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MODELING AND OPTIMUM CONTROL OF EPIDEMICS

by

© NARESH KUMAR GUPTA

A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled MODELING AND OPTIMUM CONTROL OF EPIDEMICS submitted by Naresh K. Gupta in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

This thesis concerns itself with the optimum-control study of a class of infectious diseases which are propagated through the transfer of disease micro-organism, by direct contact between diseased and healthy individuals. An improved model, generally applicable to most such diseases, reasonably accurate in representing the phenomena connected with their spread, mathematically simple, and suitable from control point of view, has been formulated. The new model, while remaining essentially deterministic in nature, incorporates a very desirable feature of stochastic models by representing the latent and infectious periods of disease by their mean values and respective standard deviations.

The resulting model consists of a set of non-linear differential equations which include functions of present values and past history of both state and control variables. Numerical solutions have been obtained for the simulated model, consisting of equivalent differential difference equations, with different sets of parameters, but without control; thus demonstrating the applicability of the model to various diseases. The effect of application and variation of each of the active and passive vaccination controls has also been studied.

The optimum control theory has been applied to the problem of finding the most economic use of active and passive

immunization controls. Application of Pontryagin's Minimum Principle to this case, involving functions of both delayed state and delayed control, has been demonstrated and a procedure has been developed for the numerical solution of the resulting control problem.

Using the numerical procedure, optimum control strategies have been obtained for different values of reported case cost, a parameter representing the personal, social and economic damage done by one active case of the disease. The influence of delay in the effectiveness of active control on the resulting optimum cost and controls has also been studied.

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TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

CHAPTER I

GENERAL INTRODUCTION

1.1 Introduction

Research conducted during the last sixty or so years in the fields of clinical medicine, biology, epidemiology, and other related disciplines has provided considerable insight into the phenomena connected with the spread of infectious diseases. A large number of text books on public health, containing this information, may be classed as non-technical from the point of view of medical sciences; references [11],* [23], [26], and [30] are a few examples of this fact. This easy access to information, coupled with the common concern of every individual for the scourge of epidemics to which humanity has been subjected from time immemorial, has attracted the attention of a considerable number of researchers from sciences other than medical.

Mechanisms of contagion can be readily classified into two sub-sections, namely, micro-mechanisms and macro-mechanisms; the former dealing with characteristic properties of pathogenic material of infection and its effects on the biological system of the victim, and the latter concerning itself with the behaviour of the intended victims as a group and the susceptibilities and defenses of this

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* Numbers in rectangular brackets indicate references listed at the end of this thesis.

group as a crowd or herd. The former is the area of major concern of only the medical or biological scientists, whereas the latter can and has benefitted most from the specialised knowledge of mathematicians, statisticians, ecologists, and system scientists. The research reported in this dissertation falls in the second category.

A beginning in the application of mathematical concepts to epidemics may be said to have been made with the studies of London Bills of Mortality by John Graunt and William Petty, in the middle of the 17th century. It was then that the term medical statistics really originated. Early attempts on the study of statistical returns of deaths from smallpox were aimed at finding some empirical laws underlying the spread of epidemics. William Farr, in fact, succeeded in fitting normal curves to quarterly data on smallpox deaths, in the middle of the nineteenth century. Successes like this, coupled with research in the biological field around the same time, laid the foundations of the present mathematical theory of epidemics.

A large number of workers have proposed a number of mathematical models to mimic the behaviour of epidemics. The work done in this field has been extensively reviewed, and good number of review articles and publications are available; prominent among them are those of Serfling [37], Bailey [2], and Deitz [10]. Bailey's monograph [2] reviews in detail the work done up to 1957, and has been updated by Deitz [10]. The major milestones in the development of this theory are

the works of Hamer, Brownlee, Lotka, Ross, Reed and Frost, Kermick and McKendrick, and E.B. Wilson. While a more detailed historical review of the subject is postponed to the later parts of the thesis, it will be useful to discuss here, in brief, the basic concepts of the epidemic theory as they are understood today.

1.2 Basic Concepts

Micro-organism of an infectious disease is carried from a diseased individual or animal to the healthy one either by direct contact and proximity, or through an intermediate agent. The intermediate agent may be an item of food, water, or a rodent or arthropod vector. Attention is here particularly restricted to those communicable diseases which pass on by direct contact or proximity. The causative agents of these diseases are bacteria or virus. It may be pointed out here, however, that the methods discussed in this thesis may be extended to other classes of infectious diseases by suitable modifications.

For the purpose of epidemic study a population, at any time, may be considered to consist of the following three sub-populations: *susceptibles*, *infectives* and *immunes*. A brief description of these three terms is in order here. *Susceptibles*, as the name implies, are the healthy individuals who have a very weak or no resistance to the disease in question. Since in most cases an individual acquires immunity to a disease after recovery, it may be assumed that a member

of the susceptible population is one who has either no experience of the disease in question or has lost his immunity obtained from earlier exposures. *Infectives* are the individuals who have sufficiently developed pathogenic material in their system so that they are capable of passing it on to their contacts, thus infecting the susceptible ones. *Immunes* are the members of population who have acquired immunity to the disease in question, either by earlier exposure or by artificial means of immunization. These members do not take any part in the process of disease spread. Therefore the individuals, once affected by the disease but since dead, recovered, or removed from circulation; either by hospitalization or effective quarantine on the appearance of symptoms, can also be considered in the immune class.

When an infective somehow gets introduced to a population of susceptibles and immunes only, the contacts of the infective pick up the disease micro-organism which then meets the biological and chemical defenses of the host. Depending upon the degree of this resistance and its own capability for multiplication, the parasite establishes itself in the system of a susceptible host after a period called *latent period*. The susceptible now himself becomes an infective and starts spreading the disease to his healthy contacts till he shows the symptoms of disease and is removed from circulation by quarantine, hospitalization, death, or recovery. If recovered, he acquires immunity to the disease, at least for the immediate future,

and enters the immune population. Some relapses in diseases like tuberculosis do, however, occur. Also, some infectives develop a tolerance to the parasite and become capable of passing the disease, at least for a limited time, without themselves ever showing the symptoms of disease; they are called *carriers*. There are others who become immune without ever becoming sick by virtue of receiving repeated but small doses of infection.

The time elapsed between the receipt of infection by a susceptible and his becoming infective is called the *latent period*, and that between first exposure and appearance of symptoms is called the *incubation period*. These two periods have definite mean values for a particular disease. The difference between the incubation period and latent period is the time during which a case is actively infective and is hence called the *infectious period*.

1.3 Modeling

The discussion so far leads to the conclusion that the dynamics of a crowd disease or an epidemic can be represented, at any time, by the numbers of susceptibles, infectives and recovered or removed individuals and the rates at which they move from one category to the other. In other words, an epidemic can be represented by a mathematical model, provided parameters for the rates of change of the above variables are known. In fact, a number of such models have been formulated during the last 60 years, as shall be discussed

in the next chapter. The primary parameters mentioned above are the rates at which effective contacts are made and infectives are removed from circulation. However, for a model to be more accurate, in addition to the consideration of chances of contact and removal, the mean values and the upper and lower limits of the latent and incubation periods should also be incorporated. Thus, mathematically, an epidemic can be specified by the effective rate of contact, and mean values and variance of the latent and incubation periods.

Since the events of contact between a susceptible and an infective (as well as various other phenomena connected with the disease spread) are probabilistic in nature, it is clear that the model representing an epidemic should ideally be stochastic in nature. However, when dealing with large populations, a deterministic model which by its nature tends to evaluate the mean values of variable at any time rather than the probabilities of these numbers is sufficiently accurate and mathematically much simpler than its stochastic counterpart. In fact, a stochastic model for a small community, when considered for households of more than two, is almost unmanageable mathematically. Therefore, when one is not dealing with very small groups, the usefulness of deterministic models can not be over stated.

As pointed out earlier, models help in understanding the mechanism of the spread of epidemics at macro level. The understanding thus gained has always been used for a better control of the epidemics. Most of the models discussed in literature, however, can be said to

be predictive in nature rather than control oriented, since they do not include parameters representing control actions. Because of the availability of methods for creating artificial immunity to disease by use of active and passive immunization, and because of the proven effectiveness of chemoprophylaxis in preventing disease, the important question of selecting the best means of control naturally arises. If only the predictive models without control parameters are used, the control strategy arrived at can, at best, be said to be a qualified guess. Whereas, with the development of control models and application of optimization techniques,a more logical control strategy can be evolved. The question of optimum control has recently started appearing in the literature, as reviewed in subsequent chapters. In fact,other attempts on some kind of optimization of epidemic control have been reported. However, to the best of this author's knowledge no model, sufficiently accurate and yet general enough for application to the control of a class of diseases, has been reported. Nor has a thorough application of the Minimum Principle of optimum control theory to this class of problem appeared in the literature.

An improved model for the spread of contagious diseases is presented in the next Chapter. The new model is basically deterministic in formulation and is derived from the standard Kermack and McKendrick model. However, latent and incubation periods and their variation for the disease in question have been incorporated in the model. The model assumes each of these periods to be normally distributed with

known mean value and standard deviation, and these values constitute important parameters of the model. Nominal controls in the form of active and passive immunizations have also been considered. The resulting model has been used to evolve a most economic control strategy.

Chapters II, III and IV contain the major contribution of this thesis. Chapter II describes the new model and its parameters in detail. Numerical solutions of the model equations, presented in this Chapter, clearly show its advantages over the earlier models. The Chapter also demonstrates the ease with which the model can be used to represent various diseases by adjusting the appropriate parameters. The introduction of control and its effect on the course of disease is discussed in Chapter III. Two different controls, active immunization and passive immunization, are separately considered, and numerical solution for various predetermined controls are presented. Chapter IV deals with the extension of optimal control theory for the determination of best control strategy between the two controls used simultaneously. The procedure developed minimizes a cost function consisting of the sum of the cost of each control and that of each case affected by disease.

It is hoped that this dissertation, in addition to presenting some new results in the field of optimum control of epidemics, also represents an extension and good example of some recent techniques in optimum control theory. The new model, incorporating the two

different controls as arrived at in Chapter III, has a finite number of delays in both state and control variables. Although considerable work on optimum control of systems with delays in state or control has been reported, and recently some papers discussing delays both in state and control have also appeared, yet the author has not come across any example of such an application in the literature. Numerical solutions presented in this thesis will, hopefully, provide a good example of practical application of optimum control to a nonlinear system with constraints, and having finite number of delays in both state and control.

CHAPTER II

NEW MODEL

2.1 Introduction

Introductory remarks made in the last chapter suggest the existance of a large number of mathematical models suitable for representing the epidemic spread. In fact, the very understanding of the mechanisms of disease spread, which we now possess, is mainly due to the liberal use of these models during the last half century. Among the available models, both deterministic and stochastic, some are specific to special cases whereas the others are more general. Again, some are relatively simple whereas the others are more complicated. Generally speaking, simple ones are less accurate in the representation of epidemic spread. Therefore a model which is accurate enough and yet mathematically simple is always desirable. One such model is introduced in this chapter.

The new model is an improved version of a well known deterministic model and incorporates many desirable features of other models, both deterministic and stochastic. This model is quite general in application to various diseases and quite suitable for introducing control parameters. Moreover, it is also suitable for the optimum control analysis.

The new model is discussed in detail in this chapter, whereas the analysis of the model with respect to controls is taken up in the subsequent chapters.

2.2 *Historical Review*

The extensive literature on the mathematical theory of epidemics has been adequately reviewed from time to time. Serfling [37] presented a comprehensive review of the state of the art as it existed in 1952. In 1957, Bailey [2] published his now famous monograph summarising all the work in the field up to that time. This work did more for the field of mathematical modeling of epidemics than any other single effort. It is no surprise, therefore, that Bailey predicted the future use of mathematical models in the economical control of epidemics, which is now receiving some attention in the literature and is also the subject of this author's present effort. Bailey's work has been adequately supplemented by the review article of Deitz [10], which updates it to 1967. These three efforts alone, not withstanding the parallel efforts of other authors, present an almost complete picture of the state of the art in the field. Any attempt to improve upon this extensive coverage of historical reviews is neither possible nor desirable here. Some general comments, necessary for the understanding of the new model, are, however, made in the next few paragraphs.

The possibility of defining some empirical relations describing the epidemic spread was first visualized by William Farr in 1840.

As pointed out in the last chapter, early efforts, including those of Farr, were devoted to the finding out of these relations from the published statistical case-report records by the use of mathematical curve fitting methods. The works of Hamer, Brownlee, Lotka and other pioneers in the field, were also directed to the same goal. These investigations helped establish the fact that the number of cases reported, at any time, depends upon the number of susceptibles and infectives in the population. This line was further advanced by Ross, Reed and Frost, Wilson et al and the Kermack-McKendrick team, among others. Most of the early attempts were deterministic in nature for the sake of mathematical simplicity. The most popular deterministic model is the one by Kermack and McKendrick [21], proposed in 1927. It was on the basis of this model that the authors proposed the now celebrated *Threshold Theorem* which states that for a disease to start the population of susceptibles should be more than a certain threshold value. This model is the one most often used, and it forms the basis of the model to be proposed in this chapter.

Dissatisfaction with deterministic models, due to their inaccuracy in representing essentially probabilistic phenomena, led to the development of mathematically more complicated stochastic models. The simple stochastic epidemic model, which led to those used today, is due to Bartlett [6] and Bailey [2], [3], [4], [5], and was first introduced by Bartlett in 1949. The accurate consideration of latent

and incubation periods was first introduced in the stochastic models, and some concepts evolved there are used in the model proposed in this chapter. Another significant but largely unexplored area is the geographical element introduced in epidemic models, mainly by Menther and Bailey [2], [4].

To sum up, two kinds of epidemic models are now available in the literature : deterministic and stochastic. The standard deterministic model is the Kermack and McKendric [21] model. The stochastic models, however, are being continuously improved upon as increasing numbers of researchers adopt them because of their better accuracy and better representation of the phenomena connected with disease spread. The immediate appeal of the stochastic models stems from the fact that everything connected with disease spread depends upon chance, and these models take this fact into account precisely. But when large populations are involved, it follows from the *law of large numbers* that the stochastic deviations are small compared to the average values, hence the argument that deterministic models are useful can not be rejected out of hand. This is especially so when the mathematical simplicity of these models far outweighs the marginal advantages of stochastic models when applied to larger populations. In fact, due to their mathematical simplicity, the deterministic models are the only ones suitable for effective optimum control studies at the present state of development.

It is due to the above considerations that the model to be introduced is kept essentially deterministic, even though the latent and incubation or infectious periods and their statistical variations are accounted for. The new model is quite general in application and suitable from the control point of view. Since the new model is based on the existing Kermack and McKendrick model and is an improvement on it, it is proposed to discuss the old model, in some detail, in the next section.

2.3 Kermack and McKendrick Model

The standard deterministic model for a closed population proposed by Kermack and McKendrick and mentioned in the last section is:

$$\frac{dx}{dt} = - \beta x y \tag{2.1}$$

$$\frac{dy}{dt} = \beta x y - \gamma y \tag{2.2}$$

$$\frac{dz}{dt} = \gamma y \tag{2.3}$$

where x, y, z are, respectively, the numbers of susceptibles, infectives, and removed or recovered cases at any time. β is the contact rate for the disease in question and γ is the removal rate. The solution of this model gives a bell shaped case report curve of the type generally observed in actual practice. This model is a landmark in the history of the mathematical theory of epidemics, since the now celebrated threshold theorem, that an epidemic will not start until and unless the number of susceptibles is more than the relative removal rate $\rho=\gamma/\beta$, was

derived from this model. In view of the non-linearity in the differential equations epidemiological conclusions, like the threshold theorem, were drawn from equilibrium conditions [29], and results were compared with those of a disease in rat populations under laboratory conditions. It may be pointed out here that the later stochastic models also arrived at a threshold theorem similar to that mentioned above, thus proving the essential correctness of the model.

Although mathematically very simple, the model is not very accurate in representing epidemics, especially in the beginning and near the end of the disease cycle. This model assumes the removals (γy) to be proportional to the population of infectives. This assumption is very inaccurate, especially at the terminals of the curve. The model, by virtue of its formulation, assumes a zero latent period and a negatively distributed (Poisson) infectious period [21]; this may be somewhat correct for quick spreading diseases like influenza and common cold, but not so for most other diseases.

Due to its mathematical simplicity this model has been used extensively, and it is also the basis of ReVelle's model for economical control of T.B. [33], [34], [23]. His model consists of nine differential equations instead of the three of the Kermack McKendrick model. The formulation of these equations in the two models is very similar. The various subpopulations considered in ReVelle's tuberculosis model are those of susceptibles, susceptibles vaccinated with B.C.G., infected

but non-active cases, non-actives with prophylaxis cured cases, and naturally recovered cases. This improved model appears to be reasonably accurate for application to the control of tuberculosis, but still does not consider latent and infectious periods explicitly. It also uses the proportional rates of the type 'γ' used in equation (2.2) to represent transfers of population from one group to the other during disease spread. Since this model is highly specialized for tuberculosis, its application to other situations would be very complicated, if not impossible.

2.4 New Model

Reference to standard text books on public health : Leavell et al [26], and epidemiology : Taylor et al[40], shows that the incubation period for every disease varies between a lower and an upper limit and these values of incubation period are so consistent that they are used for differential diagnosis of diseases. This fact is further borne out by the published results of studies conducted by Hope Simpson, [14], [15]. Reference [15] tabulates the distribution of cases against incubation period in days for three different diseases, namely : measles, mumps and chickenpox (varicella). Bailey has discussed the Hope Simpson data, in some detail, in chapter seven of reference [2], and has concluded that normal distribution curves can be fitted to the incubation period data. Continuing his discussion, on the basis of his earlier published work, he further concludes that it is reasonable to

assume a normally distributed latent period and a constant infectious period. The fact that incubation period and latent period have some kind of distribution was also proved by Abbey [1] and Sartwell [35].

Although some earlier deterministic models [44] used constant latent and infectious periods, yet it is only the recent stochastic models which use the variations in these periods as well. Bailey [2] proposed the stochastic model considering normally distributed latent period and constant infectious period (which implies a normally distributed incubation period, since incubation period is the sum of latent and infectious periods). He outlined a procedure for the estimation of parameters for this model and calculated these parameters for an epidemic of measles using Hope Simpson [15] data. Among the parameters calculated were the mean value and standard deviation of the latent period and the value of infectious period (assumed constant in his model). Significantly, Bailey and Stenberger [5] have recently (1970) revised the above procedure for estimation of parameters for the sake of better accuracy. In addition to the recalculation of parameters for measles they have also calculated parameters for infectious hepatitis using the recent (1959-67) data privately supplied by Dr. K. Peterson of Hamburg.

It is clear from the above discussion that incubation period for every disease has a distinct mean value and a definite distribution. Although incubation period is directly observable from the case histories

of the patients, the latent period can only be found indirectly. Bailey's assumption of a constant infectious period, while considering the latent period to be normally distributed, seems to have been made at least as much for mathematical simplicity of his stochastic model as for accuracy. In the opinion of this author, a more general model should have all the periods represented by their mean values and standard deviations. Consideration of a distributed rather than a constant infectious period may also be made to compensate for the fact that many reported cases may escape effective removal from circulation, and may be spreading the disease, at least for some time, after the appearance of symptoms.

We can now proceed to incorporate the above feature in the epidemic model. It may be pointed out here that for an accurate model we need the mean value and standard deviations of latent period and those for one of the other two periods, i.e. either infectious period or the incubation period. A version of the new model may be stated as follows :

$$\dot{X}_1 = - \beta_o X_1 X_2 \qquad (2.4)$$

$$\dot{X}_2 = A(t) - R(t) \qquad (2.5)$$

$$\dot{X}_3 = R(t) \qquad (2.6)$$

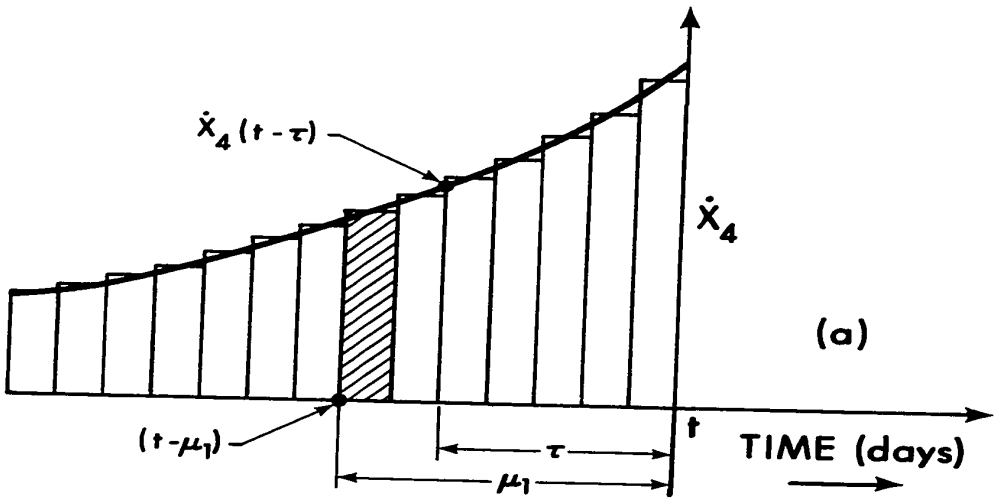
$$\dot{X}_4 = K(t) \beta_o X_1 X_2 , \qquad (2.7)$$

where X_1, X_2 and X_3 are the numbers of susceptibles, infectives and

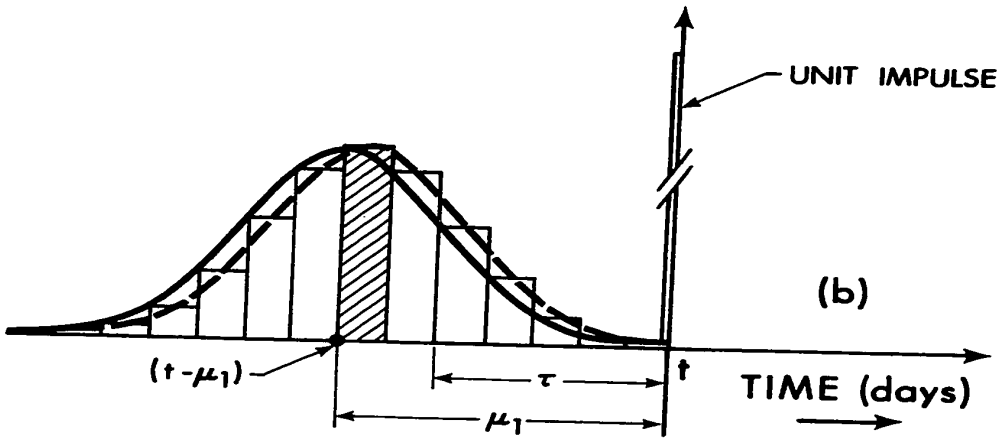
removed or recovered cases, respectively, and $\dot{X}_1$, $\dot{X}_2$, $\dot{X}_3$ are the corresponding rates of change. $\dot{X}_4$ is the rate at which infected (but not yet infective) cases are generated; β_o is the effective contact rate; K(t) is the fraction of population which finally becomes active in spreading the disease, [1-K(t)] being that fraction which becomes immune due to repeated but small doses of infection [40, page 142]. A(t) is the rate at which infected cases become infectives after their latent period is over, and R(t) is the rate at which infectives show symptoms and are reported, and hence are considered removed from circulation. Expression for variables A(t) and R(t) are derived in the next few paragraphs and are represented by equations (2.8) to (2.14).

The model is clearly based on the earlier Kermack McKendrick model. However the manner of representing the introduction of active cases and removal of reported cases is different in the two models. It is now possible to calculate the active cases and reported cases on the basis of latent and incubation periods. The expressions for these calculations are discussed next.

It was concluded in the earlier discussion that it is reasonably accurate to assume the latent, infectious and incubation periods to be normally distributed. This hypothesis will now be used to evaluate the variables A(t), and R(t). We refer to figure 2.1 for deriving the expression for the calculation of A(t). Part (a) of this figure shows a probable curve for the past history of infection rate $\dot{X}_4$



(a) CURVE REPRESENTING HISTORY OF INFECTION



(b) NORMAL DISTRIBUTION CURVE FOR LATENT PERIOD.

FIGURE 2·1

and part (b) represents a normally distributed unit impulse with its distribution parameters μ_1 and σ_1 being the mean value and standard deviation of the latent period. The two curves are drawn on the same time axis. The number of cases becoming active at a time t, from among those who picked up infection τ days back, will be the product of the ordinates of two figures at time $t-\tau$. Mathematically this number will be

$$\frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_1} \exp\left[- \frac{1}{2\sigma_1^2} (\mu_1-\tau)^2\right] \cdot \dot{X}_4(t-\tau),$$

and the total number of newly active infectives, appearing at time t will be the integral of this product over τ varying from 0 to ∞. Therefore

$$A(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_1} \int_0^{\infty} \dot{X}_4(t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_1^2} (\mu_1-\tau)^2\right] d\tau. \qquad (2.8)$$

Since the ordinate of the normal distribution curve is nearly zero for τ greater than $2\mu_1$ equation (2.8) can be approximated to

$$A(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_1} \int_0^{2\mu_1} \dot{X}_4 (t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_1^2} (\mu_1-\tau)^2\right] d\tau. \qquad (2.9)$$

Similarly, if μ_2 and σ_2 are the corresponding mean value and standard deviation of incubation period, the expression for the reported cases becomes,

$$R(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \int_0^{2\mu_2} \dot{X}_4 (t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_2^2} (\mu_2-\tau)^2\right] d\tau. \qquad (2.10)$$

R(t) can also be calculated from the past history of A(t) rather than that of $\dot{X}_4$. The corresponding expression then is,

$$R(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \int_0^{2\mu_2} A(t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_2^2} (\mu_2-\tau)^2 \right] d\tau, \qquad (2.11)$$

if μ_2 and σ_2 are the mean values and standard deviation of infectious period instead of being those of the incubation period.

Referring again to figure 2.1, we can rewrite the expressions for A(t) and R(t) in discrete form by making the valid approximation that at any time $t-n\tau$, the area under the curve between times $t-n\tau$ and $t-(n-1)\tau$, is equal to the ordinate at $(t-n\tau)$ multiplied by 1, where n is a number and τ represents an interval of one day. This area is shown shaded in the figures 2.1 (a) and 2.1 (b) for a typical period of one day. With this assumption the expressions for A(t) and R(t), in discrete form, are:

$$A(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_1} \sum_{n=0}^{2\mu_1} \dot{X}_4 (t-n\tau) \cdot \exp\left[- \frac{1}{2\sigma_1^2} (\mu_1-n\tau)^2 \right], \qquad (2.12)$$

and

$$R(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \sum_{n=0}^{2\mu_2} \dot{X}_4 (t-n\tau) \cdot \exp\left[- \frac{1}{2\sigma_2^2} (\mu_2-n\tau)^2 \right], \qquad (2.13)$$

when incubation period is used, or

$$R(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \sum_{n=0}^{2\mu_2} A (t-n\tau) \cdot \exp\left[- \frac{1}{2\sigma_2^2} (\mu_2-n\tau)^2 \right] \qquad (2.14)$$

when infectious period is used.

Normalization

Let us now examine the model for dimensional consistency. A dimensional analysis of equation (2.4) shows that for X_1, X_2 and $\dot{X}_1$ to represent actual numbers, in a population, β_o must have the dimension of inverse population. Thus other conditions being same, the value of β_o will be different for communities of different populations. The following example illustrates this point more clearly.

Suppose a community of 10,000, consisting entirely of susceptibles, has 10 infectives introduced at a given time. Using equation (2.4) and a contact rate β_{o1}, the number of infected cases generated per day (since day is the unit of time used in this dissertation) will be

$$\beta_{o1} \times 10 \times 10{,}000 = 10^5 \beta_{o1}. \qquad (2.15)$$

If we now consider the same community to be consisting of 10 subcommunities, each of 1,000 susceptibles, and one infective is introduced, simultaneously, in each of these subcommunities, the total number of cases generated per day will be

$$10 (\beta_{o2} \times 1 \times 1{,}000) = 10^4 \beta_{o2} \qquad (2.16)$$

where β_{o2} is the new contact rate for each community. Since both the above expressions represent the same situation, $\beta_{o2} = 10 \beta_{o1}$.

For the model to be more general, however, a contact rate independent of population size will certainly be better. This was achieved by ReVelle [33], in his T.B. model, by representing susceptibles as a fraction of total population but maintaining the infectives as actual number; the infection rate, then, was also in actual numbers. A still better method of achieving the same result, in the opinion of this author, is to normalize all the state (population) variables, i.e. to represent the state variables as fractions of total population rather than actual numbers.

Therefore, replacing the upper case variables by their lower case counterparts so that the new variable is the old one divided by total population N, i.e. $x = \frac{X}{N}$, the model can be rewritten as

$$\dot{x}_1 = - \beta x_1 x_2 \tag{2.17}$$

$$\dot{x}_2 = a(t) - r(t) \tag{2.18}$$

$$\dot{x}_3 = r(t) \tag{2.19}$$

$$\dot{x}_4 = K(t).\beta \; x_1 x_2 \tag{2.20}$$

where $\beta = N\beta_{o1}$

$$a(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_1} \int_o^{2\mu_1} \dot{x}_4 (t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_1^2} (\mu_1 - \tau)^2 \right] d\tau \tag{2.21}$$

$$r(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \int_0^{2\mu_2} \dot{x}_4(t-\tau) \cdot \exp\left[-\frac{1}{2\sigma_2^2} (\mu_2-\tau)^2 \right] d\tau \qquad (2.22)$$

if incubation period is used, or

$$r(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \int_0^{2\mu_2} a(t-\tau) \cdot \exp\left[-\frac{1}{2\sigma_2^2} (\mu_2-\tau)^2 \right] d\tau \qquad (2.23)$$

if infectious period is used and reported cases are calculated from the past history of active rate. Corresponding values a(t) and r(t) in discrete form are

$$a(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_1} \sum_{n=0}^{2\mu_1} \dot{x}_4(t-n\tau) \cdot \exp\left[-\frac{1}{2\sigma_1^2} (\mu_1-n\tau)^2 \right] \qquad (2.24)$$

and $$r(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \sum_{n=0}^{2\mu_2} \dot{x}_4(t-n\tau) \cdot \exp\left[-\frac{1}{2\sigma_2^2} (\mu_2-n\tau)^2 \right] \qquad (2.25)$$

or $$r(t) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \sum_{n=0}^{2\mu_2} a(t-n\tau) \cdot \exp\left[-\frac{1}{2\sigma_2^2} (\mu_2-n\tau)^2 \right] \qquad (2.26)$$

as the case may be.

The variables x_1, x_2, x_3 and x_4 now represent, respectively, the sub-populations of susceptibles, infectives, reported cases and infected cases as fractions of the total population, and $\dot{x}_1$, $\dot{x}_2$, $\dot{x}_3$ and $\dot{x}_4$ represent their respective rates of change. a(t) and r(t) are the corresponding active and report rates, again as fractions rather than actual numbers. The contact rate β is now independent of the population

size, thus making the model more universal in application.

The term: *per unit value*, commonly used in electrical engineering terminology, can be applied, successfully, to describe the normalized quantities, defined above. Here, as there, this term means that a quantity called *per unit value* is the ratio of actual value to a reference value. In the present context, if $x = \frac{X}{N}$ is a sub-population expressed as a *per unit* value, then X is the actual sub-population and N is the total population or reference population. Given a *per unit* quantity, an actual value can be found by multiplying per unit value by the corresponding reference value. All the variables represented by lower case letters, in the subsequent discussion, will represent *per unit quantities*.

Contact Rate β

The contact rate β, used in the normalized new model has the same dimension as that of *infection rate* (β) used by ReVelle [33]. Therefore both, heuristic and probabilistic, derivations of infection rates given by ReVelle [33, pp. 26-30], are equally applicable in the present case also. Physical interpretation of β is best understood by quoting ReVelle [33, p. 26].

> "β = average number of individuals per unit time that any individual (active case or not) will encounter sufficiently to cause infection. The value does not

> depend on whether the person encountered is susceptible or the individual doing the encountering is infectious. However, only if the encounterer is infectious and the encountered susceptible will a new infection arise. An individual encountered sufficiently is call a "contact"; then β is the average number of contacts any individual makes per unit time. The parameter β is characteristic of the disease and the average individual's behaviour."

Elaborating the last sentence of the above quotation we can say that β depends upon the infectiousness of the disease, weather and meteorological conditions, and living, working and social conditions of the community. A practical method of evaluating β is by curve fitting on available data. However, with sufficient knowledge of the quantitative effects of the above mentioned social and biological factors and with enough experience, an a-priori evaluation of β is possible, at least theoretically.

2.5 Comments on the model

As pointed out earlier, the important features of the new model are: (1) normalization, (2) representation of the latent, infectious and incubation periods by their mean values and standard deviations. Normalization provides a better interpretation of contact rate β and makes it independent of the size of the population to which the model is applied. The representation of sub-population as fraction has also been used to advantage by Bailey [3] for perturbation approximation to simple stochastic epidemics. A somewhat similar representation has also been suggested by Landau and Rapoport [24] in their spread of information

model; the expression arrived at there is somewhat similar to the expression we would obtain after substituting a(t) and r(t) in equation (2.18). The time 'τ' in our model is similar to the "private time" used in that paper.

Hope Simpson [15], in addition to arriving at the distribution of the incubation period for three different diseases as discussed earlier, also showed that the infectiousness of each disease is different. Thus, other conditions being equal, β for one disease can be converted to that for the other by multiplying it by the ratio of infectiousness of the two diseases. As an example, Hope Simpson [15] calculated the infectiousness of measles, varicella and mumps to be 66.5%, 48.2% and 32.1%. Thus if β for mumps is 1,

$$\beta \text{ for varicella} = 1 \times \frac{48.2}{32.1} \simeq 1.5$$

and

$$\beta \text{ for measles} = 1 \times \frac{66.5}{32.1} \simeq 2.1$$

Thus we find that, as far as the model is concerned, a disease is identified by β, μ_1, μ_2, σ_1 and σ_2, and these constants are unique for each disease. So our model can be made to represent any disease for which these constants can be identified.

The new model has available, at any time, the values of variables representing susceptibles, infectives, infected cases, reported cases, infected case rate and reported case rate. Since control of an epidemic is affected by modification of one or more of these variables,

introduction of control parameters is quite easy. Therefore the model is quite suitable for application of control. This aspect will be discussed in greater detail in the next chapter.

2.6 Analysis of the model

It was pointed out earlier that the simple model of Kermack and McKendrick already presented many difficulties for its mathematical solution. The modified model, as is apparent from equations (2.17) to (2.22), is much more complicated because of the integro-differential nature of the equations. Therefore no general, closed-form solution is attempted. The model is analysed here by digital simulation and the important results are presented.

The procedure used for solving the model numerically is to calculate the values of a(t) and r(t) for each day from the past stored values of the variables representing sub-populations (now called state variables). Expressions (2.24) to (2.26) are used for calculating the variables numerically. These expressions are greatly simplified if new weight multiplier vectors are defined as below:

$$WLP(n) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_1} \exp\left[-\frac{1}{2\sigma_1^2}(\mu_1 - n\tau)^2\right] \tag{2.27}$$

$$WIP(n) = \frac{1}{\sqrt{2\pi}} \frac{1}{\sigma_2} \exp\left[-\frac{1}{2\sigma_2^2}(\mu_2 - n\tau)^2\right] \tag{2.28}$$

Then

$$a(t) = \sum_{n=o}^{2\mu_1} WLP(n) \cdot \dot{x}_4(t-n\tau) \tag{2.29}$$

$$r(t) = \sum_{n=o}^{2\mu_2} WIP(n) \cdot \dot{x}_4(t-n\tau) \qquad (2.30)$$

for incubation period or

$$r(t) = \sum_{n=o}^{2\mu_2} WIP(n) \cdot a(t-n\tau) \qquad (2.31)$$

for infectious period.

The values WLP and WIP now represent the ordinates of the normal distribution curve at each day between the current time and 2μ days back. The normal distribution is nearly zero at μ days away on either side of the mean peak, and

$$\sum_{n=o}^{2\mu_1} WLP(n) \simeq 1$$

$$\sum_{n=o}^{2\mu_2} WIP(n) \simeq 1.$$

Keeping the calculated rates a(t) and r(t) constant for one day, the numerical solution of the differential equations is obtained for one day by using the Runga Kutta procedure. Thus the final value of variables at the end of the day is obtained from the known initial values. The final values now calculated constitute the initial values for the next day. The process is continued till the value of infectives becomes negligibly small.

The solution of the model is obtained, taking the mean values of latent and infections period to be 7 days. The standard deviations assumed are 1.4 and 2.0 respectively. Although these values are completely arbitrary, they resemble those calculated by Bailey [2] for his measles epidemic model. (Since the purpose here is only to demonstrate the applicability of the new model to various diseases, the arbitrariness of the above values does not detract from the ensuing discussion.) The model has been solved for values of β varying from 0.2 to 3.0 and for initial susceptible populations varying from 0.1 to 1.0. Since the only observable measure of disease, in actual practice, is the number of reported cases per day or week, the results of the above analysis have been plotted with x-axis representing time in days and y-axis representing the reported cases (x_3) per day.

Figure 2.2 shows the solution of the new model with a constant β but with variable initial susceptibles. The result is a family of 10 bell shaped curves, each representing the response for one value of initial susceptibles between 0.1 to 1.0. The figure shows clearly that the spread of disease is most violent when the entire population is susceptible, i.e. when disease has been introduced into a virgin population. The severity of the disease successively decreases as the initial susceptibles are assumed lesser and lesser, till a threshold value of initial susceptibles is reached below which disease does not start. The latter point is made more clear in figure 2.3, which is a

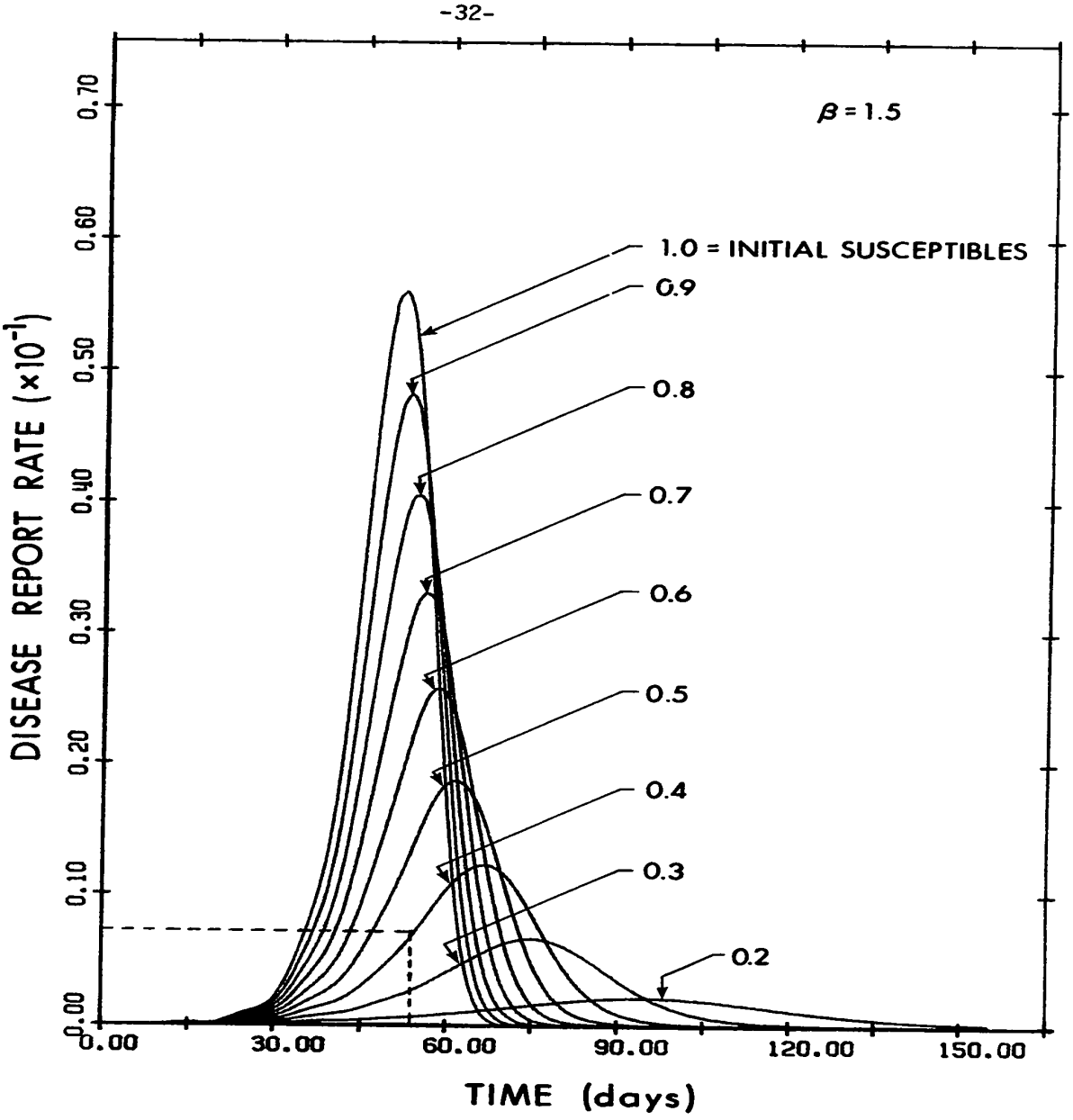


FIG. 2-2 EPIDEMIC RESPONSE FOR FIXED β AND VARIABLE INITIAL SUSCEPTIBLES

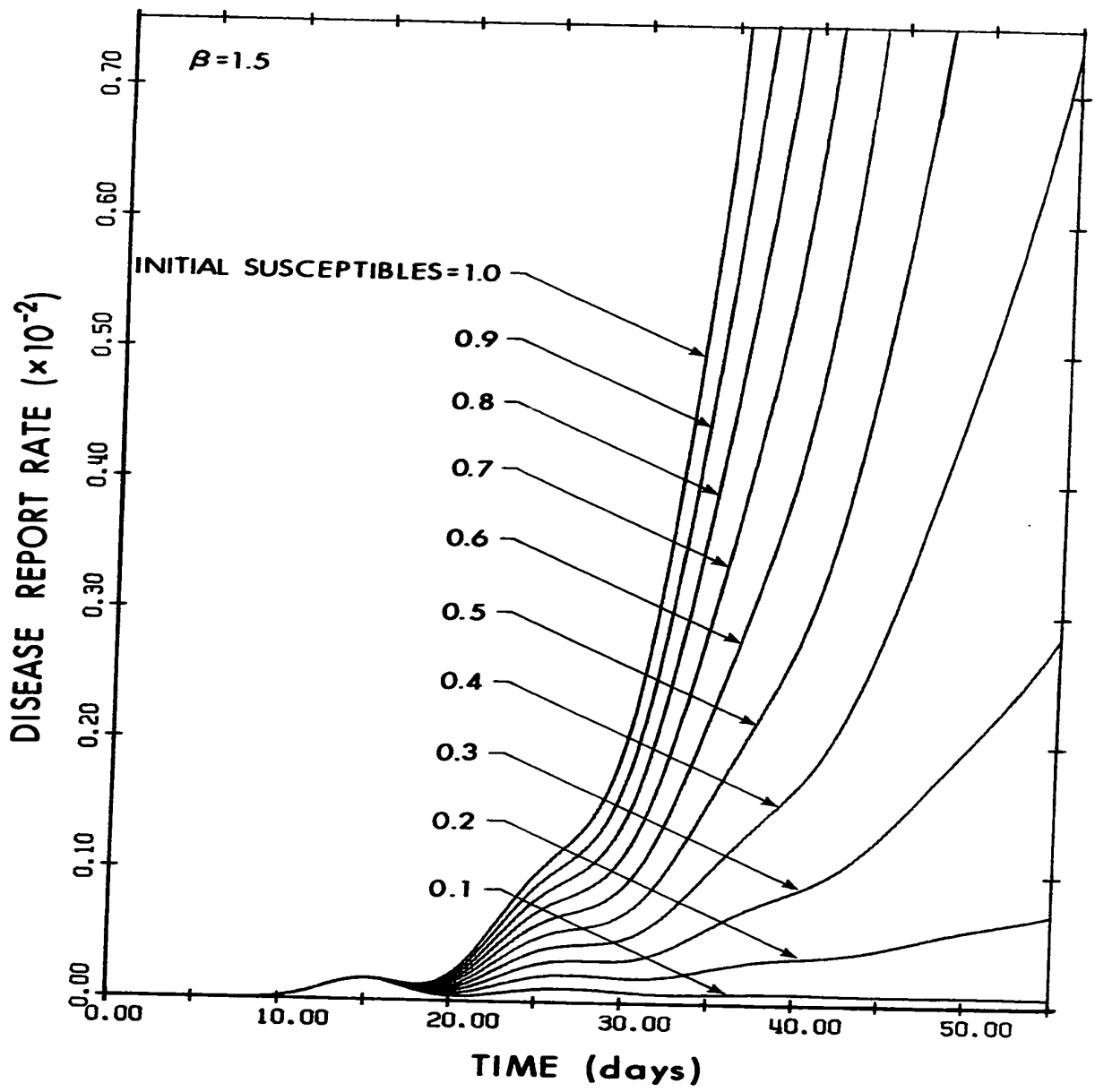


FIG. 2·3 BOXED AREA IN FIGURE 2·2 ON ENLARGED SCALE

replot, at enlarged scale, of the area enclosed by dotted lines on figure 2.2. The threshold value of initial susceptibles is 0.1 for $\beta = 1.5$. These results are in line with the known results of standard deterministic models.

In addition to the above conventional results, we observe that in the beginning of the epidemic the successive generations of cases, separated by approximately an incubation period, are also visible. This fact, generally observed during actual epidemics, is shown very clearly in figure 2.3. Therefore, we note an improvement over previous deterministic models which failed to represent this phenomenon.

Figure 2.4 shows the rate of reported cases as function of time, now with variable β and constant initial susceptibles. β is varied over a wide range (0.2 to 3.0) whereas initial susceptibles are the same (0.5) in each case. We find that for a given initial susceptibles the epidemic peak is larger for larger values of β. Figure 2.5, which is again a replot, at enlarged scale, of the area enclosed by dotted lines on figure 2.4, shows that there is a threshold value of β below which disease will not start. Thus we find that each initial-susceptibles value has a threshold value of β. This result is in line with the modified threshold theorem of Landau et al. [24], although stated differently.

The existence of threshold values of initial susceptibles and contact rate β gives a possible explanation of the flare-up of endemic

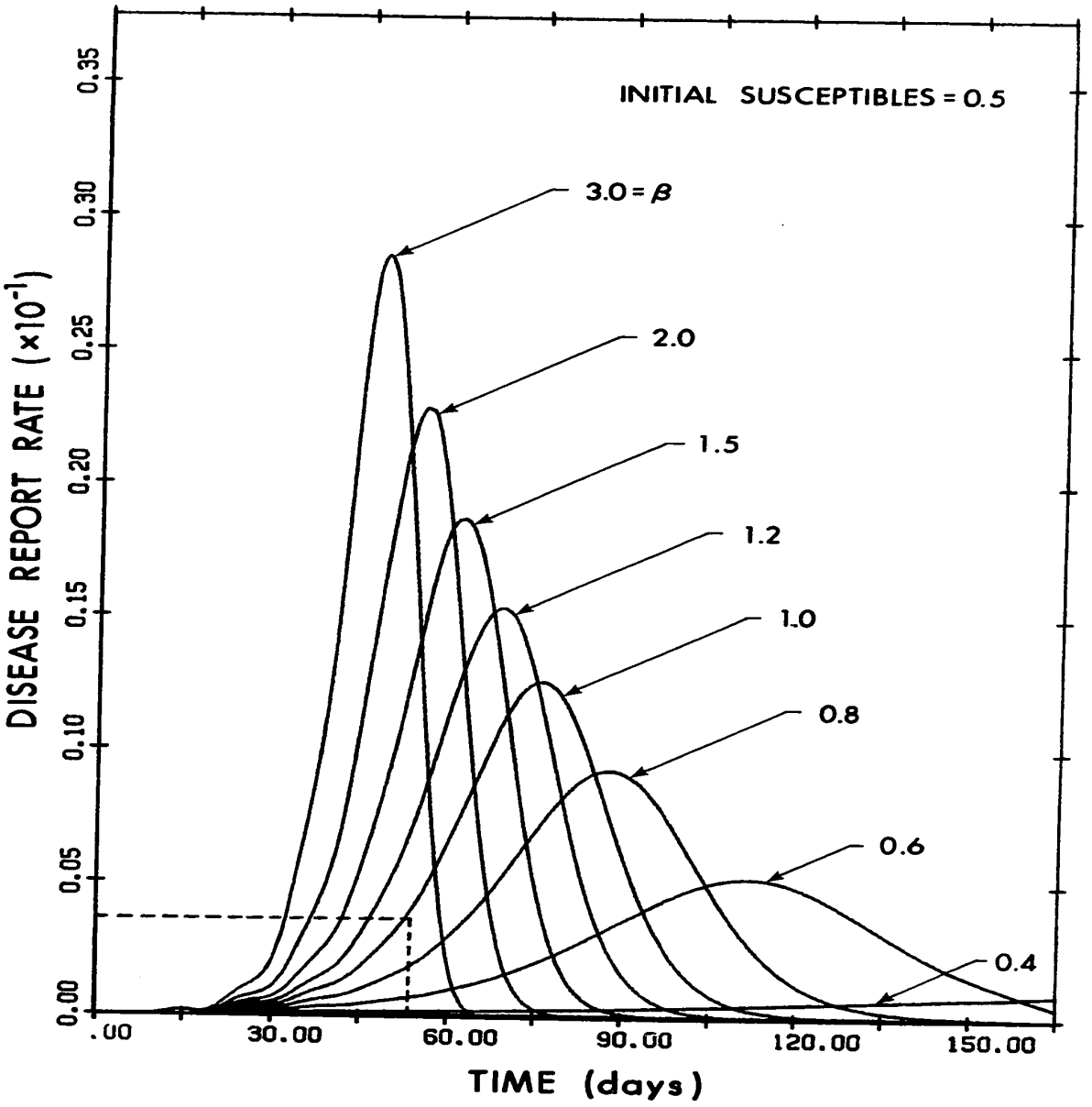


FIG. 2-4 EPIDEMIC RESPONSE FOR VARIABLE β AND FIXED INITIAL SUSCEPTIBLES

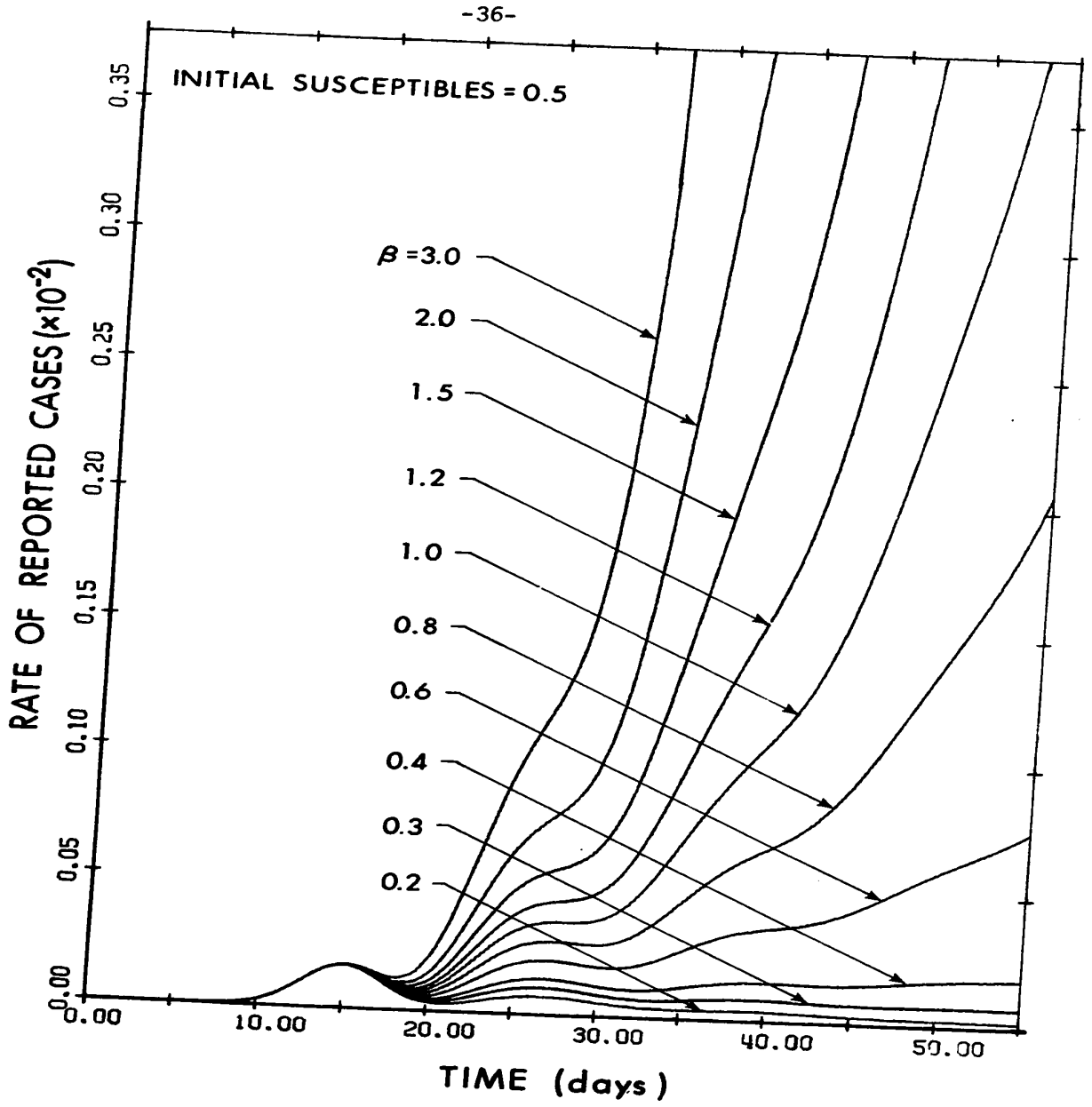


FIG. 2·5 BOXED AREA IN FIGURE 2·4 ON ENLARGED SCALE

diseases. It appears that when an epidemic wanes it leaves most people immune to the disease, i.e. the "herd immunity" is high. As time passes the herd immunity goes on decreasing, due to the addition of more susceptibles by new births and removal of immune older people by death. Some individuals also loose immunity with time. Thus the susceptible population builds up but still remains below the threshold value for the prevailing β. But when, due to meteorological changes or some other reasons, β suddenly drops, the initial susceptibles are now more than the threshold value for the new β and a flare-up of epidemic occurs. Studies of Spicer [39] and Wise [46], support the contention that weather changes and meteorological factors have definite effect on the infectiousness of diseases, thus supporting the above hypothesis.

In conclusion, we can say that the new model is quite reasonable in representing many phenomena connected with disease spread and is likely to be a useful tool in the study of epidemics. The latter is borne out by the control studies to be presented in the next two chapters. It may be mentioned here that the curves of figure 2.4 are very similar to those presented by Hopensteadt [16], where the Cook model was used with an added constant latent period. The only difference is that our model shows the successive generations of cases in the beginning, which is an improvement.

CHAPTER III

MODEL WITH CONTROL

3.1 Introduction

In his presidential address to the Royal Society of Tropical Medicine and Hygiene (1965), Dr. G. McDonald [28], while talking of mathematical models for disease spread, said: "When it comes to development of policy in such a way as to gain the initiative and ultimately gain complete mastery over an infection throughout substantial areas of populations, scientific knowledge has as yet scarcely been brought into play. There are techniques by which such policy can be developed. An important one is the study of dynamics of infections, with full evaluation of their relative susceptibility, in terms of prevalence, to alterations in different aspect of environment. In this way their sensitivity to control can be put on a scientific footing and much of the present element of "Hit and Miss" removed from the general study."

The remarks quoted above underline the fact that any advance in the art of mathematical modeling of epidemics is in itself a contribution to the control of disease spread. This is so because it helps in the understanding of mechanism of disease spread and hence helps in the formulation of control strategy. In this respect the model discussed in the previous chapter represents a significant contribution, as it shows the sensitivity of the disease spread to initial susceptibles,

to changes in β, and to the values of latent and infectious periods. A constant monitoring of the susceptible population, to keep it below its known threshold value, and control of β, to make it as low as possible, go a long way to prevent the disease spread. General notification, closing up schools and other public places, and enforcement of strict quarantine etc., are the methods commonly used to reduce β and to prevent disease spread when such a danger exists. If the quantitative effect of these measures on the value of β is known, their preventive effect can be easily estimated by the use of this model.

The above preventive methods, although universally used, have only a limited effect and are difficult to enforce, especially under the modern conditions of swift travel. They have either to be supplemented or altogether abandoned in favour of the sophisticated methods of immunization now available. These methods, which create artificial immunity or resistance to the disease, are active immunization, passive immunization, and chemoprophylaxis. This Chapter is primarily concerned with the modification of the epidemic model to include parameters representing controls by the first two of these methods. An analysis of the model with respect to the sensitivity of its response to these controls is presented.

3.2 State of the art

Although a considerable amount of work has been done in the field of mathematical modeling of epidemics, yet the incorporation of

control effects in these models is only in the beginning stages. In fact, only three serious efforts where control is incorporated in the epidemic models have come to this author's notice; those of Jacquette [17], Taylor [40] and ReVelle [33]. Among these, the last is the one closest to the situation in practice, as it studies the quantitative effect of various controls, applied at different rates, on the final cost of the disease control. The other two studies evaluate the economic benefits of stopping a disease instantaneously by massive application of control. The assumption of unlimited control for stopping the disease may be practical from the point of view of disease control in isolated cattle herds, but is hardly realistic from the public health administration point of view.

In practice, the control of disease spread in large population, always strains the resources of public health authorities. Modern practice of epidemic control consists of the administration of one or more of the three possible controls: (1) active immunization, (2) passive immunization and (3) chemoprophylaxis depending upon the disease in question. Available quantities of drugs and vaccines, their rates of production by pharmaceutical industry, and the available number of public health personnel to administer these controls,are always limited. Hence the administration of these controls is anything but instantaneous. Therefore, in the interest of evolving a useful control strategy, it is imperative that the sensitivity of the

epidemic models to these controls is studied in some detail. ReVelle's [33, 34, 23] model, though quite realistic, is not general enough (it was developed specifically for tuberculosis) and has not been used for the study of sensitivity of the disease to the controls (B.C.G. vaccination and chemoprophylaxis in the case of tuberculosis). To remedy this situation, the model presented in Chapter II is modified, in the next section, to include active and passive immunization controls, and its sensitivity to each of the two controls is analysed. The model thus obtained is similar to the one presented previously by Gupta and Rink [13].

3.3. Active Immunization

Active immunization is the process of creating artificial immunity in the system of a susceptible by injecting a vaccine of either dead or live, but attenuated, disease micro-organism. The method induces the body's defense mechanism to produce antibodies specific to the micro-organism of the disease. The experience of producing the antibodies, thus gained by the susceptible, confers on him immunity to the disease in question. This immunity is almost comparable to the one gained on recovery from the disease. Its duration depends on the disease in question and the method used for the preparation and administration of the vaccine.

The effect of administering active vaccine to susceptibles is that of transferring them from the susceptible population to the

immune population, directly, without their going through the cycle of disease. An ideal situation would be to immunize every susceptible, thus eliminating the danger of disease spread altogether. This ideal is practically impossible to achieve and is economically undesirable, as almost the same results can be obtained by a constant surveillance of the population and administration of vaccine at such a rate that the population of susceptibles is always kept below the threshold value for the disease. Considering, however, the wide variety of diseases that may strike a population and the general reluctance or negligence on the part of individuals to get immunization when the danger is not imminent, it is almost impossible to have sustained active immunization. Therefore, there is always a possibility of an epidemic outbreak catching a community inadequately protected, and control has to be applied after the first signs of epidemic appear. It is this situation for which the model is modified to account.

One way of representing the active control is to assume that vaccine is given only to known susceptibles (which can be done by giving a test before giving the actual vaccine, as in the case of B.C.G.) and each dose is effective in providing immunity, immediately after administration. Thus if $U_1(t)$ is the rate at which susceptibles are being vaccinated at time t the susceptible population can be said to be reducing at that rate, due to active control. This fact can be incorporated in the model by changing equation (2.4) from

$$\dot{X}_1 = -\beta_o X_1 X_2 \tag{3.1}$$

to

$$\dot{X}_1 = -\beta_o X_1 X_2 - U_1(t). \tag{3.2}$$

The assumption that an active vaccine is effective immediately after its administration is not wholly realistic, as all active vaccines need some latent period of their own for the immunity response. This may, however, be a reasonable assumption in the case of those diseases which have a long latent period, since in such cases immunity can develop before the disease does, even with a concurrent exposure.

Correspondingly, in the case of the normalized model equation (2.17) is changed from

$$\dot{x}_1 = -\beta x_1 x_2 \tag{3.3}$$

to

$$\dot{x}_1 = -\beta x_1 x_2 - u_1(t), \tag{3.4}$$

where $u_1 = U_{1/N}$ is the number of vaccinations given per day, expressed as a fraction of the total population, and is the per unit equivalent of U_1.

Since it is not always convenient and even in some cases not possible to give a test for susceptibility, a more general situation will be where vaccine is given at random. In such a case we can assume that of the $U_1(t)$ vaccines given per day, at time t, only the fraction proportional to the susceptible population is useful and the others are wasted. So the effective immunization rate would, in that case, be $U_1(t)$. $\frac{X_1}{N}$

for un-normalized case and $u_1(t)\ x_1$ for normalized case.

It has been assumed so far that every vaccination given to a susceptible is a success. This is not true in actual practice, as we know now that there is significant failure rate which differs from vaccine to vaccine. This situation, however, can be easily considered by assuming $U_1(t)$ as the number of effective vaccinations rather than actual vaccinations per day. Another possibility to be considered is the delay in the effectiveness of vaccine. If an active vaccine may, on the average, be considered effective τ_c days after it is administerred, the control term becomes $U_1\ (t-\tau_c)$ or $u_1\ (t-\tau_c)$, as the case may be. The equations(3.2) and (3.4) respectively, become

$$\dot{x}_1 = -\beta_1\ x_1\ x_2 - U_1\ (t-\tau_c) \cdot \frac{x_1}{N} \tag{3.5}$$

$$\dot{x}_1 = -\beta\ x_1\ x_2 - u_1\ (t-\tau_c) \cdot x_1. \tag{3.6}$$

These equations, when incorporated in the respective versions of the model, give the modified control model for active control. As an example, the normalized model with active control will be as follows:

$$\dot{x}_1 = -\beta\ x_1\ x_2 - x_1\ u_1\ (t-\tau_c) \tag{3.7}$$

$$\dot{x}_2 = a(t) - r(t) \tag{3.8}$$

$$\dot{x}_3 = r(t) \tag{3.9}$$

$$\dot{x}_4 = \beta\ K(t) \cdot x_1\ x_2 \tag{3.10}$$

$$\dot{x}_5 = u_1(t) \tag{3.11}$$

where
$$a(t) = \frac{1}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_1} \int_0^{2\mu_1} \dot{x}_4(t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_1^2} (\mu_1-\tau)^2 \right] d\tau \quad (3.12)$$

$$r(t) = \frac{1}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_2} \int_0^{2\mu_2} \dot{x}_4(t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_2^2} (\mu_2-\tau)^2 \right] d\tau, \quad (3.13)$$

and other forms of a(t) and r(t) are the same as those presented in Chapter II, equations (2.23) to (2.26). The new variable $x_5(t)$ represents the fraction of population actively immunized up to time t; $x_5(t_f)$ will, therefore, represent the total vaccine used at final time t_f.

Results of the solution

The model is now analysed for different values of active control u_1. Control delay τ_c can be assumed to be equal to zero without loss of generality, as the control is first applied on a certain day and any delay τ_c simply shifts this time of application.

Figure 3.1 shows the effect of variable control u_1 applied over a fixed interval of time. Administration of control, at rates shown on each curve, is assumed to start on the 15th day (about one mean incubation period after the start of disease) and end on the 25th day. We observe from the figure that the higher the rate of active control, the lower the total number of cases.

Figure 3.2 shows the effect of different control rates with the total amount of control administered remaining the same in each case

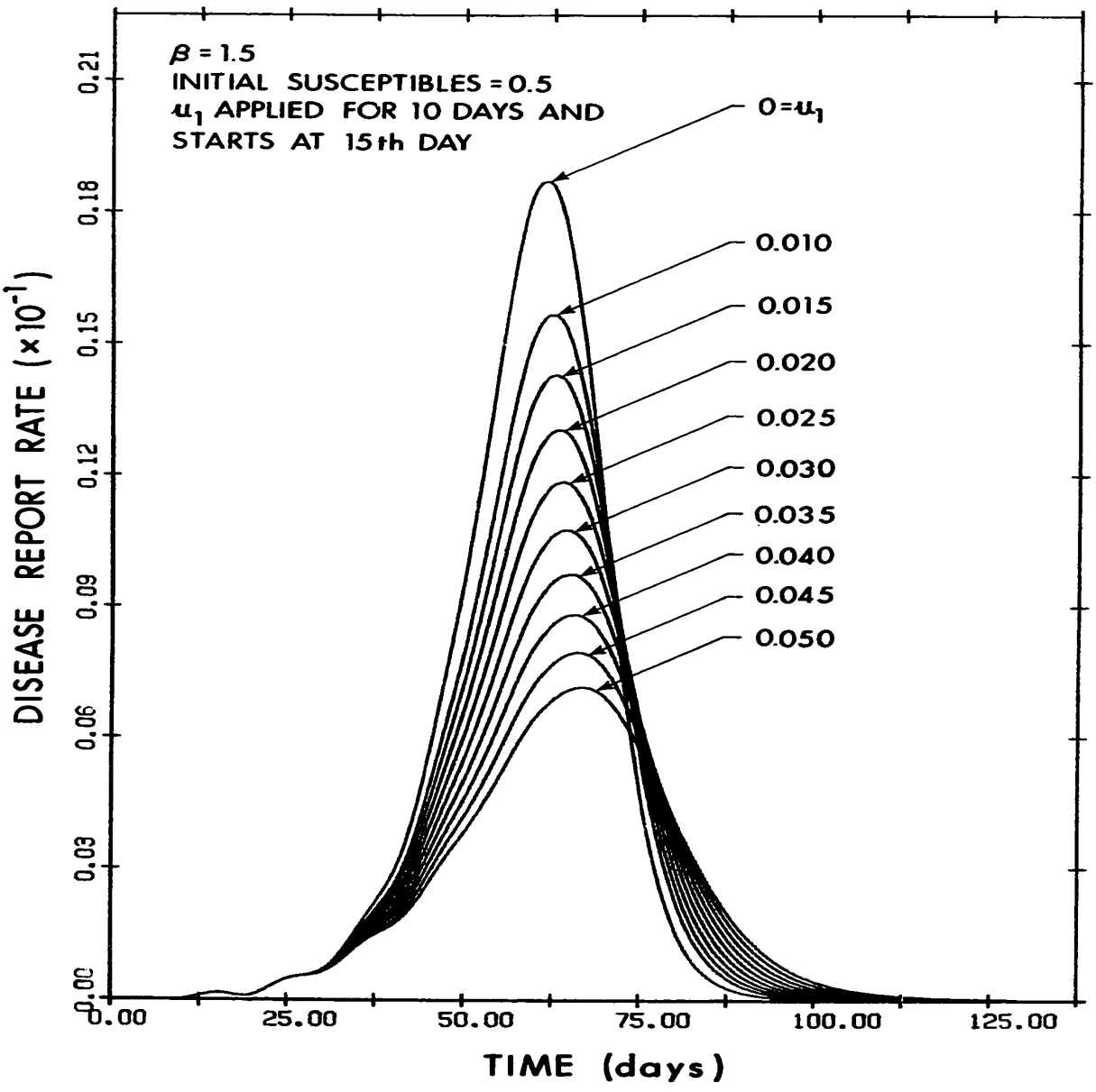


FIG. 3·1 EFFECT OF VARIABLE ACTIVE CONTROL

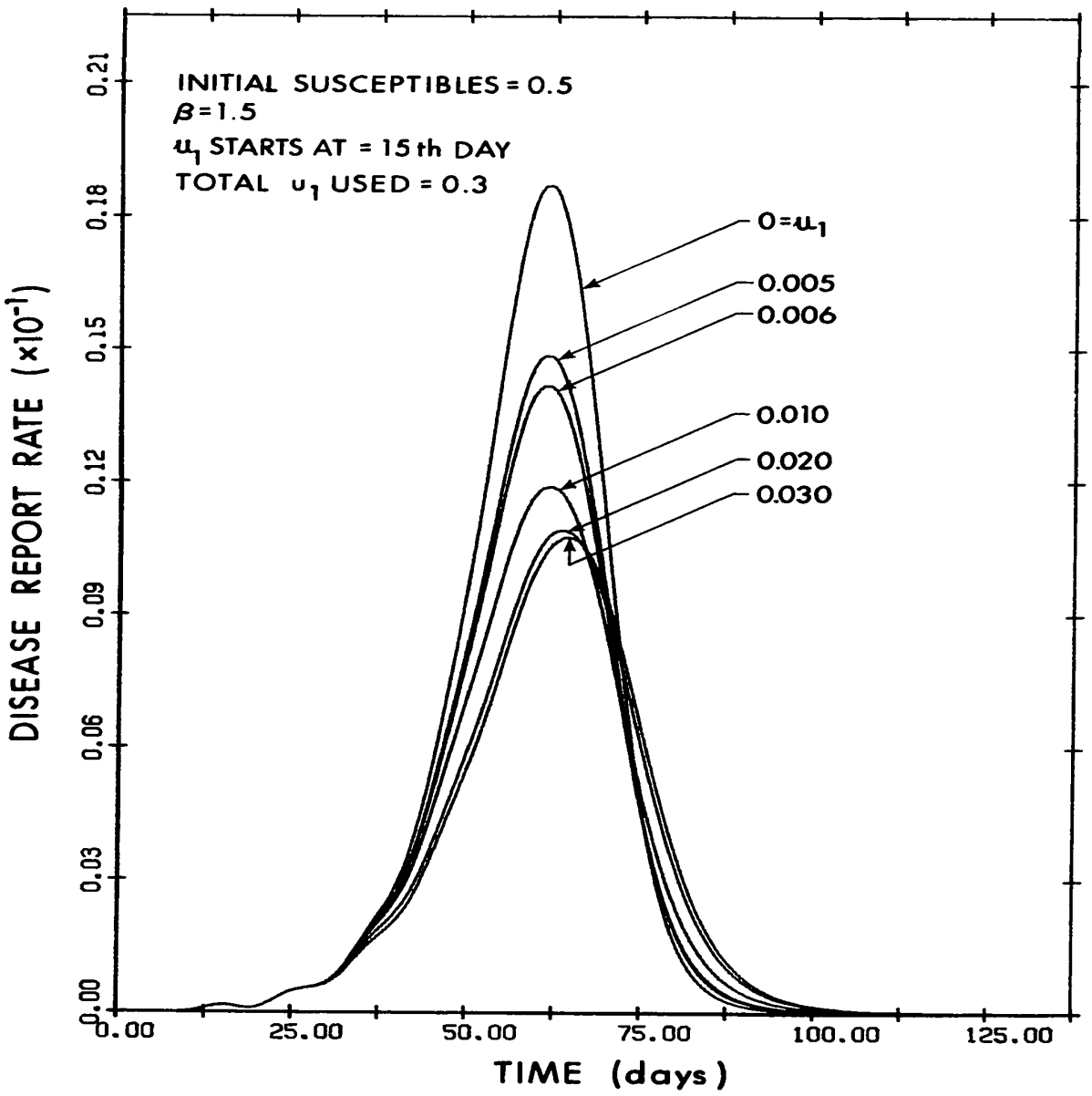


FIG. 3-2 EFFECT OF CONSTANT ACTIVE CONTROL APPLIED AT VARIABLE RATE

and, again, the control starting at the 15th day, but this time ending on a different day. The plot of the disease response, in this case, shows that best results are obtained by using the control at the highest rate although the total amount of control remains the same.

Figure 3.3 shows the effect of delay in the application of control. In each case the same amount of control (0.3) is used and at the same rate ($u_1 = 0.03$), but the control starts at different times. The delay in the start of the administration of control represents the time lag in putting the control effort in action. This time lag may be due to the immediate non-availability of the vaccine in sufficient quantities, or simply due to a failure to realize the epidemic nature of the disease. We find from figure 3.3 that the disease is best controlled by the earliest action, and the larger the delay, the less effective is the control.

Thus we conclude from these three plots that the best results are obtained by applying the available active control at the highest possible rate and at the earliest available opportunity. These results seem to be what common sense would suggest. However, since now we are able to evolve a quantitative measure of the effect of active control, the feasibility of an optimum control strategy is very clear, and the next chapter evolves this strategy by using Pontryagin's Minimum Principle.

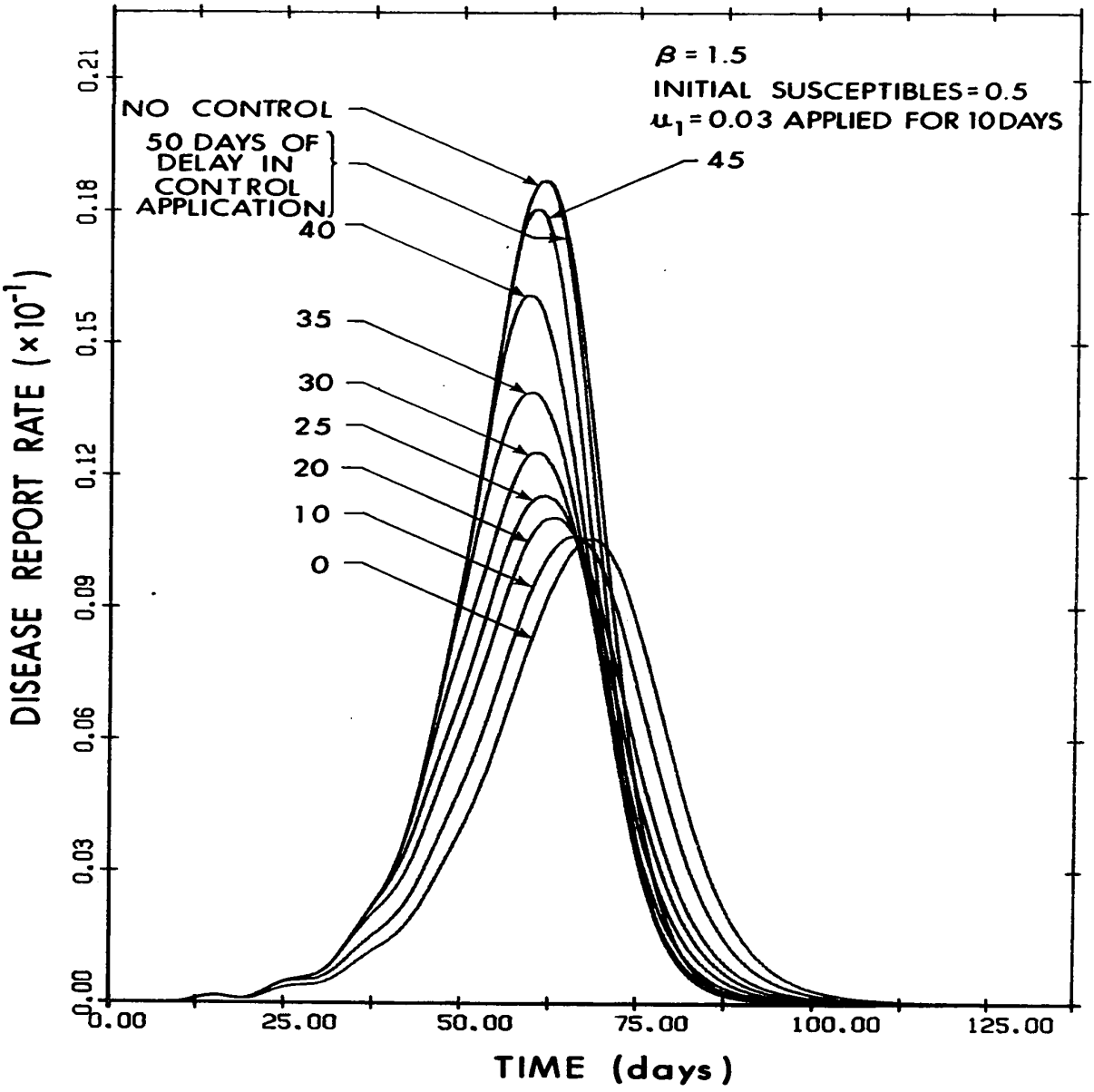


FIG. 3·3 EFFECT OF DELAY IN APPLICATION OF ACTIVE CONTROL

3.4 Passive Immunization

As opposed to active immunity, which is the process of creating antibodies in the system of a susceptible, passive immunity is provided by injecting "ready made" antibodies into the system of an individual. This form of immunity is immediately effective and is even curative in nature. The immunity provided in this manner, however, is not as permanent as one conferred by active immunization, and is liable to be lost quite soon. Other hazards of passive immunization are the possibility of introduction of other infections from the source of antibodies (human or animal blood plasma) and incompatibility of the system to foreign plasma. Notwithstanding the above difficulties, passive immunization is now an accepted method of control for those diseases for which antiserum, needed for passive immunization, can be easily produced. This antiserum is generally administered to those suspected of already carrying the disease micro-organism in their system, thus making them ineffective in spreading the disease further.

The accurate quantitative effect of the passive immunization on the latent and infectious periods of the disease, and the duration of immunity it may confer on those immunized, is not yet fully known. The methods of representation of passive control discussed in the next few paragraphs may, therefore, not be the best possible, but may serve as a guide. More over these methods of representation may, hopefully, also

be used to represent the action of chemoprophylaxis a method of control which is not discussed in this thesis for lack of knowledge about its action on various sub-populations of the model. Two different methods of representation of passive immunization have been used to adapt the model to passive control. Sensitivity of the model to changes in the passive control has been analysed in both cases.

Case 1

In this case the passive immunization is assumed to be administered at random, thus removing both susceptibles and infectives from circulation by conferring on them a temporary immunity. Representing the passive control by U_2 inoculations per day, in the same way as in the case of the active control model but with a difference that now immunity is conferred both to susceptibles and infectives, the modified model for the normalized case becomes

$$\dot{x}_1 = - \beta x_1 x_2 - u_2 x_1 \tag{3.14}$$

$$\dot{x}_2 = a(t) - r(t) - u_2 x_2 \tag{3.15}$$

$$\dot{x}_3 = r(t) \tag{3.16}$$

$$\dot{x}_4 = K(t) \cdot \beta x_1 x_2 \tag{3.17}$$

$$\dot{x}_6 = u_2 \tag{3.18}$$

where $u_2 = U_{2/N}$; $a(t)$ and $r(t)$ are the same as those given by equations

(3.12) and (3.13) respectively, and x_6 is the new variable representing the total amount of passive control. It may be noted, here, that no time delay is considered in the control variable in this case, since it is known that passive control acts almost instantaneously. In fact this is the major advantage of using this control.

Results of the solution

Figure 3.4 represents the solution of the model for different rates of passive control. We find that the higher the control rate used, the smaller the number of cases. It may also be noted that, for the same reduction in cases, the amount of u_2 used is much smaller than the amount of u_1. This is an expected result, as we know that passive control acts on the infective cases also,and as such is a more effective way of suppressing disease, at least temporarily.

Figure 3.5 shows the effect of delay in application of passive control. A constant (.01) rate of passive control is used in all the cases but it is started at different delays after the start of disease. We note that the effect of control is maximum when it is applied at the earliest time.

Case 2

In case 1 it was assumed that the passive immunization is given to the population at random. However, in practice it is preferable to give passive immunization to the known contacts of reported

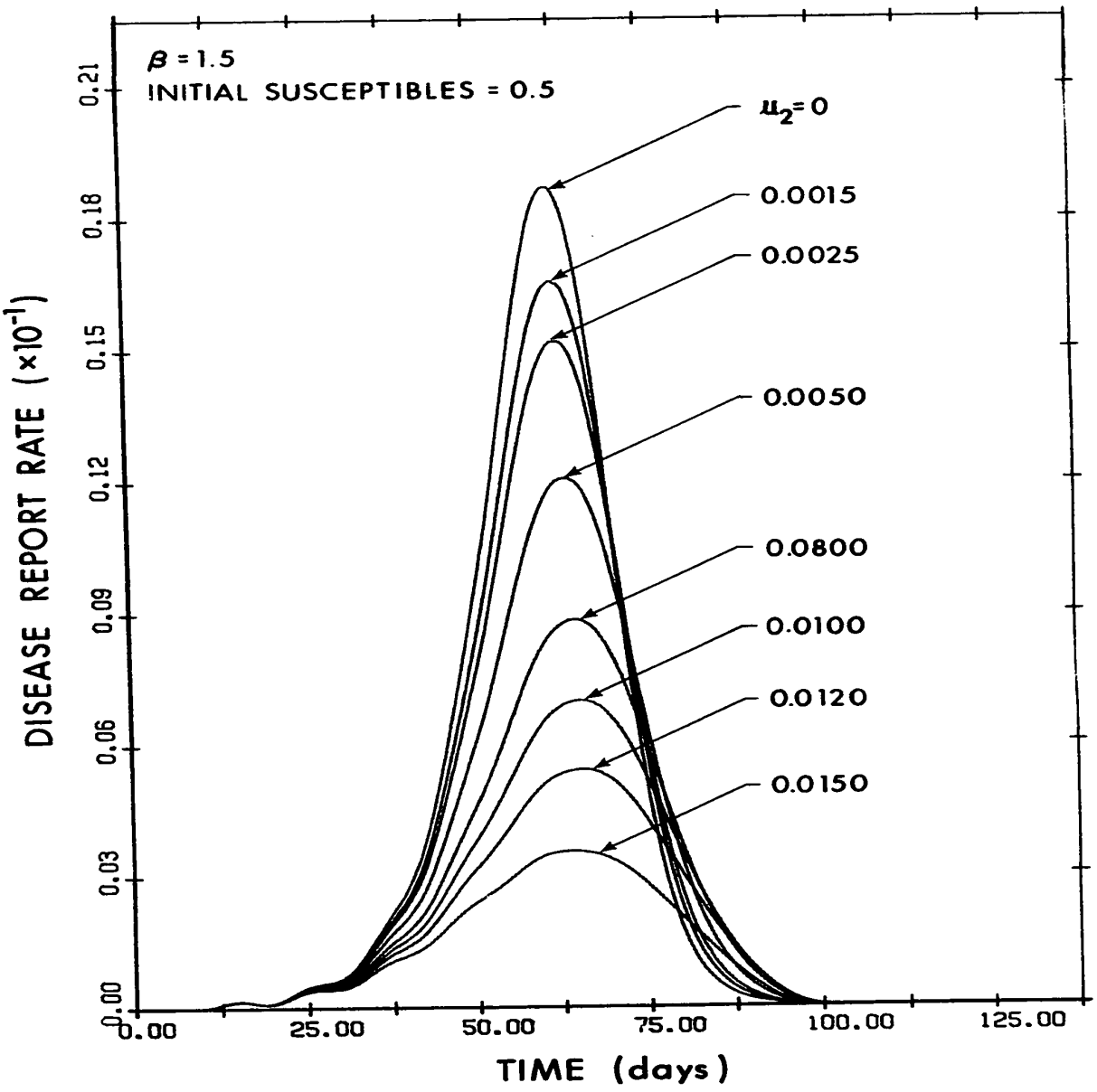


FIG. 3·4 EFFECT OF VARIABLE PASSIVE CONTROL
CASE 1

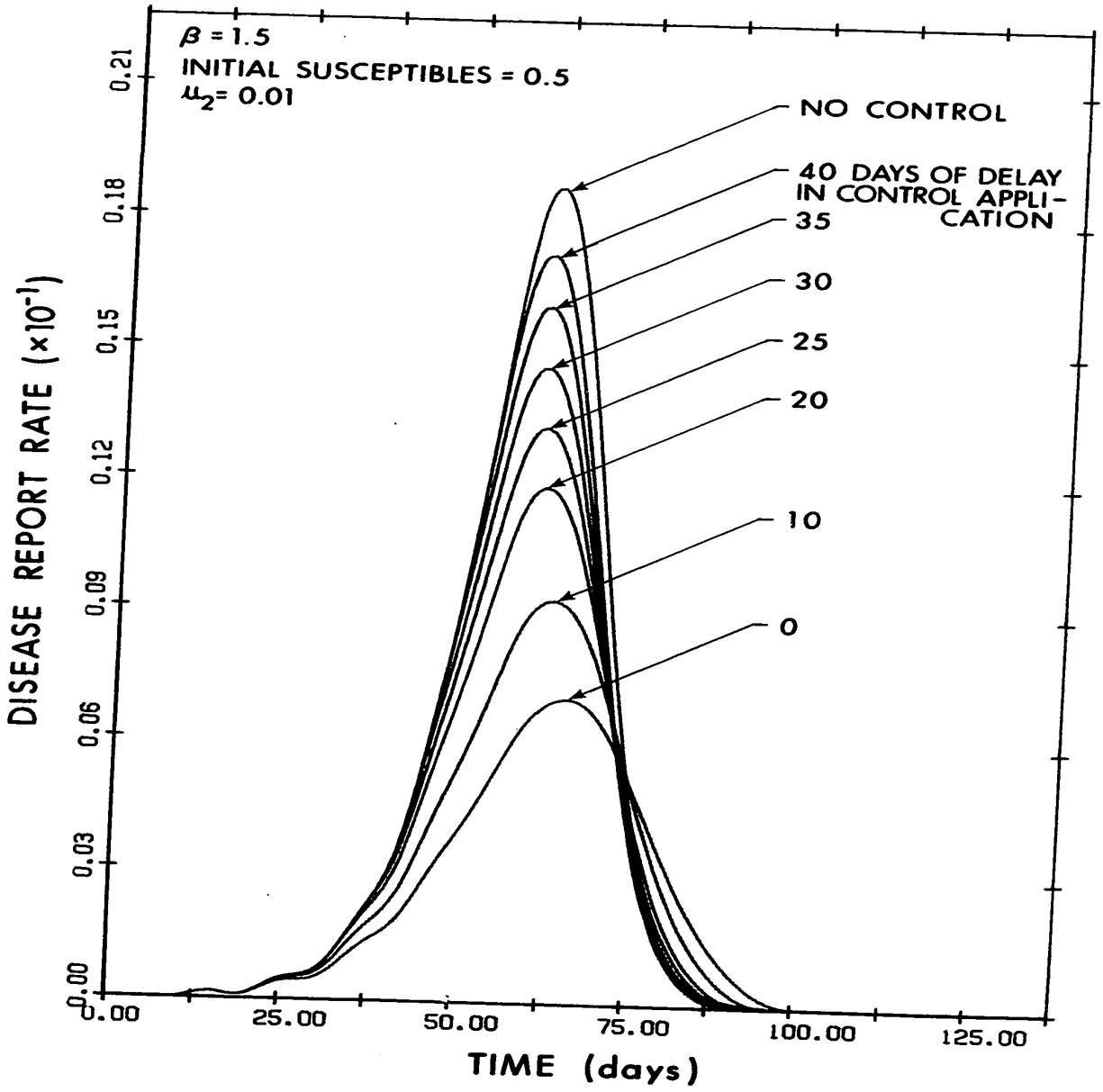


FIG. 3·5 EFFECT OF DELAY IN PASSIVE CONTROL APPLICATION CASE 1

cases. Thus, to represent a situation of this kind we assume that when a case is reported its contacts are traced and those who might have picked up the disease may be given passive immunization to suppress the disease. We can assume that on the average U_2 infectives are given passive immunization, per reported case. Thus the rate of reduction in the infective population due to passive vaccination may be assumed to be U_2 R(t) per day. This rate becomes U_2 r(t) for a normalized model. It may be noted here that in this case U_2 is a non-dimensional quantity, as it represents the number of infectives traced per reported case.

The modified normalized model now is:

$$\dot{x}_1 = - \beta x_1 x_2 \tag{3.19}$$

$$\dot{x}_2 = a(t) - r(t) - U_2 r(t) \tag{3.20}$$

$$\dot{x}_3 = r(t) \tag{3.21}$$

$$\dot{x}_4 = K(t) \beta x_1 x_2 \tag{3.22}$$

$$\dot{x}_6 = U_2 r(t), \tag{3.23}$$

where a(t) and r(t) are as defined in case 1 and x_6 corresponds to x_5.

Results of the solution

Figure 3.6 shows the result of the solution of the model for various values of U_2. We find that as U_2, the number of infectives removed per reported case, is increased the disease is better controlled.

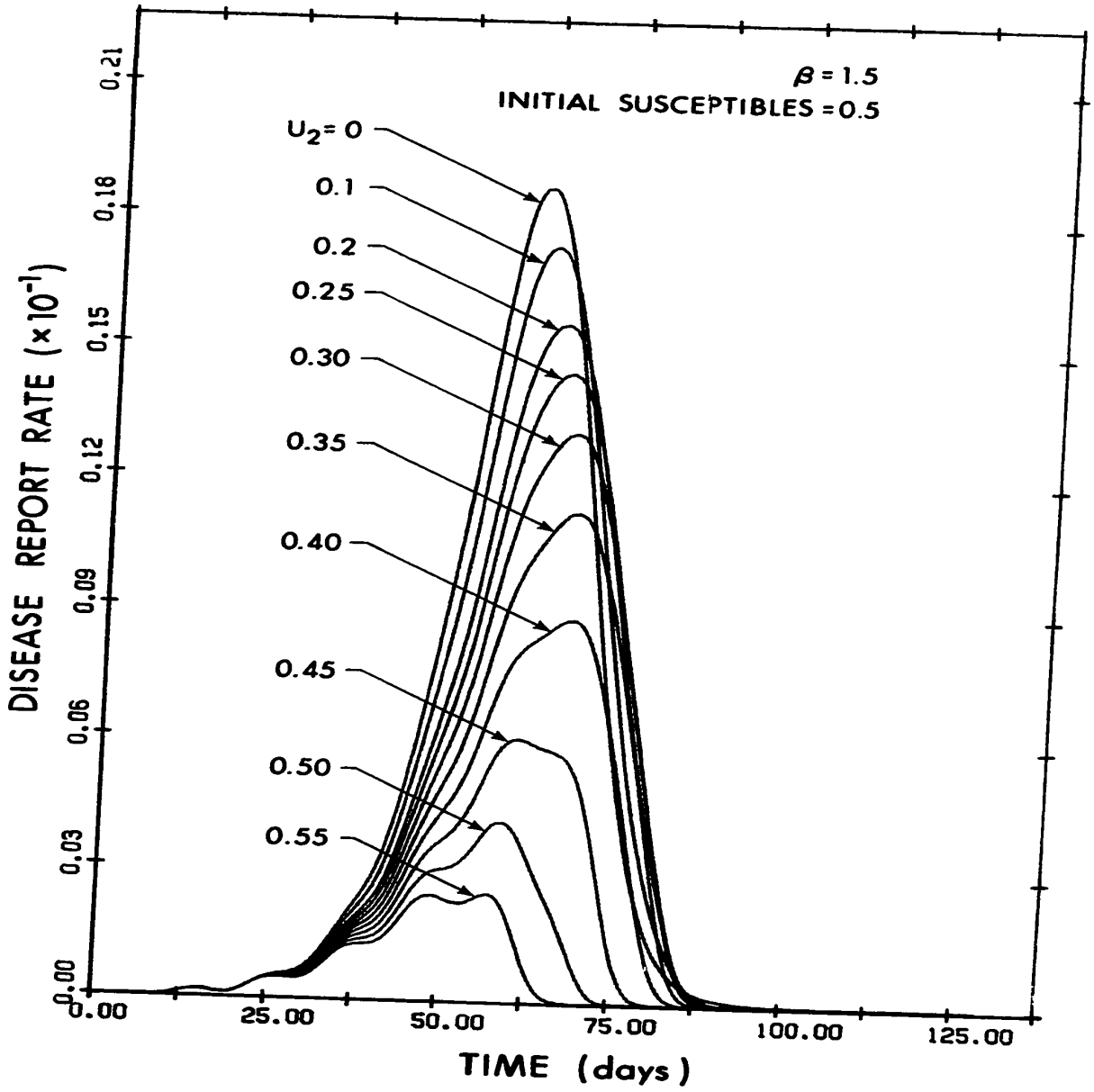


FIG. 3-6 EFFECT OF VARIABLE PASSIVE CONTROL
CASE 2

Figure 3.7 shows the effect of delay in starting the administration of passive control. As would be expected, the control is most effective when started at the earliest time. Thus we conclude, again, that for best results maximum control effort should be applied at the earliest possible time.

3.5 Conclusions

In this Chapter the sensitivity of the model to active and passive controls,each taken separately, has been analysed. Control with chemoprophylaxis was not considered. It is, however, clear that the third control can also be incorporated in the same manner as the other two. While considering the model with control, no limitations on the availability of the vaccines and antisera, and on their costs, have thus far been considered. In practice, however, the more important question is: When more than one control method is available, how much of each should be used for best results ? This problem is very difficult to solve with the methods of analysis used in this chapter, since, if various combinations of controls were to be tried in a hope of finding the best combination, we are likely to end up doing a large number of solutions of the model, yet having no certainty of finding the best combination of controls. This problem will, however, be solved in the next chapter using the method of dynamic optimization.

In conclusion, as a result of the discussion so far, we can

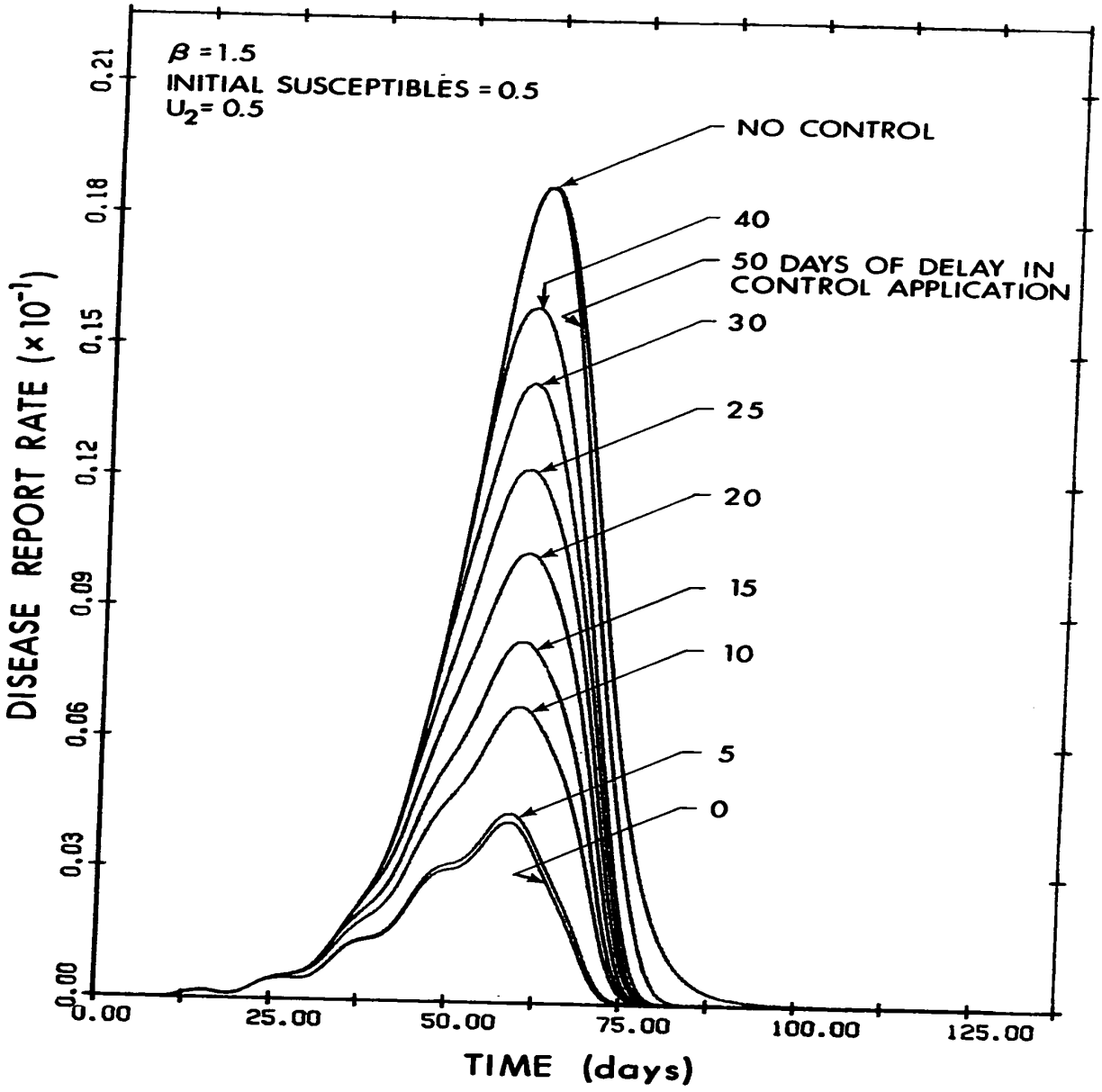


FIG. 3-7 EFFECT OF DELAY IN PASSIVE CONTROL APPLICATION CASE 2

write the model incorporating both the controls. Since we have used two different methods of representing passive control, we have two different forms of the model. Only the normalized model is given here for both the cases.

Case 1

$$\dot{x}_1 = - \beta x_1 x_2 - u_1(t-\tau_c) \cdot x_1 - u_2 x_1 \quad (3.24)$$

$$\dot{x}_2 = a(t) - r(t) - u_2 x_2 \quad (3.25)$$

$$\dot{x}_3 = r(t) \quad (3.26)$$

$$\dot{x}_4 = K(t) \cdot \beta x_1 x_2 \quad (3.27)$$

$$\dot{x}_5 = u_1(t) \quad (3.28)$$

$$\dot{x}_6 = u_2(t). \quad (3.29)$$

Case 2

$$\dot{x}_1 = - \beta x_1 x_2 - u_1 (t-\tau_c) \cdot x_1 \quad (3.30)$$

$$\dot{x}_2 = a(t) - r(t) - U_2 r(t) \quad (3.31)$$

$$\dot{x}_3 = r(t) \quad (3.32)$$

$$\dot{x}_4 = K(t) \cdot \beta x_1 x_2 \quad (3.33)$$

$$\dot{x}_5 = u_1(t) \quad (3.34)$$

$$\dot{x}_6 = U_2 r(t) \; . \quad (3.35)$$

In both the cases a(t) and r(t) are defined as in equations (2.21) to (2.26) in Chapter II, depending on the choice of representation to be used. Representative expressions for a(t) and r(t) when mean value of incubation period is used are:

$$a(t) = \frac{1}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_1} \int_0^{2\mu_2} \dot{x}_4 (t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_1^2} (\mu_1-\tau)^2 \right] d\tau \qquad (3.36)$$

$$r(t) = \frac{1}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_2} \int_0^{2\mu_2} \dot{x}_4 (t-\tau) \cdot \exp\left[- \frac{1}{2\sigma_2^2} (\mu_2-\tau)^2 \right] d\tau. \qquad (3.37)$$

CHAPTER IV

OPTIMUM CONTROL MODEL

4.1 Introduction

Constant vigil kept by the public health organizations around the world has helped to allay, considerably, the danger of full-scale epidemic outbreaks. This preventive effort, however, entails large sums of money, and efforts are always underway to improve the control procedures so as to reduce this expenditure and get maximum benefits with minimum outlay. The mathematical theory of epidemics, by providing a better insight into the mechanisms of disease spread, has indirectly contributed to the fulfilment of the above stated goal, since a better understanding of the mechanisms of disease spread, always,results in improved methods for its prevention. There is, however, a consensus in the literature that the mathematical models have not yet been used to their fullest potential for the control of epidemics. In particular, the use of these models in determining a most economical control strategy between various competing controls, by the use of dynamic optimization techniques, has been frequently predicted. This chapter presents a procedure for the application of dynamic optimization theory to the control model developed in Chapter III.

Three references, viz. ReVelle [33], Taylor [40], and Jacquette [17], were discussed in the last chapter for their contri-

bution to the field of epidemic control models. It is significant to note that the same three research efforts are also the ones that consider the question of economical control strategy, and no other work in this field has yet come to the notice of this author. ReVelle [33] considered three competing controls (prophylaxis, cures and B.C.G. vaccination) for his tuberculosis model. Four alternative control strategies, each reducing the epidemic to an assumed level in a fixed time, were considered, and the one involving minimum control cost was identified. Taylor [40] considered a herd of dairy cattle which can be immunized, at any time, to confer complete immunity, if so desired. A vaccination schedule that minimizes the long-run time-average sum of the costs of immunization and expected disease losses was determined. Jacquette [17], in turn, assumed that an epidemic can be stopped instantly by a massive dose of immunization and proceeded to find out the most economical time of this stopping.

Although the three studies, summarized above, are significant contributions to the field of economical control of epidemics, yet each stopped short of the stated ideal of determining control strategy by dynamic optimization techniques. The following quotation from the latest of these studies [17, pp. 11-12] illustrates the point:

> "We will see that the standard calculus of variation or control theory techniques for dynamic control of coefficients (or state variables) fail since the differential equations of the model are second degree. Ideally a solution consisting of an optimal control trajectory is desired, but this must be left as a topic for further work. Steady state solutions are available and controllable coefficients can be set to minimize the average cost per unit time. In cases where the model variable is a known function of time we will look at a direct form of control and discover an analogy with inventory theory."

The new model, discussed in the previous chapters, removes some of these difficulties and is used for determining an optimum control strategy by the direct application of Pontryagin's Minimum Principle. The model has been converted to a set of non-linear differential difference equations by the substitution of the variables a(t) and r(t) in their discrete form (equations 2.24 and 2.25). The resulting state equations are functions of delayed states and delayed control, both with finite number of delays. Solutions resulting from the optimum control study of this model are presented.

4.2 Formulation of the control problem

The final form of the normalized control model, incorporating both active and passive immunization controls, was presented in the concluding section of Chapter III. This model can now be modified, by reducing its dimensionality, to make it more suitable for optimization study. It may be pointed out here that the results obtained

from the normalized model, which will be the only form considered here, can easily be extended to non-normalized model, if so desired.

A quick review of equations (3.24) to (3.37), representing the model for two different formulations of passive control, reveals that the fourth equation of the model, in both the cases, can be easily eliminated by substituting it in the expressions for variables a(t) and r(t). Moreover, by introducing a new equation representing the cost of the control used, the last two equations of the model can also be dropped without, in any way, reducing the effectiveness of the model for optimization. Since it is intended to obtain the model in the differential-difference form rather than the integro-differential form, discrete versions of a(t) and r(t) (represented by equations (2.24) and (2.25) rather than those represented by equations (3.36) and (3.37)), will be used in the modified model. In addition, we can replace the 'x' variables by y to avoid confusion in the subscripts used in the previous chapters.

Thus keeping the above modifications in mind and substituting the resulting expressions for a(t) and r(t) in the main equations of the model, the model, for two cases of the last chapter, now becomes:

Case 1

$$\dot{y}_1 = - \beta\, y_1\, y_2 - u_1(t-\tau_c) \cdot y_1 - u_2\, y_1 \qquad (4.1)$$

$$\dot{y}_2 = \frac{K\beta}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_1} \sum_{n=o}^{2\mu_1} \left[\exp \{- \frac{1}{2\sigma_1^2} (\mu_1 - n\tau)^2\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau)$$

$$- \frac{K\beta}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp \{- \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau)$$

$$- u_2(t) \cdot y_2 \qquad (4.2)$$

$$\dot{y}_3 = \frac{K\beta}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp \{- \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau) \qquad (4.3)$$

$$\dot{y}_4 = A\, u_1(t) + B\, u_1^2(t) + C\, u_2(t) + D\, u_2^2(t), \qquad (4.4)$$

Case 2

$$\dot{y}_1 = - \beta\, y_1\, y_2 - u_1(t-\tau_c) \cdot y_1 \qquad (4.5)$$

$$\dot{y}_2 = \frac{K\beta}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_1} \sum_{n=o}^{2\mu_1} \left[\exp \{- \frac{1}{2\sigma_1^2} (\mu_1 - n\tau)^2\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau)$$

$$- [1+U_2(t)] \frac{K\beta}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp \{- \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2\} \right] x$$

$$y_1(t-n\tau) \cdot y_2(t-n\tau) \qquad (4.6)$$

$$\dot{y}_3 = \frac{K\beta}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp \{- \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau) \qquad (4.7)$$

$$\dot{y}_4 = A\, u_1(t) + B\, u_1^2(t) + \{C + D\, U_2(t)\}\, U_2(t) \times \frac{K\beta}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp\{-\frac{1}{2\sigma_2^2}(\mu_2 - n\tau)^2\} \right] \times y_1(t-n\tau) \cdot y_2(t-n\tau) \; . \tag{4.8}$$

Where y_1, y_2 and y_3 represent the per unit sub-populations of susceptibles, infectives and recovered or removed cases; y_4 is the cost of immunization expressed on per unit basis; τ_c is the delay, in days, in the action of active control, and τ is the unit of time, one day in this case. Again, A and C are the linear and B and D the quadrature costs for the active and passive rates of immunization, respectively. A more explicit discussion of constants A, B, C and D will be given in a later section, where the numerical values for these constants are chosen.

Using the optimum control terminology, we can now call y_1, y_2, y_3 and y_4 the states, and equations (4.1) to (4.4) (also equations 4.5 to 4.8) the state equations of the model. If the initial values of states and their history up to the initial time t_o is known, the state equations can be solved for a given control function, using the procedure described in Chapters II & III. At the final time t_f, we then obtain the final values of the states, i.e. susceptibles,

infectives, recovered or removed cases, and the cost of immunization used during the course of the epidemic.

Cost function

The final cost of an epidemic can be assessed by adding the cost of cases afflicted to the cost of control used during the epidemic period. It is not suggested here that cost to an individual struck with disease can be counted in dollars and cents, especially in a fatal case, but what we mean by cost of a case is the weighted average cost with respect to the control cost (which can be determined more accurately). In physical terms, this weighted average cost may represent the cost of average man-hours lost plus the cost of hospitalization, for each reported case. In addition, it may be argued that if the disease is well controlled the fatality rate will be negligibly small and hence the cost per case, calculated on the basis defined above, is more near to the true cost. When the model is applied to an epidemic in a herd of cattle, however, the cost per case is more straight forward. Let us, therefore, assume that the cost of one reported case is C_1. The cost function, on the per unit population basis can then be written as

$$J = C_1 \, y_3(t_f) + y_4(t_f) \tag{4.9}$$

where J is the total cost of the controlled epidemic; $y_3(t_f)$ is the final value of the reported cases, and $y_4(t_f)$ is the total cost of the control applied during the course of the epidemic. Equation (4.9) can be modified to also include the cost for the residual infectives, if any, at the final time, thus giving,

$$J = C_1\, y_3(t_f) + C_1\, y_2(t_f) + y_4(t_f). \tag{4.10}$$

A control policy which minimizes the cost J at the end of an epidemic is the optimum policy. This control policy can now be formulated by the application of Pontryagin's Minimum Principle.

We thus have a vector state equation which consists of a set of non-linear differential-difference equations with a finite number of delays in both state and control. The cost function is a function of the final values of the state only, thus giving a Meyer problem. The optimization problem, although difficult, yet is not impossible to solve, especially in view of the latest research reported in the field. A closed-form solution is, however, impossible at this stage, and hence only a numerical solution is attempted.

4.3 State of the art

A considerable amount of work has already been done in the field of optimization of time delay control systems. Yet the theory

relating to this subject is being continuously updated as the solutions to an increasing number of problems of this nature are attempted. This fact is evidenced by some recent references in the field: [36], [27], [9].

Direct application of Pontryagin's Maximum (or Minimum) Principle to systems with time delay is due to G.L. Kharatishvili. He first applied the Maximum Principle to a system having a delay in state but not control; see Pontryagin et al [32, p. 213]. Subsequently, the method was extended by him to include the case of a delay both in state and in control; see Kharatishvili [22]. More recently (1970), Budelis and Bryson [9] developed necessary conditions for an extremal path in the case where the system equations and the performance index contain a time delay in both the state and the control variables. An analytical solution for a linear system with a quadratic performance index, where control variable appears in the system equations at the present time and at a previous time, was also presented by Budelis and Bryson [9]. McAulay [27] derived the optimum control criterion for a system consisting of non-linear differential-difference equations with a finite number of delays in the state. He, furthermore, extended the application of steepest descent (gradient) technique of Kelly [20] and Bryson [7] to this case.

Concerning the gradient methods, Gottlieb [12] has brought out the relationship of these methods with the calculus of variations and Min-H (Pontryagin's Minimum Principle) methods. He has also proposed two rapid convergence gradient methods for solving Min-H problems. Lasdon et al [25] have extended the application of conjugate gradient method to the Min-H problem, thus proving the applicability of general parallel tangent methods to this problem. Shah et al [38] have applied a parallel tangent (abbreviated "PARTAN") method to the minimization of a function of several variables.

A reasonably comprehensive solution of the epidemic control problem, formulated in the last section, can be obtained using the information contained in the research reviewed above. Although some of the theories developed in the research detailed above have been successfully applied, yet many of them have not, so far, been rigorously tested with a practical application. As such, the present problem provides an excellent practical application of the techniques discussed above.

4.4 Optimization procedure

The simulated epidemic control model was solved in Chapter III with known initial conditions and a termination criterion depending on the final values of some states. Thus, the optimum control problem,

formulated in section 4.2, is essentially one of fixed initial time and free terminal time. In view of the mathematical complication introduced by the free final time, the problem is, here, simplified by converting it to one of fixed initial and fixed terminal time. This is achieved by introducing a penalty function in the state equation. The procedure applied is explained in the following paragraph.

When solving the optimum control problem with fixed terminal time, it is likely that absolute minimum of the cost function would be obtained with the final values of some states becoming negative. This is a highly undesirable situation, since negative sub-populations have no physical meaning. In other words, we can say that there is an implicit constraint on the state variables, and this constraint is that the states should, always, have values greater than zero. This difficulty can be overcome by using a penalty constraint of the type suggested by Kelly [20, p. 215]. Therefore the penalty function needed to be added to the state equation for $\dot{y}_4$ is

$$\sum_{j=1}^{3} p_j \, \delta(y_j) \, y_j^2, \tag{4.11}$$

where p_j is a positive constant, suitably selected for the corresponding state, and δ is a Heaviside unit step function of argument y_j. In practice, however, we find that for the present problem, if a heavy

penalty constant is used for y_2 (the state representing the infective population), penalties on the other two states are unnecessary.

Concentrating our attention on case 1 of the model, and incorporating the inequality constraint on state y_2, the state equations can be rewritten as:

$$\dot{y}_1 = - \beta\, y_1\, y_2 - u_1(t-\tau_c) \cdot y_1 - u_2\, y_1 \tag{4.12}$$

$$\dot{y}_2 = \frac{K\beta}{\sqrt{2\pi}} \frac{1}{\sigma_1} \sum_{n=o}^{2\mu_1} \left[\exp\left\{- \frac{1}{2\sigma_1^2} (\mu_1 - n\tau)^2\right\}\right] y_1(t-n\tau) \cdot y_2(t-n\tau)$$

$$- \frac{K\beta}{\sqrt{2\pi}} \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp\left\{- \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2\right\}\right] y_1(t-n\tau) \cdot y_2(t-n\tau)$$

$$- u_2(t) \cdot y_2 \tag{4.13}$$

$$\dot{y}_3 = \frac{K\beta}{\sqrt{2\pi}} \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp\left\{- \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2\right\}\right] y_1(t-n\tau) \cdot y_2(t-n\tau) \tag{4.14}$$

$$\dot{y}_4 = p_2\, \delta(y_2) \cdot y_2^2 + A\, u_1(t) + B\, u_1^2(t) + C\, u_2(t) + D\, u_2^2(t). \tag{4.15}$$

The above state equations can now be represented in the vector form as:

$$\dot{y} = f[y,\ y(t-\tau),\ y(t-2\tau),\ \ldots\ y(t-n\tau),\ u,\ u(t-\tau_c)] \tag{4.16}$$

where y is a state vector with four components y_1, y_2, y_3 and y_4; f is the corresponding vector of functions f_1, f_2, f_3 and f_4, each representing the right hand side of one of the above four equations; u is the control vector, and n is an integer equal to $2\mu_2$.

From physical considerations we know that u(t) is piecewise continuous with finite discontinuities and that y(t) is continuous with piecewise continuous first derivatives.

From equation (4.10) we see that the cost function J is a function of the final values of states at preselected final time t_f. Mathematically

$$J = \phi(y|^{t_f}), \tag{4.17}$$

thus giving a Meyer problem which satisfies all the conditions for application of PMP to systems with delay, as laid down by Pontryagin et al [32], Kharatishvili [22], and Budelis et al. [9]. The results of Budelis et al [9] for the gradient of Hamiltonian can thus be used directly, with extension to a multi-delay system. This extension can be carried out on the basis of results obtained by McAulay [27], since the delays encountered in equation (4.16) are similar to those assumed by him.

Therefore, assuming a co-state vector

$$\lambda = [\lambda_1, \lambda_2, \lambda_3, \lambda_4], \tag{4.18}$$

the Hamiltonian H, for the above system, becomes

$$H = \lambda_1 f_1 + \lambda_2 f_2 + \lambda_3 f_3 + \lambda_4 f_4. \tag{4.19}$$

The costate equations of the system, satisfying the conditions of optimality, and based on the results of references [9] and [27], can be written as follows:

$$\dot{\lambda} = - \sum_{k=o}^{n} \frac{\partial H}{\partial y(t-k\tau)} \Big|^{t+k\tau} \qquad t_o \leq t \leq t_f - n\tau$$

$$\dot{\lambda} = - \sum_{k=o}^{n-1} \frac{\partial H}{\partial y(t-k\tau)} \Big|^{t+k\tau} \qquad t_f - n\tau < t \leq t_f - (n-1)\tau$$

$$\vdots$$

$$\dot{\lambda} = - \sum_{k=o}^{1} \frac{\partial H}{\partial y(t-k\tau)} \Big|^{t+k\tau} \qquad t_f - 2\tau < t \leq t_f - \tau$$

$$\dot{\lambda} = - \frac{\partial H}{\partial y} \qquad t_f - \tau < t \leq t_f \tag{4.20}$$

and

$$\lambda(t_f) = \frac{\partial \phi(y(t_f))}{\partial y} \tag{4.21}$$

Moreover, the necessary conditions for an extremal (dJ=o, for arbitrary δu) are that H(t) be continuous and that

$$\frac{\partial H}{\partial u} + \frac{\partial H}{\partial u(t-\tau_c)} \Big|^{t+\tau_c} = o, \qquad t_o \leq t \leq t_f - \tau_c \tag{4.22 a}$$

$$\frac{\partial H}{\partial u} = o \ . \qquad t_f - \tau_c < t \leq t_f \tag{4.22 b}$$

The problem is now solved by the use of parallel tangent gradient method. The numerical procedure used, along with the Fortran program, is given in Appendix B. The detailed derivation of the co-state equation, as needed for the numerical computation, is given in Appendix A. The final form of the costate equation,arrived at in the appendix,is, however, given here.

The maximum number of delays in the state will be $2\mu_2$, because the mean incubation period μ_2 is larger than the mean latent period μ_1. Thus each costate equation requires $2\mu_2$ equations to represent it over the entire period from final time to initial time. As derived in Appendix A, however, each of these sets of $2\mu_2$ equations has been condensed into one equation, and the resulting four costate equations are:

$$\dot{\lambda}_1 = \lambda_1 \left[u_1(t-\tau_c) + u_2(t) + \beta\, y_2(t)\right] - RLMD \cdot y_2(t) \qquad (4.23)$$

$$\dot{\lambda}_2 = \lambda_1\, \beta\, y_1(t) + \lambda_2\, u_2(t) - 2\,\lambda_4\, p_2\, \delta(y_2) \cdot y_2(t) - RLMD \cdot y_1(t) \qquad (4.24)$$

$$\dot{\lambda}_3 = o \qquad (4.25)$$

$$\dot{\lambda}_4 = o, \qquad (4.26)$$

where

$$RLMD(t) = \sum_{n=o}^{m(t)} WLP(n) \cdot \lambda_2(t+n\tau) - WIP(n)[\lambda_2(t+n\tau) - \lambda_3(t+n\tau)],$$

$$m(t) = \begin{cases} \dfrac{t_f-t}{\tau} = 0, 1, 2 \ldots 2\mu_2, & t_f-t < 2\mu_2 \\ 2\mu_2, & t_f-t > 2\mu_2 \end{cases} . \qquad (4.27)$$

Here $m(t)=o$ at final time t_f and progressively increases by 1 each time solution proceeds one day backwards from final time.

This form of the costate equation is very suitable for the numerical solution of the problem, since the costate equations have to be solved backwards in time following a solution of the state equations in the forward direction. The initial values of the costates for backward integration (actually, values of costate at final time) are obtained from equations (4.21) and (4.10). These values are:

$$\lambda_1(t_f) = o \tag{4.28}$$

$$\lambda_2(t_f) = C_1 \tag{4.29}$$

$$\lambda_3(t_f) = C_1 \tag{4.30}$$

$$\lambda_4(t_f) = 1 \tag{4.31}$$

With the final values of costates known, RLMD can be easily computed at the start of the backward integration and is progressively updated as the solution proceeds.

4.5 PARTAN Gradient Algorithm

To obtain the control function which minimizes the cost function, the negative gradient method of Kelly [20], coupled with parallel tangent technique (PARTAN) [31], has been successfully used. Usefulness of rapid convergence methods for Min-H problems has already been demonstrated by Gottlieb [12] and Lasdon et al [25], whereas the steepest descent method has been used by McAulay [27] for systems with finite number of delays. The conjugate gradient method of Lasdon et al [25], when used for the present problem, gave good results but was abandoned in favour of the simpler and more general PARTAN technique discussed at some length by Pierre [31] and Shah et al [38]. Negative gradient, satisfying the conditions of Hamiltonian with a delayed function of control, is as follows.

Let $g(u) = [g_1(u) \quad g_2(u)]$ be the gradient vector for the two controls, where g_1 is the gradient of H with respect to control u_1 and g_2 is the same with respect to control u_2.

Then

$$g(u) = \frac{\partial H}{\partial \mu}$$

$$= [\frac{\partial H}{\partial u_1} \quad \frac{\partial H}{\partial u_2}],$$

for a no delay case. As per the conditions laid down in equation (4.22), for a delay in control u_1 only,

$$g_1(u) = \frac{\partial H}{\partial u_1} + \frac{\partial H}{\partial u_1(t-\tau_c)} \Big|^{t+\tau_c}, \quad t_o \leq t \leq t_f-\tau_c \qquad (4.32\ a)$$

$$= \frac{\partial H}{\partial u_1}, \qquad t_f-\tau_c < t \leq t_f \qquad (4.32\ b)$$

and

$$g_2(u) = \frac{\partial H}{\partial u_2}. \qquad (4.33)$$

Thus we obtain the gradient, as a function of time, as follows:

$$g_1(u) = [A + 2B\ u_1(t)]\ \lambda_4 - \lambda_1(t+\tau_c) \cdot y_1(t+\tau_c), \quad t_o \leq t \leq t_f-\tau_c \qquad (4.34)$$

$$= [A + 2B\ u_1(t)]\ \lambda_4, \qquad t_f-\tau_c < t \leq t_f \qquad (4.35)$$

$$g_2(u) = [C + 2D\ u_2(t)]\ \lambda_4 - \lambda_1\ y_1 - \lambda_2\ y_2. \qquad (4.36)$$

The gradient vector g(u), calculated from expressions (4.34) to (4.36), is an implicit function of time by virtue of u being a function of time. Based on the algorithm proposed by McAulay [27] and Lasdon et al [25], for steepest descent and conjugate gradient solution, respectively, of such problems, the following procedure for the application of negative gradient to our problem is proposed:

Assuming zero control and known initial conditions, the state equations (4.1) to (4.4) are integrated from an initial time t_o to a final time t_f which satisfies the final conditions (y_2=o). This value of t_f is now taken as the terminal time for subsequent integrations of the state equations. Cost J is evaluated using equation (4.10) and the final values of the state already obtained. Thus we get the cost of the epidemic with no control applied, and our aim is to reduce this cost to a minimum by the application of suitable control. This optimum control is generated by the use of the following iterative procedure.

(a) With the final values of costates given by expressions (4.28) to (4.31), and using the stored values of the states, just calculated (for the entire period of time), the costate equations (4.23) to (4.26) are solved by backward integration from final time t_f to initial time t_o. Thus we have the values, necessary for the

evaluation of gradient vector g(u). If the control vector for the i th iteration is represented by u^i and the corresponding gradient by $g(u^i)$, let us assume

$$s^i = - g(u^i). \tag{4.37}$$

s^i, in its present form, represents the negative gradient for the i th iteration, and has two components, s_1 and s_2, corresponding to two controls, u_1 and u_2. Reckoning of the iteration number i may start either from 0 or 1, depending upon the personal preferences. In the present case, let us assume i to start from 0.

(b) We now proceed to search for a multiplying factor α consisting of two components α_1 and α_2, such that a value of increment control (in the vector sense) may be obtained to minimize cost J. Thus choose,

$$\alpha = \alpha^i \quad \text{to minimize} \quad J(u^i + \alpha^i s^i). \tag{4.38}$$

Then the new control vector will be,

$$u^{i+1} = u^i + \alpha^i s^i. \tag{4.39}$$

The two components of α are evaluated by conducting a one dimensional search, first for one control and then for the other, to minimize J in each case.

(c) Using the new control vector obtained from equation (4.39), we proceed to solve the state equations, anew, and calculate the new value of cost J. If this new value of J is judged to be the

minimum value the solution can stop here, otherwise we proceed to the next step.

(d) Now we either calculate the new costates and new gradient using the procedure outlined in step (a) or find the acceleration step, and go to step (b). The decision as to whether this step is to be a steepest descent or an acceleration step is made on the basis of PARTAN procedure discussed, at some length, by Pierre [31] and Shah et al. [38], and outlined below:

Controls u^1 and u^2 are obtained, respectively, from u^o and u^1 by using the steepest descent. An acceleration step, which is the vector difference of controls u^2 and u^o is now obtained and treating it as negative gradient, control u^3 is obtained. Controls u^4, u^6, u^8 ... are now obtained from controls u^3, u^5, u^7 ..., respectively, by the use of steepest descent approach; whereas u^5, u^7... etc. are obtained from the corresponding pairs of controls u^4, u^1 and u^6, u^3... etc., by the use of acceleration step.

The process is iterated until the cost function J converges to a minimum value. The numerical procedure based on this algorithm is given in Appendix B. It may be pointed out here that, although the gradient method assumes an arbitrary δu, there is a constraint in the present case. Since a negative control is unthinkable in practice

(vaccinations cannot be undone!), while searching the values of α the values of trial control which would otherwise be negative were replaced by zero. The final values of cost obtained are therefore, minimum in the practical, constrained case. The results of the numerical solution, presented in the next section, prove the effectiveness of the method.

4.6 Choice of cost constants

While formulating the optimum control problem in section 4.2, the cost constants for immunization controls were represented by A, B, C and D, and that for the cost per reported case by C_1. Factors influencing the choice of numerical values for these constants are discussed in this section; a choice is also made for a representative set of values to be used for the numerical solution of the problem.

Since we are using the normalized variables in the model, the state variables y_1, y_2, y_3 and y_4 represent per unit values. The actual values are, therefore, obtained by multiplying these values by the reference value, which is, in this case, the number of individuals forming the population of the community. For y_4 to have this dimension, constants A and C should, respectively, represent the cost of one inoculation of active and passive immunization agents.

Similarly, the cost function J will also be dimensionally consistant if C_1 represents the cost of one individual falling sick with the disease.

Although the cost of immunization per inoculation is fairly constant when such inoculations are given at a slow rate, yet it is far from realistic to consider this cost to be constant in epidemic situations. In such situations the supply of vaccine or antiserum, as the case may be, has to be supplemented by creating additional manufacturing capacity, and crash immunization programs have to be initiated, thus causing the cost per injection to rise. Although the full effect of this dislocation of normal services, on the per unit cost of immunization, is not yet known precisely, yet it is certain that the cost per unit of immunization is a non-linear function of the rate of immunization. The simplest way of representing a non-linear quantity is to represent it as the first two terms of a Taylor series expansion. This fact is utilized here and, as such, the cost of active immunization is assumed to be $A + Bu_1$ per injection and that of passive immunization to be $C + Du_2$ per antiserum injection. When proceeding with the optimization process, constants B and D penalize high control effort, hence prevent the optimum control rates becoming unrealistically high.

Accurate values of constants A, B, C and D can only be determined after a sufficient experience with the model and a full knowledge of the effect of immunization rates on the unit cost of immunization. However it can be generally assumed that the cost of one injection of antiserum is relatively higher than that of the vaccine for the same disease, and that B/A and D/C are relatively large values. The following representative values have been assigned to these constants, for the numerical solution of the problem.

$A = \$ 2.00$, $B = \$ 200.00$

$C = \$ 5.00$, $D = \$ 500.00$.

This choice of relative values for linear (A and C) and quadrature (B and D) cost constants is quite consistant with the economics of vaccine and antisera production, in practice. Restricting our attention to active control only, we can say that for very small values of u_1 the cost per inoculation is approximately equal to A, whereas it is, almost, independent of A for very large values of u_1. A value of u_1 for which A and B have equal weightage is $\frac{A}{B} = \frac{1}{100}$ per day or 3.65 per year. This corresponds to a production capacity which can be geared to produce 3.65 vaccines per person per year. If a control at a higher rate is required, additional capacity has to be created at a high fixed cost, thus resulting in a relatively high per vaccine cost, which is dependent on B only. The same is also true for passive

control.

Cost per reported case (C_1) depends on the disease in question. It will be higher for a disease which causes the victim to be away from work longer. Moreover, it will be higher for those diseases which are costlier to cure and those which have higher fatality rates. Three representative values of C_1 considered in this thesis are $ 50.oo, $ 100.oo and $ 500.oo.

4.7 Results of optimization

The optimization procedure discussed in this chapter has been applied to the epidemic problem discussed in Chapter III. Results of the numerical solution of the problem are presented in this section. For the sake of clarity the parameters of the control problem are restated below:

Epidemic Parameters

Initial susceptibles ($y_1(t_o)$)	= 0.5,
initial infectives ($y_2(t_o)$)	= 10^{-4},
$y_2(t)$, $t < t_o$	= 0.0,
effective contact rate (β)	= 1.5,
factor k(t)	= 0.9,
mean value of the latent period	= 7 days,
mean value of the incubation period	= 14 days,

standard deviation of the latent period	=	1.3,
standard deviation of the incubation period	=	2.3.

Control Parameters

Per unit cost of active control (A)	=	2.0,
square law cost of active control (B)	=	200.0,
per unit cost of passive control (C)	=	5.0,
square law cost of passive control (D)	=	500.0,
penalty function (p_2)	=	10^6,
cost per reported case	=	\$ 50.0, \$ 100.0 and \$ 500.0.

The choice of these parameters has already been discussed in the various sections of this thesis. It may, however, be emphasized once more that these parameters do not represent any particular disease, but are typical values used to demonstrate the usefulness of the procedure developed in this thesis. Actual values, for a particular case, can be used to get the results appropriate to that application.

In addition to the case where the active control is assumed to be immediately effective after it is administered, two cases of delay in active control have also been considered. The delays considered are 5 days and 16 days, the latter being larger than the

mean incubation period. Thus, in all, nine cases have been considered. The results of numerical solution of these nine cases are summarized below:

Results

The solution of the model, in all the nine cases, and when no control is used, is the same as that shown by the no-control curve in figures 3.1 to 3.7. The terminal time is found to be 145 days in each case and the final extent of the epidemic, without control, is 0.4457 reported cases (per unit value). Therefore t_f used for the optimization problem is 145 days.

Figure 4.1 shows the convergence of the optimization process to an optimum cost, for a typical case, whereas the results relating to all the nine cases considered are summarized in table 4.1. This table shows the optimum, in each case, calculated against the cost without control. Optimum costs expressed as percentage of the initial cost, and the percentage saving in these costs due to the use of optimum control strategy, are shown in the next two columns. Column 6 shows the final extent of the epidemic, in each controlled case, as a percentage of that without control.

The optimum active and passive controls, determined by the optimization procedure, are plotted in figures 4.2, 4.3 and 4.4.

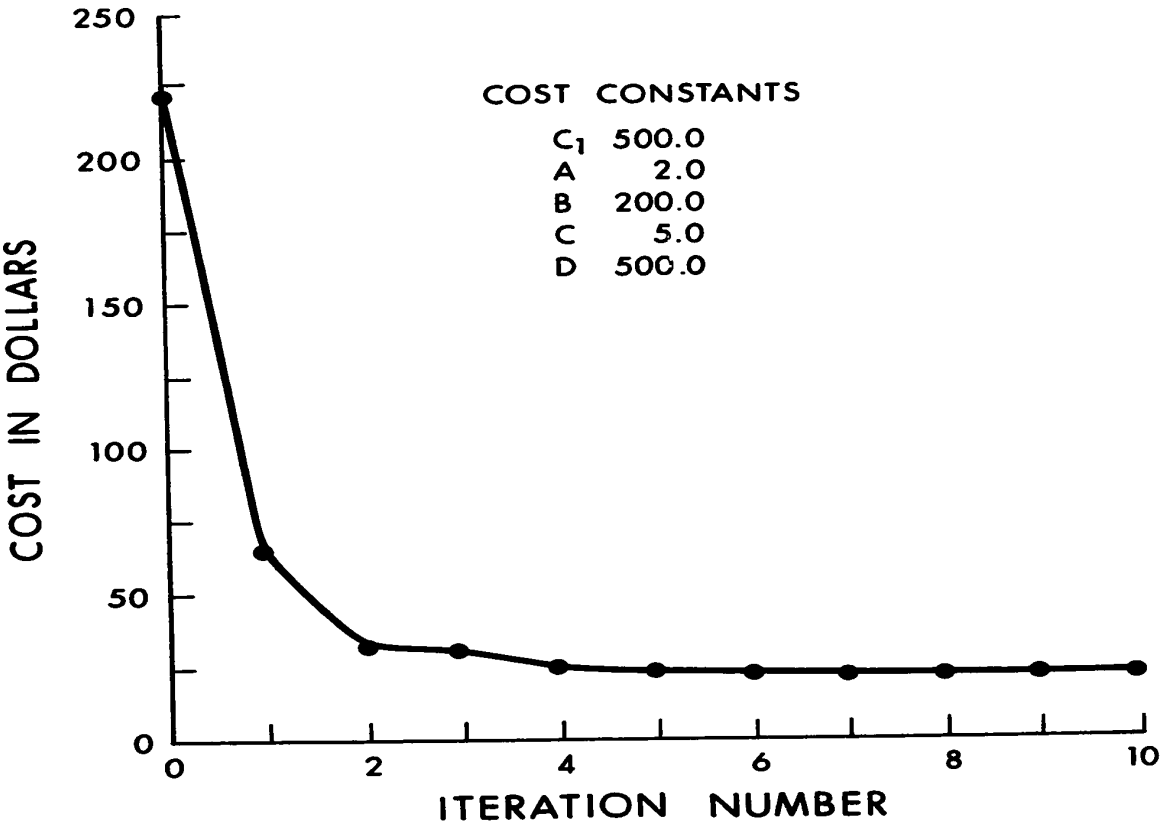


FIG. 4-1 CONVERGENCE OF THE COST TO OPTIMUM VALUE. COST PER REPORTED CASE = $ 500.00, AND NO DELAY IN ACTIVE CONTROL.

TABLE 4–1
COST CONSTANTS

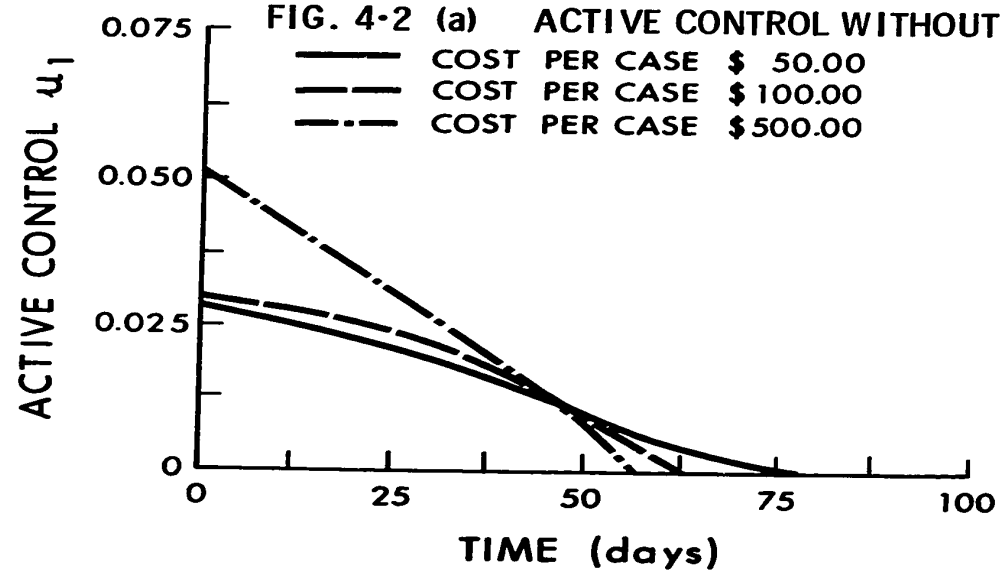
A = 2.0 B = 200.0 C = 5.0 D = 500.0

COST PER REPORTED CASE IN $	COST WITHOUT CONTROL IN $	OPTIMUM COST IN $	OPTIMUM COST AS % OF COST WITHOUT CONTROL	% SAVING IN COST, BY OPTIMIZATION	REPORTED CASES WITH CONTROL AS % OF THOSE WITHOUT CONTROL	DELAY IN ACTIVE CONTROL
50.0	$ 22.290	11.518	51.7	48.3	18.05	NO DELAY
		12.109	54.3	45.7	19.55	5 DAYS
		13.703	61.5	38.5	28.40	16 DAYS
100.0	$ 44.581	13.467	30.2	69.8	7.15	NO DELAY
		14.867	33.4	66.6	8.14	5 DAYS
		17.849	40.05	59.95	12.35	16 DAYS
500.0	$ 222.904	21.489	9.61	90.39	1.95	NO DELAY
		24.121	10.8	89.2	2.34	5 DAYS
		29.998	13.4	86.6	3.47	16 DAYS

Figure 4.2 shows the optimum controls for three different case report costs, without any delay in the effect of active control. Figures 4.3 and 4.4 show, respectively, the corresponding controls for the cases of 6 days delay and 16 days delay in active control.

4.8 Discussion of the results

The results presented in the last section clearly establish the usefulness of the optimization procedure developed in this thesis. It is apparent from figure 4.1 that the cost function converges to a minimum value (which is substantially lower than the initial cost) rapidly. A similar decrease in cost is also observed in the other cases tabulated in table 4.1. We find that the saving in the total cost ranges from 38.5% to 90.39%. The percent saving in cost is highest in the case of the most severe disease, with cost per reported case of $ 500.oo, because in this case it is economical to use more control effort to prevent the disease. This fact is also demonstrated by the observation that the actual disease cases have been reduced to less than 4%, compared to over 28% in the first case (where C_1 = $ 50.oo). Another important observation is that the saving in cost, by optimization, is reduced when delay in the active control is introduced. These results are in line with the intuitive thinking that more control should be applied for a disease which causes higher losses and that delay in control reduces its effectiveness.



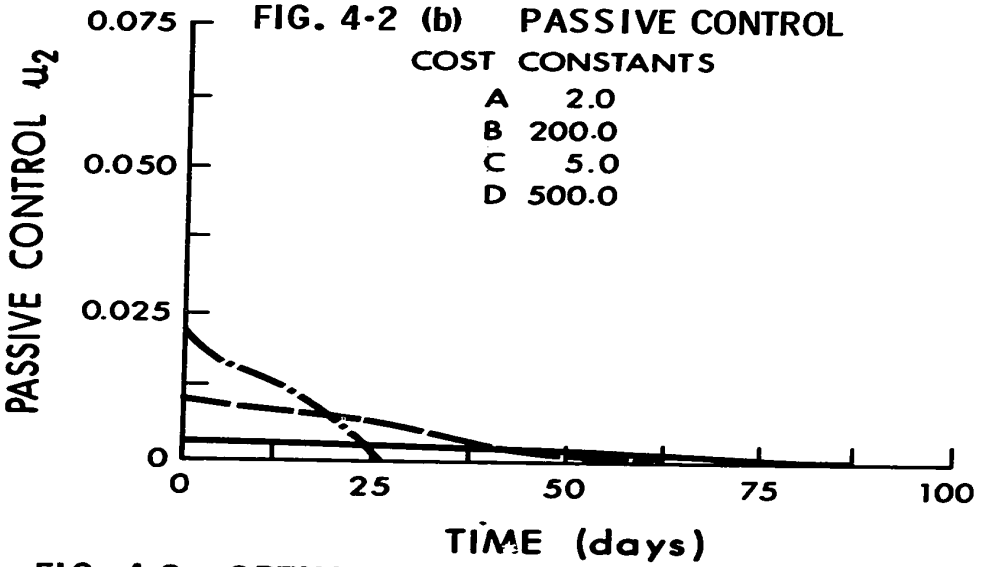
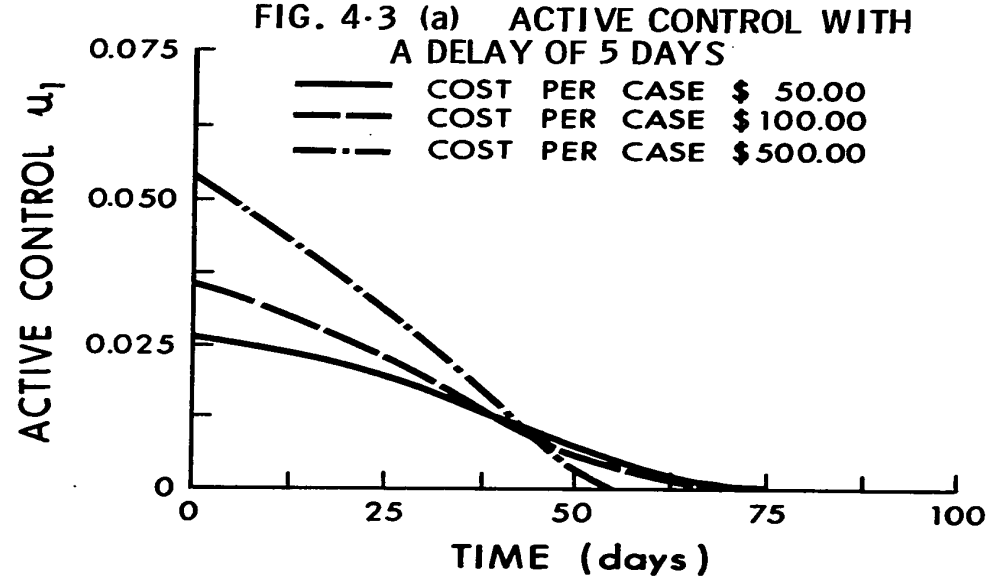


FIG. 4-2 OPTIMUM CONTROL PLOTTED AGAINST TIME. NO DELAY CASE.



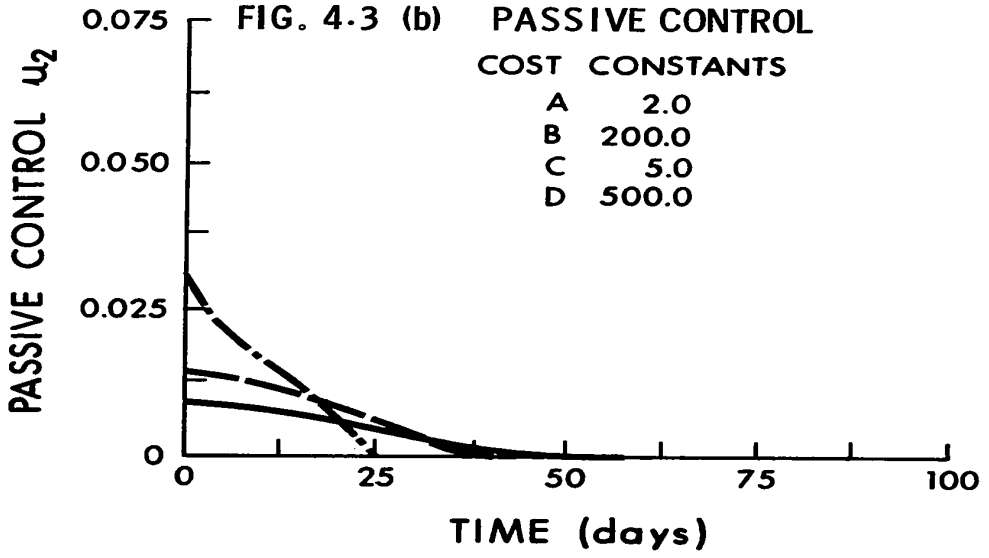


FIG. 4·3 OPTIMUM CONTROL PLOTTED AGAINST TIME. DELAY OF 5 DAYS IN ACTIVE CONTROL.

FIG. 4·4 (a) ACTIVE CONTROL WITH A DELAY OF 16 DAYS

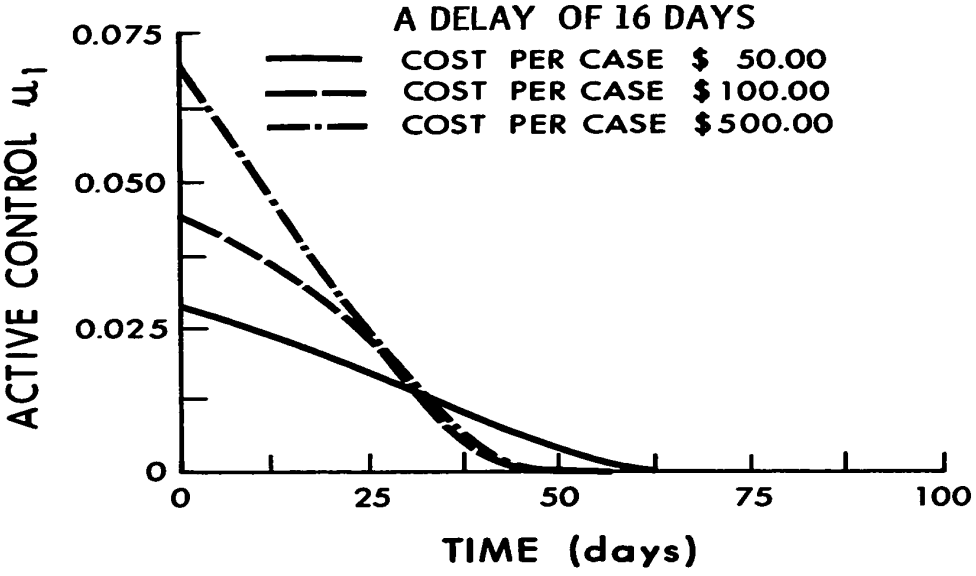


FIG. 4·4 (b) PASSIVE CONTROL

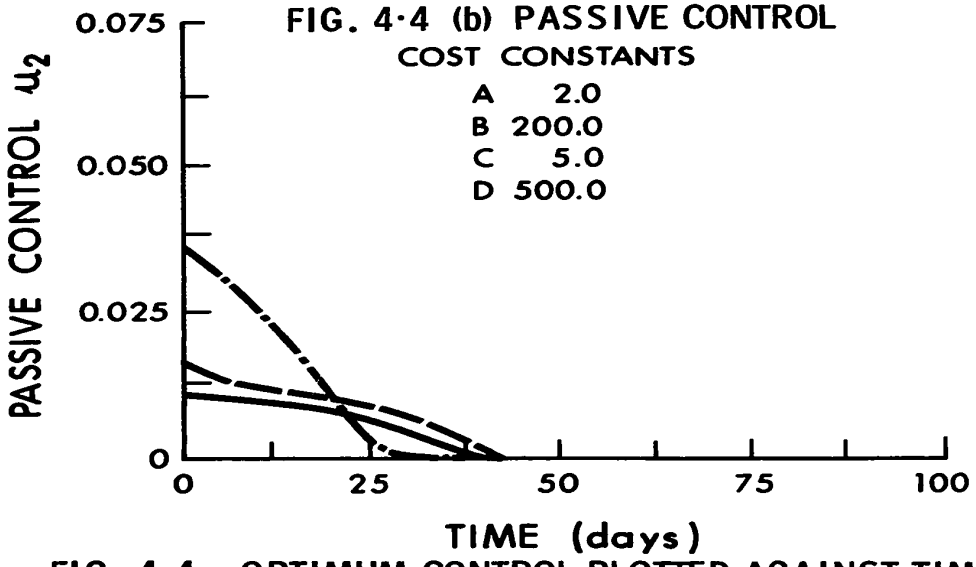


FIG. 4·4 OPTIMUM CONTROL PLOTTED AGAINST TIME. DELAY OF 16 DAYS IN ACTIVE CONTROL.

Turning to the plots of optimum control, we find that larger amounts of control are used as the cost per case increases from 50.oo to 500.oo. Moreover, we find that more active control has been used than passive control, which is, perhaps, due to the relative cheapness of the active control. We also find, as one would expect, that with delay introduced in the active control, the use of passive control is increased.

Thus we find that the optimization procedure developed in this thesis gives encouraging results that are consistant with intuition.

4.9 Optimum control procedure for case 2

We have so far restricted our attention to case 1 only. This was done to keep the discussion unambiguous. The method is, however, equally applicable to case 2. Using the procedure developed in section 4.4 and detailed in Appendix A, the corresponding costate equations for case 2 are as follows:

$$\dot{\lambda}_1 = \lambda_1 \{u_1(t-\tau_c) + \beta\, y_2(t)\} - \text{RLMD} \cdot y_2(t) \tag{4.37}$$

$$\dot{\lambda}_2 = \lambda_1 \beta\, y_1(t) - 2\lambda_4\, p_2\, \delta(y_2) \cdot y_2(t) - \text{RLMD} \cdot y_1(t) \tag{4.38}$$

$$\dot{\lambda}_3 = 0 \tag{4.39}$$

$$\dot{\lambda}_4 = 0, \tag{4.40}$$

where

$$RLMD = \sum_{n=o}^{m(t)} WLP(n) \cdot \lambda_2(t+n\tau) - WIP(n) \left[\lambda_2(t+n\tau) \{1 + u_2(t+n\tau)\} - \lambda_3(t+n\tau) - \lambda_4(t+n\tau) \{C\, U_2(t+n\tau) + D\, U_2^{\,2}(t+n\tau)\}\right], \quad (4.41)$$

m(t) is the same integer variable as in equation (4.27).

The corresponding gradient equations are:

$$g_1(u) = [A + 2B\, u_1(t)]\lambda_4 - \lambda_1(t+\tau_c) \cdot y_1(t+\tau_c), \quad t_o < t \leq t_f - \tau_c$$

$$= [A + 2B\, u_1(t)]\lambda_4, \qquad t_f - \tau_c < t \leq t_f \quad (4.42)$$

$$g_2(u) = [\lambda_4(C+2\, U_2(t) \cdot D) - \lambda_2(t)] \sum_{n=o}^{2\mu_2} WIP(n) \cdot y_1(t-n\tau) \cdot y_2(t-n\tau). \quad (4.43)$$

When the same values of constants were used in this case, substantial reductions of cost were observed. The final cost was, however, found to be relatively less sensitive to passive control which is due to the fact that the nature of U_2 here is different than that in the previous case. U_2, here, is the number of passive immunizations given per reported case, and not the actual number of immunizations. The choice of C and D should, therefore, be revised to suite this case. A reference to equation (4.8) shows that the nature of cost constant C is substantially same as that in case 1, and it is the cost of one antiserum injection. But, the choice of constant D is

more complicated. D, in the present case, not only represents the increase in the cost per inoculation due to the increase in inoculation rate, but also represents the increase in cost due to the added cost of more intensive search for the contacts of the reported case. Effect of the two factors on the choice of D is not fully known and more study is needed for a better estimation of D. It is however certain, that with a better choice of these constants, useful results can be obtained with this model also.

4.10 Conclusions

We thus conclude that the optimization procedure developed in this chapter is quite effective in determining the optimum control of an epidemic. Although the continuously changing rate of control, as observed in the results presented in section 4.7, would be difficult to implement in practice, yet it serves as a guide for the control strategy to be used in practice. If the control strategy, in practice, has to be varied due to some other considerations, the quantitative effects of this deviation can be easily assessed using this model. This will help provide, at least, a quasi-optimal control strategy in that case.

CHAPTER V

SUMMARY AND CONCLUSIONS

5.1 Summary

A mathematical model, which can be used for the prediction and optimum control of all contagious diseases that are transmitted through personal contact between infectives and susceptibles, has been developed. The new deterministic model takes into full consideration, for the first time, the latent and infections periods of the disease and their statistical variations. The model, though only applicable to closed populations, yet gives results which are nearer to disease spread observed in practice than those obtained from earlier deterministic models. A hypothesis about the possible relation of meteorological changes to disease outbreaks, based on the results obtained from the new model, has also been given.

The sensitivity of the model to active and passive immunization controls has been studied, and a procedure for charting an optimum control strategy, by the application of Pontryagin's Minimum Principle, has been developed. For the first time, dynamic optimization techniques have been successfully used for finding the optimum control strategy for this class of problems. In addition to being a practical application of the existing control theory to the

control of epidemics, the system discussed also forms an important example of the application of this theory to a non-linear case with a finite number of delays, both in state and control. The results obtained show the sensitivity of the control to delays in active control and to the severity of the disease (represented by cost per reported case).

5.2 Conclusions

From the analysis given in this thesis, we can now conclude that a contagious disease can be generally represented, mathematically, by three important parameters, viz. effective contact rate, latent period, and infective (or incubation) period. Effective contact rate (β), the first of the three parameters, is as much dependent on the social, hygienic and environmental conditions of the population as on the infectiousness of the disease, and is proportional to the infectiousness of the disease, other conditions being equal. Another important conclusion, from the solution of the model, is that for a disease to become epidemic, both the proportion of initial susceptibles in the population and β should be greater than their respective threshold values.

In the area of control application, we conclude that the available control must be applied as early as possible and at the

highest rate. Further, if the relative costs of administering each control are known,it is possible to find the best control strategy by the use of optimum control theory.

5.3 Recommendations for further research

This thesis presents many possibilities for future research. The first necessity, for getting practically applicable results, is the accurate assessment of parameters. Statistical estimation of these parameters can be done more accurately if the data of the right kind are available. It will, therefore, be advisible to record the disease data with the new models in view and develop methods for estimation of the parameters. Laboratory research about infectiousness of the diseases, their latent periods, and their incubation periods can supplement statistical research. More research is also needed to evaluate the cost constants for the cost function, more realistically. Introduction of other controls, not represented in the present study, will help make the model more useful.

The present model was restricted to closed populations. Extension of the optimization approach, used here, to models modified to include parameters relating to births, deaths and population migration, would make an interesting study. Moreover the present study was restricted to short term control of one outbreak; its

extension to endemic diseases on the long-term basis is another challenging area.

All individuals have been considered to have similar response to the disease. The effect of age groups, sex groups or any other population classification remains to be studied.

A very important factor, not considered here but already voiced in the literature [2], [4], is the question of geographical spread. In this study the population has been lumped as a single homogeneous group, which is quite far from reality when large areas are considered. Application of optimization techniques to models for geographical spread may require the use of distributed parameters, and is,thus,likely to prove a challenging but useful field of study.

Only a complete analytical solution of the control problem can really establish the limitations and full potential of the optimization techniques used; obtaining these solutions is another area where considerable research is yet needed.

If this thesis helps generate some interest in the above areas of research, it will have served a purpose.

APPENDIX A

This appendix details the derivation of costate equations and the assumptions made to arrive at the results.

With the assumption and definitions of Chapter IV, the state equations of the model can be written as:

$$\dot{y}_1 = - \beta\, y_1\, y_2 - u_1\,(t-\tau_c) \cdot y_1 - u_2\,(t) \cdot y_1 \qquad \text{(A-1)}$$

$$\dot{y}_2 = \frac{K\beta}{\sqrt{2\pi}} \; \frac{1}{\sigma_1} \sum_{n=o}^{2\mu_1} \left[\exp\left\{ - \frac{1}{2\sigma_1^2} (\mu_1 - n\tau)^2 \right\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau)$$

$$- \frac{K\beta}{\sqrt{2\pi}} \; \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp\left\{ - \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2 \right\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau)$$

$$- u_2(t) \cdot y_2 \qquad \text{(A-2)}$$

$$\dot{y}_3 = \frac{K\beta}{\sqrt{2\pi}} \; \frac{1}{\sigma_2} \sum_{n=o}^{2\mu_2} \left[\exp\left\{ - \frac{1}{2\sigma_2^2} (\mu_2 - n\tau)^2 \right\} \right] y_1(t-n\tau) \cdot y_2(t-n\tau) \qquad \text{(A-3)}$$

$$\dot{y}_4 = p_2 y_2^2 \;\; \delta(y_2) + A\, u_1(t) + B\, u_1^2(t) + [C\, u_2(t) + D\, u_2^2(t)] \,, \qquad \text{(A-4)}$$

where

$$\delta\,(y_2) = 0 \qquad y_2 \geq 0$$

$$\delta\,(y_2) = 1 \qquad y_2 < 0,$$

and p_2 is the penalty multiplier.

The constant multipliers and exponential factors in the above expressions, the latter representing the distribution of latent and incubation periods, can be calculated and stored once for all, for all values of n.

Substituting the stored vectors WLP(n) and WIP(n), defined as

$$WLP(n) = \frac{K\beta}{\sqrt{2\pi}} \frac{1}{\sigma_1} \exp\{-\frac{1}{2\sigma_1^2}(\mu_1 - n\tau)^2\}$$

$$WIP(n) = \frac{K\beta}{\sqrt{2\pi}} \frac{1}{\sigma_2} \exp\{-\frac{1}{2\sigma_2^2}(\mu_2 - n\tau)^2\}$$

the state equations become:

$$\dot{y}_1 = -\beta y_1 y_2 - u_1(t-\tau_c) \cdot y_1 - u_2(t) \cdot y_1 \qquad \text{(A-5)}$$

$$\dot{y}_2 = \sum_{n=o}^{2\mu_1} WLP(n) \cdot y_1(t-n\tau) \cdot y_2(t-n\tau) - \sum_{n=o}^{2\mu_2} \Big[WIP(n) \times y_1(t-n\tau) \cdot y_2(t-n\tau) \Big] - u_2(t) \cdot y_2 \qquad \text{(A-6)}$$

$$\dot{y}_3 = \sum_{n=o}^{2\mu_2} WIP(n) \cdot y_1(t-n\tau) \cdot y_2(t-n\tau) \qquad \text{(A-7)}$$

$$\dot{y}_4 = p_2 y_2^2 \delta(y_2) + A u_1(t) + B u_1^2(t) + C u_2(t) + D u_2^2(t) \qquad \text{(A-8)}$$

This version of the state equations is quite suitable for numerical analysis as they can be easily converted to the differential difference form. The equations can be rewritten in a concise form as

below:

$$\dot{y}_1 = - \beta\, y_1\, y_2 - u_1(t-\tau_c) \cdot y_1 - u_2(t) \cdot y_1 \qquad \text{(A-9)}$$

$$\dot{y}_2 = \text{ACTV} - \text{RMVD} - u_2(t) \cdot y_2 \qquad \text{(A-10)}$$

$$\dot{y}_3 = \text{RMVD} \qquad \text{(A-11)}$$

$$\dot{y}_4 = p_2 y_2^2\, \delta(y_2) + A\, u_1(t) + B\, u_1^2(t) + C\, u_2(t) + D\, u_2^2(t) \qquad \text{(A-12)}$$

where

$$\sum_{n=o}^{2\mu_1} \text{WLP}(n) \cdot y_1(t-n\tau) \cdot y_2(t-n\tau) = \text{ACTV} \qquad \text{(A-13a)}$$

is the rate at which latent cases become active in spreading the disease, and

$$\sum_{n=o}^{2\mu_2} \text{WIP}(n) \cdot y_1(t-n\tau) \cdot y_2(t-n\tau) = \text{RMVD} \qquad \text{(A-13b)}$$

is the rate of reported cases per unit time, at time 't'. Since the unit of time used is one day, the above rates can, respectively, be called the per day active and removal rates.

COSTATE EQUATIONS

For a complete representation of the process of disease spread, our model needs the past history of state variables for twice the incubation period. Since the values of state variables have been stored at intervals of one day, a total of $2\mu_2$ delayed values of each variable may figure in the state equations. As per the conditions for formulation of costate equations, arrived at by McAulay [27] and others [9], [22], [32] and discussed in Chapter 4, a total of $2\mu_2$ expressions are needed to completely represent each costate between the initial and final time. Working backwards in time, $2\mu_2$-1 of these expressions represent the costate in question, one for each time slot of one day duration between final time t_f and t_f-$2\mu_2$. Another one is needed for the remaining time up to the initial time.

The costate equations for the last interval, or the first one starting backwards from final time t_f, can be written from the general formula

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial y_1} = -\lambda_1 \frac{\partial f_1}{\partial y_1} - \lambda_2 \frac{\partial f_2}{\partial y_1} - \lambda_3 \frac{\partial f_3}{\partial y_1} - \lambda_4 \frac{\partial f_4}{\partial y_1} \qquad \text{(A-14)}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial y_2} = -\lambda_1 \frac{\partial f_1}{\partial y_2} - \lambda_2 \frac{\partial f_2}{\partial y_2} - \lambda_3 \frac{\partial f_3}{\partial y_2} - \lambda_4 \frac{\partial f_4}{\partial y_2} \qquad \text{(A-15)}$$

$$\dot{\lambda}_3 = -\frac{\partial H}{\partial y_3} = -\lambda_1 \frac{\partial f_1}{\partial y_3} - \lambda_2 \frac{\partial f_2}{\partial y_3} - \lambda_3 \frac{\partial f_3}{\partial y_3} - \lambda_4 \frac{\partial f_4}{\partial y_3} \qquad \text{(A-16)}$$

$$\dot{\lambda}_4 = - \frac{\partial H}{\partial y_4} = - \lambda_1 \frac{\partial f_1}{\partial y_4} - \lambda_2 \frac{\partial f_2}{\partial y_4} - \lambda_3 \frac{\partial f_3}{\partial y_4} - \lambda_4 \frac{\partial f_4}{\partial y_4} \qquad \text{(A-17)}$$

When applied to the present problem, it is apparent that the right hand sides of equations (A-16) and (A-17) are zero, so only the first two equations remain to be considered. Concentrating on equation (A-14) we find that this equation, between time $t_f-\tau$ and $t_f-2\tau$, will be

$$\dot{\lambda}_1 = - \frac{\partial H}{\partial y_1} - \frac{\partial H}{\partial y_1(t-\tau)} \Big|_{t=t+\tau}. \qquad \text{(A-18)}$$

Equation (A-18) is the same as equation (A-14) with one term added to its right hand side. This additional term is the partial derivative of Hamiltonian with respect to the delayed variable $y_1(t-\tau)$ and the resulting term advanced by τ in time. Thus an equation for the time between $t_f-k\tau$ and $t_f-(k+1)\tau$, will have k similar terms added to the right hand side of (A-14). Hence the corresponding costate equation for time $t_f-k\tau < t < t_f-(k+1)\tau$ is:

$$\dot{\lambda}_1 = - \frac{\partial H}{\partial y_1} - \frac{\partial H}{\partial y_1(t-\tau)} \Big|_{t=t+\tau} \cdots - \frac{\partial H}{\partial y_1(t-k\tau)} \Big|_{t=t+k\tau} \qquad \text{(A-19)}$$

Rewriting

$$\dot{\lambda}_1 = - \frac{\partial H}{\partial y_1} - \sum_{n=1}^{k} \frac{\partial H}{\partial y_1(t-n\tau)} \Big|_{t=t+n\tau}, \; k = 1,2,3, \ldots 2\mu_2. \qquad \text{(A-20)}$$

Similarly

$$\dot{\lambda}_2 = - \frac{\partial H}{\partial y_2} - \sum_{n=1}^{k} \frac{\partial H}{\partial y_2(t-n\tau)} \Big|_{t=t+n\tau}, \; k = 1,2,3, \ldots 2\mu_2. \qquad \text{(A-21)}$$

Substituting the expression for Hamiltonian and taking necessary partial derivatives, the costate equations for time $t_f - k\tau < t < t_f - (k+1)\tau$ become:

$$\dot{\lambda}_1 = \beta\, y_2\, \lambda_1 + \lambda_1\, u_1(t-\tau_c) + \lambda_1\, u_2(t) - y_2(t) \sum_{n=o}^{k} \lambda_3(t+n\tau) \cdot WIP(n) - y_2(t) \sum_{n=o}^{k} \lambda_2(t+n\tau) \cdot [WLP(n) - WIP(n)]$$

where $k = 0, 1, 2 \ldots\ 2\mu_2$ (A-22)

$$\dot{\lambda}_2 = \beta\, y_1\, \lambda_1 + \lambda_2\, u_2(t) - 2\lambda_4\, p_2 y_2\, \delta(y_2) - y_1(t) \sum_{n=o}^{k} \lambda_3(t+n\tau) \cdot WIP(n) - y_1(t) \sum_{n=o}^{k} \lambda_2(t+n\tau) \cdot [WLP(n) - WIP(n)]$$

where $k = 0, 1, 2 \ldots\ 2\mu_2$ (A-23)

$$\dot{\lambda}_3 = 0 \qquad \text{(A-24)}$$

$$\dot{\lambda}_4 = 0 \qquad \text{(A-25)}$$

Equations (A-22) and (A-23) simplify to

$$\dot{\lambda}_1 = \lambda_1[u_1(t-\tau_c) + u_2(t) + \beta\, y_2(t)] - y_2(t) \sum_{n=o}^{k} \lambda_2(t+n\tau) \cdot WLP(n) + y_2(t) \sum_{n=o}^{k} WIP(n)[\lambda_2(t+n\tau) - \lambda_3(t+n\tau)]$$

where $k = 0, 1, 2, 3 \ldots\ 2\mu_2$ (A-26)

$$\dot{\lambda}_2 = \lambda_1 \beta y_1(t) + \lambda_2 u_2 - 2\lambda_4 p_2 y_2 \delta(y_2) - y_1(t) \sum_{n=o}^{k} \lambda_2(t+n\tau) \cdot WLP(n)$$

$$+ y_1(t) \sum_{n=o}^{k} WIP(n)[\lambda_2(t+n\tau) - \lambda_3(t+n\tau)]$$

where $k = 0,1,2,3 \ldots . 2\mu_2$ (A-27)

Defining a variable RLMD as:

$$RLMD = \sum_{n=o}^{k} WLP(n) \cdot \lambda_2(t+n\tau) - WIP(n) \cdot [\lambda_2(t+n\tau) - \lambda_3(t+n\tau)]$$

where $k = 0,1,2,3 \ldots . 2\mu_2$ (A-28)

The costate equations reduce to

$$\dot{\lambda}_1 = \lambda_1[u_1(t-\tau_c) + u_2(t) + \beta y_2(t)] - RLMD \cdot y_2(t) \quad \text{(A-29)}$$

$$\dot{\lambda}_2 = \lambda_1 \beta y_1(t) + \lambda_2 u_2(t) - 2 \lambda_4 p_2 \delta(y_2) \cdot y_2(t) - RLMD \cdot y_1(t) \quad \text{(A-30)}$$

$$\dot{\lambda}_3 = 0 \quad \text{(A-31)}$$

$$\dot{\lambda}_4 = 0 \quad \text{(A-32)}$$

Costate equations (A-29) to (A-32) are apparently independent of time slot being considered but it is not so in reality. The newly defined variable RLMD, which figures prominently in the costate equations, is completely dependent on the time slot, and has to be up-

dated at every step as the backward integration of costate equations proceeds. A look at the expression (A-28) reveals that when $k = 0$, the summation is over only one value of n, and the value of RLMD depends, only, on the known final values of state, costate and control variables. The costate differential difference equations can now be solved for one step in time; a day in the present case. Expression (A-28) is processed again; now with $k = 1$. The value of RLMD now depends on the values of state, costate and control variables between periods t_f and $t_f-\tau$. These values are known by this time. The integration proceeds in this manner raising the value of k by one, each step of time, till it reaches $2\mu_2$. After this moment k remains fixed at this value but RLMD is still updated every step of time up to the end of integration procedure at $t=t_0$. Thus we are able to evaluate the costates for the entire period of time.

APPENDIX B

This appendix outlines the numerical procedure used for the solution of the optimum control problem discussed in this thesis. The Fortran IV program, suitable for the model IBM 360/67 digital computer, and successfully applied to the determination of an optimum control strategy, is given at the end of this appendix.

For the purpose of numerical simulation, the discretized version of the model given in Chapter IV and represented by equations (4.1) to (4.4) for case 1 and by equations (4.5) to (4.8) for case 2 has been used. A unit of time of one day has been used to make the report-rate data, generated by the simulated model, comparable to the field data. This unit of time may, however, be replaced by a week or a month in the case of slow spreading diseases like tuberculosis.

At the beginning of any given day, the values of variables a(t) and r(t) (rates of newly active cases and reported cases) are calculated using the stored values of the history of the states and the corresponding normally distributed weighting multipliers. These rates are now assumed constant for the day and the state equations are solved for one day using Runga Kutta method. Final values of the states at the end of one day form the initial values at the beginning

of the next day. This process is carried on till the stopping criterion, which is either reaching the assigned final time or reaching a value of infectives below an assigned minimum, is satisfied.

Solution of the optimum control problem is obtained by an iterative procedure. First the values of controls are assumed zero and the final time, which is the time taken by the disease to subside without any control being applied, is calculated. Using this time as the terminal time the system iterates to satisfy the cost immunization criterion, updating the control vector at the end of each iteration. The computation stops when no significant further improvement in the cost is possible; thus generating the best control strategy at the end.

The computer program consists of a supervisory main program and nine modular subroutines. A brief description of the program modules is as follows:

1. MAIN PROGRAM: It is the supervisory program which calls various subroutines, when needed, during the computation of the solution. Input to the program is the parameters of the disease, delay in control (if any), solution termination criterion and penaly constant. Final control vectors are printed at the end of the execution. The intermediate results are printed by the various subroutines.

2. SUBROUTINE WGHMLT: This subroutine calculates the normally distributed weighting multipliers from the latent and incubation periods of the disease. The resulting multiplying-constants are stored as two vectors: WLP and WIP, at intervals of one day. This subroutine is called only once, i.e. in the beginning.

3. SUBROUTINE RKST: This subroutine solves the state equations, using Runga Kutta procedure for the solution of differential equations. It uses subroutine RKGS from the SSP library and is called by both the main program and the search subroutine ASRCH. This subroutine also evaluates the cost function J.

4. SUBROUTINE FCT: This subroutine defines the state equations of the model for subroutine RKGS.

5. SUBROUTINE OUTP: This subroutine stores and prints the output of subroutine RKST. Each time RKST is called, the stored values of states are updated by this subroutine. Printing of the results is, however, skipped if variable KEY is greater than 10. This is done when subroutine RKST is called by the search subroutine ASRCH.

6. SUBROUTINE RKCST: This subroutine solves the costate equations using the Runga Kutta method. The solution is carried out backwards in time using subroutine RKGS. It also evaluates a new gradient vector each time it is called.

7. SUBROUTINE FCTCS: This subroutine supplies the costate equations to the RKGS subroutine in subroutine RKCST.

8. SUBROUTINE OUTPCS: This subroutine stores and prints the results of the solution of the costate equations.

9. SUBROUTINE ASRCH: This subroutine conducts a search for the multiplying vector α (for negative gradient or acceleration steps) to minimize the cost function J. The search is conducted both for α_1 and α_2 in turn, using a combination of bisectional search procedure and interpolation. It calls subroutines RKST (with printing of results switched off) and interpolation subroutine QDINPL.

10. SUBROUTINE QDINPL: This subroutine interpolates the value of α for minimum cost and is frequently called in subroutine ASRCH.

A list of the program described above is given in the following pages.

```
C
C
C   ** OPTIMUM CONTROL OF EPIDEMICS USING PARALLEL TANGENT TECHNIQUES **
C   ******  N.K.GUPTA, ELECTRICAL ENGG. DEPARTMENT *****
C
C   ** SST(25,200) IS THE STORAGE ARRAY.STORAGE IN ROWS 1-4 IS FOR STATES,
C      5-6 FOR INFECTIVE AND REPORT RATES,7-10 FOR CO-STATES,11-16 FOR
C      CONTROLS,17-20 ARE FOR GRADIENT VECTORS,10-20 FOR GRADIENT FOR
C      SEARCH,21-24 ARE FOR RIGHT HAND SIDE OF STATE EQUATIONS AND 25 HAS
C      STORED HAMILTONIAN **
C
C   ** WLP AND WIP ARE NORMALLY DISTRIBUTED WEIGHTAGE VECTORS **
C
      IMPLICIT REAL*8(A-H,O-Z)
      EXTERNAL FCT,OUTP,FCTCS,OUTPCS
      DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
     2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
      DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
     2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
      INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
      COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
      COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
     2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
  901 FORMAT(8F10.0)
  905 FORMAT(8I10)
  911 FORMAT(1H1///,40X,'***** OPTIMUM SOLUTION OF TIME DELAY EPIDEMIC MO
     2DEL *****')
  912 FORMAT(1H0,14X,'THE DISEASE HAS **CONTACT RATE** ',F5.2,'   INITIA
     2L SUSCEPTIBLE POPULATION  0.50  AND DISEASE FACTOR  ',F5.2)
  914 FORMAT(1H0,42X,'*** ACTIVE CONTROL BECOMES EFFECTIVE AFTER',I4,'
     2DAYS ***')
  915 FORMAT(1H ,10X,'EXPECTED MEAN  *LATENT*  AND  *INCUBATION* PERIODS
     2 ARE',2F6.2,' AND RESPECTIVE STANDARD DEVIATIONS',2F6.2//)
  916 FORMAT(1H-,60X,'COST CONSTANTS ARE'//,45X,'COST PER REPORTED CASE
     2                =',F9.2/,45X,'PER UNIT COST OF ACTIVE CONTROL      =
     3',F9.2/,45X,'SQUARE LAW COST OF ACTIVE CONTROL     =',F9.2/,45X,
     4'PER UNIT COST OF PASSIVE CONTROL      =',F9.2/,45X,'SQUARE LAW COS
     5T OF PASSIVE CONTROL    =',F9.2/,45X, 'PENALTY FOR VIOLATING CONSTR
     6AINTS    =',F9.2//)
  917 FORMAT(1H-,40X,'****** NORMALLY DISTRIBUTED WEIGHTAGE MULTIPLIERS
     2******'//)
  918 FORMAT(3(1X,'DELAY IN DAYS****',2X,10(3X,I2,6X)//,1X,'L.P.MULTIPLI
     2ERS**', 2X,10F11.6//,1X,'I.P.MULTIPLIERS**', 2X,10F11.6/////),
     3 55X,'*****  SOLUTION BEGINS *****')
  919 FORMAT(1X,'  PENALTY WEIGHTAGE MULTIPLIERS   PW1 FOR NEGATIVE INFE
     2CTIVES= ',F8.2,'      PW2 FOR RESIDUAL INFECTIVES= ',F6.2//)
  920 FORMAT(1H1///,45X,'ITERATION NUMBER',I4,'  SOLUTION WITHOUT CONTRO
     2L'//)
  921 FORMAT(1H1///,45X,'ITERATION NUMBER',I4,'  SOLUTION WITH CONTROL'/
     2/)
  922 FORMAT(1H-,10X,'DAY',7X,'REP.RATE',7X,'REPORTED',5X,'INFCT.RATE',
     2 5X,'INFECTIVES',6X,'SUSCPTBLS',5X,'ACTV CNTRL',5X,'PSSV CNTRL'/)
  925 FORMAT(1H-,10X,'*** FINAL TIME=',F8.2,' ***',10X,'*** COST=',
     2 F10.6,' *** ',10X,'*** STORAGE POSITIONS=',I5,' ***')
  935 FORMAT(1H-,10X,'ITERATIONS HAVE EXCEEDED THE LIMIT',I6)
  938 FORMAT(1H1///,55X,'*** FINAL ACTIVE CONTROL ***')
  939 FORMAT(1H-///,55X,'*** FINAL PASSIVE CONTROL ***')
  940 FORMAT(1H-,/,(2X,10F13.6))
  945 FORMAT(1H1///,50X,'*** ACCELERATION STEP FOR ACTIVE CONTROL ***')
  946 FORMAT(1H ///,50X,'*** ACCELERATION STEP FOR PASSIVE CONTROL ***')
```

```
C
C   ** READING VALUES OF LATENT AND INFECTIOUS PERIODS. THEIR MEAN VALUES
C      AND STANDARD DEVIATIONS.CONTACT RATE AND DISEASE FACTOR.  **
C   ** ALSO READING COST CONSTANTS FOR ACTIVE AND PASSIVE CONTROLS(AK.BK.
C      CK.DK).COST PER REPORTED CASE CRC. AND PENALTY CONSTANT PK. **
C
C   ** GRDSUM IS THE FLOOR LIMIT ON THE SUM OF SQUARE OF GRADIENTS. IEXIT
C      IS THE NUMBER OF ITERATIONS ABOVE WHICH ITERATION SHOULD STOP AND
C      IDELAY IS THE TIME DELAY IN THE EFFECTIVENESS OF ACTIVE VACCINE **
C
      READ(5.901) DMLP.DMIP.SDLP.SDIP.BETA.FACK.U(1).U(2)
      READ(5.901) AK.BK.CK.DK.CRC.PK.GRDSUM
      READ(5.905) IEXIT. IDELAY
C
C   ** PW1 AND PW2 ARE PENALTY  MULTIPLIERS FOR NEGATIVE AND RESIDUAL
C      INFECTIVES RESPECTIVELY. PW3 IS THE VALUE OF INITIAL INFECTIVES.
C      PW4 AND PW5 ARE CONDITION CODES USED IN THE PROGRAM. **
C
      READ(5.901) PW1.PW2.PW3.PW4
C
C   ** INITIALISING THE VARIABLES TO ZERO. **
C
      COST=0.0
      TMEND=0.0
      DO 10  I=1.50
      CST(I)=0.0
   10 CONTINUE
      DO 20 I=1.25
      DO 20 J=1.200
      IF(I.LT.11.OR.I.GT.12)   GOTO  15
      IJ=I-10
      SST(I.J)=U(IJ)
      GOTO  20
   15 SST(I.J)=0.0
      IF(I.GT.2)   GO TO   20
      USRCH(I.J)=0.0
   20 CONTINUE
      ITRN=1
      WRITE(6.911)
      WRITE(6.912) BETA.FACK
      WRITE(6.915) DMLP.DMIP.SDLP.SDIP
      WRITE(6.916) CRC.AK.BK.CK.DK.PK
      WRITE(6.919) PW1.PW2
C
C   ** EVALUATING AND STORING THE WEIGHTAGE MULTIPLIERS FOR NORMAL
C      DISTRIBLTION OF LATENT AND INFECTIOUS PERIODS. **
C
      CALL WGHMLT(WLP.WIP.DMLP.DMIP.SDLP.SDIP.BETA.FACK.MIP.MLP)
      WRITE(6.917)
      WRITE(6.918) (I.I=1.10).(WLP(I).I=1.10).(WIP(I).I=1.10).
     2(I.I=11.20).(WLP(I).I=11.20).(WIP(I).I=11.20).
     3(I.I=21.30).(WLP(I).I=21.30).(WIP(I).I=21.30)
      WRITE(6.914) IDELAY
      DO 25   K=1.200
      USRCH(1.K)=SST(11.K)
      USRCH(2.K)=SST(12.K)
   25 CONTINUE
```

```
      WRITE(6,920) ITRN
      WRITE(6,922)
      KEY=1
      CALL RKST(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
      CST(ITRN)= COST
      WRITE(6,925) TMEND,COST,INTSTR
      CALL RKCST(X,PRMT,Y,DERY,FCTCS,OUTPCS,AUX)
C
C   ** ONE DIMENSIONAL SEARCH WITH STEEPEST DESCENT FOR FIRST STAGE. **
C
      CALL ASRCH(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
C
C   ** ITERATION USING PARALLEL TANGENTS TECHNIQUE BEGINS **
C
   35 CONTINUE
      CALL RKCST(X,PRMT,Y,DERY,FCTCS,OUTPCS,AUX)
      A=BZ(1)+BZ(2)
      IF(A.LT.GRDSUM)  GOTO  60
      KEY=3
      CALL ASRCH(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
      DO 45 M=1,INTSTR
      SST(19,M)=SST(11,M)-SST(13,M)
      SST(20,M)=SST(12,M)-SST(14,M)
   45 CONTINUE
C
C   ** WRITNG ACCELERATION STEP SEARCH VALUES **
C
      WRITE(6,945)
      WRITE(6,940) (SST(19,N),N=MIP,INTSTR)
      WRITE(6,946)
      WRITE(6,940) (SST(20,N),N=MIP,INTSTR)
      KEY=5
      CALL ASRCH(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
C
C   ** ITERATION TERMINATION CRITERION. **
C
      IF(ITRN.GE.IEXIT)     GOTO  55
      GO TO  35
   55 CONTINUE
      WRITE(6,935) ITRN
   60 CONTINUE
C
C   ** WRITING FINAL CONTROL. **
C
      WRITE(6,938)
      WRITE(6,940) (SST(11,N),N=MIP,INTSTR)
      WRITE(6,939)
      WRITE(6,940) (SST(12,N),N=MIP,INTSTR)
      STOP
      END
```

TOTAL MEMORY REQUIREMENTS 0019BA BYTES

```
C
C
C
      SUBROUTINE WGHMLT(WLP,WIP,DMLP,DMIP,SDLP,SDIP,BETA,FACK,MIP,MLP)
C
C   ** THIS SUBROUTINE CALCULATES THE NORMALLY DISTRIBUTED MULTIPLIERS
C      FOR THE CALCULATION OF ACTIVE AND REPORTED CASES. **
C
      IMPLICIT REAL*8(A-H,O-Z)
      DIMENSION WLP(50),WIP(50),ST(50)
      DO 10    I=1,50
      WLP(I)=0.00000
      WIP(I)=0.00000
      ST(I) =0.0
   10 CONTINUE
C
C   ***LOADING THE MULTIPLICATION ARRAYS****
C
      MLP=2.0*DMLP+1
      MIP=2.0*DMIP+1
      DO 45   I=1,2
      IF(I-1) 20,20,22
   20 K=MLP
      SD=SDLP
      DMEAN=DMLP
      GO TO    25
   22 K=MIP
      SD=SDIP
      DMEAN=DMIP
   25 C=FACK*BETA/(SD*DSQRT(6.2831D0))
      DO 45   J=1,K
      T=J-1
C
C   ** CALCULATING THE NORMALLY DISTRIBUTED CONSTANT MULTIPLIERS. **
C
      ST(J)=C*DEXP((-0.5*(DMEAN-T)**2)/(SD**2))
C
C   ** STORING THE MULTIPLIER CONSTANTS IN PROPER ORDER. **
C
      M=MIP+1-J
      IF(I-1) 30,30,35
   30 WLP(M)=ST(J)
      GO TO 45
   35 WIP(M)=ST(J)
   45 CONTINUE
      RETURN
      END


                TOTAL MEMORY REQUIREMENTS 00062C BYTES
```

```
C
C
C
      SUBROUTINE RKST(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
C
C     **THIS SUBROUTINE INTEGRATES THE STATE EQUATIONS USING RUNGA-KUTTA
C       METHOD AND SUBROUTINE RKGS FROM SSP LIBRARY. **
C
       IMPLICIT REAL*8(A-H,O-Z)
       DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
      2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
       DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
      2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
       INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
       COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
       COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
      2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
     921 FORMAT(1H1///,45X,'ITERATION NUMBER',I4,'  SOLUTION WITH CONTROL'/
      2/)
     922 FORMAT(1H-,10X,'DAY',7X,'REP.RATE',7X,'REPORTED',5X,'INFCT.RATE',
      2 5X,'INFECTIVES',6X,'SUSCPTELS',5X,'ACTV CNTRL',5X,'PSSV CNTRL'/)
C
C    ** INITIALISING PARAMETERS AND STATES. **
C
       PRMT(1)=-1.0
       PRMT(2)=0.0
       PRMT(3)=0.25
       PRMT(4)=1.0D-5
       Y(1)=0.5
       Y(2)=PW3
       Y(3)=0.0
       Y(4)=0.0
       INT=0
       SST(1,MIP)=Y(1)
       SST(2,MIP)=Y(2)
C
C     **INT  REPRESENTS THE TIME IN DAYS **
C    ** UPDATING PARAMETERS FOR EACH INTEGRATION INTERVAL. **
C
    10 CONTINUE
       INT=INT+1
       PRMT(1)=PRMT(1)+1.
       PRMT(2)=PRMT(2)+1.
       DO 20    J=1,4
       DERY(J)=  0.25
    20 CONTINUE
       ACTV=0.0
       RMVD=0.0
C
C    ** CALCULATING ACTIVE AND REPORT RATES FOR GIVEN DAY **
C
       DO 30    J=1,MIP
       M=INT+J-1
       Y2=SST(1,M)*SST(2,M)
       ACTV=ACTV+WLP(J)*Y2
       RMVD=RMVD+WIP(J)*Y2
    30 CONTINUE
C
C    ** PRESENT VALUES ARE STORED AFTER MIP PLACES **
C
       N=INT+MIP-1
       NDELAY=N-IDELAY
```

```
      SST(5,N)=ACTV
      SST(6,N)=RMVD
      U(1)=USRCH(1,N)
      UDELAY=USRCH(1,NDELAY)
      U(2)=USRCH(2,N)
      CALL DRKGS(PRMT,Y,DERY,4,IHLF,FCT,OUTP,AUX)
      IF(KEY-1)  35,35,40
   35 IF(Y(2).GE.PW3.AND.PRMT(2).LT.12.001)    GOTO  10
C
C  ** TMEND IS THE FINAL TIME, INTEND IS THE TOTAL NUMBER OF INTEGRATION
C     INTERVALS AND INTSTR IS THE NUMBER OF STORAGE POSITIONS NEEDED. **
C
      TMEND=PRMT(2)+25.
      INTEND=INT+25
      INTSTR=MIP+INTEND
      KEY=2
   40 IF(INT.NE.INTEND)  GOTO  10
C
C  ** CALCULATING THE COST DEPENDENT ON FINAL VALUES OF STATE. **
C
      COST=CRC*(PW2*Y(2)+Y(3))+Y(4)
      RETURN
      END
```

TOTAL MEMORY REQUIREMENTS 00064E BYTES

```
C
C
C
      SUBROUTINE FCT(X,Y,DERY)
C
C  ** THIS SUBROUTINE GIVES STATE EQUATIONS WITH CONTROL **
C
      IMPLICIT REAL*8(A-H,O-Z)
      DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
     2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
      DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
     2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
      INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
      COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
      COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
     2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
C
C  ** HY2 IS THE DIRAC DELTA FUNCTION FOR NEGATIVE Y(2) PENALTY  MULTIPLIER **
C
      HY2=0.0
      DERY(1)= -BETA*Y(1)*Y(2)-UDELAY*Y(1)-U(2)*Y(1)
      DERY(2)= ACTV-RMVD-U(2)*Y(2)
      DERY(3)= RMVD
      IF(Y(2).LT.0.0)    HY2=1.0
      DERY(4)=PK*PW1*HY2*Y(2)**2+(AK+BK*U(1))*U(1)+(CK+DK*U(2))*U(2)
      RETURN
      END
```

TOTAL MEMORY REQUIREMENTS 000374 BYTES

```
C
C
C
      SUBROUTINE OUTP(X,Y,DERY,IHLF,NDIM,PRMT)
C
C  ** THIS SUBROUTINE STORES THE CURRENT VALUES OF STATE AND PRINTS
C     THE RESULTS. **
C
      IMPLICIT REAL*8(A-H,O-Z)
      DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
     2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
      DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
     2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
      INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
      COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
      COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
     2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
  910 FORMAT(1H ,F13.2,8F15.6)
      IF(X.NE.0.0.AND.X.NE.PRMT(2))    GO TO    55
      IF(X.EQ.0.0)    GOTO    40
      IK=INT+MIP
      DO 10 J=1,4
   10 SST(J,IK)= Y(J)
      IF(KEY.GE.10)    GO TO    55
      DO 20  J=1,4
      JN=20+J
   20 SST(JN,IK)=DERY(J)
      IF(Y(2).LT.0.0)    GO TO    50
      IF((INT/5*5.NE.INT)    GO TO    55
      GOTO  50
   40 IF(KEY.GE.10)    GO TO    55
      DO 45  J=1,4
      JN=J+20
   45 SST(JN,MIP)=DERY(J)
   50 WRITE(6,910) X,RMVD,Y(3),DERY(2),Y(2),Y(1),U(1),U(2)
   55 CONTINUE
      RETURN
      END

                TOTAL MEMORY REQUIREMENTS 0C0544 BYTES


C
C
C
C     SUBROUTINE RKCST(X,PRMT,Y,DERY,FCTCS,OUTPCS,AUX)
C
C  **THIS SUBROUTINE INTEGTRATES BACKWARDS THE COSTATE EQUATIONS USING
C    SUBROUTINE RKGS FROM THE SSP LIBRARY. **
C
      IMPLICIT REAL*8(A-H,O-Z)
      DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
     2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
      DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
     2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
      INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
      COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
      COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
     2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
```

```
  915 FORMAT(1H1///,24X,'*** SOLUTION OF COSTATE EQUATIONS AND CALCULATE
     2D VALUES OF HAMILTONIAN AND GRADIENT VECTORS ***')
  920 FORMAT(1H-,10X,'DAY',8X,'LEMDA-1',8X,'LEMDA-2',8X,'LEMDA-3',8X,
     2'LEMDA-4',4X,'HAMILTONIAN',5X,'GRADIENT-1',5X,'GRADIENT-2'/)
  950 FORMAT(1H0,10X,'*** GRADIENT INTEGERALS***   ',4F15.6)
C
C   ** INITIALISING THE PARAMETERS FOR BACKWARDS INTEGRATION OF COSTATES.
C      INTCS IS THE STORAGE INDEX STARTING BACKWARDS FROM LAST STORED
C      VALUE. **
C
      INTCS=INTSTR+1
      INT=0
      Y(1)=0.0
      Y(2)=PW2*CRC
      LMD3=CRC
      LMD4=1.
      PRMT(1)=TMEND+1.0
      PRMT(2)=TMEND
      PRMT(3)=-0.25
      PRMT(4)=1.0 D-5
      WRITE(6,915)
      WRITE(6,920)
      SST(7,INTSTR)=Y(1)
      SST(8,INTSTR)=Y(2)
C
C   ** UPDATING THE PARAMETERS FOR BACKWARD INTEGRATION INTERVALS. **
C
   10 CONTINUE
      INTCS=INTCS-1
      PRMT(1)=PRMT(1)-1.0
      PRMT(2)=PRMT(2)-1.0
      DERY(1)=0.5
      DERY(2)=0.5
      RLMD=0.0
      IF(INT.EQ.0)  GOTO  20
      IF(INT.GT.MIP)    INT=MIP
      DO 30  I=1,INT
      MW=MIP-I+1
      MCS=INTCS+I-1
      RLMD=RLMD+WLP(MW)*SST(8,MCS)-WIP(MW)*(SST(8,MCS)-LMD3)
   30 CONTINUE
   20 INT=INT+1
      CALL DRKGS(PRMT,Y,DERY,2,IHLF,FCTCS,OUTPCS,AUX)
      IF(PRMT(2).GT.0.)     GO TO     10
      DO 40  L=MIP,INTSTR
      SST(19,L)= -SST(17,L)
      SST(20,L)= -SST(18,L)
   40 CONTINUE
C
C   ** CALCULATING INTEGRAL OF SQUARE OF GRADIENTS **
C
      DO 50 I=1,200
      Y(I)=0.0
   50 Z(I)=0.0
      K=INTSTR+1-MIP
      DO 70  L=1,2
      J=L+18
      DO 60 I=1,K
      ML=I-1+MIP
      Y(I)= SST(J,ML)**2
   60 CONTINUE
      CALL DQSF(1.D0,Y,Z,K)
      BZ(L)=Z(K)
   70 CONTINUE
      WRITE(6,950) BZ(1),BZ(2)
      RETURN
      END

                    TOTAL MEMORY REQUIREMENTS 000708 BYTES
```

```
C
C
C
      SUBROUTINE FCTCS(X,Y,DERY)
C
C  ** THIS SUBROUTINE GIVES COSTATE EQUATIONS **
C
      IMPLICIT REAL*8(A-H,O-Z)
      DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
     2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
      DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
     2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
      INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
      COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
      COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
     2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
      HY2=0.0
      MDLAY=INTCS-IDELAY
      DERY(1)= Y(1)*(SST(11,MDLAY)+BETA*SST(2,INTCS)+SST(12,INTCS))-
     2  RLMD*SST(2,INTCS)
      IF(SST(2,INTCS).LT.0.0)     HY2=1.0
      DERY(2)= Y(1)*BETA*SST(1,INTCS)-2.0*LMD4*PK*SST(2,INTCS)*HY2*PW1
     2  -RLMD*SST(1,INTCS)+SST(12,INTCS)*Y(2)
      RETURN
      END

                    TOTAL MEMORY REQUIREMENTS 000442 BYTES


C
C
C
      SUBROUTINE OUTPCS(X,Y,DERY,IHLF,NDIM,PRMT)
C
C  ** THIS SUBROUTINE STORES THE COSTATE VALUES **
C
      IMPLICIT REAL*8(A-H,O-Z)
      DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
     2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
      DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
     2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
      INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
      COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
      COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
     2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
  910 FORMAT(1H ,F13.2,8F15.6)
      IF(X.NE.TMEND.AND.X.NE.PRMT(2))  GOTO  55
      IF(X.EQ.TMEND)  GOTO  20
C
C  ** STORING THE VALUES OF COSTATE **
C
      L=INTCS-1
      SST(7,L)=Y(1)
      SST(8,L)=Y(2)
      GOTO  30
   20 L=INTCS
   30 M=L+IDELAY
```

```
C
C   ** CALCULATING THE HAMILTONIAN **
C
      SST(25,L)=SST(21,L)*SST(7,L)+SST(22,L)*SST(8,L)+SST(23,L)*LMD3 +
     2 SST(24,L)*LMD4
C
C   ** CALCULATING AND STORING NEW GRADIENT *****
C
      SST(17,L)=-SST(7,M)*SST(1,M)+LMD4*(AK+2.0*BK*SST(11,L))
      SST(18,L)= LMD4*(CK+2.0*DK*SST(12,L))-SST(8,L)*SST(2,L)
     2 -SST(7,L)*SST(1,L)
      IF(X.EQ.TMEND)  GOTO  50
      IF(INTCS/5*5.NE.INTCS)      GOTO   55
   50 WRITE(6,910) X,Y(1),Y(2),LMD3,LMD4,SST(25,L),SST(17,L),SST(18,L)
   55 CONTINUE
      RETURN
      END

                TOTAL MEMORY REQUIREMENTS 0006FC BYTES




C
C
C
      SUBROUTINE ASRCH(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
C
C   ** THIS SUBROUTINE PERFORMS ONE DIMENSIONAL SEARCH ON ALPHA **
C
      IMPLICIT REAL*8(A-H,O-Z)
      DIMENSION SST(25,200),USRCH(2,200),WLP(50),WIP(50),CST(50),U(2),
     2Z(200),BZ(2),Y(200),DERY(5),PRMT(5),AUX(8,5)
      DOUBLE PRECISION LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,
     2PW1,PW2,PW3,PW4,PW5,UDELAY,TMEND
      INTEGER ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY,ISN
      COMMON SST,USRCH,WLP,WIP,CST,U,Z,BZ
      COMMON LMD3,LMD4,ACTV,RMVD,RLMD,BETA,AK,BK,CK,DK,CRC,PK,PW1,PW2,
     2PW3,PW4,PW5,UDELAY,TMEND,ITRN,INT,INTSTR,INTCS,MIP,MLP,KEY,IDELAY
  915 FORMAT(1H0,10X,'*** CALCULATED VALUE OF ALPHA= ',F10.6,'***',10X,
     2 '*** MINIMUM COST= ',F10.6,' ***')
  916 FORMAT(1H1,33X,'**** ONE DIMENSIONAL SEARCH ON CONTROL U',I1,
     2 ' BEGINS ****'//,40X,'SEARCH NO.',6X,'ALPHA',11X,'COST'/)
  920 FORMAT(1H ,40X,I5,2F15.6)
  921 FORMAT(1H ///,45X,'ITERATION NUMBER',I4,'  SOLUTION WITH CONTROL')
  922 FORMAT(1H-,10X,'DAY',7X,'REP.RATE',7X,'REPORTED',5X,'INFCT.RATE',
     2 5X,'INFECTIVES',6X,'SUSCPTBLS',5X,'ACTV CNTRL',5X,'PSSV CNTRL'/)
  923 FORMAT(1H ,40X,'ONLY ACTIVE CONTROL HAS BEEN SEARCHED FOR MINIMUM
     2COST')
  924 FORMAT(1H ,40X,'ONLY PASSIVE CONTROL HAS BEEN SEARCHED FOR MINIMUM
     2 COST')
  925 FORMAT(1H-,10X,'*** FINAL TIME=',F8.2,' ***',10X,'*** COST=',
     2 F10.6,' *** ',10X,'*** STORAGE POSITIONS=',I5,' ***')
  926 FORMAT(1H ,42X,'BOTH CONTROLS HAVE BEEN SEARCHED FOR MINIMUM COST'
     2)
  930 FORMAT(1H ,26X,'INTERPOLATED ALPHA')
      ICHK=0
      ITRN=ITRN+1
      ISN=1
    5 CONTINUE
```

```
      KEY=KEY+10
      ICHK=ICHK+1
      ALPHA=0.0
      PW4=1.0
C
C   ** ISRCH IS SEARCH NUMBER AND ITEST TESTS VALUES FOR INTERPOLATION **
C
      ISRCH=0
      ITEST=0
      WRITE(6,916) ISN
      WRITE(6,920) ISRCH,ALPHA,COST
      K1=ISN
      K2=ISN+10
      K3=ISN+12
      K4=ISN+14
      K5=ISN+18
      IFLAG=0
      DALPHA=0.0016
      CST1=0.0
      CST2=0.0
      CST3=0.0
      ALP1=0.0
      ALP2=0.0
      ALP3=0.0
   10 ITEST=ITEST+1
      CSTMIN=COST
      ALPMIN=ALPHA
      CST1=CST2
      CST2=CST3
      CST3=COST
      ALP1=ALP2
      ALP2=ALP3
      ALP3=ALPHA
   15 ISRCH=ISRCH+1
      PW5=1.0
      IF(ISRCH.GT.10)    GOTO  35
   18 IF(ISRCH.GT.1.AND.IFLAG.EQ.0)    DALPHA=ALPHA*PW5
      ALPHA=ALPMIN+DALPHA
C
C   ** UPDATING THE CONTROL WITH CALCULATED ALPHA FOR NEXT TRIAL. **
C
      DO 20    K=MIP,INTSTR
      USRCH(K1,K)= SST(K2,K)+ALPHA*SST(K5,K)
      IF(USRCH(K1,K).LT.0.0)    USRCH(K1,K)=0.0
   20 CONTINUE
      CALL RKST(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
      WRITE(6,920) ISRCH,ALPHA,COST
      IF(COST.LT.CSTMIN)    GOTO  10
      AALP=DABS(ALPHA)
      IF(AALP.LT.1.D-5)    GOTO  28
      IF((IFLAG.EQ.0.AND.ITEST.GT.3)  GOTO  25
      IF(ITEST.GE.2)  GOTO  30
      DALPHA=DALPHA/4.0
      IFLAG=100
      GOTO  15
   25 DALPHA=ALP3-ALP2
      IFLAG=100
      GOTO  15
   28 IF(PW4.LT.0.D0)  GOTO  45
      PW4=-PW4
      PW5=-PW5
      IFLAG=0
      ISRCH=ISRCH+1
      GOTO  18
```

```
C
C   ** INTERPOLATION RUN FOR ALPHA **
C
   30 CST1=CST2
      CST2=CST3
      CST3=COST
      ALP1=ALP2
      ALP2=ALP3
      ALP3=ALPHA
      ISRCH=ISRCH+1
   35 CALL QDINPL(ALP1,ALP2,ALP3,CST1,CST2,CST3,ALPHA)
      WRITE(6,930)
      DO 40    K=MIP.INTSTR
      USRCH(K1,K)= SST(K2,K)+ALPHA*SST(K5,K)
      IF(USRCH(K1,K).LT.0.0)    USRCH(K1,K)=0.0
   40 CONTINUE
      CALL RKST(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
      WRITE(6,920) ISRCH,ALPHA,COST
   45 IF(CSTMIN.LT.COST)        ALPHA=ALPMIN
C
C   ** STORING NEW CONTROL FOR NEXT ITERATION. **
C
      DO 70  K=MIP.INTSTR
      IF(KEY-13) 55,55,65
   55 SST(K3,K)=SST(K4,K)
      SST(K4,K)=SST(K2,K)
   65 SST(K2,K)=SST(K2,K)+ALPHA*SST(K5,K)
      IF(SST(K2,K).LT.0.0)  SST(K2,K)=0.0
      USRCH(K1,K)=SST(K2,K)
   70 CONTINUE
      KEY=KEY-10
      WRITE(6,921) ITRN
      IF(ICHK.EQ.1.AND.ISN.EQ.1)        WRITE(6,923)
      IF(ICHK.EQ.1.AND.ISN.EQ.2)        WRITE(6,924)
      IF(ICHK.EQ.2)    WRITE(6,926)
      WRITE(6,922)
      CALL RKST(X,PRMT,Y,DERY,FCT,OUTP,AUX,COST)
      CST(ITRN)= COST
      WRITE(6,925) TMEND,COST,INTSTR
      IST=1
      IF(ISN.EQ.2)     IST=-1
      ISN=ISN+IST
      IF(ICHK.EQ.1)    GOTO  5
      ISN=ISN-IST
      RETURN
      END
```

TOTAL MEMORY REQUIREMENTS 0.00E44 BYTES

```
C
C
C
      SUBROUTINE QDINPL(X1,X2,X3,Y1,Y2,Y3,Z)
C
C     ** THIS SUBROUTINE INTERPOLATES VALUES OF ALPHA MULTIPLIER FROM THREE
C        SERIAL VALUES OF ALPHA AND COSTS.  X1,X2 AND X3 ARE THE ALPHAS
C        ARRANGED IN THE ASCENDING ORDER OF ALPHA AND Y1, Y2, Y3 ARE THE
C        CORRESPONDING COSTS. Y3 BEING THE FIRST VALUE WHEN COST STARTS
C        INCREASING. Z IS THE INTERPOLATED VALUE OF ALPHA. **
C        ORDER OF ALPHA AND Y1,Y2 AND Y3 ARE CORRESPONDING COSTS Y3 BEING FIRST
C        VALUE WHEN COST STARTS INCREASING. Z IS INTERPOLATED VALUE OF ALPHA **
C
      IMPLICIT REAL*8(A-H,O-Z)
  910 FORMAT(45X,'ALPHA VALUES DO NOT SATISFY INTERPOLATION CONDITION')
  915 FORMAT(45X,'DENOMINATOR  = 0.0, INTERPOLATION NOT EXECUTED')
      X23=X2-X3
      X31=X3-X1
      X12=X1-X2
      XS23=X2**2-X3**2
      XS31=X3**2-X1**2
      XS12=X1**2-X2**2
      XD=2.0*(X23*Y1+X31*Y2+X12*Y3)
      AXD=DABS(XD)
      IF(AXD.LT.1.0D-7)  GOTO 15
      D=XD/(X23*X31*X12)
      IF(D.GT.0.0)   GO TO  10
      XN=XS23*Y1+XS31*Y2+XS12*Y3
      Z=XN/XD
      GO TO   20
   10 WRITE(6,910)
      GOTO  20
   15 WRITE(6,915)
      Z=X2
   20 CONTINUE
      RETURN
      END
```

TOTAL MEMORY REQUIREMENTS 0003E0 BYTES

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