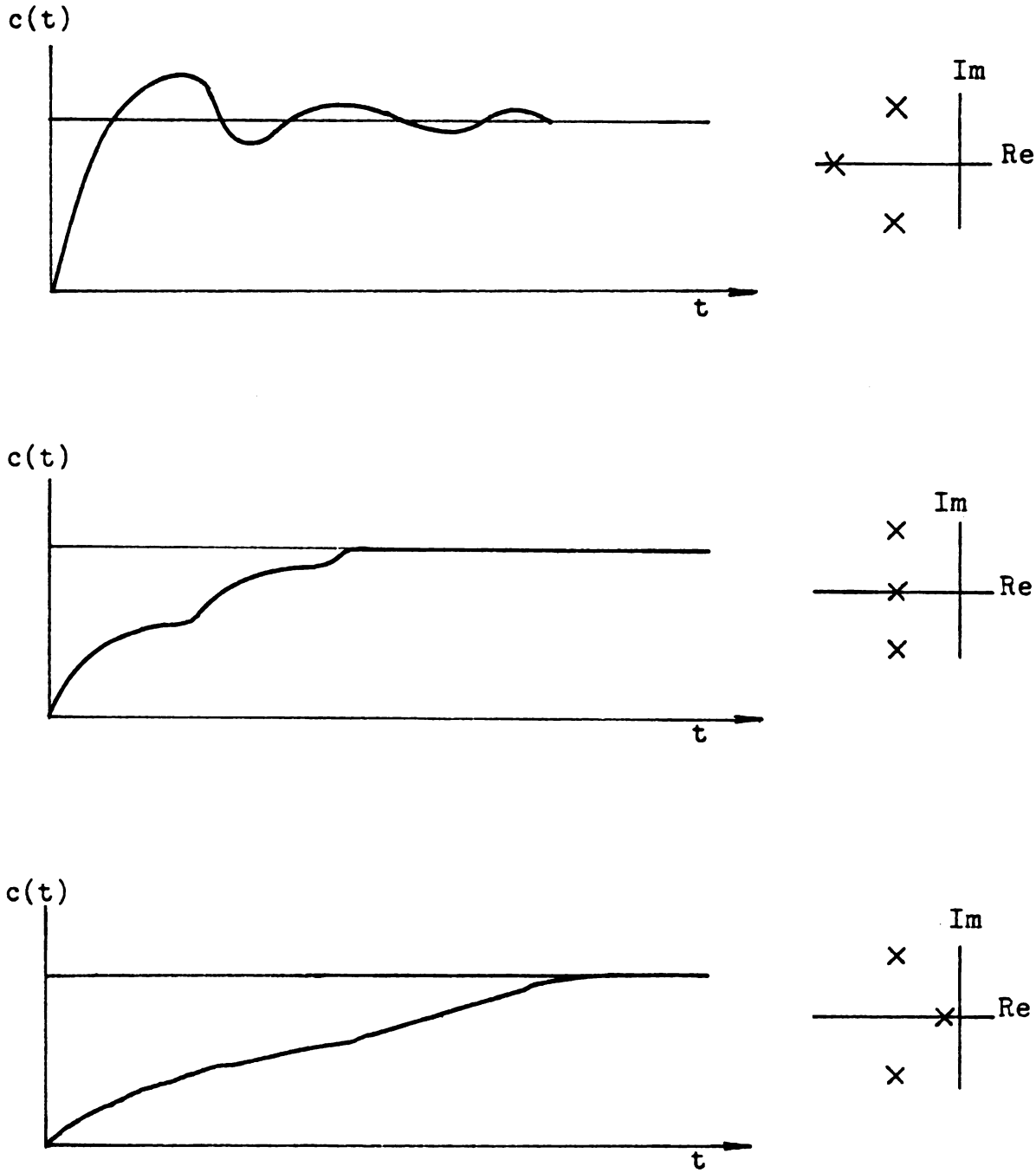


Figure 3.6. System response of a third order linear system.

$$a_2 = -(s_1 + s_2 + s_3)$$

$$a_1 = s_1s_2 + s_1s_3 + s_2s_3$$

$$a_0 = -s_1s_2s_3.$$

Assume all roots lie in the left half plane; i.e., $s_1 < 0$, $u < 0$. Then all coefficients are positive. Since a_2 is equal to the negative of the sum of the three roots, the magnitude of the real root is greater than one third of a_2 whenever the real root lies to the left of the real part of the complex roots. That is, $s_1 < -\frac{a_2}{3}$ if and only if $s_1 < u$. Note that the real part of the critical points given in Equation (3.10) is $-\frac{a_2}{3}$. Hence, if the coefficients of the characteristic polynomial f(s) satisfy Inequality (3.11) and if $s_1 < u$, then we must have $f(-\frac{a_2}{3}) > 0$. (See Figure 3.7 (a).) This inequality can be simplified to yield the relation

$$a_1 < 3\frac{a_0}{a_2} + \frac{2}{9}a_2^2.$$

Combining the above inequality with inequality (3.12), we obtain a sufficient condition for the system to be stable, oscillatory and underdamped. This condition is given by

$$\max\left\{\frac{a_0}{a_2}, \frac{a_2^2}{3}\right\} < a_1 < 3\frac{a_0}{a_2} + \frac{2}{9}a_2^2. \qquad (3.13)$$

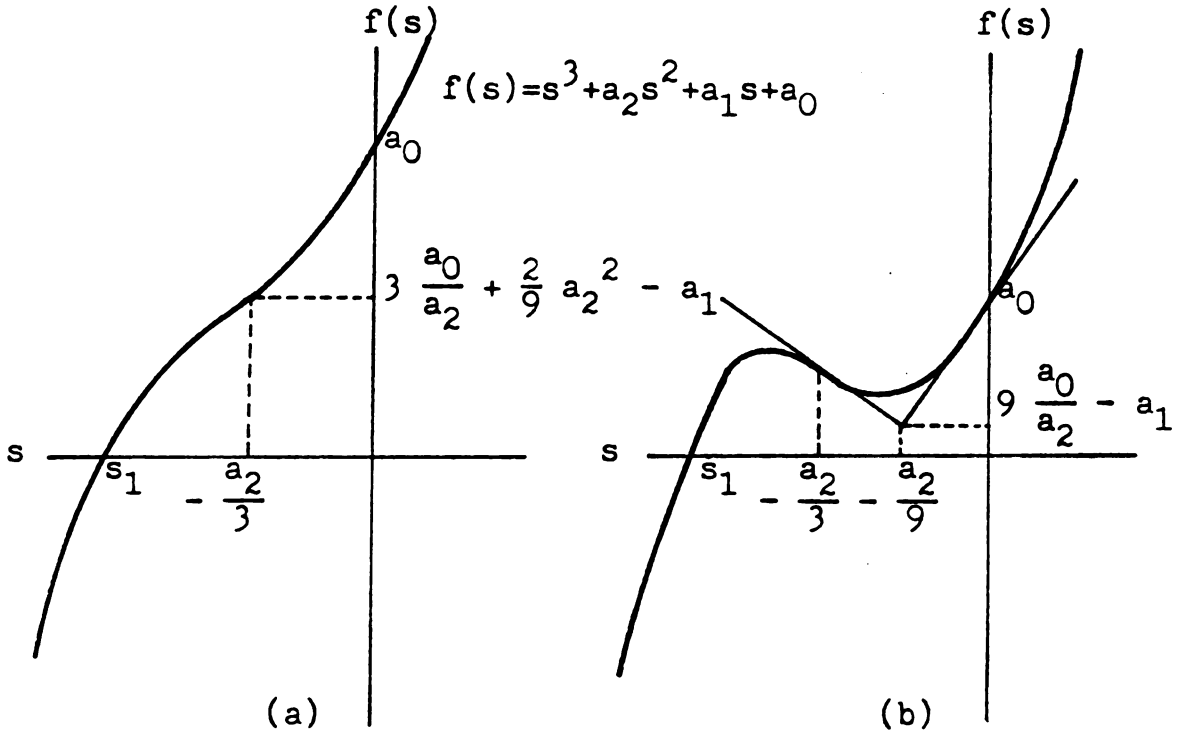


Figure 3.7. Curves of cubic polynomials having one real root and two complex roots, (a) with no relative maximum or relative minimum, (b) with a relative maximum and a relative minimum.

So far we have dealt only with the case where the characteristic polynomial has no relative maximum or relative minimum. We now relax this condition and allow it to have a relative maximum and a relative minimum (Figure 3.7 (b)). We note from Equation (3.10) that the point of inflection s_p is equal to $-\frac{a_2}{3}$. Hence, if $s_1 < u$, then the relative minimum must be positive.

To obtain a simple relationship among the coefficients of the characteristic polynomial which satisfy the above condition, we draw two lines, one tangent at the point

$(-\frac{a_2}{3}, f(-\frac{a_2}{3}))$ and the other tangent at the point $(0, a_0)$. The point of intersection of the two tangent lines is given by $(-\frac{a_2}{9}, 9\frac{a_0}{a_2} - a_1)$. Thus, a sufficient condition for the relative minimum to be positive is given by

$$9\frac{a_0}{a_2} - a_1 > 0$$

or equivalently,

$$a_1 < 9\frac{a_0}{a_2} .$$

Since the existence of the relative maximum and the relative minimum implies that $a_1 < \frac{a_2^2}{3}$, the sufficient condition for the system to be stable, oscillatory and underdamped is given by

$$\frac{a_0}{a_2} < a_1 < \min\left\{\frac{a_2^2}{3}, 9\frac{a_0}{a_2}\right\} .$$

The sufficient condition which satisfies both cases is obtained by combining inequality (3.13) and inequality (3.14) and is given by

$$\frac{a_0}{a_2} < a_1 < \max\left\{3\frac{a_0}{a_2} + \frac{2}{9}a_2^2, 9\frac{a_0}{a_2}\right\} . \qquad (3.15)$$

3.3.3 Computation for Range of Drift Rate

The following example shows the computational procedure for obtaining the range of d.

Consider the test case in which the following parameters are given:

$b = .002$ (infective rate)

$r = .8$ (removal rate)

$e = .5$ (susceptible rate)

$N = 1000$ (total population)

Then $p_1 - \frac{r}{b} = 400$ and $p_2 = \frac{e}{r} = .625$. From Equation (3.4), we can compute the steady state of the virus strain c which is the root of

$$c^3 + .6c^2 - 3.2c + .96 = 0$$

satisfying the boundary condition $0 < c < 1$. The root is $c = .3321$. Then the equilibrium point X_e given by Equation (3.3) is

$$X_e = \begin{bmatrix} 599 \\ 69 \\ 332 \\ .3321 \end{bmatrix} .$$

The coefficients of the characteristic equation of the linearized system are computed using Equations (3.7) and (3.9) and are as follows:

$a_2 = .6642\ d + .2581$

$a_1 = .2266\ d + .1550$

$a_0 = .1080\ d.$

We solve the Inequality (3.15) to obtain the range of d which gives a stable underdamped oscillation: $\frac{a_0}{a_2} < a_1$ yields

$$.1505\ d^2 + .0534\ d + .04 > 0.$$

The graph of the above parabola does not cross the real axis; i.e., the roots of the quadratic equation are complex

($d_{1,2} = -.1775 \pm j\ .484$). Hence, the solution is

$$d > 0. \tag{3.16}$$

$a_1 < 3\ \frac{a_0}{a_2} + \frac{2}{9}\ a_2^2$ yields

$$.0525\ d^2 - .2388\ d + .0252 < 0.$$

The parabola crosses at $d_1 = .1080$ and $d_2 = 4.4420$. Hence, the solution is

$$.1081 < d < 4.4420. \tag{3.17}$$

$a_1 < 9\ \frac{a_0}{a_2}$ yields

$$.1505\ d^2 - .8106\ d + .04 < 0.$$

The parabola crosses at $d_1 = .0498$ and $d_2 = 5.3357$. Hence, the solution is

$$.0498 < d < 5.3357. \tag{3.18}$$

Taking the union of the solutions (3.17) and (3.18) and then taking the intersection of the union and the solution (3.16) we obtain the range of d:

$$1.081 < d < 5.3357.$$

CHAPTER 4

SYSTEM SIMULATION AND MODEL VALIDATION

A number of simulation outputs for the influenza epidemic model developed in Chapter 3 will be presented here, and the relationship between each parameter and its corresponding system behavior will be analyzed. In particular, the peaks and the thresholds of the epidemics, the intervals between epidemics, and the drift of the virus will be discussed. Then the system output will be compared with historical data on influenza epidemics.

We have computed the equilibrium point and the range of drift rate d for underdamped oscillation for the test case in Chapter 3. The range of d is between .1080 and 5.3357. Figures 4.1, 4.2, 4.3, and 4.4 show the DYNAMO outputs for d = 1, d = .5, d = .3, d = . 1 respectively, with the initial conditions:

c_1 = 900 (susceptible population)

c_2 = 50 (infective population)

c_3 = 50 (immune population)

c_4 = .001 (virus strain)

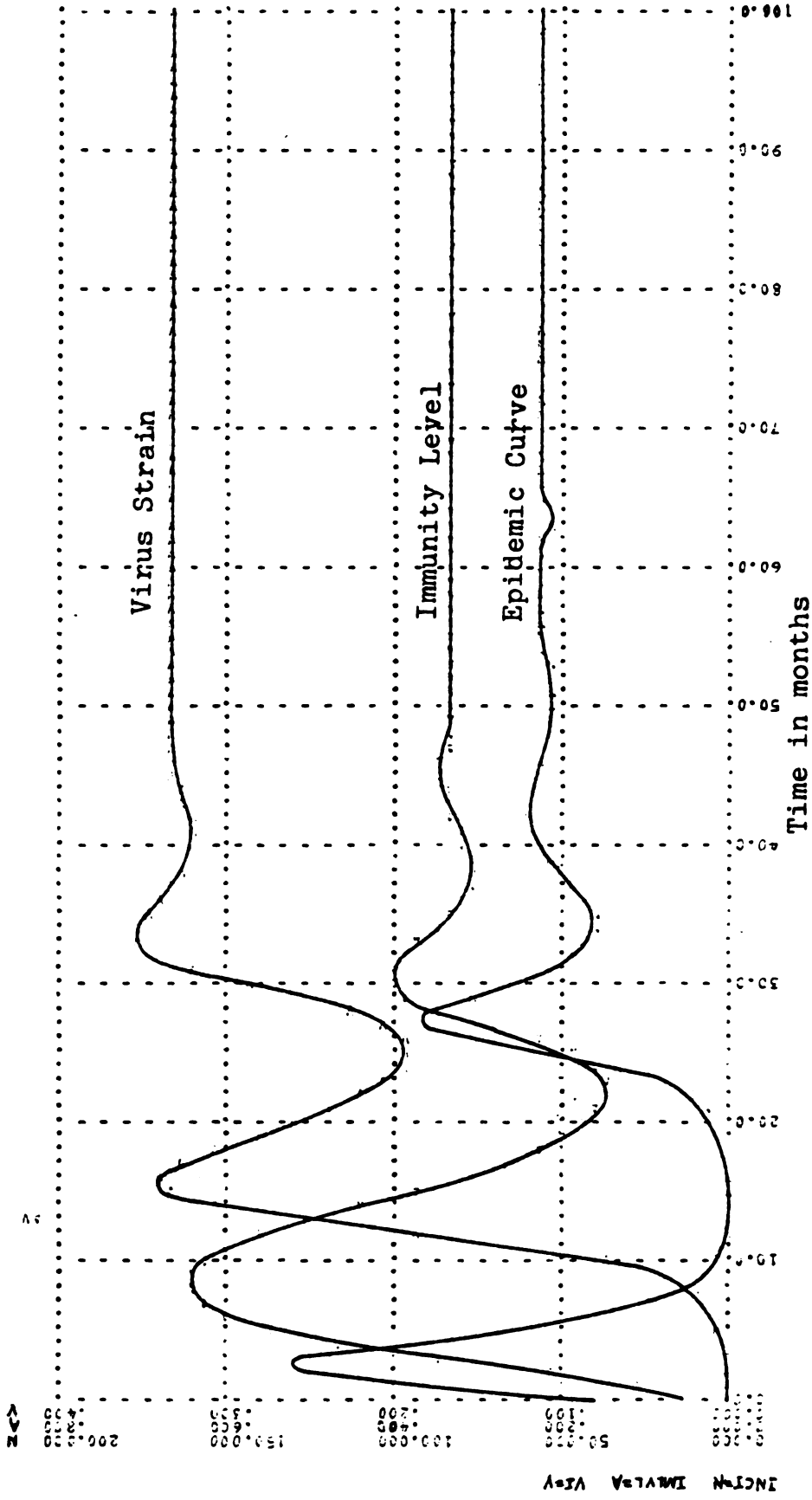


Figure 4.1. Influenza epidemic model with the drift rate d = 1.

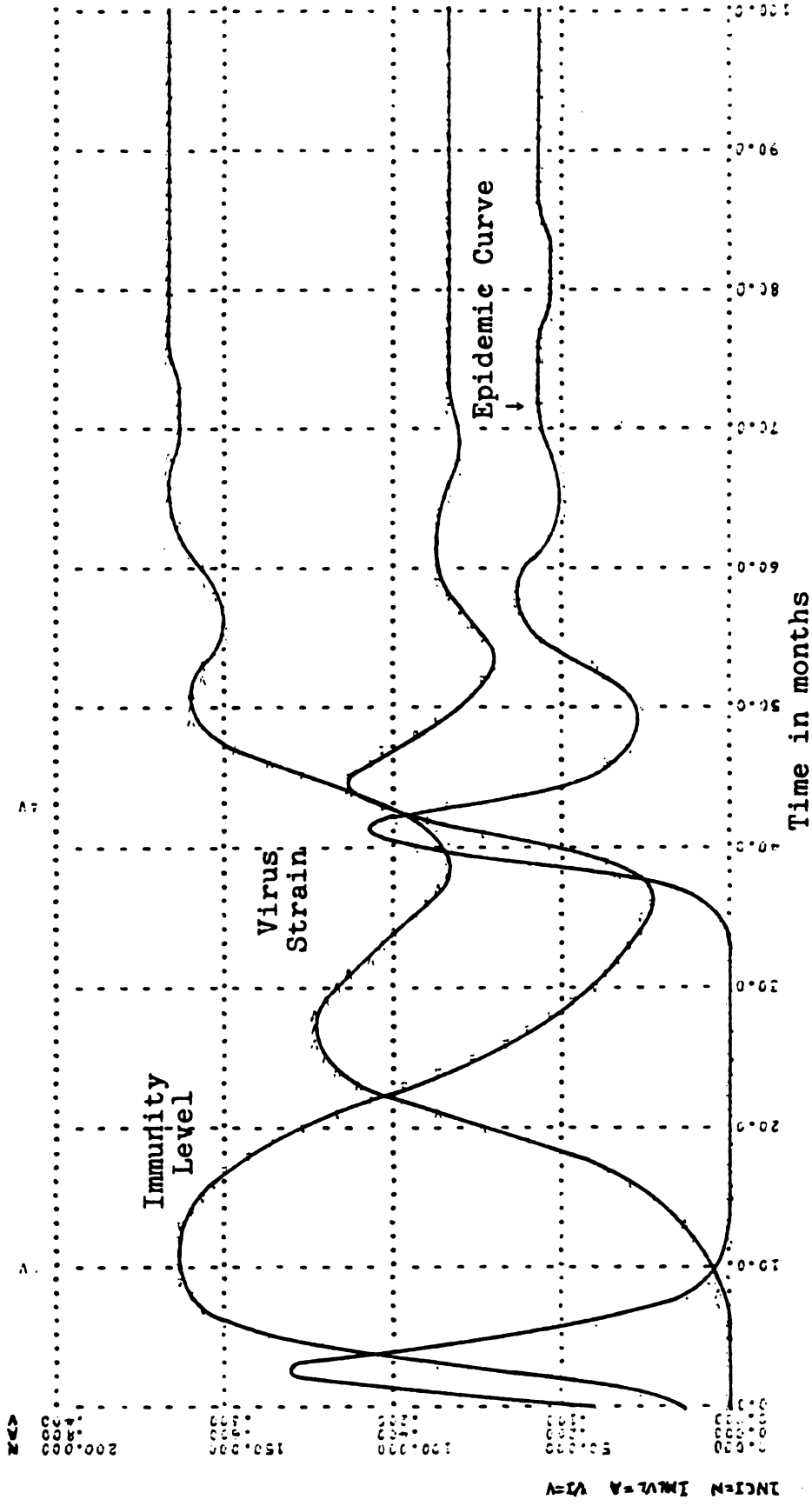


Figure 4.2. Influenza epidemic model with d = .5.

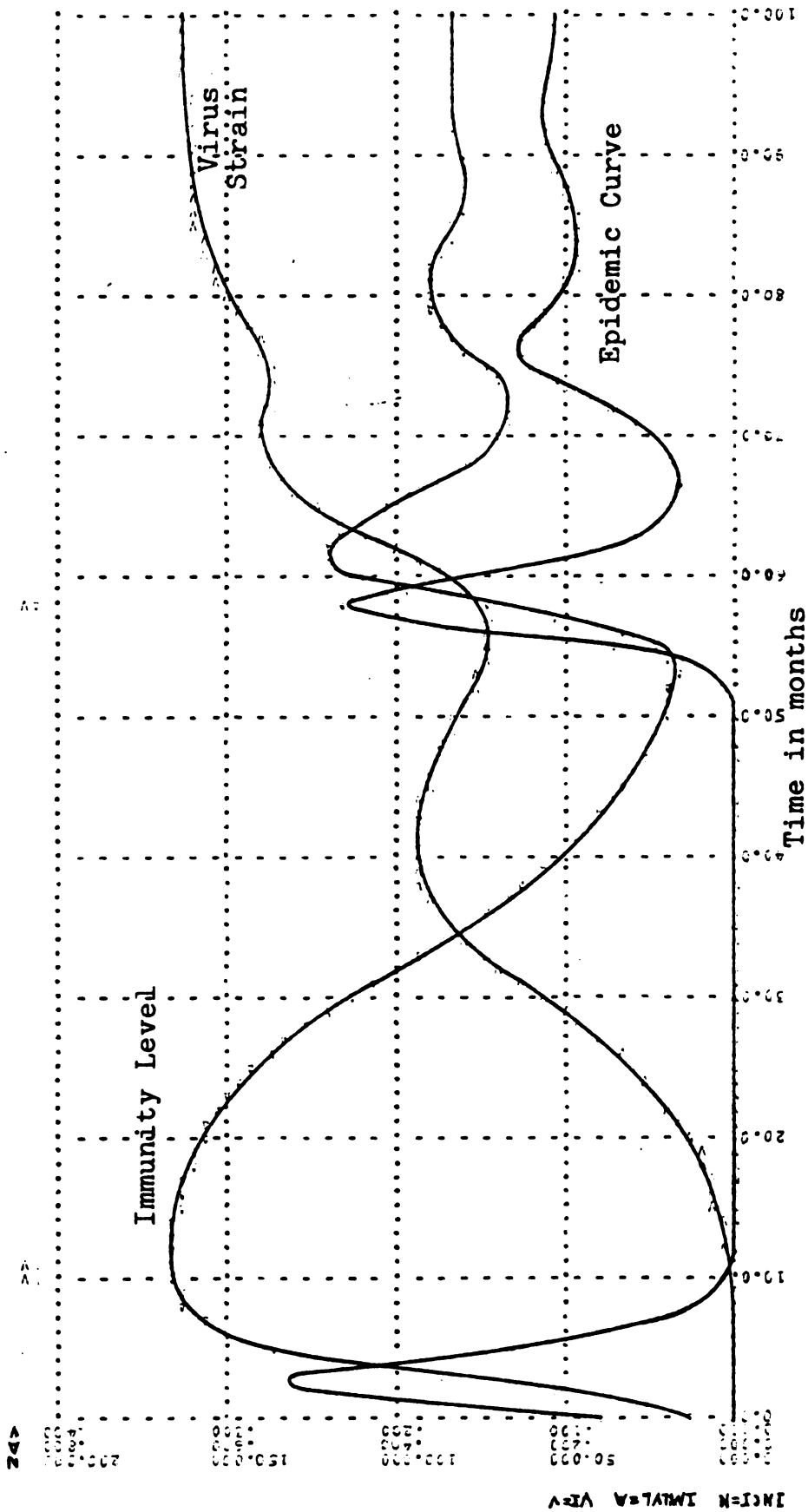


Figure 4.3. Influenza epidemic model with d = .3.

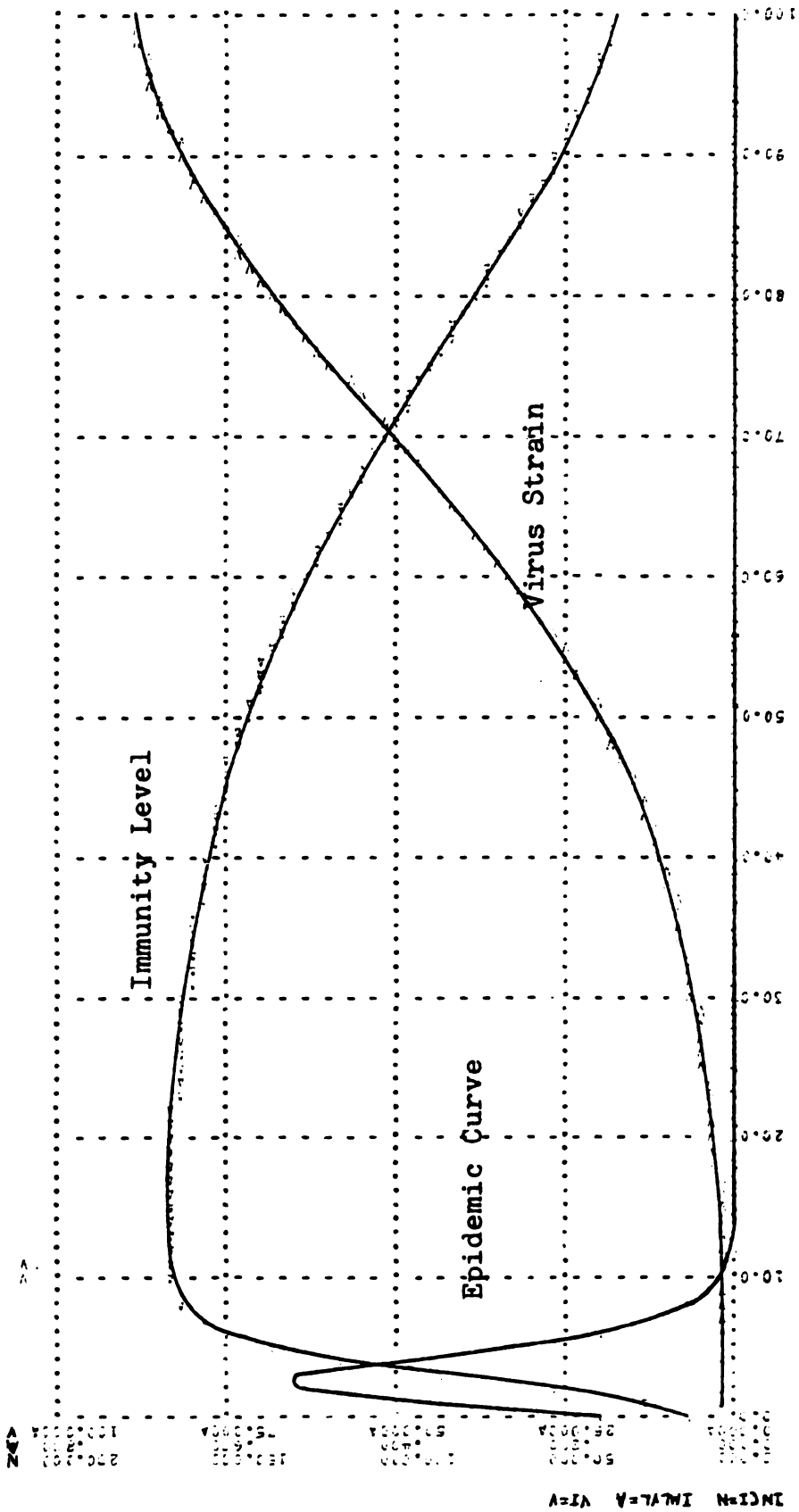


Figure 4.4. Influenza epidemic model with d = .1.

4.1 Analysis of Drift

In the case of oscillation (Figures 4.1, 4.2, and 4.3) there are three distinct epidemics before the system reaches its steady state. Also, the virus strain peaks twice, each peak occuring between the epidemics. We note that the time intervals between epidemics (measured from one peak time to the next peak time) is longer as the reciprocal of d is larger. Hence, we can consider $T = \frac{1}{d}$ as a delay constant similar to the time constant of the exponential growth as mentioned in the discussion of the equilibrium point analysis in Chapter 3. Using the basic unit of time as one month, we find that the time intervals between the epidemics for T = 1 month are 24 and 16 months; and for T = 2 months, 38 and 17 months; and for T = 3 1/3 months, 56 and 19 months.

Likewise, the virus strain reaches its peak in longer time when T is larger. In this model, drift is not only the measurement of the difference in the virus strain, but also a function of the time interval between the two virus strains. As the virus strain grows, a continuous transfer of individuals from the immune population to the susceptible population takes place. Hence, even though the difference of the virus strain from time t_1 to time t_2 may be small, if the interval $t_2 - t_1$ is large, the total transfer of individuals from the immune to the susceptible population is large, thus causing a severe epidemic. As the size of the immune population becomes smaller through this transfer, the immunity level of the population decreases which causes the growth of

the virus strain to slow down or even decrease. The occurrence of another epidemic builds up the immune population which in turn causes the virus strain to grow again.

From this causal description of the virus and the epidemics, we define the drift D to be

$$D = \frac{1}{d} (V_{max} - V_{min}), \qquad (4.1)$$

where V_{max} is a peak of the virus strain and V_{min} is the minimum value of the virus strain preceding V_{max}. (I.e., the difference of the virus strain is measured from one valley to the next peak. See Figure 4.5.) The time of the occurrence of drift T_D is defined to be the time at which the virus strain attains its peak.

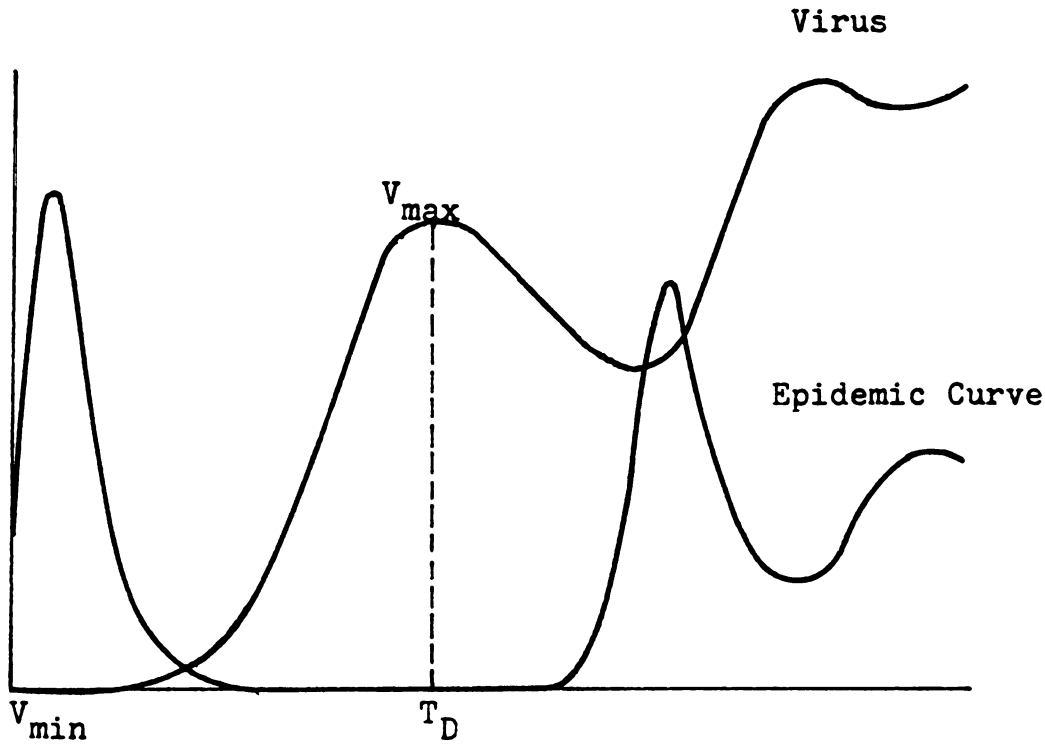


Figure 4.5. Drift and epidemic curve.

Table 4.1. Relationship between virus drifts and epidemic peaks.

d = 1				d = .5				d = .3			
t	E	V	D	t	E	V	D	t	E	V	D
0	40	•.001		0	40	•.001		0	40	•.001	
3	*130	.130		3	*129	.001		2	*158	.001	
16	1	*.339	.338	27	0	*.249	.496	40	0	*.197	.65
25	54	•.191		39	61	•.165		56	71	•.143	
27	*89	.204		41	*107	.172		58	*118	.149	
34	41	*.353	.162	50	28	*.320	.31	70	30	*.277	.447
42	*60	.320		58	*64	.306		77	*64	.282	

t = time (month)

E = epidemic curve

V = virus strain

D = drift

* peak of epidemic/virus

• minimum value of virus strain

Table 4.1 shows the numerical values of the epidemic peaks and the drifts for the oscillatory cases (Figures 4.1, 4.2, and 4.3). The relationship between the drift calculated using the above definition and the following peak of the epidemic curve confirms the reasonableness of the definition; that is, the higher the drift, the more severe the subsequent epidemic.

4.2 Threshold of Epidemics

In the general epidemics model the threshold level of the epidemic is equal to the relative removal rate p. Whenever the size of the susceptible population exceeds that level, the size of the infective population increases, thus causing the epidemic. The difference between the initial susceptible population and the threshold is the measurement for the severity of the epidemic. If the initial susceptible population is very large compared to the threshold, the peak of the epidemic is high. On the other hand, if the initial susceptible population is smaller than the threshold, the infective population decreases asymptotically to zero as shown in Figure 2.8 (b).

In the case of the influenza epidemic model, the threshold is a time varying one. Setting $\dot{x}_2 = 0$ in the state model (3.2) we obtain the threshold H(t) as

$$H(t) = \frac{p_1}{S(t)}$$

$$= \frac{Np_1}{N - x_3} \cdot \qquad (4.2)$$

The threshold is inversely proportional to the susceptible level. Even if the composition of the initial population is such that the susceptible population is below the threshold, it will not necessarily prevent epidemics because the susceptible population may cross the threshold and stay above it. If we consider the infective population negligible, the size of the susceptible population required to be equal to the threshold level can be calculated from Equation (4.2) and is given by

$$x_1 = \sqrt{Np_1} \cdot$$

Figure 4.6 shows the simulation output for the test case with the initial conditions:

$c_1 = 600$ (susceptible population)

$c_2 = 50$ (infective population)

$c_3 = 350$ (immune population)

$c_4 = .001$ (virus strain).

The initial threshold is

$$H(0) = 615.$$

An optimal immunization strategy to minimize the peak of the epidemic will be treated in the next chapter.

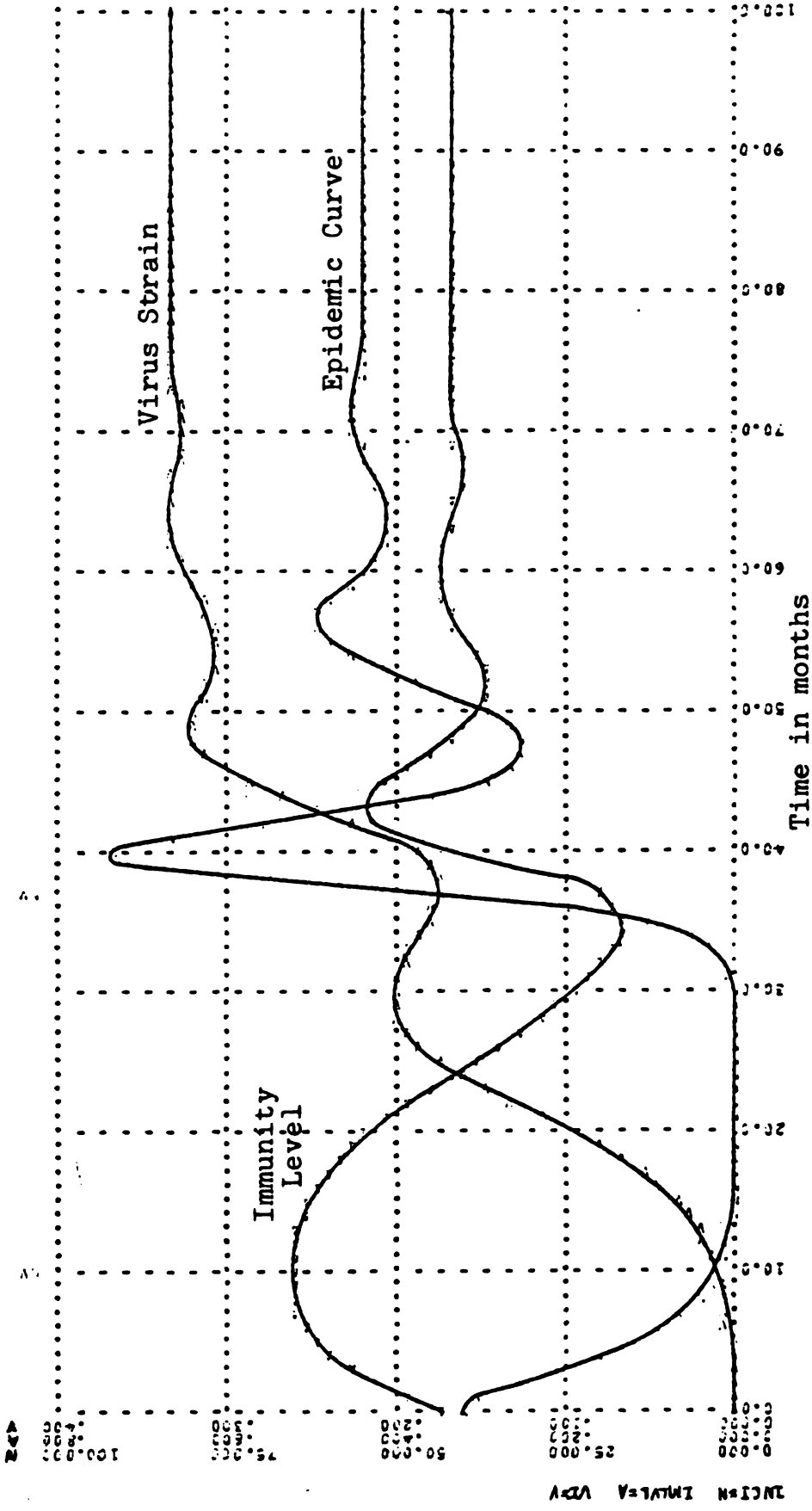


Figure 4.6. Non occurrence of initial epidemic.

4.3 Causal Loop Diagram of Parameters

Simulations are performed more efficiently in terms of the number of runs if the causal effects of the parameters on the system outputs are known. A desired response may be obtained fairly quickly by adjusting one appropriate parameter rather than making adjustments on all of them. Such effects are observed from the results of the simulation of a test case obtained by varying one parameter and fixing all others. The causal effects on the peaks and the intervals of epidemics by each parameter is demonstrated in the causal loop diagram Figure 4.6. This causal relationship was used to generate the system outputs for the model validation.

4.4 Model Validation

The Center for Disease Control (CDC) in Atlanta, Georgia maintains the weekly statistics on the number of deaths resulting from influenza pneumonia. These data are collected from 121 cities with a population in excess of 100,000. This mortality chart is also broken down into nine geographical regions. Figure 4.7 shows the mortality data from September 1968 to September 1977. The expected curve is taken from the least square method of fitting the curve to the data for the previous five years excluding epidemic periods (periods in which the number of deaths exceed the threshold).

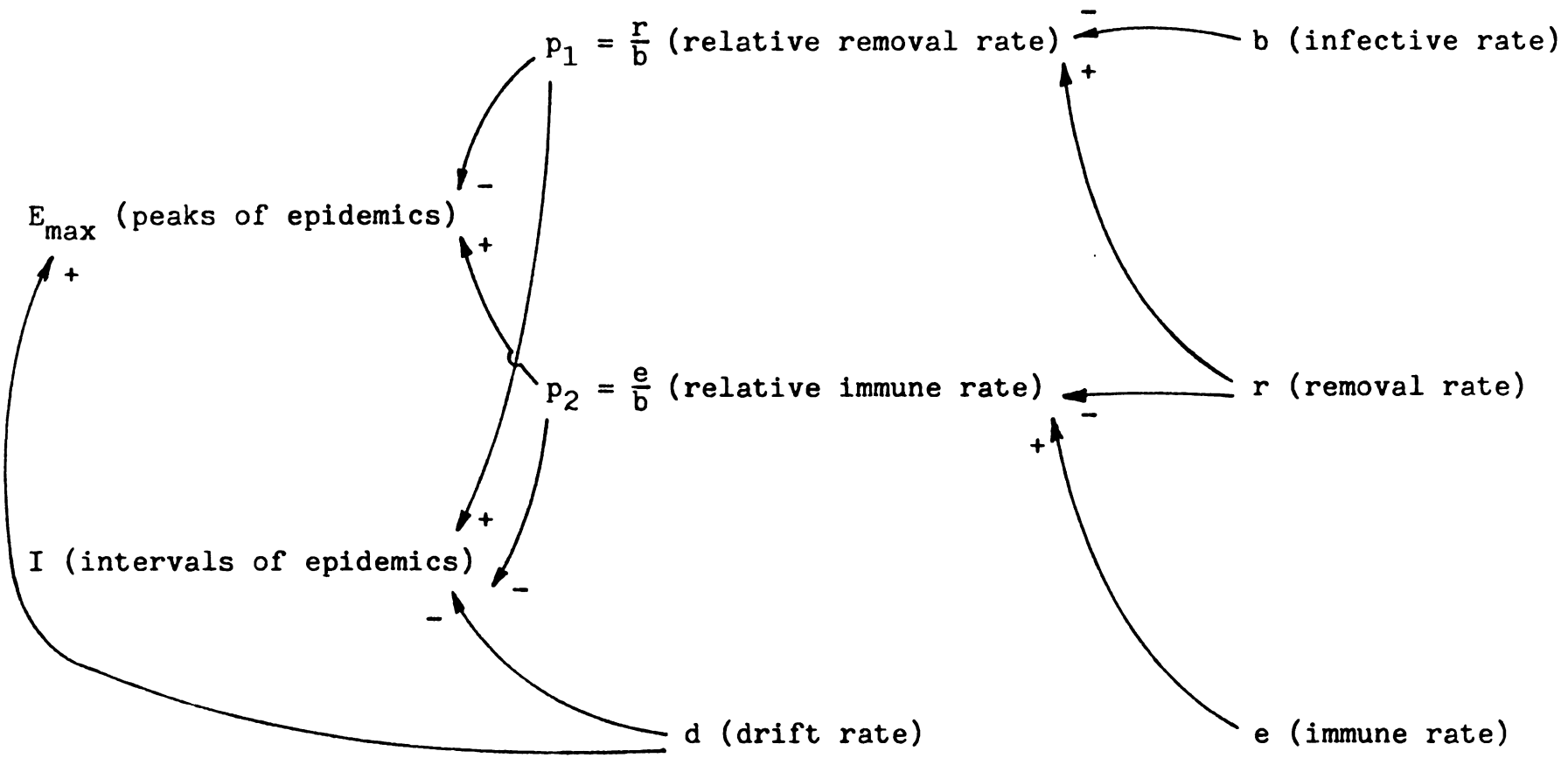


Figure 4.6. Causal loop diagram of parameters.

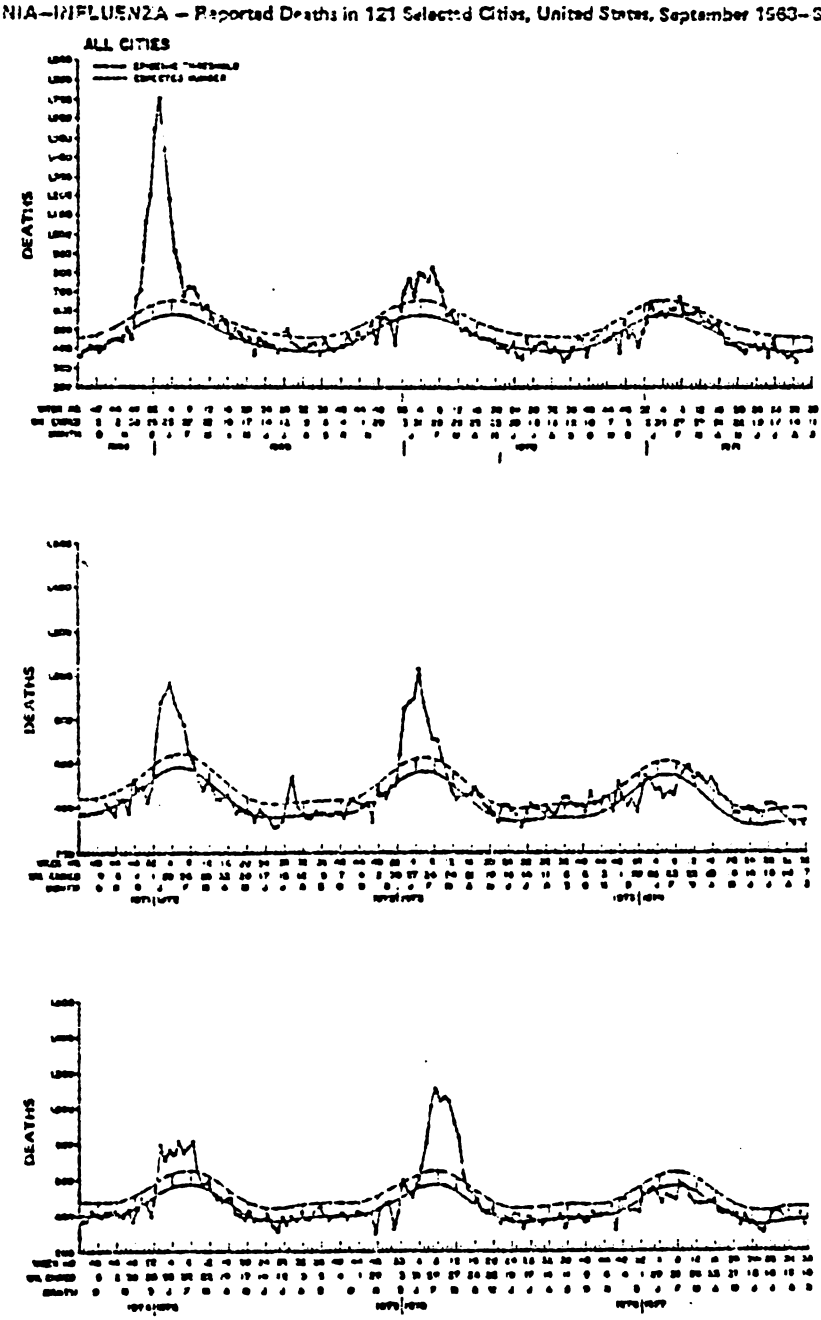


Figure 4.7. Weekly mortality rate of influenza-pneumonia.[1]

---

[1] From the Annual Summary 1977 of Morbidity and Mortality Weekly Report.

From numerous simulation results of the model, it became apparent that the oscillation dies down quickly after the third epidemic. Hence, with this model we can generate three distinct epidemics and two drifts. There were six epidemics from the onset of the 1968 Hong Kong influenza (an occurrence of the virus shift) up to 1977 excluding the small epidemic in July 1972. Of these six epidemics, we will attempt to produce the system outputs of the model to fit the data for three epidemics and compare the results with the actual figures. The three epidemics we will consider are: the outbreak of November 1968 - March 1969, that of January 1972 - March 1973, and that of January - March 1975. The difficulty in validating the model by fitting the historical curve is that data for the initial values and the parameters are not available. Nevertheless, we will estimate these values in order to generate the historical curve.

The model will be modified to accomodate the population growth and the seasonal variation of influenza. We let

POP = total population

SPOP = susceptible population

IPOP = infective population

BRTH = birth rate (people/month)

DTH = death rate (people/month).

Assuming the exponential growth of the population, we have

$$\frac{d}{dt}\ \mathrm{POP} = (\mathrm{BRTH} - \mathrm{DTH}) * \mathrm{POP}$$

and

$$\mathrm{POP} = \mathrm{SPOP} + \mathrm{IPOP} + \mathrm{RPOP}.$$

The newborns are put into the susceptible population, and the death rate is equally applied to the three groups of population. Table 4.2 gives the annual birth and death rates of the United States from 1968 to 1976. The birth rate BRTH and death rate DTH for the simulation is calculated to be the average of the actual death and birth rates of the eight year period, and this figure is converted into the monthly rate. These rates are

$$\text{BRTH} = 1.36 \times 10^{-3}$$

$$\text{DTH} = .775 \times 10^{-3}.$$

The seasonal variation of influenza is considered by making the infective rate sinosoidal, a sine curve which starts at the initial time equal to September. The sine curve represents the fact that influenza occurs most frequently during the fall and the winter and least frequently during the summer. We let

INF = infective rate (fraction/people month)

CR = contact rate (fraction/people month)

PRD = period = 12 months

H = height of the sine curve (dimensionless).

Then we can form the infective rate as

$$\text{INF} = \text{CR} * (1+\text{H} + \text{SIN}((6.25/\text{PRD}) * \text{TIME})).$$

Integrating the above changes to the influenza epidemic model and simulating by varying parameters, we obtain a reasonable fit with the historical data.

The comparison of simulation output and the actual figures for the three epidemics are given in Table 4.3 and

Table 4.2. Annual birth and death rates in the United States (per 1,000)[1].

	1968	1969	1970	1971	1972	1973	1974	1975	1976
Birth Rate	17.5	17.7	18.4	17.2	15.6	14.9	14.9	14.8	14.7
Death Rate	7.8	8.2	8.9	7.9	6.2	5.5	5.7	5.9	5.8

[1] From Monthly Vital Statistics Report.

Table 4.3. Monthly mortality rates in the three epidemics used in model validation.

Epidemic 1	Actual[1]	Simulation
NOV 68	459	919
DEC	1068	1184
JAN 69	1359	1304
FEB	677	1236
MAR	673	1037
APR	695	759
MAY	545	574

Epidemic 2	Actual[1]	Simulation
DEC 72	508	966
JAN 73	830	1029
FEB	904	1006
MAR	701	917
APR	398	796

Epidemic 3	Actual[1]	Simulation
DEC 75	479	691
JAN 76	819	710
FEB	824	714
MAR	606	702
APR	467	678

[1] From Monthly Vital Statistics Report.

plotted in Figure 4.8. The values of the parameters and initial conditions used to obtain these results are as follows:

Parameters

$b = .07 \times 10^{-6}(1 + .03 \sin .52t)$ (infective rate)

$r = .8$ (removal rate)

$e = .5$ (susceptible rate)

$d = .6$ (drift rate)

Initial conditions

$c_1 = 19.19 \times 10^6$ (susceptible population)

$c_2 = .5 \times 10^6$ (infective population)

$c_3 = .5 \times 10^6$ (immune population)

$c_4 = .001$ (virus strain).

The composition of the initial populations is 80 percent susceptible, 10 percent infective, and 10 percent immune. Since the monthly mortality data is from the 10 percent sample of the total U.S. population, the simulations were performed using that figure as the initial total population.

Figure 4.8 shows that the simulation results in terms of the epidemic peaks and the peak times are reasonably close to the actual data. This demonstrates a possible use of the model for prediction provided that the initial conditions and the values of the parameters can be measured.

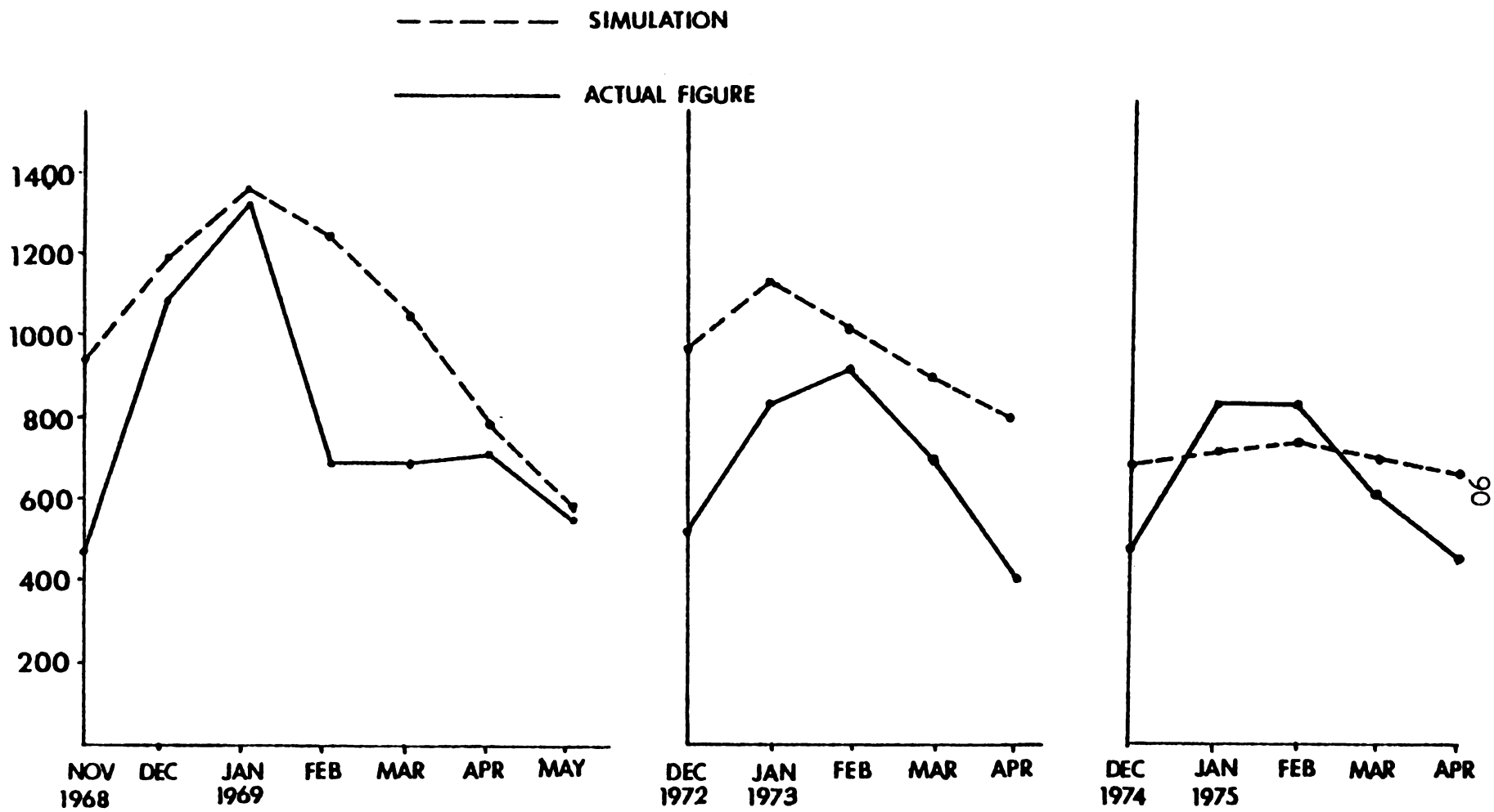


Figure 4.8. Model validation: graphical comparison of mortality rates

CHAPTER 5

IMMUNIZATION MODEL AND CONTROL SYSTEM

In the influenza epidemic model developed in Chapter 3, the cycle of epidemics begins as a result of a virus shift. The size of the susceptible population in relation to the threshold determines the severity of the initial epidemic; that is, if the difference between the initial susceptible population and the threshold is large, the peak of the epidemic curve is high. Subsequent epidemics are caused by drifts. The peaks of these epidemics are also determined by the difference between the susceptible population and the threshold. We now construct an immunization system to provide the control input to the influenza epidemic system. Figure 5.1 shows the block diagram of this control system.

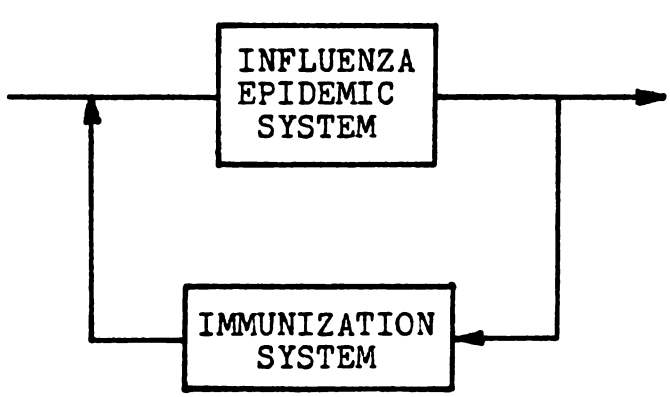


Figure 5.1. Block diagram of the control system.

The goal of the control system is to minimize the severity of the second epidemic caused by drift. One method of preventing the occurrence of the second epidemic is to remove a sufficient number of individuals from the susceptible population so that the size of the susceptible population is always below the threshold level. This method could be costly in terms of a percentage of the total population required to be immunized. We, therefore, developed an immunization system which accomplishes the goal of the control system by immunizing as few individuals as possible.

First we will examine the relationships among the variables which determine the size of the epidemic peak; then construct the state model for the immunization system; and finally, present the results of simulation.

5.1 Causal Analysis

After the initial epidemic, the susceptible population starts building up through the transfer of individuals from the immune population due to the structural change of the virus. The decrease of the immune population causes the immunity level to fall, thus increasing the susceptible level. As the susceptible level increases the threshold decreases and the difference between the susceptible population and the threshold becomes larger causing the higher peak of the next epidemic. To remedy this situation, we add the vaccinated population in the causal loop diagram (Figure 5.2). We now decrease the susceptible population and follow through the

dotted lines. The causality indicates that the difference between the susceptible population and the threshold becomes smaller, causing a smaller epidemic peak.

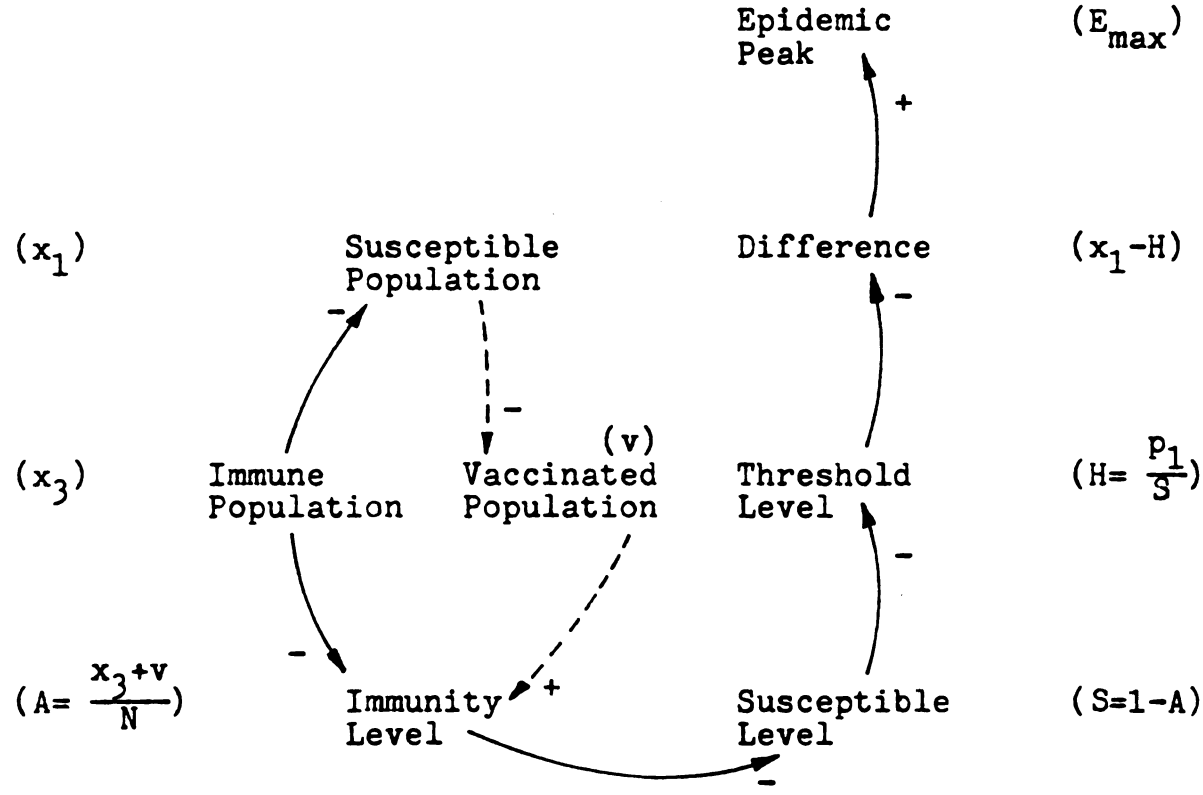


Figure 5.2. Causal loop diagram of the control system.

5.2 State Model of the Immunization System

We construct the state model in such a way that the vaccinated population behaves like a goal seeking curve. This goal is the number equal to the difference between the susceptible population and the threshold level. We let

v = vaccinated population

G = goal.

Then

$$G(t) = x_1(t) - H(t)$$

where

$x_1(t)$ = susceptible population

$H(t)$ = threshold level.

If the goal is constant; i.e. $G(t) = G$, then the state equation for the goal seeking curve is given by

$$\dot{v} = k\,(G - v) \qquad (5.1)$$

with the initial condition $v(0) = 0$. The constant k is the vaccination rate. The solution for the state equation (5.1) is

$$v = G\,(1 - e^{-kt}).$$

The graph of the vaccinated population is shown in Figure 5.3.

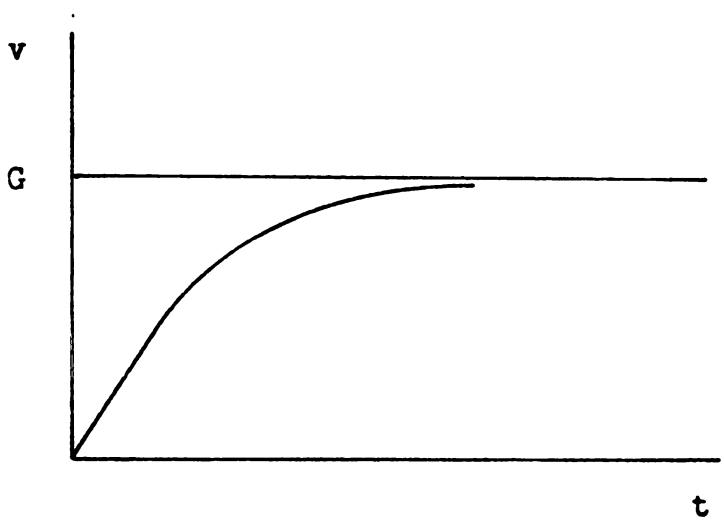


Figure 5.3. The goal seeking curve of the vaccinated population.

Using the time varying goal G(t), the state model for the immunization system is then obtained as

$$\dot{v} = k\,(G(t) - v) \qquad (5.2)$$

with the initial condition $v(0) = 0$.

The rate of immunization must be positive; hence, we consider applying the model only when the susceptible population exceeds the threshold. After the initial epidemic the susceptible population crosses over the threshold just before the drift time T_D and the next epidemic begins just after the virus strain reaches the relative minimum. Therefore, the immunization system will be initiated at the drift time T_D and continue up to the time the virus strain attains relative minimum T_{min} (see Figure 5.4). This procedure can be accomplished by using a rectangular function (the difference of two step functions) to simulate the model. The state model (5.2) becomes

$$\dot{v} = k\,(G(t) - v)\,\pi$$

where π is the rectangular function with the height equal to 1 and the length equal to the period of the immunization.

The immunity level $A(t)$ is now the sum of the immune population and the vaccinated population divided by the total population:

$$A(t) = \frac{x_3 + v}{N}.$$

As before, the susceptible level $S(t)$ is defined to be

$$S(t) = 1 - A(t).$$

Since the susceptible population decreases at the rate of immunization, the state equation for the susceptible population in the state model (3.2) is changed to

$$\dot{x}_1 = -b\,S(t)\,x_1\,x_2 + ex_3\,x_4 - \dot{v}.$$

S = Susceptible Population

H = Threshold

V = Virus

E = Epidemic Curve

I = Immunization Period

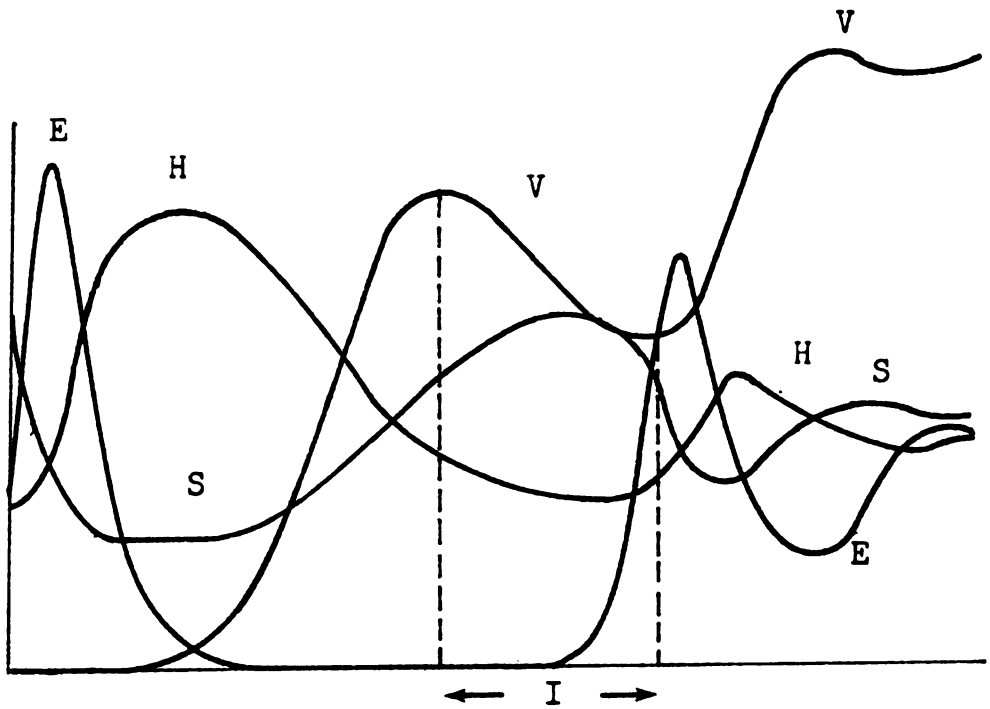


Figure 5.4. Immunization period.

5.3 Simulation Results

The control system is simulated using the three test cases given in Chapter 4, Figures 4.1, 4.2, and 4.3. In all cases, the total vaccinated population becomes larger as the vaccination rate k is set larger. However, the vaccinated population stabilized at k = 1; that is, there is very little difference in the number of the vaccinated population beyond that range of k. The simulation outputs for unvaccinated cases with the drift rate d = .5 are shown in Figure 5.5. (The epidemic curve is identical to that in Figure 4.2.) The rate of immunization $\dot{v}$ and the vaccinated population v with the vaccination rate k = 1 and the period of immunization from T_D = 27 to T_{min} = 39 are given in Figure 5.6. The epidemic curve produced after immunization is shown in Figure 5.7.

The total vaccinated population for each case and the drift calculated from Equation (4.1) are compared in Table 5.1. Note that the higher the drift, the larger the number of individuals in the susceptible population must be vaccinated to reduce the next epidemic peak to an endemic level. This observation agrees with reality.

The control system takes no consideration of the efficacy of the vaccine. According to Pereira (1979), the efficacy of vaccine ranges from 40 to 80 percent. Also, only individuals in the susceptible population are immunized in this model. In reality, individuals in the immune population are immunized as well as those in the susceptible population.

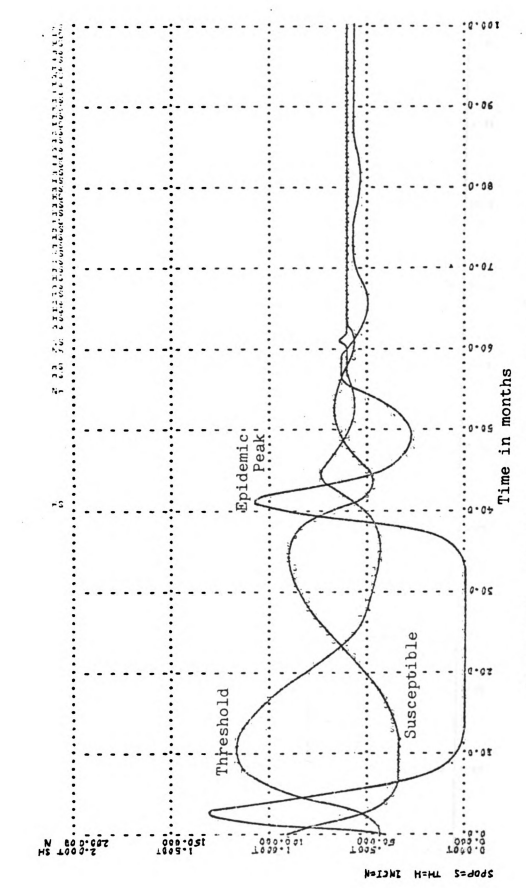


Figure 5.5. Simulation outputs before immunization.

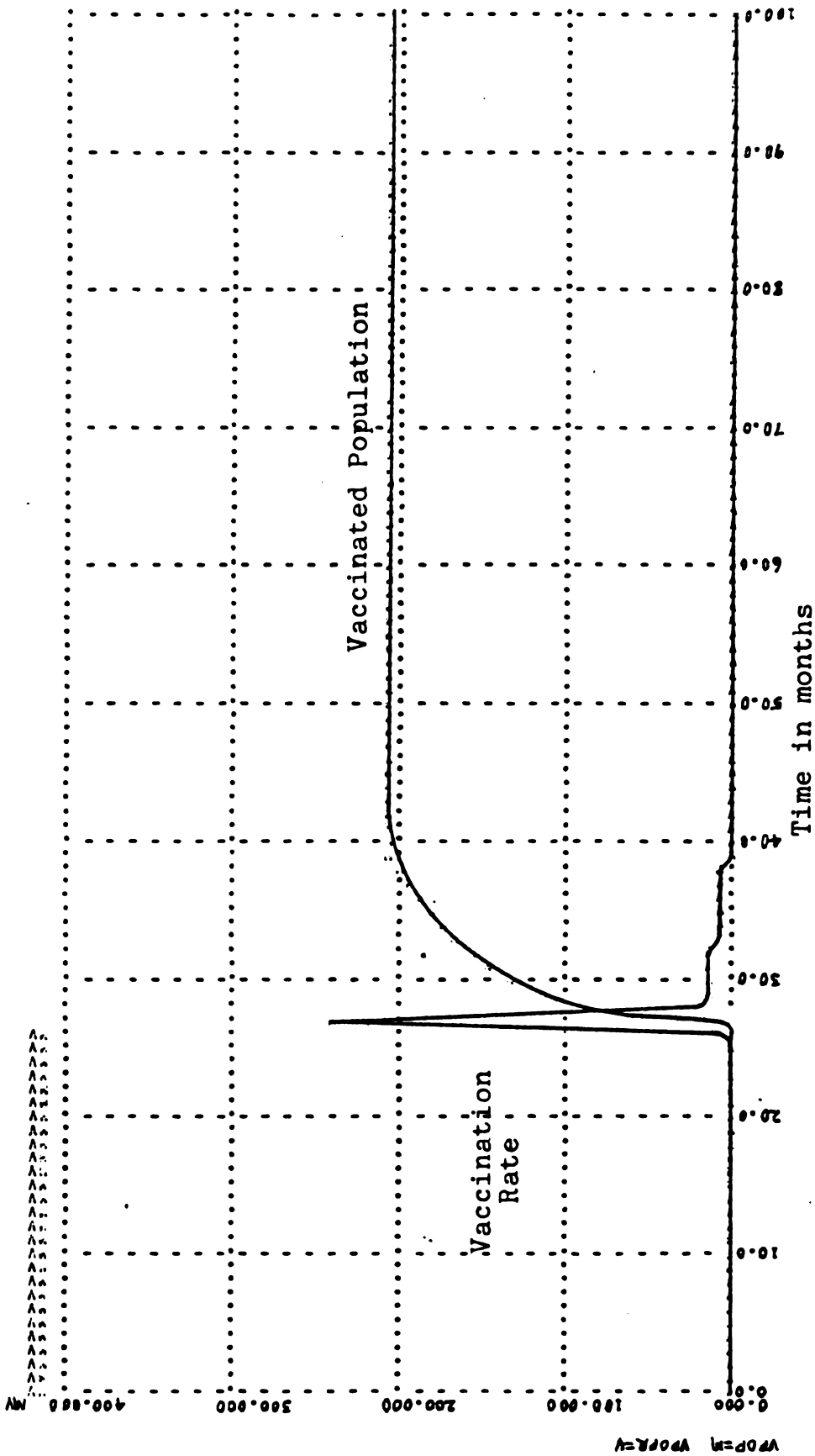


Figure 5.6. Vaccination rate and total vaccinated population.

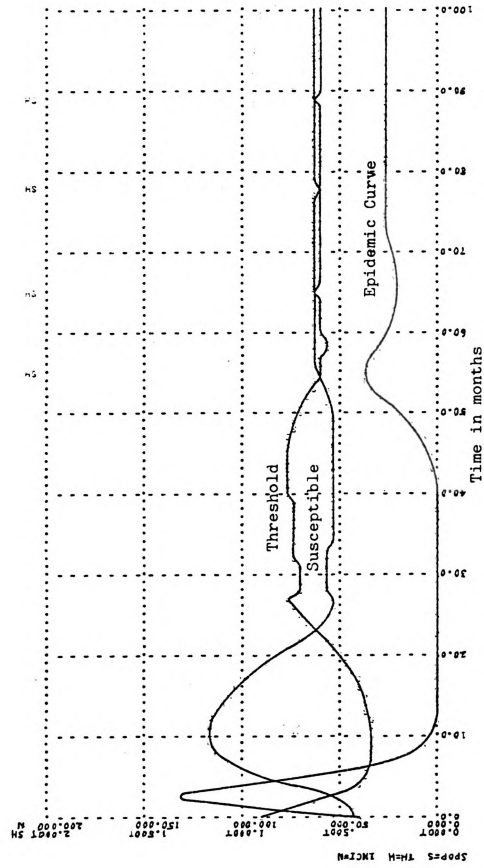


Figure 5.7. Simulation outputs after immunization.

Therefore, to compute the percentage of the total population required to be immunized, taking into consideration the efficacy of the vaccine and assuming that the immune population and the susceptible population are vaccinated proportionally, we use the formula:

$$\% \text{ POP} = \frac{1}{\text{EFF}} \times \frac{\text{VPOP}}{\text{SPOP}} \times 100$$

where

% POP = percentage of total population required to be immunized

EFF = efficacy of the vaccine (expressed in decimal)

VPOP = vaccinated population from the simulation

SPOP = the size of the susceptible population at the beginning of the immunization period.

The percentage of the total population required to be immunized are calculated for each test case using the efficacy of the vaccine to be 40 and 80 percent. The results are given in Table 5.1.

Table 5.1. Percentage of total population required to be immunized.

d	D	VPOP	SPOP	EFF	% POP	EFF	% POP
1.0	.338	178	682	.4	65	.8	33
.5	.496	205	763	.4	67	.8	34
.3	.650	215	795	.4	68	.8	34

d = drift rate
D = drift

CHAPTER 6

SUMMARY AND CONCLUSIONS

The influenza epidemic model was systematically built from the basic three epidemic models described by Bailey (1975). In the basic epidemic models, the variables which are of particular interest to epidemiologists, such as the peaks and durations of epidemics, were defined and analyzed. The numerical values of these variables computed from analysis were compared with those obtained from simulation. The results show that the Euler integration method used in DYNAMO was reasonably accurate for simulating these nonlinear models.

The influenza epidemic model is an aggregated system with four state variables which includes the structural state of the virus as one of the state variables. The state equation for the virus strain was constructed using the idea of a logistic curve, the asymptote of which is the immunity level of the population. With a proper choice of the drift rate, the system provides an epidemic curve which resembles underdamped oscillation. Linearization was used to analyze the system behavior and to compute the range of the drift rate required for this underdamped oscillation. The computational procedure for finding this range is based on a sufficient condition, expressed in terms of the coefficients of the

characteristic equation, for the third order linear system to be stable oscillatory and underdamped.

With this model three epidemic cycles can be shown. The initial epidemic results from virus shift which is represented by the presence of low immunity level in the population. The following two epidemics result from drifts which cause the susceptible population to build up above the threshold level. For the first three epidemics, the dynamic behavior of the virus, the immunity level, and the epidemic curve are similar to those graphically represented by Kilbourne.

Model validation was performed using the data taken from the Vital Statistics Report of the United States. The model was modified to accomodate population growth and the seasonal variation of the infective rate. The attempt to fit the historical data on the mortality rate of the three selected epidemics in recent time to the simulation results was reasonably successful, considering the complexity of the real world system.

The model analysis and simulation of the aggregated system provide a good insight into the behavior of the essential variables. In particular the threshold is one such variable whose behavior may not have been so obvious. The threshold is a time varying quantity which is inversely proportional to the susceptible level of the population. The size of the difference between the susceptible population and the threshold prior to an epidemic determines the severity of that epidemic.

A formula used to calculate the numerical value of

drifts was developed. It was shown from simulation results that the value of the drift is an indication of the severity of the following epidemic, measured in terms of the peak of the epidemic curve. The drift time, the time at which a drift occurs, was also defined. Knowing the drift time, the beginning of the next epidemic could be estimated.

In this model the second epidemic occurs if the susceptible population exceeds the threshold. To control this epidemic, an immunization system was developed as a subsystem of a control system. The immunization model consists of the vaccinated population as a state variable. The state equation was constructed using the idea of a goal seeking curve, the goal of which is the difference between the susceptible population and the threshold. The immunization period begins with the drift time and ends at the time the virus reaches relative minimum.

The control system is an idealized model. It takes no consideration of the efficacy of the vaccine, and only the susceptible population is immunized. To translate the total vaccinated population obtained from simulation into more realistic figures, a simple formula was used to estimate the percentage of the total population required to be immunized.

The following are suggestions for building a more complex model from this aggregated model:

(1) The susceptible level of the population may be made more precise by defining it to be a function of general health and age as well as antibody level.

(2) The infective rate may be a function of season, mobility, the density of the population and the effective contact rate.

(3) Geographical spread of infection may be modelled using partial differential equations.

(4) Population may be divided into three or four age brackets with each group having different infective removal and immune rates.

(5) Subclinical cases may be considered by having a separate immune population for those cases.

(6) Surveillance systems may be established to identify drifts and shifts of the virus.

(7) Immunization systems may include the efficacy of the vaccine which is a function of the virus and the effectiveness of surveillance. They may also include economic factors such as production, distribution and manpower costs.

(8) A more precise mathematical representation of the virus may be developed as research in this area progresses.

APPENDICES

APPENDIX A

DERIVATION OF THE FORMULA FOR THE FUNDAMENTAL MATRIX OF THE 2X2 MATRIX A IN WHICH THE EIGENVALUES ARE COMPLEX

Let $s_1 = u + jv$, $s_2 = u - jv$ be the eigenvalues. Then, from the theory of the function of matrices,

$$e^{At} = Z_1 e^{s_1 t} + Z_2 e^{s_2 t},$$

where Z_1, Z_2 are the constituent matrices given by

$$Z_1 = \frac{A - s_2 I}{s_1 - s_2}$$

$$Z_2 = \frac{A - s_1 I}{s_2 - s_1} .$$

Writing Z_1, Z_2 in terms of the real and the complex parts, we obtain

$$Z_1 = \tfrac{1}{2} \left[I - j \frac{1}{v} (A - uI) \right] \qquad (A.1)$$

and $Z_2 = \overline{Z}_1$ (conjugate of Z_1).

Hence,

$$e^{At} = Z_1 e^{s_1 t} + \overline{Z}_1 e^{\overline{s}_1 t}$$

$$= Z_1 e^{s_1 t} + \overline{Z_1 e^{s_1 t}}$$

$$= 2 \, \mathrm{Re} \, Z_1 e^{s_1 t} .$$

Now, using the Euler Formula we can write

$$e^{s_1 t} = e^{(u + jv)t}$$

$$= e^{ut}\, e^{jvt}$$

$$= e^{ut}\, (\cos vt + j \sin vt). \qquad (A.2)$$

Multiplying Equations (A.1) and (A.2) and taking twice the real part, we obtain the formula

$$e^{At} = e^{ut}\, [(\cos vt)\, I + (\tfrac{1}{v} \sin vt)\, (A - uI)].$$

APPENDIX B

DYNAMO LISTINGS

Table B.1. Simple epidemics model.

```
* SIMPLE EPIDEMICS MODEL
NOTE
NOTE          LEVELS
L SPOP.K=SPOP.J+DT*SPOPR.JK        SUSCEPTIBLE POPULATION
L IPOP.K=IPOP.J+DT*IPOPR.JK        INFECTIVE POPULATION
NOTE          RATES
R SPOPR.KL=-BETA*SPOP.K*IPOP.K     SUSCEPTIBLE
R IPOPR.KL=BETA*SPOP.K*IPOP.K      INFECTIVE
NOTE
NOTE          INITIALIZATION
N IPOP=I
N SPOP=S
C S=950
C I=50
NOTE
NOTE          PARAMETERS
C BETA=.002                        INFECTIVE RATE
PRINT SPOP,IPOP,IPOPR
PLOT SPOP=S,IPOP=I,IPOPR=N
SPEC DT=.001/PLTPER=.1/LENGTH=5/PRTPER=.1
RUN BASE
*EOF
```

Table B.2. General epidemics model.

```
* GENERAL EPIDEMICS MODEL
NOTE
NOTE          LEVELS
L SPOP.K=SPOP.J+DT*SPOPR.JK          SUSCEPTIBLE POPULATION
L IPOP.K=IPOP.J+DT*IPOPR.JK          INFECTIVE POPULATION
L RPOP.K=RPOP.J+DT*RPOPR.JK          IMMUNE POPULATION
NOTE
NOTE          RATES
R SPOPR.KL=-BETA*SPOP.K*IPOP.K
R IPOPR.KL=BETA*SPOP.K*IPOP.K-GAMMA*IPOP.K
R RPOPR.KL=GAMMA*IPOP.K
NOTE
NOTE          INITIALIZATION
N SPOP=S
N IPOP=I
N RPOP=R
C S=950
C I=50
C R=0
NOTE
NOTE          PARAMETERS
C BETA=.002                          INFECTIVE RATE
C GAMMA=.8                           REMOVAL RATE
PRINT SPOP,IPOP,RPOP,RPOPR
PLOT SPOP=S,IPOP=I,RPOP=R/RPOPR=N
SPEC DT=.001/PLTPER=.1/LENGTH=10/PRTPER=.1
RUN BASE
*EOR
C S=350
C I=100
C R=550
C BETA=.002
C GAMMA=.8
RUN CH1
*EOF
```

Table B.3. Endemic model.

```
* ENDEMIC MODEL
NOTE
NOTE          LEVELS
L SPOP.K=SPOP.J+DT*SPOPR.JK          SUSCEPTIBLE POPULATION
L IPOP.K=IPOP.J+DT*IPOPR.JK          INFECTIVE POPULATION
L RPOP.K=RPOP.J+DT*RPOPR.JK          IMMUNE POPULATION
NOTE
NOTE          RATES
R SPOPR.KL=-BETA*SPOP.K*IPOP.K+EPSLN
R IPOPR.KL=BETA*SPOP.K*IPOP.K-GAMMA*IPOP.K
R RPOPR.KL=GAMMA*IPOP.K-EPSLN
NOTE
NOTE          DISEASE INCIDENCE
S INCI.K=GAMMA*IPOP.K
NOTE
NOTE          INITIALIZATION
N SPOP=S
N IPOP=I
N RPOP=R
C S=900
C I=50
C R=50
NOTE
NOTE          PARAMETERS
C BETA=.001                          INFECTIVE RATE
C GAMMA=.8                           REMOVAL RATE
C EPSLN=50                           SUSCEPTIBLE RATE
PRINT SPOP,IPOP,RPOP,INCI
PLOT SPOP=S,IPOP=I,RPOP=R/INCI=N
SPEC DT=.1/PLTPER=1/LENGTH=100/PRTPER=1
RUN BASE
*EOR
C S=950
C R=0
C BETA=.002
C EPSLN=10
SPEC PLTPER=2/LENGTH=200
RUN CHI
*EOF
```

Table B.4. Influenza epidemic model.

```
* INFLUENZA EPIDEMIC MODEL
NOTE
NOTE          LEVELS
L SPOP.K=SPOP.J+DT*SPOPR.JK          SUSCEPTIBLE POPULATION
L IPOP.K=IPOP.J+DT*IPOPR.JK          INFECTIVE POPULATION
L RPOP.K=RPOP.J+DT*RPOPR.JK          IMMUNE POPULATION
L VI.K=VI.J+DT*VIR.JK                VIRUS STRAIN
NOTE
NOTE          RATES
R SPOPR.KL=-BETA*SLVL.K*SPOP.K*IPOP.K+EPSLN*VI.K*RPOP.K
R IPOPR.KL=BETA*SLVL.K*SPOP.K*IPOP.K-GAMMA*IPOP.K
R RPOPR.KL=GAMMA*IPOP.K-EPSLN*VI.K*RPOP.K
R VIR.KL=DELTA*(IMLVL.K-VI.K)*VI.K
NOTE
NOTE          AUX/SUPPL VARIABLES
A IMLVL.K=RPOP.K/1000                IMMUNITY LEVEL
A SLVL.K=1-IMLVL.K                   SUSCEPTIBLE LEVEL
S TH.K=(1000*(GAMMA/BETA))/(1000-RPOP.K)     THRESHOLD
S INCI.K=GAMMA*IPOP.K                DISEASE INCIDENCE
NOTE
NOTE          INITIALIZATION
N SPOP=S
N IPOP=I
N RPOP=R
N VI=V
C S=900
C I=50
C R=50
C V=.001
NOTE
NOTE          PARAMETERS
C BETA=.001                          INFECTIVE RATE
C GAMMA=.1                           REMOVAL RATE
C EPSLN=.5                           SUSCEPTIBLE RATE
C DELTA=1                            DRIFT RATE
PRINT SPOP,IPOP,RPOP,TH,INCI,VI,IMLVL
PLOT INCI=N/IMLVL=A/VI=V
SPEC DT=.1/PLTPER=1/LENGTH=100/PRTPER=1
RUN BASE
*EOR
C DELTA=.5
RUN CH1
C DELTA=.3
RUN CH2
C DELTA=.1
RUN CH3
C S=600
C R=350
C DELTA=.5
RUN CH4
*EOR
```

Table B.5. Model validation.

```
* MODEL VALIDATION
NOTE
NOTE            LEVELS
L SPOP.K=SPOP.J+DT*SPOPR.JK          SUSCEPTIBLE POPULATION
L IPOP.K=IPOP.J+DT*IPOPR.JK          INFECTIVE POPULATION
L RPOP.K=RPOP.J+DT*RPOPR.JK          IMMUNE POPULATION
L VI.K=VI.J+DT*VIR.JK                VIRUS STRAIN
NOTE
NOTE            RATES
R SPOPR.KL=-INF.K*SLVL.K*SPOP.K*IPOP.K+EPSLN*VI.K*RPOP.K
X +BRTH*POP.K-DTHS*SPOP.K
R IPOPR.KL=INF.K*SLVL.K*SPOP.K*IPOP.K-GAMMA*IPOP.K-DTHI*IPOP.K
R RPOPR.KL=GAMMA*IPOP.K-EPSLN*VI.K*RPOP.K-DTHR*RPOP.K
R VIR.KL=DELTA*(IMLVL.K-VI.K)*VI.K
NOTE
NOTE            AUX/SUPPL VARIABLES
A INF.K=CR*(1+H*SIN(6.28/PRD)*TIME.K))      INFECTIVITY
S MORT.K=DTHI*IPOP.K                 MORTALITY RATE
A POP.K=SPOP.K+IPOP.K+RPOP.K         TOTAL POPULATION
S INCI.K=GAMMA*IPOP.K                DISEASE INCIDENCE
A IMLVL.K=RPOP.K/POP.K               IMMUNITY LEVEL
A SLVL.K=1-IMLVL.K                   SUSCEPTIBLE LEVEL
NOTE
NOTE            SEASONAL VARIATION
C CR=.07E-6                          CONTACT RATE
C H=.03                              HIGHT STEP FUNC
C PRD=12                             PERIOD SINE
NOTE
NOTE            INITIALIZATION
N SPOP=S
N IPOP=I
N RPOP=R
N VI=V
C S=17.19E6
C I=.5E6
C R=.5E6
C V=.001
NOTE
NOTE            PARAMETERS
C GAMMA=.9                           REMOVAL RATE
C EPSLN=.5                           SUSCEPTIBLE RATE
C DELTA=.6                           DRIFT RATE
C BRTH=1.36E-3                       BIRTH RATE
C DTHS=7.78E-4                       DEATH RATE
C DTHI=7.78E-4
C DTHR=7.78E-4
PRINT POP,SPOP,IPOP,RPOP,INF,VI,IMLVL,MORT,INCI
PLOT POP=P,SPOP=S,RPOP=R,IPOP=I/VI=V/IMLVL=A/MORT=M/INCI=N
SPEC DT=.1/PLTPER=1/LENGTH=120/PRTPER=1
RUN BASE
*EOF
```

Table B.6. Immunization model.

```
* IMMUNIZATION MODEL AND CONTROL SYSTEM
NOTE
NOTE          LEVELS
L SPOP.K=SPOP.J+DT*SPOPR.JK          SUSCEPTIBLE POPULATION
L IPOP.K=IPOP.J+DT*IPOPR.JK          INFECTIVE POPULATION
L RPOP.K=RPOP.J+DT*RPOPR.JK          IMMUNE POPULATION
L VI.K=VI.J+DT*VIR.JK                VIRUS STRAIN
L VPOP.K=VPOP.J+DT*VPOPR.JK          VACCINATED POPULATION
NOTE
NOTE          RATES
R SPOPR.KL=A.K-VPOPR.JK
R IPOPR.KL=BETA*SLVL.K*SPOP.K*IPOP.K-GAMMA*IPOP.K
R RPOPR.KL=GAMMA*IPOP.K-EPSLN*VI.K*RPOP.K
R VPOPR.KL=KSAI*(DIFF.K-VPOP.K)*VAC.K
R VIR.KL=DELTA*(IMLVL.K-VI.K)*VI.K
NOTE
NOTE          AUX/SUPPL. VARIABLES
A A.K=-BETA*SLVL.K*SPOP.K*IPOP.K+EPSLN*VI.K*RPOP.K
A VAC.K=STEP(HGHT1,STTM1)-STEP(HGHT1,STTM2)   VACCIN PERIOD
C HGHT1=1
C STTM1=27
C STTM2=59
A IMLVL.K=(RPOP.K+VPOP.K)/1000       IMMUNITY LEVEL
A SLVL.K=1-IMLVL.K                   SUSCEPTIBLE LEVEL
A TH.K=RHO1/SLVL.K                   THRESHOLD
A DIFF.K=SPOP.K-TH.K                 SUSCEP-THRESH
A INCI.K=GAMMA*IPOP.K                DISEASE INCIDENCE
NOTE
NOTE          INITIALIZATION
N SPOP=S
N IPOP=I
N RPOP=R
N VPOP=M
N VI=V
C S=900
C I=50
C R=50
C M=0
C V=.001
NOTE
NOTE          PARAMETERS
C RHO1=400                           RELATIVE REMOVAL RATE
C BETA=.002
C GAMMA=.8
C EPSLN=.3
C DELTA=.5
C KSAI=1                             VACCIN RATE
PRINT SPOP,IPOP,RPOP,VPOP,TH,DIFF,INCI,VI,IMLVL,VPOPR
PLOT SPOP=S,TH=H/INCI=N
SPEC DT=.1/PLTPER=1/LENGTH=100/PRTPER=1
RUN BASE
*EOR
PLOT VPOP=M/VPOPR=V
RUN CHI2
*EOF
```

BIBLIOGRAPHY

Aggarway, J. K. 1972. Notes on nonlinear systems. Van Hostrand Reinhold Company, New York.

Bailey, Norman T. J. 1957. The mathematical theory of epidemics. Hafner Publishing Company, New York.

_____. 1964. The elements of stochastic process. John Wiley and Sons, Inc., New York.

_____. 1975. The mathematical theory of infectious disease. Hafner Press, New York.

Barker, D. J. P., and G. Rose. 1976. Epidemiology in medical practice. Churchill Livingston, New York.

Baroyan, O. V., et. al. 1971. Computer modeling of influenza epidemics for the whole country (USSR). Adv. Appl. Prob. 3: 224-6.

Bartlett, M. S. 1960. Stochastic population models. Methuen and Co., LTD., London.

Beveridge, W. I. B. 1977. Influenza. Prodis, New York.

Center for Disease Control: Influenza surveillance report no. 91, issued July 1977.

Center for Disease Control: Morbidity and mortality weekly report, annual summary 1977, issued September 1978. 26 (53): 61-63.

Dayananda, P. W. A., and W. L. Hogarth. 1978. Optimal health programs of immunization and isolation for some approximations to chain-bronomial epidemic models. Mathematical Biosciences. 41: 24-251.

D'Azzo, John J., and Constantine H. Houpis. 1975. Linear control system analysis and design. McGraw-Hill, New York.

Dickson, L. E. 1922. First course in the theory of equations. John Wiley and Sons, Inc., New York.

Elveback, Lila R., John P. Fox, and Eugene Ackerman. Stochastic simulation models for two immunization problems, p. 90-103 in Ludwig, D., and K. L. Cooke, eds. 1975. Epidemiology: Proceedings of a SIAM Conference on Epidemiology. Alta, Utah, July 8-12, 1974. Society for Industrial and Applied Math, Philadelphia, Pennsylvania.

Fenner, F. J., and D. O. White. 1970. Medical virology. Academic Press, New York.

Fenner, F. J., et. al. 1974. The biology of animal viruses. 2nd ed. Academic Press, New York.

Forrester, J. W. 1968. Principles of systems. Wright-Allan Press, Cambridge, Massachusetts.

Fox, J. P., et. al. 1968. Epidemiology. Macmillan, London.

Goodman, Michael R. 1974. Study notes in system dynamics. Wright-Allan Press, Cambridge, Massachusetts.

Hinshaw, V. S., et. al. 1978. The prevalence of influenza viruses in swine and the antigenic and genetic relatedness of influenza viruses from man and swine. Virology. 84: 51-62.

Holland, W. W., ed. DATA handling in epidemiology. 1970. Oxford University Press, London.

Kendall, D. B. 1956. Deterministic and stochastic epidemics in closed populations. Proc. Third Berkeley Symp. Math. Statist. and Prob. 4: 149-65. Univ. California Press, Berkeley.

Kilbourne, E. D. 1975. Epidemiology of influenza, p. 483-538 in Kilbourne, E. D., ed., 1975. The influenza viruses and influenza. Academic Press, New York.

Kojima, K., ed. 1970. Mathematical topics in population genetics. Springer-Verlag, New York.

Laver, W. G., and R. G. Webster. 1979. Ecology of influenza viruses in lower mammals and birds. British Medical Bulletin 35 (1): 29-33.

May, R. M. 1974. Model eco-systems. 2nd ed. Princeton University Press, Princeton, New Jersey.

Olinick, Michael. 1978. An introduction to mathematical models in the social and life sciences. Addison-Wesley, Reading, Massachusetts.

Oxford, J. S., and J. D. Williams. 1976. Chemotherapy and control of influenza. Academic Press, New York.

Pereira, M. S. 1978. 'Flue: the mutant virus. World Health, July 1978, WHO, Geneva, Switzerland.

_____. 1979. Global surveillance of influenza. British Medical Bulletin 35 (1): 9-14.

Perkins, F. T., and R. H. Regamey, eds. 1977. International symposium on influenza immunization. International Association of Microbiological Societies, New York.

Pugh, Alexander. 1976. DYNAMO user's manual. The MIT Press, Cambridge, Massachusetts.

Sage, A. P. 1977. Methodology for large scale systems. McGraw-Hill, New York.

Sanders, M., and M. Schaeffer. 1971. Viruses affecting man and animals. Warren H. Green, Inc., St. Louis, Missouri.

Saucedo, Robert, and Earl E. Schiring. 1968. Introduction to continuous and digital control systems. Macmillan, New York.

Savageau, M. A. 1976. Biochemical systems analysis. Addison-Wesley, Reading, Massachusetts.

Selby, P., ed. 1976. Influenza: Virus, vaccines, and strategy. Sandoz Institute for Health and Socio-Economic Studies, Academic Press.

Smith, Gordon C. E. 1976. Epidemiology and infections. Meadowfield Press, Busbey, England.

Spicer, C. C. 1979. The mathematical modeling of influenza epidemics. British Medical Bulletin 35 (1): 23-28.

Stuart-Harris, D. H., and G. C. Schild. 1976. Influenza. Publishing Sciences Group, Inc., Littleton, Massachusetts.

Supplement. 1977. The Journal of Infectious Diseases. 136 (December 1977).

Susser, Mervyn. 1973. Causal thinking in the health sciences. Oxford University Press, New York.

Tyrrell, D. A. J., and J. W. G. Smith. 1979. Vaccination against influenza. British Medical Bulletin 35 (1): 77-85.

Volk, W. A. 1978. Essentials of medical microbiology. J. B. Lippincott Company, New York.

Waltman, P. 1974. Deterministic threshold models in the theory of epidemics. Springer-Verlag, New York.

Wilkinson, James H. 1965. The algebraic eigenvalue problem. Clarendon Press, Oxford.