MODELS FOR THE MANAGEMENT OF ASTHMA

by

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ABSTRACT

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Asthma is a serious health problem. Its prevalence varies markedly between different countries, with figures of 0.09% for all ages in the highlands of Papua New Guinea and 75% for children in the Western Carolines in the pacific ocean. In the United kingdom, about 10% of children suffer from the disease. Adults also suffer from asthma.

There is no curative treatment for asthma. A good management of asthma would mean the prevention or the control of the degree of severity of an attack.

There are two approaches for the management of asthma, acute care and preventive care. With preventive care, usually by inhaled steroids, a General Practitioner may have higher prescribing costs, but this can be justified if it leads to reduced mortality, fewer admissions to hospital and fewer days off work or school. The problem is determining what the optimum balance between the two should be. In this thesis, we attempt to reslove this problem among others by describing deterministic and stochastic models for the management of the disease.

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CONTENTS

CHAPTER 1

INTRODUCTION

In this chapter we discuss the effects of diseases on the populations of both developed and developing countries by giving a historical survey of some selected diseases. The problem of asthma is introduced in section 1.2 and a brief outline of the modelling work reported in this thesis is given in section 1.3.

1.1. The Effects of Diseases

The lives of many millions of people all over the world have been changed by diseases. In some of the more severe epidemics, families and villages have been destroyed and many of those who have survived have had their health and lifestyles changed as a result.

The first example of the impact of such widespread epidemics is that of smallpox in the Aztec Empire. The smallpox virus was entirely unknown to the Aztec Empire before the sixteenth century, even though it was relatively common in Europe at that time, with a 0.25 death to case ratio. After the Spanish invasion in 1519, the disease wiped-out about half of the Aztec Empire. The Black death of fourteenth century Europe, estimated to have killed 25 million out of 100 million people, is another example. Other examples are: typhus epidemic of Russia from 1918 to 1921, in which there were 25 million cases of typhus with a death rate of about 10%; and the widespread influenza epidemic of 1920, during which 20 million people were estimated to have died

world wide (Bailey, 1975).

These infectious diseases need a critical population size to survive. They survive in a community that contains sufficient numbers of susceptible and infective people at all times, otherwise new people will not become infected and the disease will "die out". In Britain and North America, the critical community size is from 200,000 to 300,000 people (Anderson and May, 1982). Some of these diseases are still a major problem in both developed and developing countries. The following is a historical survey of some selected diseases.

Measles occurs throughout the world, with community outbreaks taking place about two to four years. For example, in 1983, the United States experienced its lowest level of reported numbers of cases of the disease following the inception of an aggressive national measles elimination strategy. This accomplishment was the result of an effective vaccination strategy coupled with surveillance and control efforts by local, state, and national public health agencies. Since then, however the reported numbers of measles cases fluctuated between 2,500 and 6,300 until 1989 when over 16,000 cases were reported (Thacker and Miller, 1991). Although a safe and effective measles vaccine has been available for several decades, measles is still a major cause of death.

Malaria is a world wide disease, but it is most common in the tropics, where climatic conditions are favourable for the mosquito and for transmission of the disease throughout the year. Administrative, economic and political problems have frustrated the eradication of this disease in some countries, as has problems of insecticide resistance in the vector and drug resistance in the malaria parasite. In Pakistan, malaria is endemic with up to 30 to 40 percent of the population infected, with 0.4 to 0.5 percent of the patients expected to die as a result (Strickland et al., 1987). The position in most countries in Africa is almost similar if not worse.

Cholera is a disease of poverty and insanitation and is rare in people of upper socio-economic groups even in endemic countries. The true endemic

cholera centres are found in lower Bengal. A similar place is found in Oju Local Government Area of Benue State, Nigeria. Cholera is also endemic in rural Bangladesh and is primarily a disease of children two to nine years of age. Between 1966 and 1980, children in this age group had age-specific hospitalization rates of 4.5 and 6.5 hospitalized cases/1000 children/year, and adults were hospitalized for cholera less frequently than two to nine year olds, and the rates among women in their childbearing years (15-35) were approximately twice those of men of the same age (Glass et al., 1982).

Typhoid fever is another world wide disease and is particularly prevalent throughout the tropics where it is one of the commonest causes of "fever". It is a disease of major importance in areas of the world that have not attained high standards of sanitation and public health. It is particularly predominant in Africa.

Rubella, considered a childhood disease is only moderately contagious, and young children often escape the illness. In the USA, the attack rate is highest in the 5 to 9 year age group, but is also high in older children and adolescents. In addition, local outbreaks are relatively common in colleges and military installations, because of the significant number of young adults (10 to 20 percent) who have no serologic evidence of immunity. In USA, there was an epidemic of Rubella in 1964, when approximately 12,500,000 people were affected.

Trachoma represents a serious public health problem in parts of Africa, Asia, and Latin America. About 500 million people suffer from the disease worldwide with some 7 million blind as a direct result. It is a major problem in the village of Jali, in the Gambia (Ward et al., 1990).

Cancer is one of the unsolved medical problems. The scale of the cancer problem is huge and it is a major cause of death in many countries. In the United Kingdom, about 15,000 women die from breast cancer annually. The indication that early detection reduces breast cancer mortality has created interest in breast cancer screening in many countries including the United Kingdom (Ouinten and Shahani, 1987).

Acute respiratory diseases are extremely common in the younger age groups of the third world countries and cause a large number of deaths. In Medan, Indonesia, a diphtheria case fatality rate of 36.5% was found in patients admitted in the hospital, with 75% of the patients aged less than 5, (Lubis et al., 1987). The incidence of whooping cough in rural areas of India was shown to be strongly related to overcrowding and the number of children in family groups (Singh et al., 1987). Cvjetanovic et al., (1978) in their simulation modelling of whooping cough; stated that fatality rates are dependent on socioeconomic states and age. In addition, they assumed that in general, for developing countries, the fatality rate was approximately 13.5% for people of age less than 1; 3.5% for ages 1 to 4; and 1.0% for ages 5 to 19.

AIDS is not entirely a sexually transmitted disease. In fact it is not just one disease but a collection of different diseases (a syndrome). AIDS is now a major health problem in many areas of the world. In Africa, the AIDS virus is chiefly transmitted via heterosexual intercourse, and in some central African countries AIDS is equally prevalent amongst men and women (Piot et al., 1988). In the West the main routes of transmission are homosexual intercourse and intravenous injection (mainly by drug users but also by unsafe medical practice, as in Rumania), although prevalence is increasing fastest amongst the heterosexual population. The virus can also be passed from mother to child during pregnancy. AIDS is now a major cause of death in people under 40 in many cities in the USA.

1.2. The Asthma Problem

Asthma is a disease of the lungs. The problem of asthma can be likened to that of other chronic diseases, but there is however one way in which it is notably diferrent. Despite the increase in knowledge about the underlying mechanisms of asthma (Holgate and Finnerty, 1988), the development of new drugs and their delivery systems for its management (Jones, 1990), the mortality, prevalence and morbidity of asthma have increased over the past two decades in contrast to other chronic conditions.

It is a serious health problem. Asthma prevalence varies markedly between different countries, with figures of 0.09% for all ages in the highlands of Papua New Guinea and 75% for children in the Western Carolines in the Pacific Ocean. In the United Kingdom, about 10% of children suffer from the disease. Adults also suffer from asthma.

There are two approaches for the management of asthma, acute care and preventive care. With preventive care, usually by inhaled steroids, a General Practitioner may have higher prescribing costs, but this can be justified if it leads to reduced mortality, fewer admissions to hospital and fewer days off work or school. The problem is determining what the optimum balance between the two should be. In this thesis, we attempt to resolve this problem among others by describing deterministic and stochastic models for the management of the disease.

Markov chain models have been developed by Jain (1986) and Jain (1988) to aid policy makers to plan their resources for the management of asthma. These models do not consider how much time an asthmatic may spend in a state before making a transition to another state. The model developed by Jain (1986) has constant transition probabilities and for a given season the one developed by Jain (1988) also involves constant probabilities of moving from a given state to another. In the two models the transition probabilities do not depend on how long the asthmatic has been in a state. In reality these probabilities may depend on the durations in states. This led us to the use of semi-Markov processes (section 5.2) to analyse the problem.

One of the aims of building a model for this disease is to help medical people plan for resources, so that there is the need for the incorporation of these resources and treatments used for the disease. With that kind of model, given a set of treatment strategies, one can decide on the ones that are worthwhile, in terms of costs, days off work or school and the number of admissions to hospital. An investigation of the effect of these treatment strategies on durations of stay in each state can also be made. The Markov chain models developed by Jain (1986) and Jain (1988) do not incorporate these factors and the semi-Markov model considered in section 5.2 can not also capture these

additional features of the disease. A simulation approach will therefore be preferable in these circumstances involving complexities.

Data is also a major setback in constructing mathematical models for disease processes. If there is no data and we want to produce models that can be used, especially by people who are not themselves numerate, then simulation on the microcomputer is a very attractive approach because one can put in a variety of distributions for durations in states. In addition, a simulation model would help the medical people to study the situation closely and thus gather the necessary data. With simulation one could also have quite complicated disease state structure. Treatment options and resources used and the costs incurred can be very easily handled. Markov chain models cannot handle these complexities.

A survey of analytical models is carried out in chapters 4, 5 and 6 and the general conclusion is that a practically fruitful work will be simulation. Simulation models are therfore developed in chapter 8.

1.3 An Outline of the Modelling Work

Mathematical and simulation models are needed for the natural history of asthma. Lack of adequate data is a major challenge in the modelling work reported in this thesis. Though the models represent an approximation to reality they could give medical planners some insight into the management of the disease.

In the modelling work attempted in this research only asthmatics who are at least three years old are considered. The models attempt to determine a management strategy that is beneficial, under scarce resources. They could also be used to predict the number of asthmatics in each disease state in order to plan for the efficient use of these resources.

The results obtained from these models are essentially the expected number of people in each disease state and the expected cost of management strategies adopted. The linear programming model discussed in chapter 4 gives information

about the number of asthma clinics that could be established under limited resources.

Chapter 2 examines the issue of modelling for the control of disease. In this chapter deterministic and stochastic models are discussed in detail. The need for stochastic models is explained and some of the models developed for specific diseases are mentioned.

The disease asthma is discussed in some detail in chapter 3. Here it becomes evident that asthma is a complex disease and hence the modelling approach of Operational Research is well suited for the disease. Chapter 4 considers the asthma process as a deterministic process in discrete time. Difference equations are used in a novel approach to understand, in quantitative terms, the asthma problem. The chapter ends with the problem of how many asthma clinics should be established given limited available resources.

Asthma involves a lot of uncertainty and variability. Deterministic models may therefore be inappropriate to describe this process. Stochastic models are thus developed in chapter 5. These are basically Markov chain models. The extension of these models is given in chapter 6 by considering the process in continuous time. A non-Markovian approach is also investigated in this chapter. Thus chapters 4, 5, and 6 explore the possibility of constructing mathematical models for asthma and reveal that these models need highly simplifying assumptions. There will also be the problem of communication between the model builder and the model user. Therefore simulation is more appropriate for asthma.

The techniques of simulation are discussed in chapter 7 where, among other things, the three-phase approach used for the simulation model is briefly discussed and the techniques of random number generation and distribution sampling is also mentioned.

Chapter 8 discusses the development of the simulation models. Models I and II concentrate on asthma in children while models III and IV consider children and adults separately and in combination. Model V considers asthmatics in a

community and also allows the incidence of new cases. The model is used in determining management strategies that are beneficial, in terms of cost, for the management of asthma.

Chapter 9 gives a description of one of the simulation shells, TOCHSIM used in the development of the simulation models.

Chapter 10 gives a summary, conclusion and suggests further work needed to make the models more realistic.

The simulation programs for model V are described in the appendix. A decsription of how models III and V can be run is also given in the appendix.

CHAPTER 2

MODELLING FOR DEALING WITH DISEASE

This chapter gives a short historical account of modelling for dealing with disease. The development of mathematical theories of the spread of diseases is reviewed in section 2.1 and some deterministic and stochastic analytic models are reported in section 2.2. The advancement in computer technology has eased the construction of simulation models for the control of disease. These models are reviewed in section 2.3.

2.1. The Beginnings

According to Bailey (1975), disease modelling started as far back as the ancient Greeks, with the epidemics of Hippocrates [459-377 B.C.]. The work of John Graunt [1620-74] and William Petty [1623-87] could be considered the beginning of medical statistics and the understanding of large-scale phenomena connected with disease and mortality, but the time was not yet ripe for anything approaching a connected theory of epidemics. Firstly, the requisite mathematical techniques were themselves only then in process of development, and secondly there was insufficient knowledge about the spread of disease. Although a good start was made in the field of physics, particularly mechanics and astronomy, nearly 200 years passed before any real progress was achieved in the biological sciences (Bailey, 1975). It is true however that in 1760 Daniel Bernoulli used a mathematical method to evaluate the effectiveness of inoculation against smallpox, with a view to influencing public health policy.

The outstanding feature of the beginning of modern scientific achievement in this field was the rise of the science of bacteriology in the 19^{th} century. Researches of Pasteur [1822-95] and Koch [1843-1910] involved mainly the statistical appraisal of records showing the incidence and locality of known cases of disease.

Apart from the highly specific studies made by men like Snow [1855] and Budd [1873], we have the more careful investigation by Farr [1840] whose work was mathematically more sophisticated. He fitted a normal curve to quarterly data on deaths from smallpox. Later Brownlee [1866] used a similar method to predict the course of an outbreak of rinderpest amongst cattle. The curve was fitted to four rising successive monthly totals and extrapolated values used for prediction. Although observed and predicted curves were both bell-shaped, agreement in detail was not very good.

Similar curve-fitting methods used by Evans [1875] on the smallpox of 1871-1872 also met with little success. More intensive studies of the same type were later undertaken by Brownlee [1906], who fitted various Pearson curves to epidemic data on many diseases occuring at different times and places.

The work of Farr, Brownlee and Evans involved more of curve fitting and prediction. Deterministic and stochastic models were studied in the early part of the 20^{th} century. This is reviewed extensively in the next section.

It is worth mentioning that there are in general three modelling approaches for disease control :

Deterministic
Analytical Stochastic
Simulation, usually Stochastic

2.2. Mathematical Modelling

The first models presented by Hammer [1906] and later elaborated by Soper [1929] were deterministic. Ross (1911) developed a mathematical model of malaria, which attempted to take into account a set of measures describing various aspects of transmission. The study of respiratory disease using a deterministic approach to the heterogeneity of spread of infection was provided by Becker and Hopper (1983). An epidemiologic application of sophisticated control theoretic deterministic modelling was provided by Hethcote (1983).

This age-dependent immunization model was designed to predict appropriate strategies for disease control. Hethcote utilized data on measles and rubella to determine vaccination strategies appropriate for their control at various levels of immunization coverage.

Deterministic models fell into disfavor because of their inability to accurately describe recurrent cycles of disease (Bailey, 1982). When data became more extensive and much smaller groups were considered, elements of "chance and variation" became more prominent. Mckendrick (1926) was the first to construct stochastic models of epidemic processes. Greenwood (1931) gave an alternative probability treatment five years later, (Bailey, 1975).

"Continuous infection" and "chain binomial" stochastic models were introduced next. These probability models were more appropriate for dealing with smaller groups in which random variation would play a larger role. Although these models achieved popularity, they are usually mathematically and computationally more complex than are simple deterministic models.

Stochastic models now appear more frequently in the study of diseases, (Bailey, 1975). Greenwoods chain-binomial model was used to model group A beta hemolytic streptococcal infections (Poku, 1979). Kimber and Crowder (1984) proposes a model to analyse resistance times to infection under treatment. A general stochastic model was proposed by Hillis (1979, and models specific for toxoplasmosis (Papoz et al., 1986) and a measles outbreak (Riley, 1978) were

also published.

Several stochastic models have been presented to describe distributions of infectious disease over time and space. Catalytic models were used to assess the force of infection (age-specific infection rates) for measles in Tanzania (Remme et al., 1984) and hepatitis A in Europe (Shenzle et al., 1979) using cross-sectional data. Goldacre (1977) attempted an analysis of meningitis using space-time clustering techniques introduced by Knox (1964) to detect the existence of factors associated with infection.

Trend surface analysis, a polynomial regression technique developed for use in geology, was applied to smallpox data from Brazil (Angulo et al, 1977) to determine if general trends in what appeared to be random spatial patterns could be detected. A centrifugal pattern, emerging from the center of a city and spreading outward, was detected. Box-Jenkins models, variants of the ARIMA (autoregressive integrated moving average) models utilized in economics, were applied in a novel fashion to describe patterns of infection in chickenpox and mumps (Helfenstein, 1986) and to forecast mortality due to influenza (Choi et al., 1981). Time-series data also provided the data base for models of epidemic velocity proposed by Cliff and Haggett (1982).

The etiology of disease is of primary concern to many epidemiologists and can be viewed either in a deterministic or stochastic framework. A deterministic perspective is one in which factor x causes y if (all other factors being held constant) a change in the value of x results in a change in the values of y, in a completely prescribed way tracing out a mathematical function of some form. In practice, probability theory and statistical techniques are used to assess evidence regarding causality. In any causal analysis of data, the goal is to account for variation in the dependent variable.

Several models of this sort have been utilized to analyse data in studies of infectious disease, including most commonly linear regression, log-linear analysis and logistic regression, discriminant analysis, and proportional hazards modelling. Few examples include the work of Stevens and Lee (1978) who used a generation effect model to assess the impact of antitubercular

chemotherapy on mortality. The generation effect model assumes that the mortality pattern for each cohort is set early in life; rates vary only according to birth cohort. This model was used to project current mortality experience using past cohort data. The large differences noted by Stevens and Lee between the expected and the observed rates were ascribed to the effect of intervention with chemotherapy.

Discriminant analysis was used in studies of herpes simplex types 1 and 2 (McClung et al., 1976), chronic obstructive pulmonary disease (Lebowitz and Burrows, 1977), and leprosy (Serjeanston and Woodfield, 1978). Linear regression models were utilized for analyses of risk associated with influenza mortality (Clifford et al., 1977) and childhood diarrhoea (Koopman, 1978) and to model the effect of influenza on ischemic heart disease. A model of risk factors in a noninfectious disease, skin cancer, has been constructed using logistic regression (Vitaliano, 1978).

The following year, log-linear models were used to analyse data from a cohort study of acute respiratory illness (Melia et al., 1979 and Florey et al.,1979). Other examples using logistic regression include (Stavraky et al., 1983 and Lugosi, 1985); and those using log-linear modelling include (McGlynn et al., 1985 and Perillo et al., 1986).

Markov chain models have also been applied to study the progression of disease. Fix and Neyman (1951) constructed a simple stochastic model of recovery, relapse, death and loss of patients. They were concerned with the difference in effect either of the same treatment applied to different categories of patients or of different treatments applied to specified category of patients. In all cases the criterion for comparison was the frequency of surviving specified periods of time. This model was used to study the effects of treatment of cancer of the breast. Marshall and Goldhamer (1955) applied Markov process to study the epidemiology of mental disease. Other similar studies include the work of Sverdrup (1965) and Sacks and Chiang (1977). Badger et al. (1987) proposed a time-homogeneous Markov process for modelling the clinical course of recurrent genital herpes and is used to obtain estimators for various characteristics of the disease. The model has a

finite, discrete time parameter and discrete state space, with six transient states corresponding to the six stages a herpes lesion may enter. The healed condition was represented as an absorbing state. The number of lesions present at the outset of the clinical episode and the number of lesions appearing during the course of the episode are assumed to have negative binomial distributions. Clinical trial data are used to examine the assumptions of the model and to estimate its parameters. Estimates of clinical variables based on the model are computed and are compared with those calculated directly to assess how well the model represents the biological process of the disease. Markov chain models have also been constructed to study the effect of weather on asthma (Jain, 1986 and Jain, 1988). See chapter 3 for more details on asthma models.

Many disease models have yielded valuable information, examples being measles (Fine and Clarkson, 1982a, 1982b), rubella (Anderson and May, 1983), Hepatitis (Farrington, 1989), Leukaemia (Birkhead, 1985),and Cancer (De Sena and Shahani, 1984; Ouinten and Shahani, 1987).

However, mathematical modelling is only suitable for very simple systems or situations that allow high simplifying assumptions and not for systems or situations that involve uncertainty, complexity, and scarce resources. In such cases simulation models are often appropriate.

2.3. Simulation Modelling

Simulation is a process for studying or finding a solution for a problem or calculating the effect of a course of action, by representing it in mathematical terms, especially using the computer, (Readers Digest Universal Dictionary, 1989). A simulation model is an abstract model which represents some system in the real word.

Simulation methods have developed since early 1960s and may well be the most commonly used of all the analytical tools of Operational Research, (Pidd, 1992). The simulation technique is discussed in some detail in chapter 7.

In sufficiently small communities complete fade-out of infection may occur if fresh cases are not introduced, whereas in communities above a certain critical size it will merely happen that infection reaches a low level before building up again for a fresh outbreak, (Anderson and May, 1982). These conclusions are in agreement with both observed data and with the results of empirical investigations using Monte Carlo methods in conjunction with the electronic computer. This perhaps marks the beginning of the use of computer simulation for disease control. One of the first simulation studies was conducted by Bartlett (1961) in the area of recurrent epidemics and endemicity with special reference to the interpretation of real public health measles data.

Computerized simulation studies of both simple and general epidemics over a square lattice were carried out by Bailey (1967). The simulation work of Williams and Bjerknes (1971, 1972) on the growth of tumour cells in two dimensions can also be found in the literature. This has close analogy with two dimensional epidemic spread.

Computerized simulations have been extremely valuable in elucidating the properties of multistate models of disease and in shedding light on proposed intervention strategies. Extensive studies of this type have been made in tuberculosis control by Waaler, Geser and Andersen (1962); BrØgger (1967); ReVelle, Lynn and Feldmann (1967). Similar applications have also been utilized for a number of other bacterial diseases, such as typhoid fever, tetanus and cholera, in the works of Cvjetanovic', Grab and Uemura (1971); Cvjetanovic', Grab, Uemura and Bytchenko (1972); Cvjetanovic', Grab and Uemura (1978).

Another area of some public health consequence is the interference and interaction phenomena that may occur between different disease organisms. Lila Elveback and her co-workers have developed a series of six fundamental models of increasing complexity that can be used for the study by computerized simulations of public health control of poliomyelitis by means of live polio vaccine, including the situation where the effect of the vaccine is inhibited by enterovirus infections. The chief references are (Elveback, Fox and Varma,

1964; Elveback and Varma, 1965; Elveback, Ackerman, Gatewood and Fox, 1971), just to mention a few.

Frerichs and Prawda (1975) developed a simulation model describing the transmission of cannine rabies within and between 116 spatially distributed neighborhoods in Cali, Colombia. Various cannine vaccination strategies were tested in the model over a ten-year planning horizon for their cost-effectiveness with regard to the prevention of cannine rabies. A deterministic model in the form of a computer simulation model for predicting the global spread of influenza was presented by Longini et al., (1985).

Today, simulation modelling is a very attractive powerful method for dealing with the complications of a variety of diseases including asthma (Yates, 1989), and has been used for a variety of diseases such as Rubella (Flahault et al., 1988), Cancer (Mandurah, 1988), AIDS (Brailsford and Shahani, 1990). The simulation technique has also been used to investigate the effect of trachoma control strategies (Hawkins, 1989).

The evolution of modern (more powerful, less expensive and easier to use) computers and high level languages has popularized (Zeiglier, 1979) the application of simulation for solving real-life problems in several descriptions, and the expected advances in computer technology indicate that this trend will continue.

A realistic model of the disease asthma would be a simulation model for the following basic reasons :

(a) the development and possible control of asthma attacks and the concept of growing out of asthma are complex processes. Applying mathematical modelling approach would require many simplifying assumptions e.g. assumptions about transition probabilities from, say mild attack to a severe attack. Such assumptions would have adverse effects on the validity of the mathematical model of the real problem.

(b) the successful use of an asthma model would require joint work by medical people and Operational Researchers. The problem of communication between these two groups of people is greatly eased by the use of the simulation approach.

CHAPTER 3

THE DISEASE ASTHMA AND A REVIEW OF ITS MODELS

Asthma has been recognized since the begining of medicine. The word was first used by "the father of medicine", the Greek physician Hippocrates, over 2000 years ago. But despite doctors' ability to identify the disease when they see it, they have always remained unable to define it, (Sinclair, 1987).

In this section, we shall examine some of the characteristics of asthma, and explain how it is being managed in general medical practice. Some of these ideas are used in the asthma simulation models described in chapter 8. We shall also give a review of the modelling work in the management of the disease.

3.1. Definition of Asthma

Asthma is a disease characterised by wide variations over short periods of time, in resistance to flow in intrapulmonary airways, (Weiss et al.,1985). The disease's chief sympton is wheezing which is caused by the narrowing of the bronchi and bronchioles in the lungs; a process known as bronchoconstriction. In an individual with asthma, this narrowing is not permanent but episodic, and it varies either spontaneously or as a result of treatment.

It is a disease that may begin at any age, and different types of people can develop wheezing. In half of the cases the onset is before age 10. In over

one-third of patients, there is a history of asthma in members of the immediate family.

When there is clear association with allergy, asthma is referred to as allergic (or atopic or extrinsic) asthma. In other patients, the role of exogeneous allergens can not be clearly shown, and the relationship of asthma attacks to exposure to such agents is not evident. There is however frequent association with respiratory tract infection. This type of asthma is generally known as intrinsic (or non-atopic or non-allergic) asthma.

3.2. Stimuli Causing Attacks of Asthma

In this section we explain some of the trigger factors that cause the smooth muscle in the walls of the airways to contract, thus bringing on an asthma attack.

3.2.1. Allergic Factors

The word allergy was coined by Von Pirquet (Banszky, 1950), to connote the condition in which one is abnormally sensitive to a particular substance. Allergic factors are more effective in children with a history of eczema and asthma, and are often prominent in individuals whose asthma starts in later childhood, adolescence or early adult life. Many different types of allergens have been identified in individuals with asthma. The most common being pollens; and many asthmatics who are hypersensitive to pollens have a history of hay fever.

In children, sensitivity to food allergens, such as eggs, wheat, cow's milk or chocolate is relatively common. Nevertheless, food as the sole precipitating factor in asthma is rare. In a study (Chobot et al., 1951), it was found that food as the sole identifiable allergen occurred only in 0.25% of the series. However, in children under the age of 3, 15% were found to be allergic to food as well as other substances.

House dust, fungi and their spores are other allergic factors in asthma. They are more common in older individuals.

It is now believed that the factor responsible for the hypersensitivity of reaction may be due to an allergen derived from mites of the "*Dermatophagoides*" species which subsist on human skin peelings and are commoner in damp houses and in damp years. The relief often obtained by asthmatics in high altitudes may be due to the absence of mites. In Britain the house dust mite is proving to be the most frequent allergen in asthma, and it tends to be at its worst between July and November.

Other common allergens are animal dander, especially from cats, dogs, and horses. About 1% of asthmatics are said to be sensitive to aspirin and also to other analgesics. Other allergens reported within the last few years include antibiotics and many other drugs, wood dust, and isocyanates in the chemical industry.

In a sudy of 375 cases of allergic asthma (Crofton and Douglas, 1975), Pearson found that sensitivity to house dust was present in 45% to 60% regardless of age. Other allergens, in descending order of frequency, were pollens, feathers, animal hair, food, and moulds.

In many cases, no hypersensitivity to specific allergens can be demonstrated, either by clinical history or by skin or inhalation tests.

3.2.2. Infection

This is one of the most common stimuli causing an asthma attack. It is most important in those in whom asthma first comes on in early childhood, and in those, particularly women in whom it starts in middle age.

It is not always possible to demonstrate an allergic reaction to any specific infecting agent but it may be that in these cases inflammation of the bronchial tubes from the infection starts off a chain of reactions resulting in asthma. It is known that sensitizing antibodies tend to accumulate in

inflamed tissues and it may be that such antibodies are responsible for the asthmatic reaction to an agent which in a normal person would only produce an upper respiratory infection or at most an attack of simple bronchitis.

It has been found that respiratory tract infections account for about two-thirds of asthma attacks in children, and one - third in adults, (Lambert and Stern, 1972). In a study conducted by Gregg, it was found that less than 10% of healthy adults had a wheezy experience during virus infections of the nose and pharynx, (Yates, 1989). In a group of asthmatics, 80% were found to have the same experience with a similar infection.

In another study of children with asthma (Minor et al., 1974), it was found that about 69% of episodes of asthma were caused by respiratory tract infection. This was actually confirmed in about 57% of the cases.

In yet another study of adults who were admitted in hospital with acute asthma, 37% had had a respiratory infection and 23% had possible respiratory infection.

3.2.3. Psychological Factors

These are other trigger factors in asthma. In two surveys in the general population in Britain, it was found that psychiatric disturbance was commoner in asthmatic children than in controls, (Crofton and Douglas, 1975). Families of asthmatics seemed to have a higher prevalence of neurosis and other psychiatric illnesses. In (Zealley et al., 1971), it is reported that the distribution of neurosis in asthmatics was similar to that in a control group. Graham and others found that asthmatic children in the general population were more intelligent than controls, but that their educational achievements were no greater, (Crofton and Douglas, 1975). However, Rees (1967) found the distribution of measured intelligence the same in asthmatics and controls. These were hospital patients, so possibly a selective factor operates in hospital cases, but the frequent clinical impression of an association with intelligence may be exaggerated. He found evidence of major psychological stress, of a wide variety of types, immediately preceeding the onset of asthma

in 35% of 800 asthmatics, a significantly higher proportion than in a control group. Under hypnosis, suggestions of fear and anger have been shown to increase airways resistance, (Smith et al., 1970).

There is no doubt that attacks of asthma can be precipitated by psychological upset, although it is doubtful whether psychological upset alone is ever the only factor responsible for an asthma attack. However it is believed that emotional episodes are liable to aggravate asthma, especially in children. Nevertheless, it must be emphasized that multiple factors often operate in asthma.

In a review of 487 cases, Williams and his colleages found that there was a psychological factor in 70% of the asthmatics, (Crofton and Douglas, 1975).

3.2.4. Air Pollution

The quality of air we breath can have major effects on asthmatics. Asthmatics tolerate atmospheric pollution or cigarette smoke badly. Cigarette smoke induces bronchoconstriction in normal individuals (Rees et al., 1982), and asthmatics most often show a much greater degree of bronchoconstriction than normal people. An asthmatic attack can also occur when low concentrations of surphur dioxide and oxidants in the air are produced by industry. Outbreaks of asthma, as in the U.S. servicemen stationed in the Tokyo - Yokohama area and in the inhabitants of New Orleans, seem likely to have been due to atmostpheric pollutants (Crofton and Douglas, 1975), though the evidence is incomplete and the disease induced may have been more of bronchitis than asthma. Nevertheless, asthma is often worse in foggy weather.

As discussed earlier, inhaled allergens are the most common triggers of asthma and they can be divided into seasonal allergens, e.g. from plants and pollens, and perennial allergens, e.g. from house dust mites, animals, and foods. These vary greatly in different parts of the world.

3.2.5. Exercise

Exercise quite frequently induces asthma, provided that it is hard enough. There is some variation between individuals. It requires walking slowly for some asthmatics, to sustained hard running for others. The asthma attack happens mostly after the exercise.

The exercise effect is greatest after running, somewhat less after cycling, and substantially less after swimming. The exercise effect can be diminished or prevented by preliminary inhalation of sodium cromoglycate, (Clarke, 1971).

3.2.6. Other Non-Specific Factors

There are some stimuli that cause an asthma attack which may not be classified. In section 3.2.4., we mentioned that cigarette smoke induces bronchoconstriction in asthmatics. Other smoke may have a similar effect, as may such things as the smell of fresh paint, strong perfume or cold air, (Aas, 1969). In a study by Tiffenan, it was discovered that irritable cough and decrease in FEV is much more readily induced in asthmatics than in normals, (Crofton and Douglas, 1975). He found that cough, often with pricking and tickling, developed in 75% of asthmatics, at least with the largest dose of acetylcholine, where as it occurred in normals with only about 100 mcg inhalation (Asmundsson et al., 1971), the bronchial tubes of asthmatics being more sensitive than those of normal people.

Occasionally drugs used to treat asthma can themselves cause bronchoconstriction. Such effects have been noticed with aminophylline, ipratropium bromide, sodium cromoglycate, and propellants in metered dose inhalers.

Sometimes pregnancy may cause a deterioration or an improvement in asthma, (Turner et al., 1980). In a study conducted by Gluck and his colleague, it was found that 43% of asthmatics experienced a deterioration in their asthma during pregnancy. The deterioration started around the fourth month of pregnancy, (Gluck and Gluck, 1976). If asthma deteriorates during one

pregnancy, then it is likely to deteriorate during the next and if it improves, it is also likely to improve during further pregnancies.

Beta blocking agents may also cause bronchoconstriction when given to asthmatics, and this happens even when they are administered as eye drops.

3.3. Effects of Asthma

Which ever factors trigger an attack, the airways of an asthmatic narrow and breathing out becomes a problem. The bronchial smooth muscles contract, there is an increased secretion from bronchial glands and globlet cells, and swelling of the mucosa, all of which contribute to airway narrowing, (Farzan, 1978). This causes wheezing as the asthmatic tries to obtain more air by using the accessory muscles of respiration.

Because of the difficulty of breathing out, the air gets trapped in the lungs resulting in hyperinflation. Breathing becomes difficult and the asthmatic is unable to talk. There is also a shortage of oxygen in the blood and the asthmatic starts to go blue - a condition known as cyanosis, (Sinclair, 1987).

Bronchial asthma has not, until recently been considered as a disease that can cause fatalities. It was thought to cause only moderate morbidity and negligible mortality.

Sir William Oster stated in 1901 (Diggle, 1983) that "death did not occur from Asthma". Coope in 1948 said "the prognosis of the acute attack of asthma is usually good, it is sometimes said that no one ever dies of asthma, but this is not entirely true" and Witts in 1963 said "when status asthmaticus persist for two days, the risk of sudden death should be seriously considered, (Williams, 1959). It has now been generally agreed that attack of asthma could result in asthma death. About 2000 asthmatics die of asthma every year in the United Kingdom alone, (Jones, 1989).

Childhood asthma, when it becomes severe or is poorly controlled, may retard growth. Days are lost from schooling and/or work if asthma is severe, and many asthmatics experience night attacks which keep them awake. Inability to take part in sports and other activities is common in many asthmatics.

Martin and others found, and as quoted in (Yates, 1989), that one-third of a large group of asthmatics were missing substantial time from work and has a restriction on their sports activities.

In U.S. in 1970, over 30% of the asthmatic population spent one or more asthma-induced days in bed. 20% spent from 1 to 7 days, 5.8% spent from 8 to 14 days, 3.6% from 15 to 30 days, and 1.6% 31 or more days in bed. In the same year the average asthmatic spent 15 days of restricted activity and 5.8 days in bed owing to asthma. This represented 90 million days of restricted activity and about 34 million bed days due to asthma. In the same country asthma was a major cause of school absences in 1980. In 1964, 25% was estimated as school days lost due to asthma, (Patterson, 1980). However, if asthmatics are given correct treatment, they can expect to lead a normal lifestyle.

3.4. Incidence and Prevalence

There is a relative paucity of data concerning the incidence of asthma. As a chronic disease, it is responsible for a great many days of absence from school or work, and thus is an important socio-economic disease. Among diseases that result from allergy, asthma is the most important source of morbidity and mortality. The incidence of fatalities increased in the decade of the 1960s, and it continues to increase. In England and Wales, the annual number of death from asthma in patients between the ages of 5 and 64 increased from 720 in 1959 to 1401 in 1966, with almost a doubling of the death rate from 2.0 to 3.7 per 100,000 population, (Speizer et al., 1968). Now about 2000 people die from asthma each year and the disease is increasing because of pollution and allergy to the house dust mite, (Medicom, 1990).

In the U.S., Lawrence showed, and is quoted in (Patterson, 1980), that there were 4441 deaths from asthma in 1964, representing a death rate of 2.3 per 100,000 population. Even more significant was the fact that an additional 13,000 death certificates listed asthma as an underlying cause, a figure which may signify that this disease is an even greater cause of death than is suspected.

A further breakdown of these U.S. statistics of asthma mortality in 1964, revealed that significantly more males than females died during the period. The rate for non-whites was from 2 to 3 times higher at every age than for whites, with an exception of the oldest age-group where the rates for these two groups were about the same.

If we look at the amount of morbidity caused by asthma, the disease assumes an even greater importance. In the U.S. in 1970, there were 6 million people with asthma, and it was estimated that 17% of these had some limitation of their activity due to their disease.

Summarised data, quoted in (Yates, 1989), showed differences in childhood asthma prevalence in different countries : 0.7% to 2.0% in Scandinavia, 2.0% to 5.1% in U.K. and U.S., and 5.4% to 7.4% in Australia and New Zealand.

Some communities have much lower rates, such as rural Indians, Papua New Guinea highlanders, Eskimos, and North American Indians.

3.5. Natural History of Asthma

Asthma is a most common disease that may begin at any age. In half of the cases, the onset is before age 10. In over one-third of patients, there is a history of Asthma in members of the immediate family.

Spontaneous recovery is not uncommon in childhood asthma and in approximately one-third of cases in early childhood will recover by their adult age. Beyond this age, tendency to spontaneous recovery is much less. Many asthmatics who have the onset of their asthma later in life will continue to be vexed by it

throughout their existence.

Blair (1977) followed a series of asthmatic children to the age of 20 and found that 52% were then completely free of symptons, 21% still suffered from asthma and in 22%, the disease had remitted in adolescence but then reappeared after several years.

A similar study was conducted by Martin and others, (Yates, 1989). They followed wheezy children to the age of 21. Over half of the children with infrequent wheeze lost their symptons by early adult life. Of those with frequent wheezing, 20% became sympton-free and a further 30% were much improved. Of those who wheezed frequently at 14, 25% had a more severe disease at 21. Almost all the children with persistent wheeze in childhood continued to wheeze into adult life, but many became less persistent.

Much confusion still exists as to whether the chances of growing out of asthma or having remissions are affected by sex, age at onset, breast feeding, family history of atopic disease, presence of associated atopic disease or of positive prick skin test results to external allergens.

In many studies it is not known whether the results were due to the treatment employed or whether the improvement or lack of it represented the natural course of the disease.

3.6. Treatment of Asthma

At present there is no actual curative treatment for the disease asthma. Thus what we will call treatment here will be the prevention or the control of the degree of severity of an attack.

In this section we shall outline some of the drugs used in the treatment of asthma and their prescribing costs in general medical practice.

3.6.1. Drugs Used in the Treatment of Asthma

The main process involved in any asthmatic attack is the narrowing of the airways. It is likely that any drug which can prevent or even reverse this process will be effective in the treatment of asthma. Inflammatory reaction that sets in also causes the lungs to produce more than the usual amount of phlegm or mucus. This lodges in the narrowed airways, blocking them still further. Finally, most asthmatics react to external allergens. No single drug will deal with all these reactions.

It is thus convenient to divide anti-asthma drugs into two groups : "relievers" - which relieve constriction by relaxing the airway muscle, and "preventers" - which prevent or reverse the inflammation. This last group also includes anti - allergic drugs.

Classifying drugs on the basis of their types of action leads to three categories :-

1. Bronchodilators which include adrenergic drugs (e.g. Salbutamol), Methylxanthines (e.g. theophylline), and anticholinergic agents (e.g. ipratropium)

2. Corticosteroids which are divided into two main subgroups :- glucocorticoids (e.g. hydrocortisone) and mineralocorticoids. These are the main steroids used in medicine. Glucocorticosteroids are the most effective drugs in the treatment of asthma.

3. Mast - cell Stabilizers (e.g. Sodium cromoglycate (Intal)) which act by preventing bronchoconstrictor responses to certain forms of provocation, usually allergic or exercise.

3.6.1.1. Administration of Drugs

Most of the anti-asthma drugs can be administered by more than one route. At least one of each category of the drugs can be taken by inhalation, with the

exception of the methylxanthines.

Inhaled drugs are available in three forms :- aerosols, micronised powders, and nebulised solutions and can be taken by means of spinhaler, rotahaler or diskhaler. Inhalation is nearly always preferable in the treatment of asthma.

3.6.1.2. Prescibing Costs in General Medical Practice

Having an interest in asthma in general practice is associated with higher respiratory prescribing costs when compared with the calculated national average, (The General Practitioners in Asthma Group, 1990). Individual GPs with an interest in asthma have on average higher respiratory and prophylactic medicine prescribing costs than their practice averages. Having an interest in asthma care can be associated with an increase in respiratory prescribing costs without any increase in the overall costs. These comparisons (expressed as percentages) are shown in table 3.1, (Source : The General Practitioners in Asthma Group, 1990):-

Table 3.1. Percentage relationship between costs of prescribing : GPs, Practice averages and caculated National average

	Individual Versus Practice Average		
Total	mean	106%	95% CI 98 - 115%
Respiratory	mean	129%	95% CI 115 - 143%
	Practice Average Versus National Average		
Total	mean	95%	95% CI 89 - 101%
Respiratory	mean	118%	95% CI 106 - 130%

CI - confidence interval.

In the United Kingdom the returns made by General Practitioners suggest that a group practice with about 10, 000 registered patients will result in an annual expenditure of about 20, 000 pounds on Bronchodilators and about 30, 000 pounds on steroids for treating severe attacks and for preventive treatment.

Drugs used in the modelling process are assumed to be taken by inhalation and therefore for model I the number of units of a drug is regarded as the number of puffs of the drug. Facilities like inhalation devices and peak flow meters are assumed to be replaced after two years. Using published data, (BNF, 1992) we can estimate the costs of some of these resources. Table 3.2 shows the number of units used per day and the cost of salbutamol (a bronchodilator), budesonide and prednisolone (corticosteroids).

Drug	Number of units per day	Cost of 1 unit (pounds)
Salbutamol	8	0.010
Budesonide	2	0.095
Prednisolone	1	0.010

Table 3.2. Drugs used for model I

For models II - V the costs of the drugs were estimated per month (for models II-IV) and per day (for model V). The result is given in table 3.3.

Drug	Cost per month (pounds)	Cost per day (pounds)
Salbutamol	2.40	0.08
Budesonide	11.40 (22.80*)	0.38 (0.76*)
Ketotifen	16.80	0.56
Adrenaline	4.20	0.14

* For severe attack

Table 3.3. Drugs used for models II-V

The costs of some facilities were also estimated and are presented in table 3.4.

Facility	Cost per month (pounds)	Cost per day (pounds)
Inhalation device	0.30	0.01
Peak flow meter	0.30	0.01

Table 3.4. Facilities used for models II-V

Note that for a more severe attack some of these costs may increase.

3.7. A Review of Asthma Models

There has been widespread use of statistical techniques in clinical trials and in attempting to determine variables which are relevant to the prognosis of asthma, but the application of Operational Research modelling techniques to the study of asthma has been minimal.

In (Ware, Lipsitz and Speizer, 1988), statistical methods for the analysis of repeated observations of categorical variables (no wheeze, wheeze with colds, and wheeze without colds) as they might arise in longitudinal studies were discussed. Two general models were used :-

1. marginal models that give representations for the marginal distribution of response at each occasion, and

2. transitional models that give representations for the transition probabilities between outcome states at successive occasions were described.

A discussion on the conceptual and technical differences was made and recent work advancing both approaches was reviewed. The two approaches were illustrated through analysis of repeated observations on interval history of

the respiratory sympton "persistent wheeze" in pre - adolescent children.

Korn and Whittemore (1979) presented new methods for analysing repeated binary health measurements of individuals exposed to varying levels of air pollution. The methods involved a separate logistic regression of response against environmental covariates for each individual. Estimates of parameters reflecting individual susceptibility to pollutants and weather were made using Cox's regression techniques. The individual parameters were combined to yield summary estimates of environmental effects. The approach did not require independence of successive health measurements. It was illustrated with data on asthma and air pollution in Los Angeles area in U.S.

Stochastic models had been used for a long time for studying the progression of disease. Fix and Neyman (1951) were the first to use a four state Markov model to study human cancer. Marshall and Goldhamer (1955) discussed a Markov chain model for characterizing the age distribution of mental patients. Recently several stochastic models have been proposed for the study of the progression of diseases (Sacks and Chiang, 1977 and Tolley et al., 1978), just to mention a few. The rate of progression of disease for allergic patients induced by allergenic pollen is an area which require a great deal of attention from the medical point of view (Lebowitz, 1973). The amount of allergenic pollen in the environment can be associated with the time of the year. The severity of chronic bronchial asthma is related to the changing pattern of the season (Lebowitz, 1973, 1981).

Based on the above facts, Jain (1988) proposed a time-varying Markov chain model with periodically changing transition probability matrix (non-homogeneous Markov chain) to predict the behaviour of those diseases which are periodic with respect to the year.

The model was used to characterize the behaviour of chronic bronchial asthma, and the behaviour of the severity of asthma attack was compared with the seasonal pattern of the weather.

The states of his model were classified as follows :-

S_1 : Leading normal life,
S_2 : Mild attack (i.e. slight interference with normal activities),
S_3 : Severe attack (i.e. considerable interference with normal activities).

Five Canadian seasons were considered : Winter (November 1 to April 15); Trees (April 16 to May 31); Grass (June 1 to July 20); Ragweed (July 21 to September 7); and Fall (September 8 to October 7).

Seasons were determined on the basis of daily airbone allergenic pollen as appropriate transition times, each with its own transition probability matrix.

Accordingly, a Markov process with periodically changing transition probability matrices based on the five seasons was considered. Limiting state probabilities at the end of each season were computed and the results were analysed. The results demonstrate that the time-varying Markov chain model reproduced the high probability for suffering severe attack of chronic bronchial asthma during a high pollen count season.

Jain (1986) used a similar approach to develop a finite Markov model with discrete time parameter for the study of seasonal patterns affecting the state of health of chronic bronchial asthma patients. He considered the condition of an asthmatic patient to be modelled by a three state Markov chain :- a patient in state 1 : under self- care, state 2 : under intermediate care, and state 3 : under intensive care. He considered the same Canadian seasons:- winter, trees, grass, ragweed, and fall with their duration as given above. He showed (using the likelihood ratio test) that the transition probabilities were stationary (homogeneous Markov chain).

He used the maximum likelihood estimates for the one - step transition probability matrix. Thus given the patients' health states for the season T, the model could be used to predict future states of patients' health. These

predictions can be used by doctors, hospital administrators, and policy makers to device a strategy for the treatment of asthmatics at a minimum cost.

Mao et al.(1990) conducted a similar study of the disease using data from the province of Ontario, Canada. These data were collected on asthmatics aged 15 to 34 during the period 1979 to 1986. Seasonality in mortality and hospital admission rates were evaluated using time series methods. The evaluation involved fitting a series of Box-Jenkins regression - ARIMA (autoregressive integrated moving average) models. Hospital admission rates were highest in the fall (September - October). There was a smaller peak in the spring (April-May). The rates were lowest during the summer (June - August) and during the winter (December-March). Mortality was higher in October. The test for seasonality for hospital admission rates was highly significant while that for mortality was not significant.

CHAPTER 4

DETERMINISTIC MODELS

In this chapter we develop deterministic models for asthma. In section 4.1 we construct models in discrete time and in section 4.2 we consider asthma as a continuous time process.

4.1. Deterministic Models in Discrete Time

In this section we consider asthma as a process in discrete time. A two state model will be developed in section 4.1.1. The implications of preventive treatment will be considered in section 4.1.2. The extension of this model to a five state model will be discussed in section 4.1.3.

4.1.1. A Two State Model

Let us assume that we have N asthmatics, some of which are in state 0 (No attack) and the others in state 1 (Attack) on day n. Thus if on day n, X_1 are in state 1, then $X_0 = N - X_1$ are in state 0. We therefore have the following flow diagram :

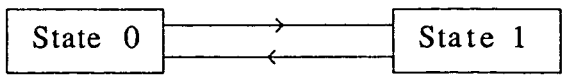


Figure 4.1. The flow diagram for the two state model

We suppose that state changes occur discretely in time and that a day is the appropriate unit of time. We therefore consider the daily rates of exit to be the parameters controlling the movement of the asthmatics from one state to the other. These parameters are listed and discussed below :

(1) Time between attacks.

We take the mean time between attacks to be μ_1 days (say) and the corresponding daily rate of exit to be $\alpha_1 = 1/\mu_1$ per asthmatic in state 0.

(2) Duration of an attack.

Let the mean duration of an attack be μ_2 days (say) and the corresponding daily rate of exit to be $\alpha_2 = 1/\mu_2$ per asthmatic in state 1.

Following Cvjetanovic et al.(1978), the mathematical expression of the dynamics of the disease, as illustrated in figure 4.1, is given by the following system of difference equations

$$\begin{aligned} \Delta X_0 &= \alpha_2 X_1 - \alpha_1 X_0 \\ \Delta X_1 &= \alpha_1 X_0 - \alpha_2 X_1 \end{aligned} \qquad (1)$$

Here ΔX_i, i = 0, 1, represent the daily changes of patients in the two states.

4.1.2. The Implications of Preventive Treatment

Let us consider the possibility of the asthmatics being on preventive treatment. We suppose that when an asthmatic is under this treatment, the time between attacks is extended. The corresponding daily rate of exit α_1 is calculated as follows :

$$\alpha_1 = (1 + k)\ 1/\mu_1 \qquad (2)$$

where k is a positive real number and is taken as the efficacy of the preventive treatment. α_2 however remains the same, since attacks are always treated.

Example 4.1.

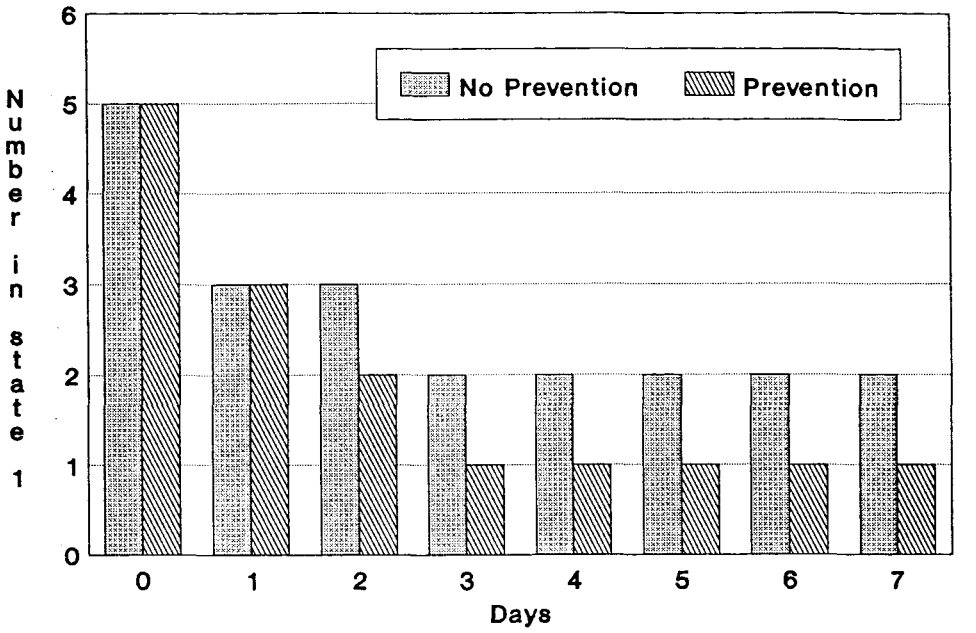
Suppose that the mean time between attacks, without treatment, is 30 days. If we now give preventive treatment with k = 0.95 then the time between attacks with this treatment is 58.5 days. Assume that the duration of an attack is 2 days. Then μ_1 = 30 (without treatment) and μ_1= 58.5 (with treatment). Therefore α_1 = 0.0333 per asthmatic in state 0 (without treatment) and α_1 = 0.0171 per asthmatic in state 0 (under preventive treatment). α_2 = 0.5 per asthmatic in state 1. If we let N = 30, X_0 = 25, X_1 = 5 on day 0, then using equations (1) we can compute the number of asthmatics in state 1 on each day, both under prevention and when preventive treatment is not given. The result of this is displayed in table 4.1 for a seven day period.

Day	No prevention	Prevention (k = 0.95)
0	5	5
1	3	3
2	3	2
3	2	1
4	2	1
5	2	1
6	2	1
7	2	1

Table 4.1. A comparison of the number of asthmatics having an attack on day n under no prevention and that under prevention.

The result displayed in table 4.1 is shown graphically in figure 4.2.

Figure 4.2. Number of asthmatics in state 1



4.1.3. An Extension of the Two State Model

Now suppose that when an asthmatic has an attack, treatment is not just given to bring this attack under control, treatment is given according to the type of the attack. Thus when an asthmatic is in state 1, some tests are performed and the attack is classified as mild, moderate or severe depending on the results of these tests. We also allow the possibility of death occurring from a severe attack that is not well treated. We then define the following states

State 0 No attack
State 1 Mild attack
State 2 Moderate attack
State 3 Severe attack
State 4 Death

The flow of asthmatics through these states is presented in figure 4.3.

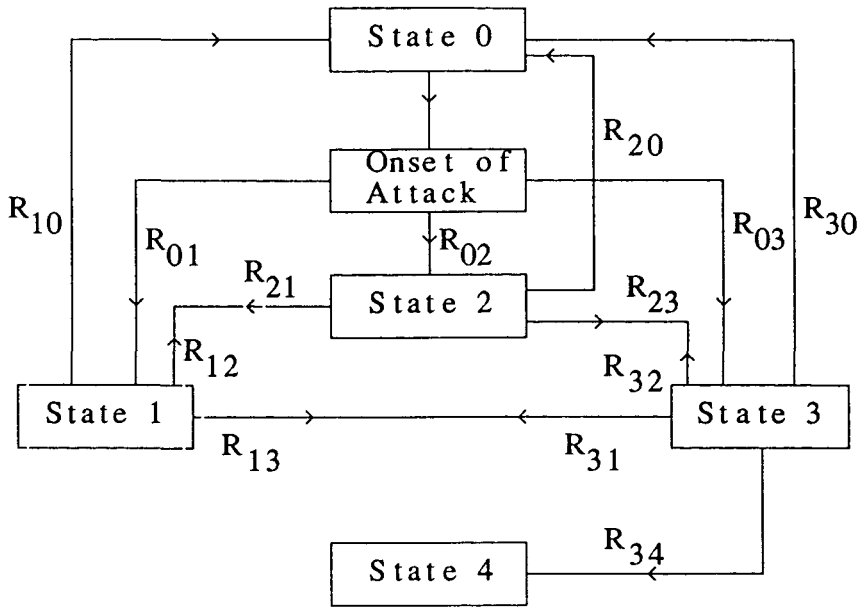


Figure 4.3. The flow diagram for the five state model

Let X_i , i = 0, 1, ..., 4 be the number of asthmatics in state i on day n. It is not easy to estimate the rates of transition from one state to the other. We consider these rates as the product of the daily rate of exit from a state, and the coefficient of transfer R_{ij}. R_{ij} is the fraction of those leaving state i and going into state j. These transition parameters are discussed below :

(1) Duration in state 0.

Let the mean duration in state 0 be μ_1 days when preventive treatment is not given. The corresponding daily rate of exit is $\alpha_1 = 1/\mu_1$ per asthmatic in this state . The daily rate of exit when preventive treatment is given is calculated from equation (2).

(2) Duration in state 1.

Let the mean duration in this state be μ_2 days. The daily rate of exit is thus $\alpha_2 = 1/\mu_2$ per asthmatic in this state.

(3) Duration in state 2.

Assume that the mean duration in state 2 is μ_3 days. Therefore the daily

rate of exit is $\alpha_3 = 1/\mu_3$ per asthmatic in this state.

(4) Duration in state 3.

We take the mean duration in state 3 to be μ_4 days. The daily rate of exit is therefore $\alpha_4 = 1/\mu_4$ per asthmatic in state 3.

(5) Mortality from asthma.

There are about 45 deaths from asthma per year in the 5-14 years age group in England and Wales, Clark and Godfrey (1983). The daily rate of exit is thus 0.123 per asthmatic in state 4. This is taken to be R_{34}.

(6) Coefficient of transfer.

All the transfers are represented in figure 4.3 by R_{ij}. Clark and Godfrey, (1983) mentioned that about 25% of asthmatic children have moderate form of the disease, while 2.5% fall into the most severe group. Thus R_{02} is taken to be 0.25 and R_{03} is taken to be 0.025. R_{01} therefore comes to 0.725. These and other values of R_{ij} are displayed in table 4.2.

State of origin	Coefficient of transfer to destination state j					
i	0	1	2	3	4	Total
0	-	0.725	0.25	0.025	-	1.000
1	0.70	-	0.20	0.10	-	1.000
2	0.66	0.20	-	0.14	-	1.000
3	0.51	0.177	0.19	-	0.123	1.000
4	-	-	-	-	-	0.000

Table 4.2. Matrix of coefficients of transfer R_{ij}.

As in section 4.1.1 the disease dynamics can be expressed mathematically by the following system of difference equations (ΔX_i being the daily changes of the asthmatics in the different states).

$$\Delta X_0 = \alpha_2 X_1 R_{10} + \alpha_3 X_2 R_{20} + \alpha_4 X_3 R_{30} - \alpha_1 X_0$$

$$\Delta X_1 = \alpha_1 X_0 R_{01} + \alpha_3 X_2 R_{21} + \alpha_4 X_3 R_{31} - \alpha_2 X_1$$

$$\Delta X_2 = \alpha_1 X_0 R_{02} + \alpha_2 X_1 R_{12} + \alpha_4 X_3 R_{32} - \alpha_3 X_2 \qquad (3)$$

$$\Delta X_3 = \alpha_1 X_0 R_{03} + \alpha_2 X_1 R_{13} + \alpha_3 X_2 R_{23} - \alpha_4 X_3$$

$$\Delta X_4 = \alpha_4 X_3 R_{34}$$

Example 4.2.

Assume that the mean time between attacks is 30 days without treatment. This is increased to 58.5 days when a 95% effective preventive treatment is given (use equation (2) with k = 0.95). We further suppose that the duration in states 1 to 3 is 2 days each (we assume that the duration of an attack is independent of its severity). Thus α_1 = 0.0333 (without treatment) and α_1 = 0.0171 (with treatment), $\alpha_2 = \alpha_3 = \alpha_4 = 0.50$. Let $X_0 = 550$, $X_1 = 300$, $X_2 = 200$, $X_3 = 150$, $X_4 = 0$ on day 0. Then using equations (3) we compute the number of asthmatics in state 1, 2, and 3 both when preventive treatment is given and when it is not. The result is displayed in table 4.3.

The result in table 4.3 is better illustrated in figures 4.4, 4.5, and 4.6.

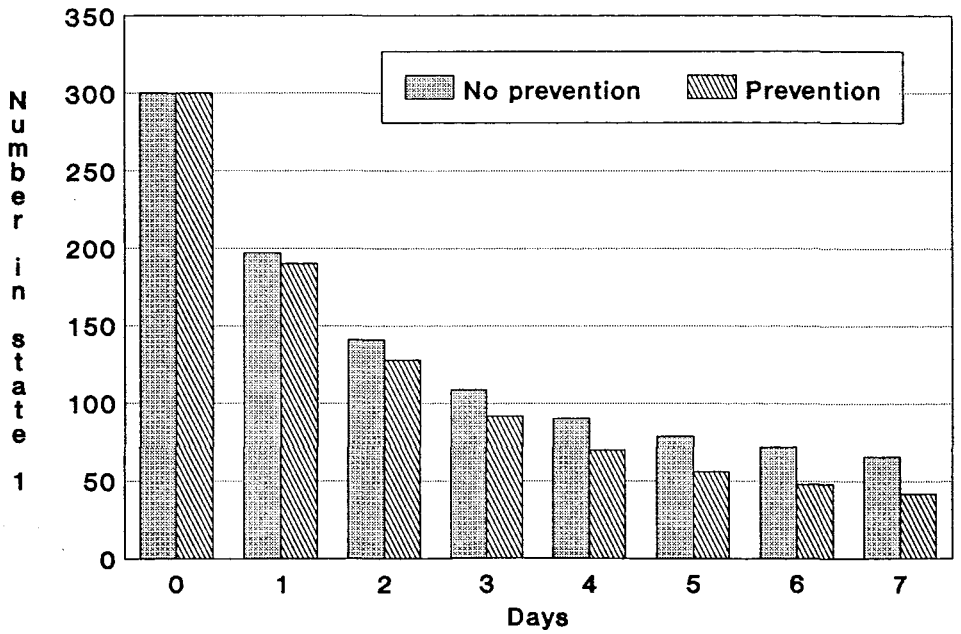
4.2. A Two state Deterministic Model in Continuous Time

In this section we develop a deterministic model of asthma in continuous time. This model is an extension of that given in section 4.1.1 since the condition of the asthmatic can be determined at any time t rather than just on any given day. The model is constructed in section 4.2.1 and the implications of preventive treatment is considered in section 4.2.2.

Day	No prevention State			Prevention State		
	1	2	3	1	2	3
0	300	200	150	300	200	150
1	197	149	105	190	147	104
2	141	110	77	128	106	72
3	109	84	54	92	76	50
4	90	66	39	70	56	35
5	79	54	29	56	43	25
6	72	46	23	48	34	19
7	66	41	19	42	28	15

Table 4.3. A comparison of the number of asthmatics in states 0, 1, and 2 on day n under no prevention and that under prevention.

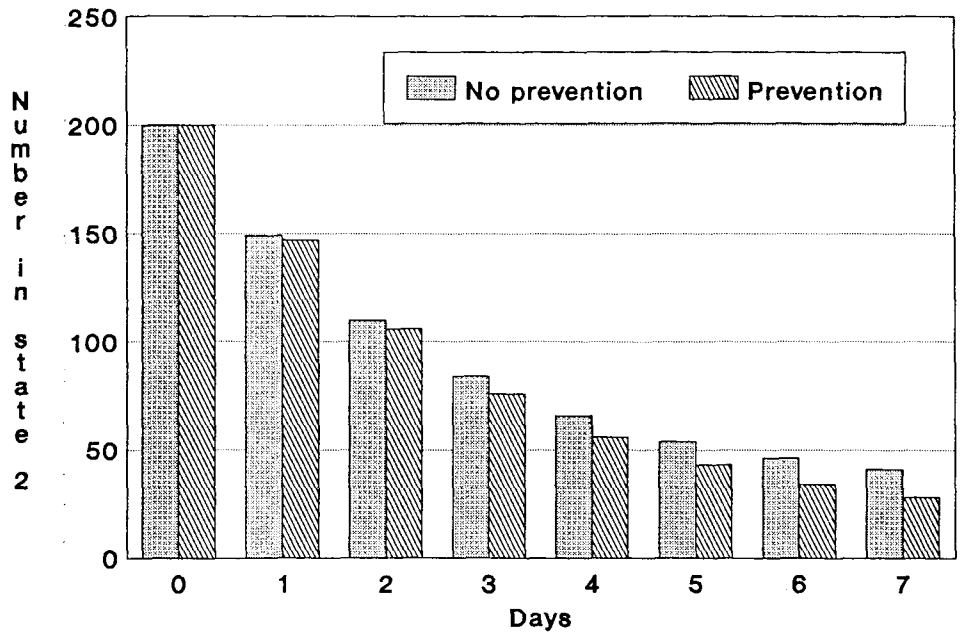
Figure 4.4. Number of asthmatics in state 1



4.2.1. Construction of The Model

Suppose we have N asthmatics and out of these, M are experiencing an attack at time t = 0. The remaining N-M are attack-free. At time t, we let $X_0(t)$ and $X_1(t)$ represent the number experiencing no attack and the number experiencing an attack , respectively, so that $X_0(t) + X_1(t) = N$. Let state 0 and state 1 represent "no attack" and "attack" respectively, then at any given time t, M asthmatics are in state 0 and N-M are in state 1. Let α be the rate at which attacks occur and β be the rate at which attacks are treated. The flow diagram for this process is the same as that shown in figure 4.1.

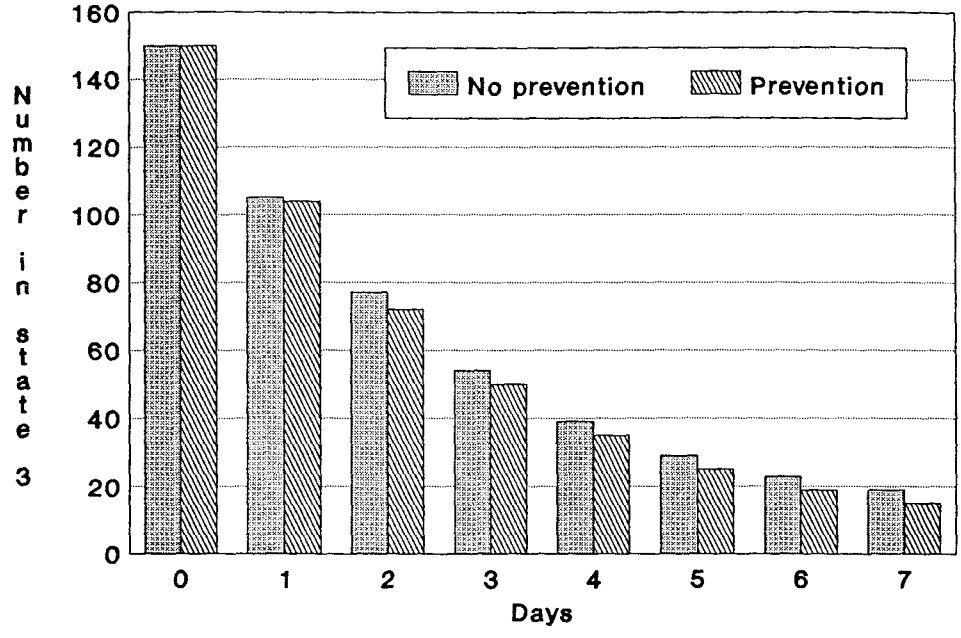
Figure 4.5. Number of asthmatics in state 2



We assume that the rate of occurrence of attacks is proportional to the number experiencing no attack and the rate at which attacks are treated is proportional to the number having an attack at time t. It follows that

$$\Delta X_0 = -\alpha X_0 \Delta t + \beta X_1 \Delta t$$
$$\Delta X_1 = -\beta X_1 \Delta t + \alpha X_0 \Delta t \qquad (4)$$

Figure 4.6. Number of asthmatics in state 3



So that the process is described by the following system of differential equations

$$\frac{dX_0}{dt} = -\alpha X_0 + \beta X_1$$
$$\frac{dX_1}{dt} = \alpha X_0 - \beta X_1 \qquad (5)$$

with initial conditions $X_0(0) = N\text{-}M$, $X_1(0) = M$.

The solution of equations (5), subject to the initial conditions is

$$X_0(t) = \frac{\beta N}{\alpha+\beta} - \left(M - \frac{\alpha N}{\alpha+\beta}\right) \exp[-(\alpha+\beta)t]$$
$$X_1(t) = \frac{\alpha N}{\alpha+\beta} + \left(M - \frac{\alpha N}{\alpha+\beta}\right) \exp[-(\alpha+\beta)t] \qquad (6)$$

4.2.2. The Implications of Preventive Treatment

In section 4.2.1 the idea of giving preventive treatment to the asthmatics was not considered. Treatment of the attacks was however looked at. In this section, we consider the implications of treatment given to the asthmatics in order to prevent attacks.

We suppose that when preventive treatment is given, the rate α at which attacks occur is now reduced to γ (say). This reduction depends to a greater extent, on the effectiveness of this treatment. An appropriate measure of this effectiveness is obtained from the following expression

$$1/\gamma = (1 + k)\ 1/\alpha \qquad (7)$$

Here k is a positive real number. The rate β, at which attacks are treated remains the same, since medication is always given for an attack.

The equations for this new process are similar to those developed in section 4.2.1 with α replaced by γ.

Thus

$$X_0(t) = \frac{\beta N}{\gamma+\beta} - (M - \frac{\gamma N}{\gamma+\beta}) \exp[-(\gamma+\beta)t]$$

$$X_1(t) = \frac{\gamma N}{\gamma+\beta} + (M - \frac{\gamma N}{\gamma+\beta}) \exp[-(\gamma+\beta)t] \qquad (8)$$

Example 4.3.

Suppose $\alpha = 1/30$, $\beta = 1/2$, $N = 30$, $M = 5$. Equations (6) become

$$X_0(t) = \frac{225}{8} - \frac{25}{8} \exp(-8/15t)$$

$$X_1(t) = \frac{15}{8} + \frac{25}{8} \exp(-8/15t)$$

When we give preventive treatment that is 95% effective (k = 0.95), the rate α is reduced to γ. Using equation (7), we get

$$\gamma = 2/117$$

Equations (8) therefore become

$$X_0(t) = \frac{3510}{121} - \frac{485}{121} \exp(-121/234t)$$

$$X_1(t) = \frac{121}{121} + \frac{485}{121} \exp(-121/234t)$$

The number of people having an attack at time t under no prevention is compared to that under prevention, for seven days in table 4.4.

Time (in days)	No prevention	Prevention (k = 0.95)
0	5	5
1	4	3
2	3	2
3	3	2
4	2	2
5	2	1
6	2	1
7	2	1

Table 4.4. A comparison of the number of asthmatics havin an attack at time t under no prevention and that under prevention.

The result in table 4.4 is shown in figure 4.7.

4.2.3. Comments

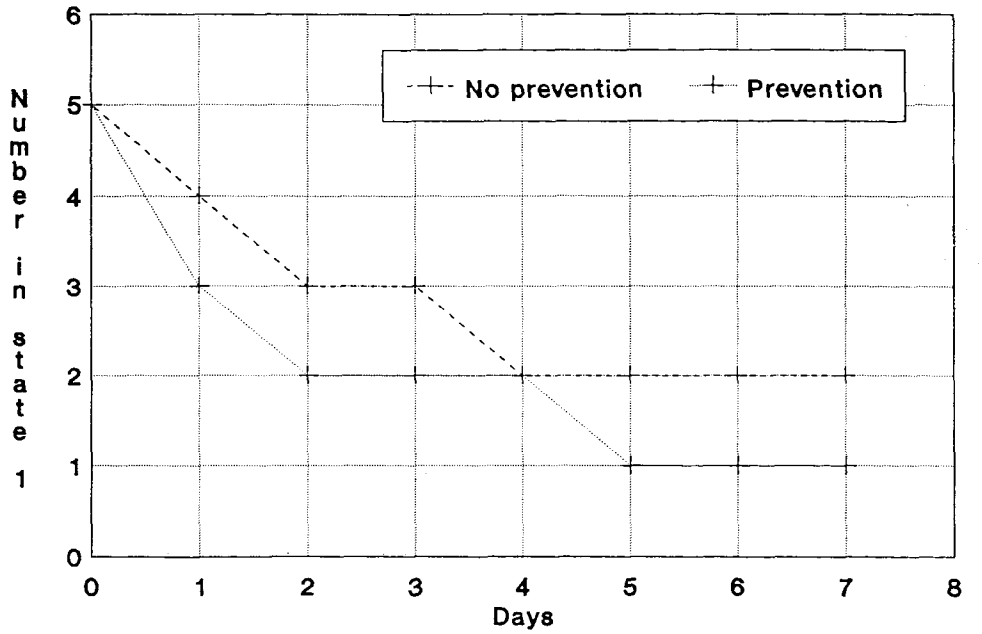
Since one of the solutions of $|\lambda I - A| = 0$

where

$$A = \begin{bmatrix} -\alpha & \beta \\ \alpha & -\beta \end{bmatrix}$$

is zero and the other negative and real (no pure imaginary roots), all solutions of equation (5) are bounded and asymptotically stable.

Figure 4.7. Number of asthmatics in state 1



4.3. A Mathematical Programming Model

Mathematical programming and particularly linear programming is a widely known and used Operational Research technique. This technique has proved itself to be a valuable aid to decision making in the industrial sector. Its application is not uncommon to health services, (Boldy, 1976). It has however generally not lived up to the expectations of health planners. In section 4.3.1 the background leading to the application of this technique is discussed and the model is developed in section 4.3.2. An application of the model is given in section 4.3.3 and a sensitivity analysis is carried out in section 4.3.4.

4.3.1. Background to the Problem

Asthmatics often experience attacks at night or at weekends and so are exposed to a variety of doctors. Sometimes they even require referral or admission to the hospital. These may make asthmatics become more confused as to how to manage their condition.

There is therefore a need to develop systems of asthma care in general practice in order that GPs, nursing staff and patients become acquainted with the management of the condition.

The establishment of asthma clinics has been suggested as one approach to this organised system of asthma care, (Charlton, 1989). Here patients are called to an organised consultation with doctors and nurses who have special interest in asthma care. One clinic set up in 1987 in Aylsham in Norfolk has been shown to be performing well, (Charlton, 1991).

Assuming that this approach is accepted, the problem now remains as to the number of asthma clinics to be established in a given area (say). The number of clinics that can be established is however limited given scarce resources. This problem is formulated as a linear programming problem in the next section.

4.3.2. Mathematical Programming Formulation

As discussed in section 4.3.1, suppose a Regional Health Authority has seen the need to establish asthma clinics in the United Kingdom. However the number of clinics that can be established is restricted by the limited availability of three resources : doctors, nurses, and money. The question is, how many clinics should be established in the region in order to make the best possible use of these resources.

Let R_1, R_2 ,..., R_k represent districts in the region. The number of doctors and nurses required to run a clinic varies from clinic to clinic, and the amount of money needed to run a clinic per unit time is known. Let D_1, D_2,

...,D_k be the number of doctors and N_1, N_2, ...,N_k be the number of nurses required to run a clinic in the respective districts. Let M_1, M_2, ..., M_k be the amount of money needed to run a clinic per unit time in the districts respectively. Suppose that d, n, and m is the number of doctors, the number of nurses and the amount of money (per unit time) the region can provide. Let b_1, b_2, ..., b_k be the number of patients who would benefit from the establishment of one clinic in the respective districts. This may be regarded as the number of patients a single clinic can accommodate. The objective is therefore to establish a number of clinics in order to maximize the number of patients who would benefit from this system of care. These data are summarized in table 4.5.

Resources	Amount used per clinic				Regional resources available
	C_1	C_2	....	C_k	
Doctors	D_1	D_2	...	D_k	d
Nurses	N_1	N_2	...	N_k	n
Money (in (Pounds)	M_1	M_2	...	M_k	m
Number of beneficia-ries	b_1	b_2	...	b_k	

Table 4.5. Data for asthma clinic problem

Let x_1, x_2, ..., x_k be the number of clinics to be established in the districts, respectively. Suppose that a policy decision is that there must be at least one clinic and not more than 5 clinics in each district. The objective is therefore to maximize the total number of beneficiaries in the region. The objective function is thus

$$Z = b_1x_1 + b_2x_2 + ... + b_kx_k$$

and from table 4.5, we construct the constraints as follows :

$$D_1x_1 + D_2x_2 + \ldots + D_kx_k \leq d$$

$$N_1x_1 + N_2x_2 + \ldots + N_kx_k \leq n$$

$$M_1x_1 + M_2x_2 + \ldots + M_kx_k \leq m$$

and $1 \leq x_i \leq 5$, i = 1, 2, ..., k are integers.

It can be readily seen that each resource contributes one constraint to the problem.

The above problem can be formulated as a linear integer programming problem as follows :

Maximize $Z = b_1x_1 + b_2x_2 + \ldots + b_kx_k$

Subject to

$$D_1x_1 + D_2x_2 + \ldots + D_kx_k \leq d$$

$$N_1x_1 + N_2x_2 + \ldots + N_kx_k \leq n$$

$$M_1x_1 + M_2x_2 + \ldots + M_kx_k \leq m$$

and $1 \leq x_i \leq 5$, i = 1, 2, ..., k are integers.

This formulation is in terms of these resources and no constraints on b_i, i = 1, 2, ..., k. Additional resources and constraints can be taken into account in an obvious manner and so discussion is restricted to this simple model.

4.3.3 An Application of the Model

Suppose we would like to apply this technique to determine the number of asthma clinics to be established in a region. As an illustration consider a region with 10 districts, say S_i, i = 1, 2, ..., 10. Suppose data has been collected on the availability of resources in each district and the amount of

resources the region is able to provide. The money needed to run one clinic in each district is obtained as follows :

Suppose a doctor earns about 30 thousand pounds in a year. Assume that the doctor works for 2 hours on asthma in a clinic in a week comprising of 5 x 8 = 40 working hours. Then the doctor spends 2/4 = 5 % of his time on asthma. 5 % of 30 thousand pounds is 1.5 thousand pounds (1,500 pounds). This is the cost of running one clinic with one doctor per year. We suppose that the nurse earns 10 thousand pounds per year. With a similar analysis it costs the district 0.5 thousand pounds (500 pounds) to run one clinic with one nurse. We let the general cost per clinic be 2 thousand pounds. This may be the cost of housing, equipment and other costs that may be incurred. Thus the cost of D doctors/clinic is 1500 x D and the cost of N nurses/clinic is 500 x N, the total cost/clinic being 1500 x D + 500 x N + 2000 pounds. Let us assume that the number of patients a clinic can accomodate depends on the number of doctors and the number of nurses. We further assume that a doctor and nurse team is required for the care of patients. Suppose, for the sake of argument, the capacity of a clinic is 140 x D + 70 x N. This gives the number of patients who would benefit from the establishment of one clinic. The data is presented in table 4.6.

Resources	Amount used per clinic										Regional resources available
	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9	S_{10}	
Doctors	2	1	2	1	2	2	2	2	2	3	30
Nurses	2	3	2	2	2	3	2	1	3	2	70
Money (in thousand pounds)	6	5	6	4.5	6	6.5	6	5.5	6.5	7.5	120
Number of beneficiaries	420	350	420	280	420	490	420	350	490	560	

Table 4.6. Data for the region

Using the data in table 4.6, the linear programming problem becomes

$$\text{Maximize} \quad Z = 420x_1 + 350x_2 + 420x_3 + 280x_4 + 420x_5 + 490x_6 + 420x_7 + 350x_8 + 490x_9 + 560x_{10}$$

Subject to

$$2x_1 + x_2 + 2x_3 + x_4 + 2x_5 + 2x_6 + 2x_7 + 2x_8 + 2x_9 + 3x_{10} \leq 30$$

$$2x_1 + 3x_2 + 2x_3 + 2x_4 + 2x_5 + 3x_6 + 2x_7 + x_8 + 3x_9 + 2x_{10} \leq 70$$

$$6x_1 + 5x_2 + 6x_3 + 4.5x_4 + 6x_5 + 6.5x_6 + 6x_7 + 5.5x_8 + 6.5x_9 + 7.5x_{10} \leq 120$$

and $\quad 1 \leq x_i \leq 5,\ i = 1, 2, \ldots, k$ are integers.

The solution of the above problem is found, by the Branch and Bound method, using LINDO, (Schrage, 1989), to be $x_1 = 1$, $x_2 = 5$, $x_3 = 1$, $x_4 = 4$, $x_5 = 1$, $x_6 = 1$, $x_7 = 1$, $x_8 = 1$, $x_9 = 3$, $x_{10} = 1$. Consequently a total of 7,420

asthmatics would benefit from the 10 districts with all the doctors and only 46 nurses used. The total cost being 106 thousand pounds.

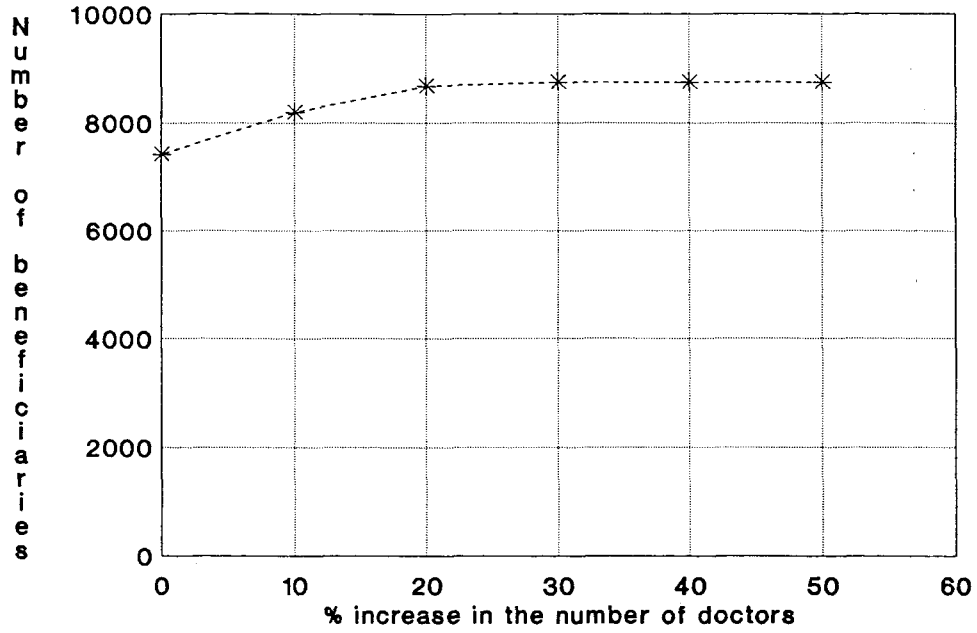
4.3.4. Sensitivity Analysis of the Problem

We now perform a sensitivity analysis to investigate the effect on the number of beneficiaries if the regional resources available take on other possible values. We first of all consider increasing the number of doctors that can be made available. This may mean training additional doctors to understand the disease asthma, with the hope that more clinics would be established, taking into account the cost of training and running a clinic per unit time with these additional doctors. We consider increasing the number of doctors without altering other available regional resources (nurses, money). The result of this exercise is given in table 4.7. Some of the values in this table are plotted in figure 4.8.

Percentage increase in the number of doctors	Number of beneficiaries	Number of clinics per region									
		x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	x_{10}
0	7,420	1	5	1	4	1	1	1	1	3	1
10	8,190	1	5	1	5	1	4	1	1	1	1
20	8,680	1	4	1	1	1	4	1	1	5	1
30	8,750	1	1	1	1	1	4	1	1	5	3
40	8,750	1	1	1	1	1	4	1	1	5	3
50	8,750	1	1	1	1	1	4	1	1	5	3

Table 4.7. The effect of increasing the number of doctors on the number of beneficiaries.

Figure 4.8. The effects of the number of doctors on the number of beneficiaries



We can see from the graph that the number of beneficiaries increase with the number of available doctors. The number of clinics also increase. Thus the total cost of running the clinics will also increase.

Sensitivity analysis was also performed on the number of nurses, and the amount of money that could be made available. It was however discovered that if we fix the other regional resources available, an increase in the number of nurses has no effect on the number of beneficiaries. Similarly, if we fix the other resources available and increase the amount of money provided by the region, we see that there is also no change in the number of beneficiaries. This is obvious since the solution of the problem with 30 doctors (the number available) make the number of availabe doctors a binding constraint. That is, the number of available doctors is exhausted. Since a clinic cannot operate without a doctor in our model, the optimal number of patients cannot increase, because more clinics cannot be established. Even if we make more money available, there would be no effect on the number of clinics established and hence no effect on the number of beneficiaries. If we however use this money to train more doctors and nurses, then the optimal number of patients

benefiting would be increased since we can now establish more clinics. The effect of increasing all the available resources on the number of beneficiaries is shown in table 4.8.

Percentage increase in the number of doctors and nurses	Percentage increase in the amount of money					
	0	10	20	30	40	50
(0,0)	7,420	*	*	*	*	*
(10,10)	8,190	*	*	*	*	*
(20,20)	8,680	8,890	*	*	*	*
(30,30)	8,750	9,520	9,660	*	*	*
(40,40)	+	9,590	10,220	10,360	*	*
(50,50)	+	+	10,360	11,060	*	*

Table 4.8. The effect of increasing all the available resources on the number of beneficiaries.

* Indicate no changes in the row

+ Indicate no changes in the column

CHAPTER 5

STOCHASTIC MODELS IN DISCRETE TIME

In chapter 4 we developed deterministic models for the asthma process. These models do not take into account the considerable degree of uncertainty and variability arising in the disease process. They are therefore bound to give inaccurate results. In this chapter we construct stochastic models in discrete time for the disease. Markov chain models are developed in section 5.1 and a semi-Markov model is constructed in section 5.2.

5.1. Markov Chain Models for the Asthma Process

Markov chain models have been applied to many areas of health-related problems. Some of the early applications are discussed by Fix and Neyman (1951), Marshall and Goldhamer (1955), and Sacks and Chiang (1977).

A finite Markov chain is a discrete time parameter stochastic process in which the future state of the system is dependent only on the present state and is independent of the past history, where the number of states are finite or countably infinite, (Cox and Miller, 1987).

In this section we construct two models for the asthma process. The first, treated in section 5.1.1 will be a model for the prevention and treatment of asthma attacks and the second, given in section 5.1.2 will be a model to study the effect of weather on the disease.

5.1.1. A Four State Model

Let us suppose that at any time t an asthmatic is having an attack or is not. If the asthmatic has an attack, the severity of the attack is assessed in order to give appropriate treatment. Some tests are performed and the attack is classified as being mild, moderate, or severe depending on the results of these tests. To make matters simple, we assume that the possibility of death from an attack is small and could be neglected. We therefore have a four state process :-

State 0 No attack
State 1 Mild attack
State 2 Moderate attack
State 3 Severe attack

The transition diagram for this process is shown in figure 5.1.

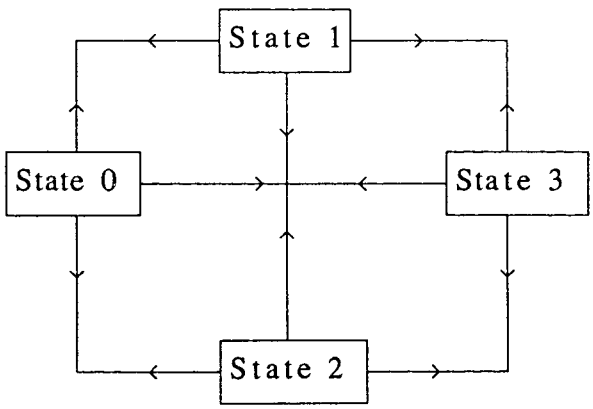


Figure 5.1 The state transition diagram for the process.

We use the Markov chain technique to analyse the process with the above mutually exclusive set of states. The transitions can be readily identified from the transition diagram.

To study this process, we must specify the probabilistic nature of the state

transition. Since the Markov chain analysis requires that the process be considered at discrete uniformly spaced intervals of time, we assume that the time between transitions is one day. The underlying assumption of Markov chain is that the probability of making a transition from state i to state j in the next time interval is a function only of i and j and not of any history of the process before its arrival in state i. Thus we may define a Markov chain as a sequence X_0 X_1, ... of discrete random variables with the property that the conditional distribution of X_{n+1} given X_0, X_1, ..., X_n depend only on the value of X_n but not further on X_0, X_1,...,X_{n-1}. That is, for any set of values h,i,...,j in the discrete state space,

$$\text{Prob}(X_{n+1} = j | X_0 = h,...,X_n = i) = \text{prob}(X_{n+1} = j | X_n = i)$$

$$= P_{ij} \quad i,j = 0,1,2,3.$$

Let **P** be the transition matrix, then for the four state process, **P** takes the form :

$$\mathbf{P} = \begin{bmatrix} P_{00} & P_{01} & P_{02} & P_{03} \\ P_{10} & P_{11} & P_{12} & P_{13} \\ P_{20} & P_{21} & P_{22} & P_{23} \\ P_{30} & P_{31} & P_{32} & P_{33} \end{bmatrix}$$

Here we assume that the P_{ij}'s do not depent on time, which is the case of a homogeneous Markov chain.

Let $\mathbf{P}^{(n)} = \left[P_0^{(n)},...,P_3^{(n)}\right]$ denote the probabilities of finding the asthmatic in any of the states 0,...,3 on day n. Then

$$\mathbf{P}^{(n)} = P^{(n-1)}\ \mathbf{P} \qquad (1)$$

On iteration therefore, we have

$$\mathbf{P}^{(n)} = P^{(0)}\ \mathbf{P}^{n} \qquad n = 0,1,2,... \qquad (2)$$

where $P^{(0)}$ is any starting vector of probabilities.

For the derivation of these equations see Cox and Miller (1987). Thus when the initial probabilities $P^{(0)}$ and the matrix of transition probabilities **P** are given, we can find the state occupation probabilities on any day n using equation (2).

Example 5.1.

Suppose the following data were collected on a single asthmatic over 1460 days.

		Actual day				
		state 0	state 1	state 2	state 3	
Preceding day	state 0	1210	75	40	10	1335
	state 1	48	15	9	3	75
	state 2	25	5	8	2	40
	state 3	2	3	4	1	10

Table 5.1. Transition count for asthma attacks

Transition probabilities are then estimated from this data using relative frequencies. Thus

$$\mathbf{P} = \begin{bmatrix} 0.906 & 0.056 & 0.030 & 0.008 \\ 0.640 & 0.200 & 0.120 & 0.040 \\ 0.625 & 0.125 & 0.200 & 0.050 \\ 0.200 & 0.300 & 0.400 & 0.100 \end{bmatrix}$$

Calculating $\mathbf{P}^n$ we find that

$$\mathbf{P}^2 = \begin{bmatrix} 0.877 & 0.068 & 0.043 & 0.012 \\ 0.791 & 0.103 & 0.083 & 0.023 \\ 0.781 & 0.100 & 0.094 & 0.025 \\ 0.643 & 0.151 & 0.162 & 0.044 \end{bmatrix}$$

$$\mathbf{P}^4 = \begin{bmatrix} 0.864 & 0.073 & 0.049 & 0.014 \\ 0.855 & 0.076 & 0.054 & 0.015 \\ 0.854 & 0.076 & 0.055 & 0.015 \\ 0.838 & 0.082 & 0.063 & 0.017 \end{bmatrix}$$

$$\mathbf{P}^8 = \begin{bmatrix} 0.863 & 0.073 & 0.049 & 0.015 \\ 0.862 & 0.074 & 0.049 & 0.015 \\ 0.862 & 0.074 & 0.049 & 0.015 \\ 0.862 & 0.074 & 0.049 & 0.015 \end{bmatrix}$$

$$= \begin{bmatrix} 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \end{bmatrix} \text{ to 2dp.}$$

and for $n > 8$ we find that $\mathbf{P}^n$ gets closer and closer to exactly

$$\begin{bmatrix} 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \end{bmatrix} \text{ to 2dp.}$$

as n increases.

This means that for $n \geq 8$

$$\mathbf{P}^{(n)} = P^{(0)}\,\mathbf{P}^{n} = \left[P_0^{(0)}, P_1^{(0)}, P_2^{(0)}, P_3^{(0)}\right] \times \begin{bmatrix} 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \\ 0.86 & 0.07 & 0.05 & 0.02 \end{bmatrix}$$

$$= \left[\, 0.86,\ 0.07,\ 0.05,\ 0.02 \,\right]$$

Again as n increases this approximation becomes more and more accurate. That is

$$\mathbf{P}^{(n)} \longrightarrow \left[\, 0.86,\ 0.07,\ 0.05,\ 0.02 \,\right] \text{ as } n \longrightarrow \infty.$$

5.1.1.1. Limiting State Probabilities

As illustrated in example 5.1 the state-occupation probabilities appear to be independent of the starting state of the process if the number of state transitions is large. Thus the process reaches a steady state after a sufficiently large period of time (n = 8 in the above example). If this is so then there is an equilibrium probability distribution $\Pi = (\Pi_0,\ldots,\Pi_3)$ and

letting $n \longrightarrow \infty$ in equation (1), we have

$$\Pi = \Pi \mathbf{P} \tag{3}$$

and the sum of the components of Π must be 1, that is

$$\sum_{i=0}^{3} \Pi_i = 1 \tag{4}$$

We therefore use (3) and (4) to find the limiting state probabilities for this process.

5.1.1.2. Modelling the Effect of Preventive Treatment

Suppose preventive treatment is given to prevent an attack, and the effect of this preventive treatment is that the probabilities of making transitions from state 0 to state 1, 2, or 3 are reduced. This reduction depends on the effectiveness of this preventive treatment. A good measure of this effectiveness is obtained by defining

$$E_{0j} = (1\text{-}k)\ P_{0j}\ ,\ j = 1, 2, 3. \tag{5}$$

where k is a positive real number in the interval [0,1).

Then

$$E_{00} = 1 - \sum_{j=1}^{3} E_{0j}$$

and the transition matrix is **P** with the first row replaced by E_{0j} , j = 0, 1, 2, 3.

5.1.1.3. Extension of the Four State Model

To make the four state model more realistic, we may allow the possibility of death occurring from an attack, if it is not well treated. We also allow an asthmatic to "grow out" of his disease at some point in time. Here we consider $N > 1$ asthmatics, N large enough. Thus instead of recording the number of times an asthmatic moves from one state to another, we record the number of asthmatics that move from one state to another. We would therefore have a four state process with the additional states :

State 4 Grow out
State 5 Death

These two additional states are absorbing states. This process has the following transition probability matrix

$$\mathbf{P} = \begin{bmatrix} P_{00} & P_{01} & P_{02} & P_{03} & P_{04} & 0 \\ P_{10} & P_{11} & P_{12} & P_{13} & 0 & 0 \\ P_{20} & P_{21} & P_{22} & P_{23} & 0 & 0 \\ P_{30} & P_{31} & P_{32} & P_{33} & 0 & P_{35} \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

In constructing this matrix we assumed that before an asthmatic grows out of his disease he must pass through state 0. In other words an asthmatic can only go to state 4 from state 0 and once he is in this state he remains there forever (reappearance of the disease is not considered). We also assumed that the asthmatic can only die from a severe attack (natural death is also not considered).

This is an absorbing Markov chain with a non-regular matrix **P**. State 4 and state 5 are absorbing states. State 0, state 1, state 2, and state 3 are transient states. Thus no matter where the process starts, the probability

that it is absorbed tends to 1 as n tends to infinity. Since **P** is not regular it means that 1 is an eigenvalue of multiplicity k > 1. **P** will be ergodic if it possesses k linearly independent (left) eigenvectors associated with this eigenvalue. This depends on the entries of **P**. If **P** is ergodic then the limiting state probabilities can be obtained as in (Bronson, 1982). If **P** is not ergodic then the limiting state probabilities do not exist. We may however like to determine the number of days an asthmatic will be in each transient state before being absorbed. This can easily be obtained by writing **P** in canonical form

$$\mathbf{P} = \begin{bmatrix} \mathbf{I} & \mathbf{O} \\ \mathbf{R} & \mathbf{Q} \end{bmatrix} = \left[\begin{array}{cc|cccc} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ \hline P_{04} & 0 & P_{00} & P_{01} & P_{02} & P_{03} \\ 0 & 0 & P_{10} & P_{11} & P_{12} & P_{13} \\ 0 & 0 & P_{20} & P_{21} & P_{22} & P_{23} \\ 0 & 0 & P_{30} & P_{31} & P_{32} & P_{33} \end{array}\right]$$

For this chain the fundamental matrix is given by

$$\mathbf{N} = (\mathbf{I} - \mathbf{Q})^{-1}$$

Matrices **Q**, **R**, and **N** can be used to provide a variety of results, for example the mean number of days an asthmatic is in a given transient state before being absorbed. For more details see (Kemeny and Snell, 1976).

5.1.2. A Model of Seasonal Effect

The rate of progression of disease for allergic patients induced by allergenic pollen is an area which requires a great deal of attention from the medical point of view, (Lebowitz, 1973). The relationship between air pollution and weather with respect to mortality has been discussed by Lebowitz (1973).

It is well known that the amount of allergenic pollen in the environment is associated with the time of the year, and the condition of asthmatic patients is dependent on the changing patterns of the seasons.

Based on the above, Jain (1986) proposed a homogeneous Markov chain model using the five Canadian seasons as transition times, and Jain (1988) used the five Canadian seasons to develop a non-homogeneous Markov model.

The model we shall construct here will be a more general model. Thus it could be used in any country and in any situation. It will be used to study the effect of seasonal patterns on the severity of chronic bronchial asthma. The formulation of this model will be given in section 5.1.2.1. In section 5.1.2.2, we consider the model when the transition probabilities are constant with respect to the seasons - homogeneous Markov chain model, and in section 5.1.2.3, we consider the model when the transition probabilities vary with the seasons - non-homogeneous Markov chain model. In section 5.1.2.4, we show how to find the limiting probabilities in either of the above cases. We shall end by giving two illustrative examples on how the model can be applied.

5.1.2.1. Formulation of the Model

Asthma is a disease which occurs intermittently. It is therefore not present all the times even in severe cases. The course and outcome of the disease changes periodically and could be measured by periodic assessment according to the complication of the disease based on respiratory indicators, (Lebowitz 1973, 1981) which can be classified into the following states:

State 1 Leading Normal Life - no interference with normal activities;

State 2 Mild Asthma - slight interference with normal activities;

State 3 Severe Asthma - considerable interference with normal activities.

The transition between states is described below.

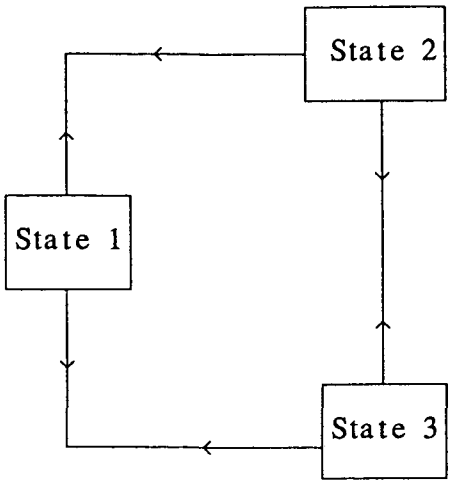


Figure 5.2. Possible transitions between states

Let these transitions be described by the following transition probability matrix :

$$P = \begin{bmatrix} P_{11} & P_{12} & P_{13} \\ P_{21} & P_{22} & P_{23} \\ P_{31} & P_{32} & P_{33} \end{bmatrix} \qquad (1)$$

As earlier on mentioned, the probable course and outcome of the disease asthma change with the seasons. Seasons are accordingly classified on the basis of daily pollen counts. In this study, we simply consider two seasons as the appropriate transition times :-

1. Low pollen count season,
2. High pollen count season.

Each of the seasons therefore has its own transition count matrix and transition probability matrix. We denote these matrices as follows :

$\mathbf{M}_1$: transition count matrix for the low pollen count season,

$\mathbf{M}_2$: transition count matrix for the high pollen count season,

$\mathbf{P}_1$: probability transition matrix corresponding to the low pollen count season, and

$\mathbf{P}_2$: probability transition matrix corresponding to the high pollen count season.

Let

$$\mathbf{M}_k=\left[f_{ij}(k)\right], \quad i,j=1,2,3. \ k=1,2. \tag{2}$$

and

$$\mathbf{P}_k=\left[p_{ij}(k)\right], \quad i,j=1,2,3. \ k=1,2. \tag{3}$$

Thus $f_{ij}(k)$ denotes the transition count from state i to state j for the season k and $p_{ij}(k)$ the transition probability from state i to state j for the season k.

The transition probabilities are estimated as follows

$$\hat{p}_{ij}(k) = f_{ij}(k)/f_{i.}(k) \quad , k = 1, 2. \ i,j = 1,2,3. \tag{4}$$

Where $$f_{i.} = \sum_{j=1}^{3} f_{ij}(k), \ i = 1, 2, 3.$$

We assume here that the severity of asthma does not depend on the previous state. For intance if an asthmatic patient has mild asthma during season k, then an improvement (going to state 1) or the worsening (going to state 3) does not depend on his previous state. It is only dependent on his present state (state 2).

Thus the model assumes that the movement of the patients from one state to another is dependent only on the present state and is independent of the past history. This gives us the Markov chain model.

We now test for the stationarity of the transition probability matrices $\mathbf{P}_k$. That is, we test for the independence of $\mathbf{P}_k$ on k. To do this we formulate the following null hypothesis :

$$H_0: p_{ij}(k) = p_{ij}, \text{ for all } k; \qquad (5)$$

$$H_1: \text{depend on } k.$$

We use the likelihood ratio test for the above hypothesis. For this

let

$$\mathbf{M} = \sum_{k=1}^{2} \mathbf{M}_k = \left[f_{ij}\right], \qquad (6)$$

where

$$f_{ij} = \sum_{k=1}^{2} f_{ij}(k).$$

Maximum Likelihood estimate of the stationary transition probability matrix is

$$\hat{p}_{ij} = f_{ij}/f_{i.} \qquad (7)$$

where

$$f_{i.} = \sum_{j=1}^{3} f_{ij}$$

Therefore λ, the likelihood ratio criterion is given by

$$\lambda = \prod_{i,j}^{3} \prod_{k=1}^{2} \left[\frac{\hat{p}_{ij}}{\hat{p}_{ij}(k)}\right]^{f_{ij}(k)} \qquad (8)$$

and we have that, (Bhat, 1972)

$$-2\ln\lambda \simeq \chi^2_{m(m-1)(T-1)}$$

where m is the number of states and T is the time parameter. Here m = 3, T = k = 2. Therefore

$$-2\ln\lambda \simeq \chi^2_{3(3-1)} = \chi^2_6 \qquad (9)$$

Thus we evaluate λ in (8) and calculate $-2\ln\lambda$. We then get the critical value of χ^2_6 at α significance level and compare it with $-2\ln\lambda$. We then decide whether to accept or reject the null hypothesis H_0. With the acceptance of H_0, we have a homogeneous Markov chain model. In this case we can represent the model by a single transition count matrix given in (6) and the p_{ij}'s are estimated from equation (7).

5.1.2.2. Non-Homogeneous Markov Chain Model

We may wish to develop a non-homogeneous Markov chain model because of the understanding of the disease asthma. Or we may reject the null hypothesis of constant transition probability matrix, then we have a time - varying Markov model or non - homogeneous Markov model. For these cases we cannot represent the model by a single transition count matrix given in (6). We then seek for alternative means of obtaining the p_{ij}'s in (1).

Following Howard (1971a), the stochastic matrix **P** in (1) can be written as

$$\mathbf{P} = \mathbf{P}_1\,\mathbf{P}_2 \qquad (10)$$

and the p_{ij}'s are estimated from (4).

We can now carry out further helpful calculations.

Case 1. The homogeneous case.

In this case the transition probabilities do not depend on the season. The limiting state probability vector, Π can be found from the following

$$\Pi = \Pi \mathbf{P}$$

and

$$\sum_{i=1}^{3} \Pi_i = 1. \tag{11}$$

Case 2. The non-homogeneous case.

Here we consider the process to be governed in succession by transition probability matrices $\mathbf{P}_1$ and $\mathbf{P}_2$ and then the cycle is repeated in that order. To obtain the limiting state probabilities for this process, we consider the stochastic matrix given in (10). Then we obtain the state probability vector Π_0 that holds at the end of each cycle of two seasons from

$$\Pi_0 = \Pi_0 \mathbf{P}$$

and

$$\sum_{i=1}^{3} \Pi_0{}^{i} = 1. \tag{12}$$

see Chorafas (1965).

The limiting state probability vectors Π_1 and Π_2 for the low pollen count season and the high pollen count season respectively, are then obtained from the following

$$\begin{aligned} \Pi_1 &= \Pi_0 \mathbf{P}_1 \\ \Pi_2 &= \Pi_1 \mathbf{P}_2 \end{aligned} \tag{13}$$

Because of the nature of the process, we have

$$\Pi_0 = \Pi_2 .$$

5.1.2.3. Illustrative Examples

Suppose at the begining of the low pollen count season, we record the number of asthmatic patients in each of the states. Then at the end of the season we register the possible transitions from one state to another. We take note of the number in each state for the high pollen count season, and at the end of the high pollen count season we record the possible transitions.

Example 5.2.

Suppose the results are displayed in the following tables:

Table 5.2 Distribution of Patients' States of Health According to Seasonal Variations.

Season (k)	State of Health		
	State 1	State 2	State 3
Low Pollen Count (1)	20	18	9
High Pollen Count (2)	18	18	11

Table 5.3 Transition Count Matrices for the Two Seasons.

$$M_1 = \begin{bmatrix} 17 & 1 & 2 \\ 3 & 10 & 5 \\ 1 & 1 & 7 \end{bmatrix}, \quad M_2 = \begin{bmatrix} 13 & 2 & 3 \\ 3 & 12 & 3 \\ 1 & 1 & 9 \end{bmatrix}$$

Therefore $$M = \begin{bmatrix} 30 & 3 & 5 \\ 6 & 22 & 8 \\ 2 & 2 & 16 \end{bmatrix}$$

From (9) we have that

$$-2\ln\lambda \simeq \chi^2_6.$$

Thus using (8), we get

$$-2\ln\lambda = 2.257 .$$

The critical value of χ^2_6 at $\alpha = 0.05$(say) is 12.59. Therefore the null hypothesis of constant transition probability matrix can not be rejected. The model can then be represented by a single transition count matrix given in (6). Thus, the maximum likelihood estimate of the transition matrix **P** is the following:

$$\mathbf{P} = \begin{bmatrix} 0.789 & 0.079 & 0.132 \\ 0.167 & 0.611 & 0.222 \\ 0.100 & 0.100 & 0.800 \end{bmatrix}$$

Then the limiting state probability vector, Π is obtained from (11) as

$$\Pi = \begin{bmatrix} 0.3619 & 0.1890 & 0.4491 \end{bmatrix}$$

This shows that in the long run 36.19% of the asthmatics will have mild asthma, 18.90% will have moderate asthma, while 44.91% of asthmatics will have severe asthma.

Example 5.3.

Suppose the probability transition count matrix for the low pollen count season ($\mathbf{M}_1$) and the probability transition count matrix for the high pollen count season ($\mathbf{M}_2$) are given as follows:-

$$\mathbf{M}_1 = \begin{bmatrix} 86 & 6 & 8 \\ 18 & 55 & 27 \\ 15 & 9 & 76 \end{bmatrix}, \quad \mathbf{M}_2 = \begin{bmatrix} 72 & 11 & 17 \\ 16 & 67 & 17 \\ 0 & 6 & 94 \end{bmatrix}$$

Then we proceed as in example 5.1.

$$\mathbf{M} = \begin{bmatrix} 158 & 17 & 25 \\ 34 & 122 & 44 \\ 15 & 15 & 170 \end{bmatrix}$$

Using (8) we get

$$-2\ln\lambda = 32.9414.$$

The number of states m = 3 and the seasons (time) k = 2. Thus

$$-2\ln\lambda \simeq \chi^2_{3(3-1)} = \chi^2_6.$$

The critical value of χ^2_6 at $\alpha = 0.05$ (say) is 12.59. Therefore, the null hypothesis of constant transition probability cannot be accepted. Thus the model is a time varying model and can be represented by a single transition probability matrix given in (10).

The maximum likelihood estimates of the transition probability matrices $\mathbf{P}_1$ and $\mathbf{P}_2$ are as follows :

$$\mathbf{P}_1 = \begin{bmatrix} 0.86 & 0.06 & 0.08 \\ 0.18 & 0.55 & 0.27 \\ 0.15 & 0.09 & 0.76 \end{bmatrix}, \quad \mathbf{P}_2 = \begin{bmatrix} 0.72 & 0.11 & 0.17 \\ 0.16 & 0.67 & 0.17 \\ 0.00 & 0.06 & 0.94 \end{bmatrix}$$

Hence from (10)

$$\mathbf{P} = \mathbf{P}_1\mathbf{P}_2 = \begin{bmatrix} 0.6288 & 0.1396 & 0.2316 \\ 0.2176 & 0.4045 & 0.3779 \\ 0.1224 & 0.1224 & 0.7552 \end{bmatrix}$$

Thus from (12) and (13) we get

$$\Pi_1 = \begin{bmatrix} 0.3556 & 0.1631 & 0.4813 \end{bmatrix}$$

$$\Pi_2 = \begin{bmatrix} 0.2821 & 0.1773 & 0.5406 \end{bmatrix}$$

Here we see that the severity of the disease increases with the amount of airborne allergens. For instance, the probability of severe asthma during high pollen count season is 54.06%, while the corresponding probability is 48.13% during the low pollen count season. The probability of leading normal life during low pollen count season is 35.57%. This probability is reduced to 28.22% during the high pollen count season.

5.1.2.4. Comments

We can readily see that in theory it is easy to formulate the above models. In practice we may however run into many difficulties in trying to estimate the parameters of the models. The first problem will be the determination of the seasons. For instance, it may not be possible to know when the low pollen count season starts and when it ends. The transition probabilities can be estimated by observing a number of asthmatics for a year and counting the number that move from one state to another at the end of each season as done

by Jain (1986). In practice this exercise is not easy.

The results obtained from the non-homogeneous model confirms an establish fact that the probability of suffering from severe asthma during high pollen count season is higher than that obtained during the low pollen count season. The model can therefore be used as a predictive device for studying the health status of asthmatics. The predictions can then be used by policy makers in the health service to plan for resources used in the management of the disease.

From the management point of view, a realistic time unit is a day rather than a season. We therefore need transition probabilities that govern day to day transitions. Given the set of states defined by Jain (1986) and Jain (1988), which are also used in this section, we cannot observe the process day by day. These models are therefore interesting from a theoretical rather than a practical point of view.

5.2. A Semi-Markov Process Model for the Disease Asthma

The models developed in section 5.1 have the property that state changes can only occur at the appropriate discrete time instant. In section 5.1.1 the time instant was taken to be one day, while in section 5.1.2 the time instant was the season. However, given the nature of the disease asthma, transitions may not necessarily occur at these time instants. We therefore consider a situation where the time between transitions may be several of the unit time intervals, and where this transition time can depend on the transition that is being made. This lead us to a generalization of a Markov process called a semi-Markov process, (Howard, 1971b).

5.2.1. The Formulation of the Model

To formulate this model, we retain the assumptions made for the Markov chain model developed in section 5.1.1. We therefore have the same states and hence the same transition diagram. We shall however think of this process as a process whose successive state occupancies are governed by the transition probabilities of a Markov chain, but whose stay in any state is described by a

discrete random variable that depends on the state to which the next transition will be made.

To make this notion precise, let P_{ij} be the probability that the asthmatic, who entered state i on his last transition, will enter state j on his next transition, i,j = 0, 1, 2, 3. The transition probabilities must satisfy the same equations of the transition probabilities for a Markov chain,

$$P_{ij} \geq 0 \qquad i, j = 0, 1, 2, 3; \tag{14}$$

and

$$\sum_{j=0}^{3} P_{ij} = 1, \qquad i = 0, 1, 2, 3. \tag{15}$$

Whenever the asthmatic enters a state i, he remains for a time T_{ij} in state i before making a transition to state j. The holding times are positive, integer-valued random variables each governed by a probability mass function $f_{ij}(.)$ called the holding time mass function for a transition from state i to state j. Thus

$$P(T_{ij} = m) = f_{ij}(m), \quad m = 0,1,2,... \qquad i,j = 0, 1, 2, 3. \tag{16}$$

The k^{th} moment, about the origin, μ_{ij}^{k} of the holding time T_{ij} is defined by

$$\mu_{ij}^{k} = \sum_{m=0}^{\infty} m^{k} f_{ij}(m) \tag{17}$$

Variance

$$Var(T_{ij}) = \mu_{ij}^{2} - (\mu_{ij})^{2}$$

We assume that the means μ_{ij} of all holding time distributions are finite and that all holding times are at least one day in length, that is

$$f_{ij}(0) = 0 \tag{18}$$

We therefore must specify 4 holding time mass functions (since for a fixed value of i, T_{ij} is the same for each value of j, i,j = 0,1,2,3.) in addition to the transition probabilities, to describe this process completely.

The figure 5.3 shows a portion of a possible trajectory for the semi-Markov process.

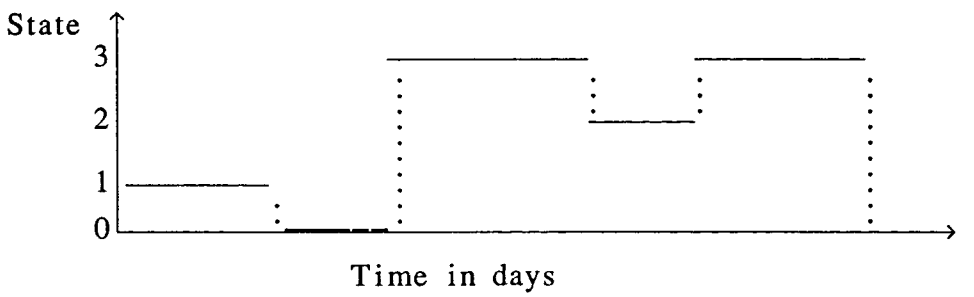


Figure 5.3. A possible trajectory for the process.

Let $F_{ij}(.)$ be the cumulative probability distribution of T_{ij},

$$F_{ij}(n) = P(T_{ij} \leq n) = \sum_{m=0}^{n} f_{ij}(m) \qquad (19)$$

and

$\overline{F}_{ij}(.)$ be the complementary probability distribution of T_{ij}

$$\overline{F}_{ij}(n) = 1 - F_{ij}(n) = P(T_{ij} > n) = \sum_{m=n+1}^{\infty} f_{ij}(m) \qquad (20)$$

Suppose now that the asthmatic enters state i. Let Y_i be the time spent in state i before moving out of state i. We let $w_i(.)$ be the probability mass function of Y_i, then

$$w_i(m) = \sum_{j=0}^{3} P_{ij}\, f_{ij}(m) = P(Y_i = m) \qquad (21)$$

We call Y_i, the waiting time in state i. The mean waiting time υ_i and the mean holding time μ_{ij} are related as follows

$$\upsilon_i = \sum_{j=0}^{3} P_{ij}\, \mu_{ij} \tag{22}$$

and the variance of the waiting time is given as

$$\mathrm{Var}(Y_i) = \upsilon_i^2 - (\upsilon_i)^2 \tag{23}$$

where υ_i^2 is the second moment of the waiting time and is computed using the second moments of the holding time as follows

$$\upsilon_i^2 = \sum_{j=0}^{3} P_{ij}\, \mu_{ij}^2 \tag{24}$$

The cumulative probability distribution $W_i(.)$ and the complementary cumulative probability distribution $\overline{W_i}(.)$ for the waiting times are

$$W_i(n) = \sum_{m=0}^{n} w_i(m) = \sum_{m=0}^{n} \sum_{j=0}^{3} P_{ij}\, f_{ij}(m) = \sum_{j=0}^{3} P_{ij}\, F_{ij}(n)$$

$$= P(Y_i \leq n) \tag{25}$$

$$\overline{W_i}(n) = \sum_{m=n+1}^{\infty} w_i(m) = \sum_{m=n+1}^{\infty} \sum_{j=0}^{3} P_{ij}\, f_{ij}(m) = \sum_{j=0}^{3} P_{ij}\, \overline{F_{ij}}(n)$$

$$= P(Y_i > n) \tag{26}$$

5.2.2. The Interval Transition Probabilities

We define $\phi_{ij}(n)$ as the probability that the asthmatic will be in state j on day n given that he entered state i on day zero. We call this probability the interval transition probability from state i to state j in the interval (0,n).

Then

$$\phi_{ij}(n) = \delta_{ij}\overline{W}_i(n) + \sum_{k=0}^{3} P_{ik} \sum_{m=0}^{n} f_{ik}(m)\, \phi_{kj}(n-m) \qquad (27)$$

$$i,j=0,1,2,3;$$
$$n=0,1,2,...$$

$$\delta_{ij} = \begin{cases} 1 & i=j \\ 0 & i\neq j \end{cases}$$

We write equation (27) in matrix form as

$$\Phi(n) = \overline{W}(n) + \sum_{m=0}^{n} \left[P \square H(m)\right] \Phi(n-m), \quad n = 0,1,2,... \qquad (28)$$

where $\square$ denotes congruent matrix multiplication, that is, multiplication of corresponding components. $\overline{W}(n)$ is the matrix comprising of elements $\overline{W}_i(n)$ obtained from equation (26).

5.2.3. Counting the Number of Attacks

Since the semi-Markov model allows us to distinguish between the number of time units that have passed and the number of transitions that have occurred, we have the opportunity of asking not only the probability of being in each state on day n but also the probability distribution of the number of transitions made by that day. For this we let N(n) be the number of transitions that the asthmatic has made between day 0 and day n. Let S(n) be the index of the state that the asthmatic occupies on day n, and let t(k) be

the time at which the k^{th} transition occurs. Then define $\phi_{ij}(k/n)$ by

$$\phi_{ij}(k/n) = P\{N(n)=k, S(n)=j \mid S(0)=i, t(0)=0\} \qquad (29)$$

$$i = 0,1,2,3.;\ k,n = 0,1,2,...$$
$$j = 1,2,3.$$

$\phi_{ij}(k/n)$ is the joint probability that the asthmatic is in state j and that he has made k transitions given that the day is n and that on day zero the asthmatic entered state i on his zeroth transition. This probability satisfies the following recursive equation,

$$\phi_{ij}(k/n) = \delta_{ij}\ \delta(k)\overline{W}_i(n) + \sum_{r=0}^{3} P_{ir} \sum_{m=0}^{n} f_{ir}(m)\ \phi_{rj}(k-1/n-m) \qquad (30)$$

$$i = 0,\ 1,\ 2,\ 3;\ j = 1,2,3.;\quad n,k = 0,\ 1,\ 2,\ ...$$

$$\delta(k) = \begin{cases} 1\ , & k=0 \\ 0\ , & k\neq 0 \end{cases} \qquad \text{and}$$

$$\phi_{ij}(0/n) = \delta_{ij}\overline{W}_i(n)\ \ i = 0,1,2,3.;\ n = 0,1,2,... \qquad (31)$$
$$j = 1,2,3.$$

Showing that the only way to have made no transitions within (0,n) is to have i = j and a holding time in state i that is greater than n.

Equation (30) can be written in matrix form by defining a matrix $\Phi(k/n)$ with elements $\phi_{ij}(k/n)$:

$$\Phi(k/n) = \delta(k)\overline{W}(n) + \sum_{m=0}^{n} \left[P \square H(m)\right] \Phi(k-1/n-m), \qquad (32)$$
$$n,k = 0,1,2,...$$

Where H(m) is a matrix of holding times with elements $f_{ij}(m)$.

The calculation of $\Phi(n)$ and $\Phi(k/n)$ is very tedious but appropriate computer packages could be used to evaluate them. See Howard (1971b) for some illustrative examples.

5.2.4. The Effect of Preventive Treatment

If preventive treatment is given in order to prevent asthma attacks, then the transition probability matrix **P** is recalculated using equation (5) of section 5.1.1. An alternative could be to extend the holding time in state 0 using the following :

$$\upsilon_{0j} = (1+k)\ \mu_{0j}$$

Where k is as defined in equation (5) of section 5.1. Then replacing μ_{0j} by υ_{0j}. This involves specifying new holding time mass functions $f_{0j}(.)$ with mean υ_{0j}.

CHAPTER 6

STOCHASTIC MODELS IN CONTINUOUS TIME

The models developed in chapter 5 were in discrete time. The transition time was in days. Therefore one could know the condition of the asthmatic only on a given day. However we might be interested in the condition of the asthmatic at any time t. In this chapter we construct models of the asthma process in continuous time. A two state model is considered in section 6.1. This model is extended in section 6.2 to a three state model. A non-Markovian approach is considered in section 6.3.

6.1. A Two State Model for the Asthma Process

In this section we look at asthma as a two state process. The model is developed in section 6.1.1 and we introduce the concept of prevention and treatment of the disease in section 6.1.2. Cost is incorporated into the model in section 6.1.3. In each section a hypothetical example is given.

6.1.1. The Development of the Model

Consider a single asthmatic. We assume that at any time t the asthmatic is either experiencing an attack or is attack-free. If he is experiencing an attack, he then stays with this attack for a certain period of time called the duration of the attack. Treatment is given during this attack and the asthmatic gets cured. If he was attack-free at time t = 0, he stays in this state for a certain period of time, then develops an attack. He gets treated

and becomes attack-free again. For the sake of simplicity, we assume that the probability of death from attack is negligible. We thus have a two state process

State 0 No attack
State 1 Attack - the asthmatic is currently experiencing an attack

The transitions between these states are represented in the following diagram.

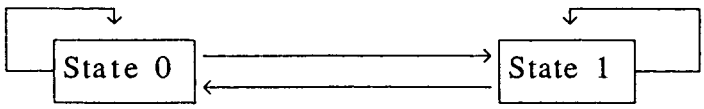


Figure 6.1. The transition diagram for the process.

The asthmatic may spend some time in each state, and as time progresses states 0 and 1 alternate.

Suppose that if the asthmatic is in state 0 at time t then the probability that he may switch to state 1 in time interval $(t,t+\Delta t)$ is, to the first order, $a_{01}\Delta t$ independent of all occurrencies before time t. Similarly, the probability that he may switch from state 1 to state 0 in time interval $(t, t+\Delta t)$ is $a_{10}\Delta t$. Let us call a_{01} the transition rate of the asthmatic from state 0 to state 1 and a_{10} the transition rate of the asthmatic from state 1 to state 0. Note that the probability of two or more transitions in the time interval $(t,t+\Delta t)$ is of the order of $(\Delta t)^2$ or higher. This is assumed to be zero when Δt is small. Let A be the transition rate matrix for the process with components a_{ij}. Following Howard (1960), the diagonal elements a_{jj} of A are given as

$$a_{00} = - a_{01} \text{ and } a_{11} = - a_{10} . \qquad (1)$$

Let $P_0(t)$ be the probability that at time t the asthmatic is in state 0 and $P_1(t)$ be the probability that at time t the asthmatic is in state 1. The

probability that state 0 is occupied at time $t+\Delta t$ is the sum of the probabilities that

(i) state 0 is occupied at time t and no transition occurs in the time interval $(t,t+\Delta t)$. See figure 6.2 below.

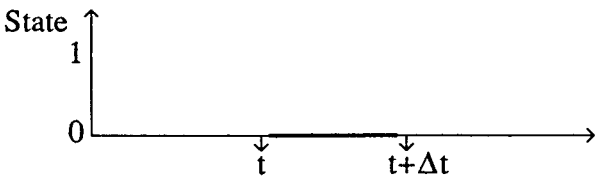


Figure 6.2. A possible trajectory for $P_0(t+\Delta t)$

(ii) state 1 is occupied at time t and a transition from state 1 to state 0 occurs in the time interval $(t, t+\Delta t)$. See figure 6.3 below.

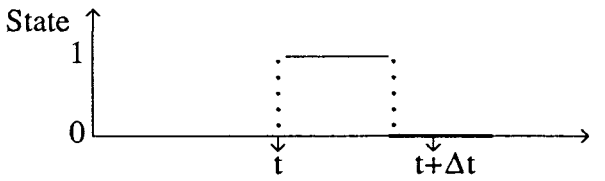


Figure 6.3. Another possible trajectory for $P_0(t+\Delta t)$

A similar argument is applied to $P_1(t+\Delta t)$ and elementary probability considerations lead us to the following equations

$$P_0(t+\Delta t) = (1-a_{01}\Delta t)\, P_0(t) + a_{10}\Delta t\, P_1(t)$$

$$P_1(t+\Delta t) = a_{01}\Delta t\, P_0(t) + (1-a_{10}\Delta t)\, P_1(t) \qquad (2)$$

Dividing by Δt and taking limits as $\Delta t \to 0$ in equations (2), we have that $P_0(t)$ and $P_1(t)$ satisfy the following differential equations

$$\frac{dP_0(t)}{dt} = -a_{01}P_0(t) + a_{10}P_1(t)$$

$$\frac{dP_1(t)}{dt} = a_{01}P_0(t) - a_{10}P_1(t) \qquad (3)$$

In matrix form we may write equations (3) as

$$\frac{d\mathbf{P}(t)}{dt} = \mathbf{P}(t)\,\mathbf{A}$$

Where $\mathbf{P}(t)$ is the vector of state probabilities at time t. i.e. $\mathbf{P}(t) = [P_0(t)\ P_1(t)]$. Since states 0 and 1 are mutually exclusive, we have that $P_0(t) + P_1(t) = 1$, for all t, (Syski, 1989). With this condition, the differential equations (3) have the following solution

$$P_0(t) = \frac{a_{10}}{a_{01}+a_{10}} + \left\{P_0(0) - \frac{a_{10}}{a_{01}+a_{10}}\right\} \exp\left[-(a_{01}+a_{10})t\right]$$

$$P_1(t) = \frac{a_{01}}{a_{01}+a_{10}} + \left\{P_1(0) - \frac{a_{01}}{a_{01}+a_{10}}\right\} \exp\left[-(a_{01}+a_{10})t\right] \qquad (4)$$

Note that $P_0(t) + P_1(t) = 1$ as it should be. $P_0(0)$, $P_1(0)$ are the probabilities of being in states 0 and 1 at time $t = 0$, respectively; and $P_0(0) + P_1(0) = 1$.

We can see clearly that as $t \to \infty$ the probabilities in (4) approach the limiting values

$$P_0 \equiv \lim_{t\to\infty} P_0(t) = \frac{a_{10}}{a_{01}+a_{10}}$$

$$P_1 \equiv \lim_{t\to\infty} P_0(t) = \frac{a_{01}}{a_{01}+a_{10}} \qquad (5)$$

These limiting values provide the equilibrium probability distribution for the process.

An alternative formulation of the process is in terms of two sequencies of mutually independent random variables $\{ X_1, X_2 \ldots \}$ and $\{ Y_1, Y_2, \ldots \}$ exponentially distributed with parameters equal to a_{01} and a_{10} respectively. This means that the time between attacks is exponentially distributed with mean $1/a_{01}$, while the duration of an attack is exponentially distributed with mean $1/a_{10}$. If, for example, the asthmatic starts in state 0, there is a transition to state 1 at time X_1, a transition back to state 0 after a further time Y_1, and so on.

Figure 6.4 shows a realization of this process.

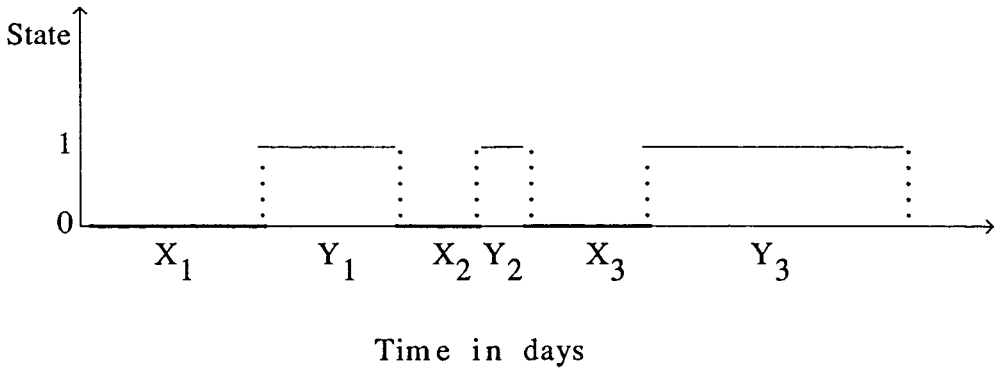


Figure 6.4 A possible trajectory for the asthma process.

Example 6.1.

Suppose that if the asthmatic is in state 0, there is a probability $1/30\Delta t$ that he will be in state 1 in a short interval Δt; and if he is in state 1, there is a probability $1/2\Delta t$ that he will be free of attack in Δt. Thus $a_{01} = 1/30$, $a_{10} = 1/2$ and we obtain the following transition rate matrix

$$A = \begin{bmatrix} -1/30 & 1/30 \\ 1/2 & -1/2 \end{bmatrix}$$

This is equivalent to saying that the time between attacks is exponentially distributed with mean 30 days, while the duration of an attack is exponentially distributed with mean 2 days. For this problem we would like to find, for example, the probability that the asthmatic will be in state 0 at time $t > 0$ if he is in state 0 when $t = 0$. If the asthmatic is in state 0 at time $t = 0$, so that $P(0) = [P_0(0) \quad P_1(0)] = [1 \quad 0]$, then from equations (4), we see that

$$p_0(t) = \frac{15}{16} + \frac{1}{16} \exp(-16/30t)$$

$$p_1(t) = \frac{1}{16} - \frac{1}{16} \exp(-16/30t)$$

Both $P_0(t)$ and $P_1(t)$ have a constant term plus an exponentially decaying term. The constant term represent the limiting state probability as t becomes very large. Thus the probability that the asthmatic is in state 0, $P_0(t)$, falls exponentially from 1 to 15/16 as t increases.

Similarly, if the asthmatic is in state 1 at time $t = 0$, $P(0) = [0 \quad 1]$, and from equations (4)

$$p_0(t) = \frac{15}{16} - \frac{15}{16} \exp(-16/30t)$$

$$p_1(t) = \frac{1}{16} + \frac{15}{16} \exp(-16/30t)$$

Note that the probability that the asthmatic is in state 0 rises exponentially from 0 to its steady-state value of 15/16 as t becomes large. The limiting state probabilities of the process are 15/16 and 1/16 for states 0 and 1, respectively. They are independent of the state of the asthmatic at $t = 0$.

Suppose that the asthmatic is initially in state 0. As shown in figure 6.4, each period spent in a state is a random variable. The random variable has mean $1/a_{01}$ for state 0 and $1/a_{10}$ for state 1. In a very long time , say after 2N transitions, the total time spent in state 0 will be the sum of a large number N of quantities, each with expectation $1/a_{01}$, and hence will be asymptotically N/a_{01}; similarly the time spent in state 1 will be

asymptotically N/a_{10}. Thus the proportion of a very long time spent in state 1 is asymptotically

$$\frac{N/a_{10}}{N/a_{01}+ N/a_{10}} = \frac{a_{01}}{a_{01}+ a_{10}} = P_1 \qquad (6)$$

Therefore, if we observe the process for a long period of time, the proportion of time which the asthmatic spends in state 1 is approximately the stationary probability P_1 of finding the asthmatic in state 1. Similarly for a long period of time, the proportion of time spent in state 0 is approximately P_0.

6.1.2. A Two State Model with Preventive Treatment

In section 6.1.1 we assumed that treatment was given during an attack but there was no treatment to prevent this attack. In this section we allow a situation where the asthmatic could be under preventive treatment.

Suppose as in section 6.1.1 that if the asthmatic is in state 0 at time t then the probability he may switch to state 1 in time interval $(t,t+\Delta t)$ is $a_{01}\Delta t$. This is equivalent to saying that the duration in state 0 is exponentially distributed with mean $1/a_{01}$. Now suppose that preventive treatment is given to the asthmatic. This treatment reduces this probability of switching from state 0 to state 1 in $(t,t+\Delta t)$ to $b_{01}\Delta t$. How much this probability is reduced depends on the effectiveness of this treatment. A convenient measure of the effectiveness of the treatment is obtained by the definition

$$1/b_{01} = (1 + k)\ 1/a_{01} \qquad (7)$$

where k is a positive real number. With $k = 0$ the treatment has no effect at all, and with $k > 0$ the treatment is beneficial. The probability $a_{01}\Delta t$ is reduced to $b_{01}\Delta t$ accordingly. The probability of switching from state 1 to state 0 in time interval $(t,t+\Delta t)$, namely $a_{10}\Delta t$ remains the same since an attack is assumed to be always treated. To be consistent with notations,

however, we use $b_{10}\Delta t$ instead of $a_{10}\Delta t$. Thus

$$b_{10} = a_{10}. \tag{8}$$

Let $P_0(t)$ and $P_1(t)$ be as defined in section 6.1. Following equations (4), we have for this process

$$P_0(t) = \frac{b_{10}}{b_{01}+b_{10}} + \left\{P_0(0) - \frac{b_{10}}{b_{01}+ b_{10}}\right\} \exp\left[- (b_{01}+ b_{10})t\right]$$

$$P_1(t) = \frac{b_{01}}{b_{01}+b_{10}} + \left\{P_1(0) - \frac{b_{01}}{b_{01}+b_{10}}\right\} \exp\left[- (b_{01}+b_{10})t\right] \tag{9}$$

Where b_{01} and b_{10} are found from (7) and (8) respectively. The transition rate matrix is **B** with components b_{ij}. The diagonal elements of **B** are $b_{00} = - b_{01}$ and $b_{11} = - b_{10}$, analogous to equation (1).

Example 6.2.

Suppose that an asthmatic has a probability $1/30\Delta t$ of moving from state 0 to state 1 in a short interval $(t,t+\Delta t)$ under no preventive treatment. Suppose a preventive treatment for which $k = 0.95$ is given to this asthmatic. With this preventive treatment the probability of switching from state 0 to state 1 is reduced to $b_{01}\Delta t$, where $b_{01} = 2/117$ with $a_{01} = 1/30$ and $k = 0.95$ subtituted in equation (7). Suppose the probability of moving from state 1 to state 0 in a short interval $(t,t+\Delta t)$ is $1/2\Delta t$. Then $b_{10} = a_{10} = 1/2$ and we obtain the following transition rate matrix

$$\mathbf{B} = \begin{bmatrix} -2/117 & 2/117 \\ 1/2 & -1/2 \end{bmatrix}$$

This is equivalent to saying that the time between attacks has an exponential distribution with mean 58.5 days, while the duration of an attack is

exponentially distributed with mean 2 days (as in example 1). Note that the mean duration in state 0 is increased from 30 days to 58.5 days (a 95 % increase) as a result of this preventive treatment.

Suppose the asthmatic is in state 0 at time t = 0, so that $[P_0(0)\ P_1(0)] = [1\ 0]$, then from equations (9), we have

$$P_0(t) = \frac{117}{121} + \frac{4}{121} \exp(-121/234t)$$

and

$$p_1(t) = \frac{4}{121} - \frac{4}{121} \exp(-121/234t)$$

Similarly, if the asthmatic is in state 1 at time t = 0, $[P_0(0)\ P_1(0)] = [0\ \ 1]$, and from equations (9)

$$p_0(t) = \frac{117}{121} - \frac{117}{121} \exp(-121/234t)$$

and

$$p_1(t) = \frac{4}{121} + \frac{117}{121} \exp(-121/234t)$$

The probability of being in state 1 having started in state 0, under no prevention is compared to that under prevention, for a week in the following table.

Time (in days)	No prevention	Prevention (k = 0.95)
0	0.00000	0.00000
1	0.02580	0.01335
2	0.04099	0.02131
3	0.04988	0.02605
4	0.05510	0.02888
5	0.05815	0.03057
6	0.05950	0.03157
7	0.06101	0.03217

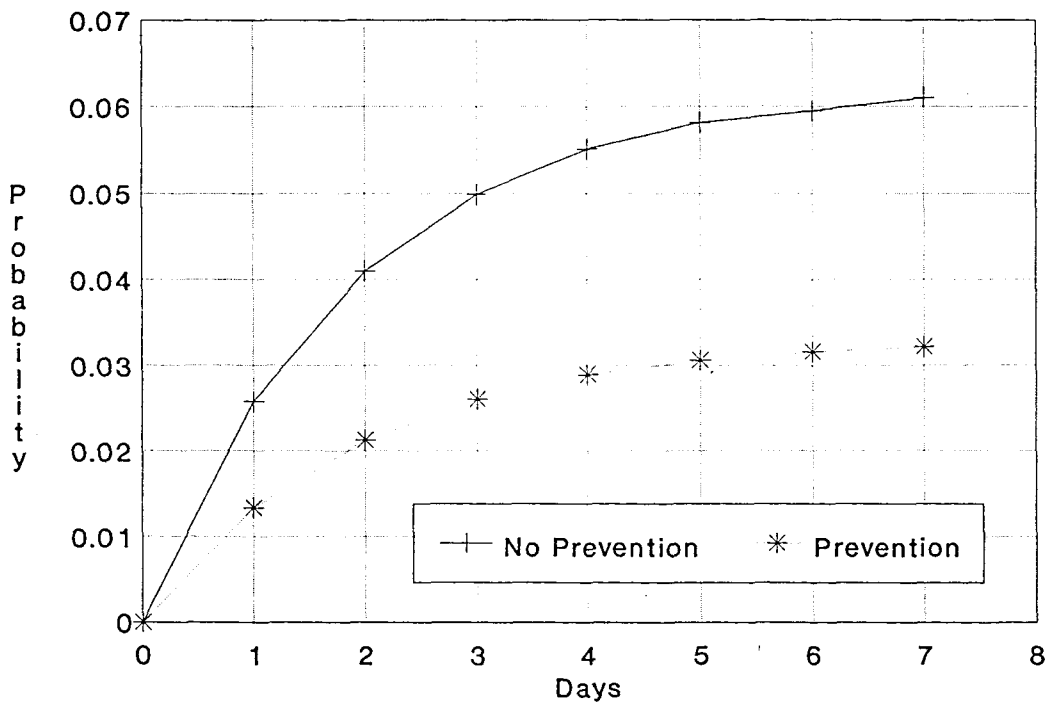
Table 6.1. A comparison of the probability of being in state 1 having started in state 0, under no preventive treatment and that under preventive treatment.

Values shown in table 6.1 are displayed graphically in figure 6.5 for clarity.

6.1.3. A Two State Model with Cost Implications.

Let us suppose that the asthmatic incurs a cost of c_{ii} pounds per unit time during all the time he is in state i, i = 0, 1. We are interested in the expected cost the asthmatic incurs for a time t. For this, let $K_0(t)$ be the expected total cost that the asthamtic incurs in a time t if he starts in state 0, and $K_1(t)$ be the expected total cost that the asthmatic incurs in a time t if he starts in state 1. Then following Howard (1960), the total expected cost in a time $t+\Delta t$ for states 0 and 1, denoted by $K_0(t+\Delta t)$ and $K_1(t+\Delta t)$ respectively, are given as

Figure 6.5. Probability of being in state 1 having started in state 0



$$K_0(t+\Delta t) = (1 - a_{01}\Delta t)\left[c_{00}\Delta t + K_0(t)\right] + a_{01}\Delta t\, K_1(t)$$

and

$$K_1(t+\Delta t) = (1 - a_{10}\Delta t)\left[c_{11}\Delta t + K_1(t)\right] + a_{10}\Delta t\, K_0(t) \qquad (10)$$

The above equations can be interpreted as follows : consider first of all $K_0(t+\Delta t)$. During the time interval (t, t+Δt) the asthmatic may remain in state 0 or make a transition to state 1. If the asthmatic remains in state 0 for a time Δt, a cost of $c_{00}\Delta t$ will be incurred plus the expected cost incurred in the remaining t units of time, $K_0(t)$. The probability that the asthmatic remains in state 0 for a time Δt is 1 minus the probability he makes a transition in Δt, i.e. $1 - a_{01}\Delta t$. On the other hand, the asthmatic may make a transition to state 1 during the time interval (t,t+Δt) with probability $a_{01}\Delta t$. In this case he incurs a cost $K_1(t)$ for t units of time remaining. A similar argument holds for $K_1(t+\Delta t)$. The product of probability and cost must then be added in order to obtain the total contribution to the expected values.

Using equation (1) we write equations (10) as

$$K_0(t+\Delta t) = (1 + a_{00}\Delta t)\left[c_{00}\Delta t + K_0(t)\right] + a_{01}\Delta t\, K_1(t)$$

and

$$K_1(t+\Delta t) = (1 + a_{11}\Delta t)\left[c_{11}\Delta t + K_1(t)\right] + a_{10}\Delta t\, K_0(t)$$

or

$$K_0(t+\Delta t) = c_{00}\Delta t + K_0(t) + a_{00}K_0(t)\Delta t + a_{01}\Delta t\, K_1(t)$$

and

$$K_1(t+\Delta t) = c_{11}\Delta t + K_1(t) + a_{11}K_1(t)\Delta t + a_{10}\Delta t\, K_0(t) \qquad (11)$$

where terms of higher order than Δt have been ignored.

Dividing equations (11) by Δt and taking limits as Δt -> 0 with appropriate rearrangement gives

$$\frac{d}{dt} K_0(t) = c_{00} + a_{00}\, K_0(t) + a_{01}\, K_1(t)$$

$$\frac{d}{dt} K_1(t) = c_{11} + a_{11}\, K_1(t) + a_{10}\, K_0(t) \qquad (12)$$

We thus have a set of constant-coefficient differential equations that define $K_0(t)$ and $K_1(t)$ completely when $K_0(0)$ and $K_1(0)$ are specified. Obviously $K_0(0) = 0$ and $K_1(0) = 0$ since the cost incurred at time $t = 0$ is zero.

Let $\mathbf{K}(t)$ represent the column vector with elements $K_i(t)$, the total expected cost, then equations (12) can be written in matrix form as

$$\frac{d}{dt}\mathbf{K}(t) = \mathbf{C} + \mathbf{A}\,\mathbf{K}(t) \qquad (13)$$

where $\mathbf{C} = \begin{bmatrix} c_{00} \\ c_{11} \end{bmatrix}$ is a column vector of transition costs.

To obtain a solution to (13), we use the Laplace transform method. For this we let K(s) be the Laplace transform of K(t), then if we take the Laplace transform of equation (13), we have

$$s\mathbf{K}(s) - \mathbf{K}(0) = 1/s\ \mathbf{C} + \mathbf{A}\,\mathbf{K}(s)$$

or

$$(s\mathbf{I} - \mathbf{A})\mathbf{K}(s) = 1/s\ \mathbf{C} + \mathbf{K}(0)$$

or

$$\mathbf{K}(s) = 1/s\ (s\mathbf{I} - \mathbf{A})^{-1}\ \mathbf{C} \quad \text{since } \mathbf{K}(0) = \mathbf{0}. \qquad (14)$$

The cost vector $\mathbf{K}(t)$ is found by inverse transformation of equation (14).

Example 6.3.

Suppose as in example 6.2 that a preventive treatment for which $k = 0.95$ is given to the asthmatic. Thus the probability of switching from state 0 to state 1 in a short time interval $(t,t+\Delta t)$ is reduced to $2/117\Delta t$. The probability of moving from state 1 to state 0 in a short interval $(t,t+\Delta t)$ is $1/2\Delta t$, see example 6.2. Then the transition rate matrix is given by

$$\mathbf{A} = \begin{bmatrix} -2/117 & 2/117 \\ 1/2 & -1/2 \end{bmatrix}$$

Suppose further that the asthmatic incurs a cost of 5 pounds per unit time during his stay in state 0 and 8 pounds per unit time during his stay in state 1. Then $c_{00} = 5$, $c_{11} = 8$ and

$$C = \begin{bmatrix} 5 \\ 8 \end{bmatrix}.$$

Thus we have

$$(sI - A)^{-1} = \begin{bmatrix} \frac{s+1/2}{s(s+121/234)} & \frac{2/117}{s(s+121/234)} \\ \frac{1/2}{s(s+121/234)} & \frac{s+2/117}{s(s+121/234)} \end{bmatrix}$$

$$1/s(sI - A)^{-1} = \begin{bmatrix} \frac{s+1/2}{s^2(s+121/234)} & \frac{2/117}{s^2(s+121/234)} \\ \frac{1/2}{s^2(s+121/234)} & \frac{s+2/117}{s^2(s+121/234)} \end{bmatrix}$$

Using partial fraction expansion, we get

$$1/s(sI - A)^{-1} = \begin{bmatrix} \frac{936/14641}{s} + \frac{117/121}{s^2} + \frac{-936/14641}{s+121/234} & \frac{4/121}{s^2} + \frac{-936/14641}{s} + \frac{936/14641}{s+121/234} \\ \frac{117/121}{s^2} + \frac{-27378/14641}{s} + \frac{27378/14641}{s+121/234} & \frac{4/121}{s^2} + \frac{27378/14641}{s} + \frac{-27378/14641}{s+121/234} \end{bmatrix}$$

$$= \frac{1}{s^2}\begin{bmatrix} 117/121 & 4/121 \\ 117/121 & 4/121 \end{bmatrix} + \frac{1}{s}\begin{bmatrix} 936/14641 & -936/14641 \\ -27378/14641 & 27378/14641 \end{bmatrix}$$

$$+ \frac{1}{s+121/234}\begin{bmatrix} -936/14641 & 936/14641 \\ 27378/14641 & -27378/14641 \end{bmatrix}$$

Since $\mathbf{K}(s) = 1/s(s\mathbf{I} - \mathbf{A})^{-1}\,\mathbf{C}$, we have by inverse transformation that

$$\mathbf{K}(t) = t\begin{bmatrix} 5.10 \\ 5.10 \end{bmatrix} + \begin{bmatrix} -0.19 \\ 5.61 \end{bmatrix} + \begin{bmatrix} 0.19 \\ -5.61 \end{bmatrix}\exp(-121/234t)$$

The total expected cost in time t if the asthmatic started in state 0 is thus

$$K_0(t) = 5.10t - 0.19 + 0.19\ \exp(-121/234t)$$

and the total expected cost in time t if he started in state 1 is given by

$$K_1(t) = 5.10t + 5.61 - 5.61\ \exp(-121/234t)$$

We can see that irrespective of the starting state the asthmatic will incur an average cost of 5.10 pounds per unit time when t is large.

6.1.4. Possible Extension of the Two State Model.

In reality, when the asthmatic is in state 1, the severity of the attack is assesed in order to give appropriate treatment. Some tests such as the lung function tests are performed and the attack is classified as mild, moderate, or severe depending on the results of these tests, see chapter 8 for detailed analysis. In addition the asthmatic might die if the attack is not well treated. There is also a possibility that an asthmatic might "grow out" of

asthma by adult age. When all these possibilities are allowed, the two state model developed in section 6.1.1 becomes inadequate for the problem and hence a model for more than two states is needed. This model is therefore developed in section 6.2.

6.2. A Three State Model for the Asthma Process

In this section we give an extension of the two state model taking into account some of the possibilities mentioned in section 6.1.4. The model is developed in section 6.2.1 and the concept of prevention and treatment of asthma attacks with the resulting costs is highlighted in section 6.2.2. In each case an example is given for the sake of clarity.

6.2.1. The Development of the Model

Consider as in section 6.1.1 that we have a single asthmatic. At time t the asthmatic is either experiencing an attack or is attack-free. When the asthmatic develops an attack, some lung function tests and other measurements are performed, and depending on the results of these measurements the attack is classified as mild, or severe (we do not distinguish between mild and moderate attacks). The asthmatic then stays with this attack for a period of time called the duration of the attack. Treatment is given during this attack and the asthmatic gets cured. If the asthmatic was attack-free at time t = 0, he stays in this state for a certain period of time, then develops an attack. The asthmatic gets treated and becomes normal again. As in section 6.1.1 we assume that the probability of death from an attack is negligible. Therefore we have a three state process :-

State 0 No attack
State 1 Mild attack
State 2 Severe attack

The likely transitions between these states are shown in figure 6.6

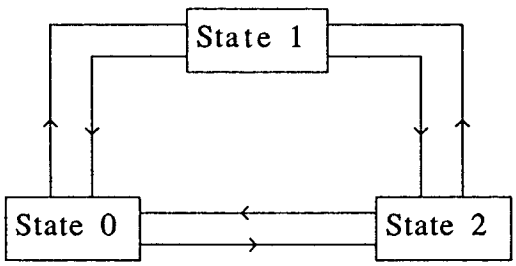


Figure 6.6. The transition diagram for the three state process.

This is a three state process whose time between transitions is random. Figure 6.7 shows a portion of a possible trajectory for this process.

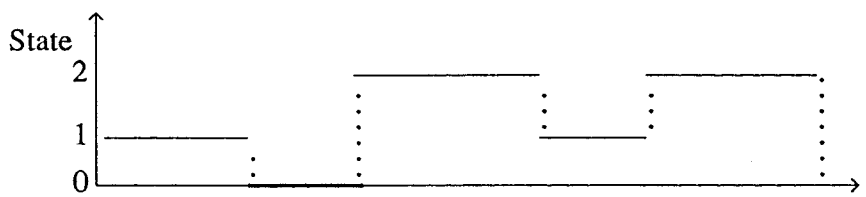


Figure 6.7. A possible trajectory for the three state process

Following Howard (1960), let a_{ij} be the transition rate of the asthmatic from state i to state j, $i \neq j$. By this we mean that in a short time interval $(t,t+\Delta t)$, the asthmatic, now in state i will make a transition to state j with probability $a_{ij}\Delta t$ $(i \neq j)$. Symbolically, if X_t represent the state of the process at time t, then we have

$$P(X_{t+\Delta t} = j \mid X_t = i) = a_{ij}\Delta t \qquad (15)$$

The probability of two or more state transitions is of the order of $(\Delta t)^2$ or higher and could be neglected if Δt is sufficiently small. We assume that the a_{ij}'s are constants, that is, the transition rates do not change with time. We define

$$a_{jj} = -\sum_{i \neq j} a_{ji} \qquad i,j = 0,1,2. \qquad (16)$$

We thus describe this process by a transition-rate matrix A with components a_{ij}. Those who are familiar with Markov chains, as discussed in chapter 5, will see that this matrix is analogous to the transition probability matrix in Markov chain analysis. The assumption that the transition rates are constant is also equivalent in the discrete-time case to the assumption that the transition probabilities do not change with time.

Let $P_i(t)$ be the probability that the asthmatic is in state i at time t after the start of the process. Let $P_i(t+\Delta t)$ be the probability that the asthmatic is in state i a short time Δt later.

$$\text{Then} \quad P_j(t+\Delta t) = P_j(t)\left[1-\sum_{i\neq j} a_{ji}\Delta t\right] + \sum_{i\neq j} P_i(t)\, a_{ij}\Delta t \qquad (17)$$
$$j = 0,1,2.$$

Equation (17) can be explained as follows : there are basically two mutually exclusive ways in which the asthmatic can be in state j at time $t+\Delta t$. First, he could have been in state j at time t and made no transition during the interval $(t,t+\Delta t)$. These events have respective probabilities $P_j(t)$ and $1-\sum_{i\neq j} a_{ji}\Delta t$ since the probability of multiple transitions is of the order higher than Δt and is negligible. Note also that the probability of making no transition in $(t,t+\Delta t)$ is 1 minus the probability of making a transition in $(t,t+\Delta t)$ to some state $i\neq j$. Another way the asthmatic could be in state j at time $t+\Delta t$ is to have been in state $i\neq j$ at time t and then made a transition from i to j during the time Δt. Equation (17) is obtained by multiplying the probabilities and adding over all i that are not equal to j because the asthmatic could have entered j from any other state i.

Substituting equations (16) in (17), we have

$$P_j(t+\Delta t) = P_j(t)\left[1+ a_{jj}\Delta t\right] + \sum_{i\neq j} P_i(t)\, a_{ij}\Delta t$$

or

$$P_j(t+\Delta t) - P_j(t) = \sum_{i=0}^{2} P_i(t)\, a_{ij}\Delta t$$

Dividing by Δt and taking limit as $\Delta t \longrightarrow 0$, we obtain

$$\frac{d}{dt} P_j(t) = \sum_{i=0}^{2} P_i(t)\, a_{ij} \qquad j = 0,1,2. \tag{18}$$

This is a set of three linear constant-coefficient differential equations that relate the state probabilities to the transition rate matrix **A**. In matrix form therefore we may write equation (18) as

$$\frac{d}{dt} \mathbf{P}(t) = \mathbf{P}(t)\, \mathbf{A} \tag{19}$$

P(t) is a row vector of state probabilities at time t. Note that the matrix **A** is also called a differential matrix. This is bacause its rows sum to zero. The initial distribution conditions $P_i(0)$, i = 0,1,2. must be specified in order to obtain the solution for equation (19). The Laplace transform technique is usually employed to obtain this solution.

Example 6.4.

We suppose that if the asthmatic is in state 0, he has a probability of $1/30\Delta t$ of being in state 1, and a probability of $1/50\Delta t$ of being in state 2 in a short time interval $(t,t+\Delta t)$. If the asthmatic is in state 1, he has a probability of $1/2\Delta t$ of making a transition to state 0 and a probability of $1/5\Delta t$ of making a transition to 2 in a short interval of time $(t,t+\Delta t)$. When the asthmatic is in state 2, the probabilities are $1/15\Delta t$ and $1/10\Delta t$ of making transitions to states 0 and 1 respectively in a short time interval of length Δt. Therefore $a_{01} = 1/30$, $a_{02} = 1/50$; $a_{10} = 1/2$, $a_{12} = 1/5$; and $a_{20} = 1/15$, $a_{21} = 1/10$. The transition matrix is given as

$$A = \begin{bmatrix} -0.05 & 0.03 & 0.02 \\ 0.50 & -0.70 & 0.20 \\ 0.07 & 0.10 & -0.17 \end{bmatrix}$$

This is equivalent to saying that the time between state 0 and state 1 is exponentially distributed with mean 30 days, the time between states 2 and 3 is exponentially distributed with mean 5 days etc. The problem is therefore to find the probability that the asthmatic will be in state i at time t given that he was in state j at time t = 0. For this, we solve equation (19) by the Laplace transform method.

Taking the Laplace transform of (19), we have

$$\mathbf{sP}(s) - \mathbf{P}(0) = \mathbf{P}(s)\ \mathbf{A}$$

or

$$\mathbf{P}(s)\ (s\mathbf{I}-\mathbf{A}) = \mathbf{P}(0)$$

and

$$\mathbf{P}(s) = \mathbf{P}(0)\ (s\mathbf{I}-\mathbf{A})^{-1} \qquad (20)$$

Thus $\mathbf{P}(t)$ is obtained as the inverse transform of $\mathbf{P}(s)$. Following this method, we first write (sI-A),

$$(s\mathbf{I}-\mathbf{A}) = \begin{bmatrix} s+0.05 & -0.03 & -0.02 \\ -0.50 & s+0.70 & -0.20 \\ -0.07 & -0.10 & s+0.17 \end{bmatrix}$$

and then find its determinant,

$$|(s\mathbf{I}-\mathbf{A})| = s^3 + 0.92\ s^2 + 0.13\ s = s(s+0.17)(s+0.75)$$

Therefore

$$(s\mathbf{I}-\mathbf{A})^{-1} = 1/s(s+0.17)(s+0.75)$$

$$\times \begin{bmatrix} s^2+0.87s+0.1 & 0.03s+0.01 & 0.02s+0.02 \\ 0.5s+0.1 & s^2+0.22s+0.01 & 0.2s+0.02 \\ 0.07s+0.1 & 0.1s+0.01 & s^2+0.75s+0.02 \end{bmatrix}$$

and write it in partial fraction expansion form,

$$(sI-A)^{-1}=\frac{1}{s}\begin{bmatrix} 0.77 & 0.08 & 0.15 \\ 0.77 & 0.08 & 0.15 \\ 0.77 & 0.08 & 0.15 \end{bmatrix}+\frac{1}{s+0.17}\begin{bmatrix} 0.20 & -0.05 & -0.15 \\ -0.14 & 0.00 & 0.14 \\ -0.88 & 0.07 & 0.81 \end{bmatrix}$$

$$+\frac{1}{s+0.75}\begin{bmatrix} 0.03 & -0.03 & 0.00 \\ -0.63 & 0.92 & -0.29 \\ 0.11 & -0.15 & 0.04 \end{bmatrix}$$

We therefore have, by inverse transformation

$$\mathbf{P}(t) = \mathbf{P}(0)\left\{\begin{bmatrix} 0.77 & 0.08 & 0.15 \\ 0.77 & 0.08 & 0.15 \\ 0.77 & 0.08 & 0.15 \end{bmatrix}+\exp(-0.17t)\right.$$

$$\left.\times\begin{bmatrix} 0.20 & -0.05 & -0.15 \\ -0.14 & 0.00 & 0.14 \\ -0.88 & 0.07 & 0.81 \end{bmatrix}+\exp(-0.75t)\begin{bmatrix} 0.03 & -0.03 & 0.00 \\ -0.63 & 0.92 & -0.29 \\ 0.11 & -0.15 & 0.04 \end{bmatrix}\right\}$$

Thus $\mathbf{P}(t)$ is completely specified whenever the initial probability matrix $\mathbf{P}(0)$ is known. The first matrix is a stochastic matrix and the other two matrices are differential matrices except for round off errors.

Suppose the asthmatic is in state 0 at time t = 0. Then

$$\mathbf{P}(0) = \begin{bmatrix} P_0(0) & P_1(0) & P_2(0) \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \text{ and}$$

$$\mathbf{P}(t) = \begin{bmatrix} 0.77 & 0.08 & 0.15 \end{bmatrix} + \begin{bmatrix} 0.20 & -0.05 & -0.15 \end{bmatrix}\exp(-0.17t)$$

$$+\begin{bmatrix} 0.03 & -0.03 & 0.00 \end{bmatrix}\exp(-0.75t) \qquad (21)$$

The constant terms in equations (21) represent the limiting state probabilities as t becomes large.

Similarly, if the asthmatic starts in state 1 at time t = 0. Then

$$\mathbf{P}(0) = \begin{bmatrix} 0 & 1 & 0 \end{bmatrix} \text{ and}$$

$$\mathbf{P}(t) = \begin{bmatrix} 0.77 & 0.08 & 0.15 \end{bmatrix} + \begin{bmatrix} -0.14 & 0.00 & 0.14 \end{bmatrix} \exp(-0.17t)$$

$$+ \begin{bmatrix} -0.63 & 0.92 & -0.29 \end{bmatrix} \exp(-0.75t)$$

The asthmatic may also start in state 2 at time t = 0. Then

$$\mathbf{P}(0) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \text{ and}$$

$$\mathbf{P}(t) = \begin{bmatrix} 0.77 & 0.08 & 0.15 \end{bmatrix} + \begin{bmatrix} -0.88 & 0.07 & 0.81 \end{bmatrix} \exp(-0.17t)$$

$$+ \begin{bmatrix} 0.11 & -0.15 & 0.04 \end{bmatrix} \exp(-0.75t)$$

6.2.2. Implications of Preventive Treatment

Here we introduce the concept of prevention of asthma attacks. By this we mean treatment is given to the asthmatic in order to prevent him from asthma attacks. To do this we suppose as in section 6.1.2 that if the asthmatic occupies state 0 at time t then he has probabilities $a_{01}\Delta t$ and $a_{02}\Delta t$ of switching to state 1 and state 2 in time interval $(t,t+\Delta t)$, respectively. This is the same as saying that the times taken for the asthmatic to make a transition from state 0 to states 1 and 2 are exponentially distributed with mean $1/a_{01}$ and $1/a_{02}$ respectively. If preventive treatment is given to this asthmatic, these mean times are increased to $1/b_{01}$ and $1/b_{02}$ respectively, and the probabilities of switching from state 0 to states 1 and 2 in $(t,t+\Delta t)$ are therefore reduced to $b_{01}\Delta t$ and $b_{02}\Delta t$ accordingly. The reduction is however dependent on the effectiveness of this preventive treatment. As discussed in section 6.1.2, a measure of this effectiveness is obtained from the following expression

$$1/b_{0j} = (1+k)\ 1/a_{0j}\ ,\ j = 1,2. \qquad (22)$$

with k defined in section 6.1.2. The probabilities of switching from states 1 or 2 to state 0 in time interval $(t,t+\Delta t)$, namely $a_{10}\Delta t$ and $a_{20}\Delta t$ remains the same. For consistency we use $b_{10}\Delta t$ and $b_{20}\Delta t$ instead of $a_{10}\Delta t$ and $a_{20}\Delta t$.

Therefore $b_{10} = a_{10}$ and $b_{20} = a_{20}$ (23)

and the b_{jj}'s are obtained from equation (16).

Let $P_i(t)$, i = 0,1,2. be as defined in section 6.2.1. Then we have

$$\frac{d}{dt}\mathbf{P}(t) = \mathbf{P}(t)\,\mathbf{B} \tag{24}$$

with analogy to equation (19). In this case the matrix B has components b_{ij}, i,j = 0,1,2.

Example 6.5.

Let $1/30\Delta t$ and $1/50\Delta t$ be the probabilities that the asthmatic will switch from state 0 to states 1 and 2 without preventive treatment, respectively. When preventive treatment is given these probabilities reduce to $b_{01}\Delta t$ and $b_{02}\Delta t$, respectively, where b_{01} and b_{02} are found from (22) with $a_{01} = 1/30$ and $a_{02} = 1/50$. Let the other probabilities be as in example 6.4. That is, $b_{10} = 1/2$, $b_{12} = 1/5$; $b_{20} = 1/15$, $b_{21} = 1/10$. Then with b_{00}, b_{11} and b_{22} obtained with the use of (16), we have that the matrix of transition rates is

$$\mathbf{B} = \begin{bmatrix} -0.03 & 0.02 & 0.01 \\ 0.50 & -0.70 & 0.20 \\ 0.07 & 0.10 & -0.17 \end{bmatrix}$$

$$(s\mathbf{I}-\mathbf{B}) = \begin{bmatrix} s+0.03 & -0.02 & -0.01 \\ -0.50 & s+0.70 & -0.20 \\ -0.07 & -0.10 & s+0.17 \end{bmatrix}$$

and

$$(sI-B)^{-1} = 1/s\ (s+0.1532)(s+0.7468)$$

$$x \begin{bmatrix} s^2+0.87s+0.099 & 0.02s+0.0044 & 0.01s+0.011 \\ 0.5s+0.099 & s^2+0.2s+0.0044 & 0.2s+0.011 \\ 0.07s+0.099 & 0.1s+0.0044 & s^2+0.73s+0.011 \end{bmatrix}$$

The partial fraction expansion is of the form,

$$(sI-B)^{-1} = \frac{1}{s}\begin{bmatrix} 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \end{bmatrix} + \frac{1}{s+0.1532}\begin{bmatrix} 0.12 & -0.02 & -0.10 \\ -0.25 & 0.03 & 0.22 \\ -0.97 & 0.12 & 0.85 \end{bmatrix}$$

$$+ \frac{1}{s+0.7468}\begin{bmatrix} 0.02 & -0.02 & 0.00 \\ -0.62 & 0.93 & -0.31 \\ 0.11 & -0.16 & 0.05 \end{bmatrix}$$

Thus we have that

$$\mathbf{P}(t) = \mathbf{P}(0)\left\{\begin{bmatrix} 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \end{bmatrix} + \exp(-0.1532t)\right.$$

$$\left. x \begin{bmatrix} 0.12 & -0.02 & -0.10 \\ -0.25 & 0.03 & 0.22 \\ -0.97 & 0.12 & 0.85 \end{bmatrix} + \exp(-0.75t)\begin{bmatrix} 0.02 & -0.02 & 0.00 \\ -0.62 & 0.93 & -0.31 \\ 0.11 & -0.16 & 0.05 \end{bmatrix}\right\}$$

If the asthmatic is in state 0 at time t = 0. Then

$$\mathbf{P}(0) = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \text{ and}$$

$$\mathbf{P}(t) = \begin{bmatrix} 0.86 & 0.04 & 0.10 \end{bmatrix} + \begin{bmatrix} 0.12 & -0.02 & -0.10 \end{bmatrix}\exp(-0.1532t)$$

$$+ \begin{bmatrix} 0.02 & -0.02 & 0.00 \end{bmatrix}\exp(-0.7468t)$$

If the asthmatic starts in state 1 at time t = 0. Then

$$\mathbf{P}(0) = \begin{bmatrix} 0 & 1 & 0 \end{bmatrix} \text{ and}$$

$$\mathbf{P}(t) = \begin{bmatrix} 0.86 & 0.04 & 0.10 \end{bmatrix} + \begin{bmatrix} -0.25 & 0.03 & 0.22 \end{bmatrix} \exp(-0.1532t)$$

$$+ \begin{bmatrix} -0.62 & 0.93 & -0.31 \end{bmatrix} \exp(-0.7468t)$$

The asthmatic may also start in state 2 at time t = 0. Then

$$\mathbf{P}(0) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \text{ and}$$

$$\mathbf{P}(t) = \begin{bmatrix} 0.86 & 0.04 & 0.10 \end{bmatrix} + \begin{bmatrix} -0.97 & 0.12 & 0.85 \end{bmatrix} \exp(-0.16t)$$

$$+ \begin{bmatrix} 0.11 & -0.16 & 0.05 \end{bmatrix} \exp(-0.7468t)$$

The probability of being in states 1 and 2 having started in state 0, under no prevention is compared to that under prevention, for a week in tables 6.2 and 6.3 respectively.

Time (in days)	No prevention	Prevention (k = 0.99)
0	0.00000	0.00000
1	0.02365	0.01336
2	0.03772	0.02079
3	0.04681	0.02524
4	0.05318	0.02815
5	0.05792	0.03023
6	0.06164	0.03180
7	0.06319	0.03305

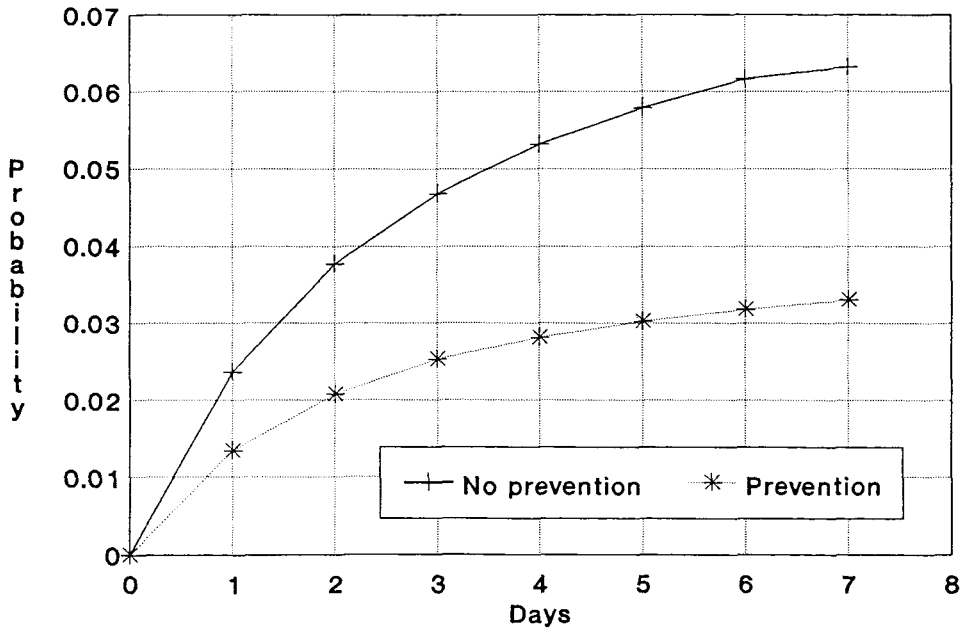
Table 6.2. A comparison of the probability of being in state 1 having started in state 0, under no preventive treatment and that under preventive treatment.

Values shown in tables 6.2 and 6.3 are displayed graphically in figures 6.8 and 6.9 respectively.

Time (in days)	No prevention	Prevention (k = 0.99)
0	0.00000	0.00000
1	0.02345	0.01420
2	0.04324	0.02639
3	0.05993	0.03685
4	0.07401	0.04582
5	0.08589	0.05351
6	0.09591	0.06012
7	0.10437	0.06578

Table 6.3. A comparison of the probability of being in state 2 having started in state 0, under no preventive treatment and that under preventive treatment.

Figure 6.8. Probability of being in state 1 having started in state 0



Now, cost may be incurred when this treatment is given. We let c_{ii} pounds be the cost incurred by the asthmatic per unit time during all the time he is in

state i, i = 0,1,2. The concern here is the expected cost the asthmatic incurs for a time t. Let $K_i(t)$ be the expected total cost that the asthmatic incurs in a time t if he starts in state i. The total expected cost in a time $t+\Delta t$ for state i may be found in the following way :

(i) In the time interval $(t,t+\Delta t)$, the asthmatic may remain in state i or move to some state j. If the asthmatic stays in state i for a time Δt, he will incur a cost $c_{ii}\Delta t$ plus the expected cost that will be incurred in the remaining t units of time, $K_i(t)$. The probability that the asthmatic remains in state i for a time Δt is $1-\sum_{j\neq i} b_{ij}\Delta t$.

(ii) The asthmatic may make a transition to some state $j\neq i$ during the time interval $(t,t+\Delta t)$ with probability $b_{ij}\Delta t$. In this case he would incur a cost $K_j\Delta t$, for the remaining t units of time.

The product of probability and cost must be summed up in order to obtain the total contribution to the expected values. We then get

$$K_i(t+\Delta t) = (1-\sum_{j\neq i} b_{ij}\Delta t)\left[c_{ii}\Delta t + K_i(t)\right] + \sum_{j\neq i} b_{ij}\Delta t K_j(t) \qquad (25)$$

Using equation (16), we have

$$K_i(t+\Delta t) = (1+ b_{ii}\Delta t)\left[c_{ii}\Delta t + K_i(t)\right] + \sum_{j\neq i} b_{ij}\Delta t K_j(t)$$

or

$$K_i(t+\Delta t) = c_{ii} + K_i(t) + b_{ii}K_i(t)\Delta t + \sum_{j\neq i} b_{ij}\Delta t K_j(t) \qquad (26)$$

Where terms of higher order than Δt have been neglected. Dividing (26) by Δt and taking limit as $\Delta t \longrightarrow 0$, we have

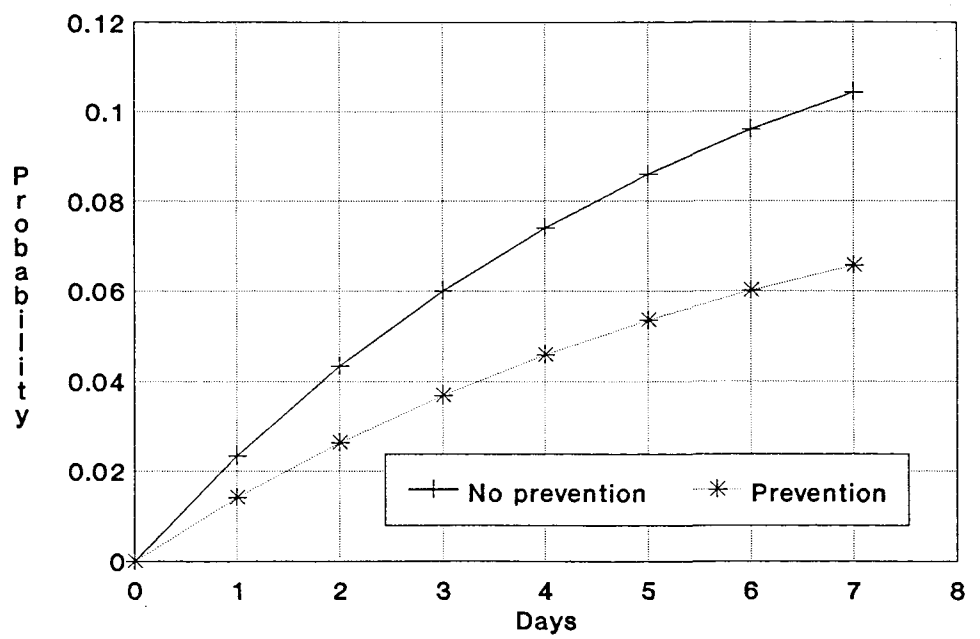
$$\frac{d}{dt} K_i(t) = c_{ii} + \sum_{j=0}^{2} b_{ij} K_j(t) \qquad (27)$$

Equation (27) is a set of three constant-coefficient differential equations that define $K_i(t)$. Since $K_i(0) = 0$, $i = 0,1,2.$, this set is completely specified.

Let $\mathbf{K}(t)$ be a column vector with elements $K_i(t)$. Then (27) can be written in matrix form as follows

$$\frac{d}{dt} \mathbf{K}(t) = \mathbf{C} + \mathbf{B}\, \mathbf{K}(t) \qquad (28)$$

Figure 6.9. Probability of being in state 2 having started in state 0



Where $\mathbf{C}$ is a column vector of transition costs. The solution of (28) is obtained by the use of Laplace transform method, see equation (14), for a more detailed analysis of how the method is applied.

Example 6.6.

Suppose all the transition probabilities are as in example 6.5. We assume that the asthmatic incurs a cost of 5 pounds per unit time during his stay in state 0, 8 pounds per unit time during his stay in state 1, and 12 pounds per unit time during his stay in state 2. Then the transition rate matrix is as given in example 6.5. That is

$$\mathbf{B} = \begin{bmatrix} -0.03 & 0.02 & 0.01 \\ 0.50 & -0.70 & 0.20 \\ 0.07 & 0.10 & -0.17 \end{bmatrix}$$

The vector of transition costs is $\mathbf{C} = \begin{bmatrix} 5 \\ 8 \\ 12 \end{bmatrix}$

Therefore

$$(\mathbf{sI-B})^{-1} = 1/s\ (s+0.1532)(s+0.7468)$$

$$\times \begin{bmatrix} s^2+0.87s+0.099 & 0.02s+0.0044 & 0.01s+0.011 \\ 0.5s+0.099 & s^2+0.2s+0.0044 & 0.2s+0.011 \\ 0.07s+0.099 & 0.1s+0.0044 & s^2+0.73s+0.011 \end{bmatrix}$$

Thus the partial fraction expansion is of the form,

$$(\mathbf{sI-B})^{-1} = \frac{1}{s}\begin{bmatrix} 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \end{bmatrix} + \frac{1}{s+0.1532}\begin{bmatrix} 0.12 & -0.02 & -0.10 \\ -0.25 & 0.03 & 0.22 \\ -0.97 & 0.12 & 0.85 \end{bmatrix}$$

$$+ \frac{1}{s+0.7468}\begin{bmatrix} 0.02 & -0.02 & 0.00 \\ -0.62 & 0.93 & -0.31 \\ 0.11 & -0.16 & 0.05 \end{bmatrix}$$

Therefore

$$1/s(sI-B)^{-1} = \frac{1}{s^2}\begin{bmatrix} 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \\ 0.86 & 0.04 & 0.10 \end{bmatrix} + \frac{1}{s}\begin{bmatrix} 0.81 & -0.16 & -0.65 \\ -2.46 & 1.45 & 1.01 \\ -6.18 & 0.57 & 5.61 \end{bmatrix}$$

$$- \frac{1}{s+0.1532}\begin{bmatrix} 0.78 & -0.13 & -0.65 \\ -1.63 & 0.20 & 1.43 \\ -6.33 & 0.78 & 5.55 \end{bmatrix} - \frac{1}{s+0.7468}\begin{bmatrix} 0.03 & -0.03 & 0.00 \\ -0.83 & 1.25 & -0.42 \\ 0.15 & -0.21 & 0.06 \end{bmatrix}$$

and

$$\mathbf{K}(t) = t\begin{bmatrix} 5.82 \\ 5.82 \\ 5.82 \end{bmatrix} + \begin{bmatrix} -5.03 \\ 11.42 \\ 40.98 \end{bmatrix} - \begin{bmatrix} -4.94 \\ 10.61 \\ 41.19 \end{bmatrix}\exp(-0.1532t)$$

$$- \begin{bmatrix} -0.09 \\ 0.81 \\ -0.21 \end{bmatrix}\exp(-0.7468t)$$

The asthmatic will incur an average cost of 5.82 pounds when the process is observed for a long time. This cost is independent of the starting state.

6.2.3. Modelling Complexities

If the model was extended to cover all the possibilities discussed in section 6.1.4, we would have had a six state model as a result. There would have been no problem with the formulation of this model. The solution would however have been a tedious task since the use of Laplace transform requires that matrices be inverted. The inverse of matrices of this nature with dimension more than 3 will need appropriate computer packages. Numerical work will be subject to round off errors.

6.3. Non-Markovian Modelling for the Asthma Process

The discussions in sections 6.1 and 6.2 have been subject to the Markov restriction that the future probability behaviour of the asthma process is uniquely determined once the state of the process at the present stage is given. This restriction makes the process mathematically tractable since with discrete states and continuous time, the "life-times" of the process have exponential frequency distributions. The life-times are the time between attacks and the durations of attacks. It may, however be that a more accurate representation of this process will make the process non-Markovian. By this we mean that the probability of making a transition from state 0 to state 1 for instance, may also depend on how long the asthmatic has been in state 0. Models of such processes are usually rather difficult to handle. In section 6.3.1 we discuss methods of converting these kind of processes to Markov processes and in section 6.3.2 we give an alternative formulation for a two state process.

6.3.1. The Conversion to a Markov Process

There are, fortunately, a number of methods by which it may be possible to restore the Markov property without abandoning the basic model, (Cox, 1955). Some of these methods are as follows :

(i) Imbedded Markov process method : Here the behaviour of the process is considered at a discrete set of time instants, chosen so that the resulting process is Markovian.

(ii) Erlang's method : Here the "life-time" is divided into stages, and the time spent in each stage is assumed to have an exponential distribution. When the specification of the state of the process includes an account of which stage of life has been reached, the process becomes Markovian.

(iii) Supplementary variable method : Here the expended "life-times" are included in the specification of the state of the process to make the whole process Markovian. Using this method we could specify the two

state process discussed in section 6.1.1 as being in state 0 or in state (1,u), where state (1,u) is occupied when the asthmatic is in state 1 and has been there a time u. For a simple illustration of this method see Cox and Miller (1987).

To give an illustration of the Erlang's method, consider as in section 6.1.1 that we have a two state process

State 0 No attack
State 1 Attack

The transitions between these states are given in figure 6.1. The probability of making a transition from state 0 to state 1 in the interval of time $(t,t+\Delta t)$ is $a_{01}\Delta t$ (say). Thus the duration in state 0 follows an exponential distribution with mean $1/a_{01}$. We suppose that the time spent in state 1 is non-exponential. Thus the process is non-Markovian. To convert the process to a Markov one using the Erlang's method, we would take attack to consist of k fictitious stages, the durations of which are independently exponentially distributed with probability density function $a_{10}\exp(-a_{10}y)$. The probability density function of the duration in state 1 is thus the sum of the durations in each stage, that is

$$\frac{a_{10}(a_{10}\, y)^{k-1}\, \exp(-a_{10}y)}{(k-1)!}$$

which is the Erlang distribution with index k. For instance, if we take an attack (state 1) to consist of 3 stages, namely

Stage 1 Attack has just started
Stage 2 Attack is at its peak
Stage 3 Attack has died down

Then k = 3. Thus the duration in each stage has the exponential distribution with mean $1/a_{10}$ and the total duration has the Erlang distribution with index

k = 3, the mean being $3/a_{10}$.

If the state of the process includes a specification of the stage of the attack reached, the possible states are 0; (1,1), (1,2), (1,3). We could then redefine our states as follows :

State 0 No attack
State 1 The asthmatic is experiencing an attack and the attack is in stage 1
State 2 The asthmatic is experiencing an attack and the attack is in stage 2
State 3 The asthmatic is experiencing an attack and the attack is in stage 3 (29)

The methods for a discrete state Markov process already discussed in section 6.2.1 can now be applied directly. The probability of being in the original state 1 will now be the sum of the probabilities of being in (1,1), (1,2), and (1,3) since these states are mutually exclusive. That is, if $P_1(t)$ is the probability of being in state 1 and $P_{1j}(t)$ is the probability of being in state 1 stage j, j = 1,2,3; then

$$P_1(t) = \sum_{j=1}^{3} P_{1j}(t) \qquad (30)$$

The probability of being in state 0 remains the same as given in section 6.1.1.

This idea could be applied to the three state model described in section 6.2.1. Here each state except state 0, could be divided into 3 stages given in (29). The states could then be redefined resulting in a seven state process, and the probabilities of being in the original states calculated with the aid of a formula analogous to equation (30). However, the probabilities of being in each stage may be difficult to obtain.

6.3.2. An Alternative Formulation

The two state process discussed in section 6.3.1 could be formulated in an alternative way. The process could be looked at as an alternating renewal process as follows : After the nth attack the asthmatic takes a period of time, length Y_n, to get treated; he subsequently takes a period of length Z_n before developing another attack. We assume that the Y's and Z's are independent of each other, the Y's having a non-exponential distribution with a common distribution function F_Y and the Z's having the exponential distribution with a common distribution function F_Z. This makes the process non-Markovian. With this process we have the opportunity of asking not only the probability of being in a state at time t, but also the number of attacks by time t. If we let N(t) represent the number of treated attacks by time t, then N(t) is a renewal process with times between treated attacks X_1, X_2, ..., given by

$$X_n = Z_{n-1} + Y_n$$

This process is illustrated in figure 6.10.

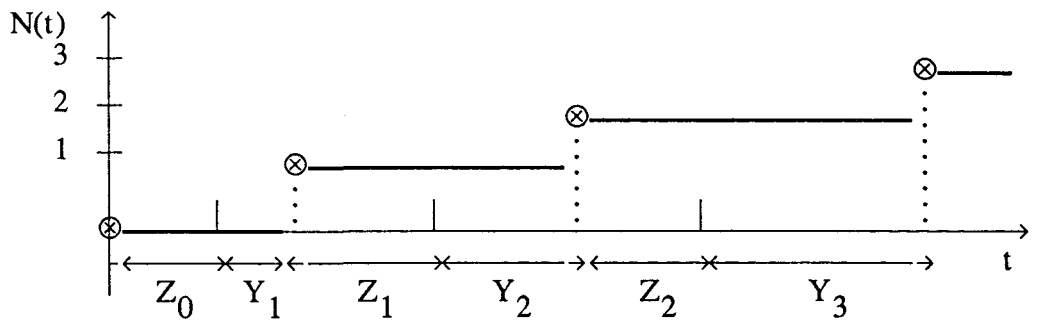


Figure 6.10. Asthma as an alternating renewal process

The distribution function being

$$F(x) = \int_0^x F_Y(x-y)\, dF_Z(y)$$

Let $P_0(t)$ and $P_1(t)$ be the probabilities of being in states 0 and 1 at time t respectively, then

$$P_0(t) = 1 - F_Z(t) + \int_0^t P(t-x)\, dF(x) \qquad (31)$$

and hence

$$P_0(t) = 1 - F_Z(t) + \int_0^t [1-F_Z(t-x)]\, dM(x) \qquad (32)$$

where M is the renewal function of N.

To obtain $P_1(t)$, we simply have $P_1(t) = 1 - P_0(t)$. Since the density function of Y and hence that of X is non exponential, the evaluation of (31) or (32) could be very difficult. It is however mentioned in Grimmett and Stirzaker (1982) that, subject to certain conditions,

$$P_0(t) \longrightarrow 1/(1+\rho) \quad \text{as } t \longrightarrow \infty$$

Where $\rho = E(Y)/E(Z)$ is the ratio of the mean duration of an attack and the mean time between attacks.

CHAPTER 7

COMPUTER SIMULATION TECHNIQUES

Simulation modelling was briefly described in chapter 2, section 2.3. In the same chapter it was argued that a realistic model for asthma would be a simulation model. Mathematical models for the disease were explored in chapters 4, 5, and 6 and we can see that many simplifying assumptions were needed. In this chapter, different methods of discrete stochastic simulation, the generation of random numbers and random variates, and verification and validation of simulation models will be discussed briefly. For more details, see (Neelamkavil, 1987; Pidd, 1992; and Davies and O'Keefe, 1989). The purpose of this chapter is to outline some of the methods used in the asthma simulation models.

7.1. Types of Simulation

A system is a set of elements or components interrelated to each other and to the whole so as to achieve a common goal (Neelamkavil, 1987). Simulation generally deals with study of systems over time. It is based on the idea of experimentation. Instead of experimenting with the real system, the trials are made on the dynamic model. This is similar to observing the real system but with the advantage that the simulation of the real system over a year, say, could be performed on a computer within minutes. The process of simulation can be thought of as three stages (Pidd, 1992) :

modelling
programming
experimentation

These stages are not entirely distinct and could be time consuming.

There are basically three types of model-building simulations :

(i) statistical
(ii) continuous
and (iii) discrete

A statistical simulation is used to estimate values that cannot be easily deduced mathematically. This type of simulation is most often called a Monte Carlo simulation. For instance, the area of an amorphous shape can be estimated using statistical simulation by drawing a rectangle on the map so as to enclose it. Suppose the area of the rectangle is 800 square units. The rectangle is then mapped on to the X and Y co-ordinates. If a pair of co-ordinates is chosen at random, it will result in a 'success' (inside the area) or 'failure' (outside the area). Thus if S is the size of the amorphous area and n is the number of successes in N generations of random pairs, then

$$n/N = S/800 \text{ as } N \longrightarrow \infty$$

A continuous simulation is used for systems which vary continuously over time. Thus the simulation model for this system can be thought of as changing values smoothly and the values taken are accessible at any time point within the simulation. In discrete simulation the system is simulated by observing various characteristic changes at discrete points of time. These points coincide with the occurrence of certain events which change the system's performance.

The type of simulation used for the disease asthma is the discrete type and will be described in the following section.

7.2. Discrete Event Simulation

As the name suggests, a discrete event simulation employs a next event technique to control the behaviour of the system. In modelling such systems, there are certain distinct elements, each of which possesses properties of interest. The elements of the system being simulated which can be individually identified and processed are known as *entities* whilst the term *attribute* denotes a property of an entity. Thus each entity may possess one or more attributes which convey extra information about the entity. As time progresses, the entities co-operate and thence change state. The instant of time at which a significant state change occurs in the system is called an *event*. Thus the operations and procedures which are initiated at each event are known as *activities*. The *state of the system* refers to a description of all the entities, attributes, and activities at any one point in time. Table 7.1 gives some examples of systems.

Table 7.1. Examples of entities, attributes, and activities for a number of systems.

SYSTEM	ENTITIES	ATTRIBUTES	ACTIVITIES
bank	customers	balance credit status	depositing withdrawing
hospital	patients	emergency cases	waiting for admission hospital stay
machine repair shop	machines	type of job processed on the machine	waiting for repair
traffic	cars	speed distance	driving
University	students staff	department	reading in the library

If a hospital is considered as a system, then individual patients can be

regarded as entities, with emergency or non-emergency case as an attribute. Typical activities would be the action of waiting for admission or in hospital stay. Similarly, in the case of a University system, the students and staff in the University are entities with department as an attribute. Among the activities is the action of reading in the library.

The main interest in system simulation is to study the dynamic behaviour of the sytem. It is therefore necessary to construct an appropriate model for the system and the interrelationships of its distinct elements. This model could be

(i) numerical or analytical
(ii) static or dynamic
(iii) stochastic or deterministic

A dynamic model is one in which the relationships between the attributes or entities of the system, and the model's behaviour vary with time whereas one that does not incorporate this variation is said to be static. A model which does not take into account the random processes of the system is deterministic whereas one that allows entities to have random attributes is stochastic. In a deterministic model all relationships between attributes or entities of the system are described by fixed mathematical functions.

In a discrete event simulation, changes in the state of an entity only occur at specific instants of time. There are two ways of controlling the speed at which a simulation experiment proceeds. These are as follows :

(a) The uniform time increment method, where the simulation clock is advanced from time t to $t+\Delta t$, where Δt is a uniform fixed time increment. The operations that occurred from time t to $t+\Delta t$ are performed and then the clock is incremented again. This method is referred to as *time slicing*.

(b) The next-event time increment method, where the simulation clock is incremented from time t to the next event time t_1, whatever may be the value of t_1. The state changes are at the next event time t_1, and this process is continuously repeated.

The first method detects the events that occur during the interval $(t,t+\Delta t)$ only at time $t+\Delta t$, thereby introducing errors in the simulation. Another problem of this method is that if the interval between two events is very large compared to Δt, then the simulator goes through several unproductive clock increments (during periods of inactivity) and the associated computing effort which will not bring any change in system states. The second method involves sorting of event activation times and maintaining the current and future event lists. Most simulations and simulation packages are developed with this type of clock (Bratley et al., 1987). The simulation shell, TOCHSIM, used in the asthma modelling also incorporates this more flexible method of time update.

7.3. Modelling Approaches

We have already mentioned in section 7.2 that the next event time increment method is generally used in most of the discrete event simulation and simulation packages for advancing the time. The scheduling of the next event and updating the system state by this method can be implemented in several ways (Fishman, 1978; Zeigler, 1979). The major approaches are :

(i) event approach;
(ii) activity approach;
(iii) process interaction approach;
and (iv) three phase approach;

The three phase approach succeeds in combining the simplicity of the activity approach with the efficient execution of the event approach. This approach is used for the development of TOCHSIM and is described in section 7.3.4.

7.3.1. Event Approach

In this approach the time is advanced to the time of occurrence of the next event and the simulation is completed by the execution of ordered (by time) event sequences. A list of events numbered 1, 2, ..., k in ordered form and the time in which they will occur t_1, t_2, ..., t_k is maintained and the

appropriate list of event routine is executed at time $t_i = \min(t_1, t_2, \ldots t_k)$. This approach is embodied in the simulation languages SIMSCRIPT (Markowitz, et al., 1963) and GASP (Pristsker, 1975). To make this concept clearer, consider an asthma clinic with one doctor where the arrival of asthmatics to the clinic is a Poisson process and the doctor treats the asthmatics on a first come first served basis. Here we have two state changes :

(1) arrival of an asthmatic;
(2) departure of the asthmatic (when treatment is completed).

With the event scheduling approach, each of these events will need an event routine in the simulation. The arrival event routine is shown in figure 7.1 and the departure (end of treatment) routine in figure 7.2. The inter-arrival and treatment times are generated from sampling routines and the events themselves are scheduled by interfacing with the executive.

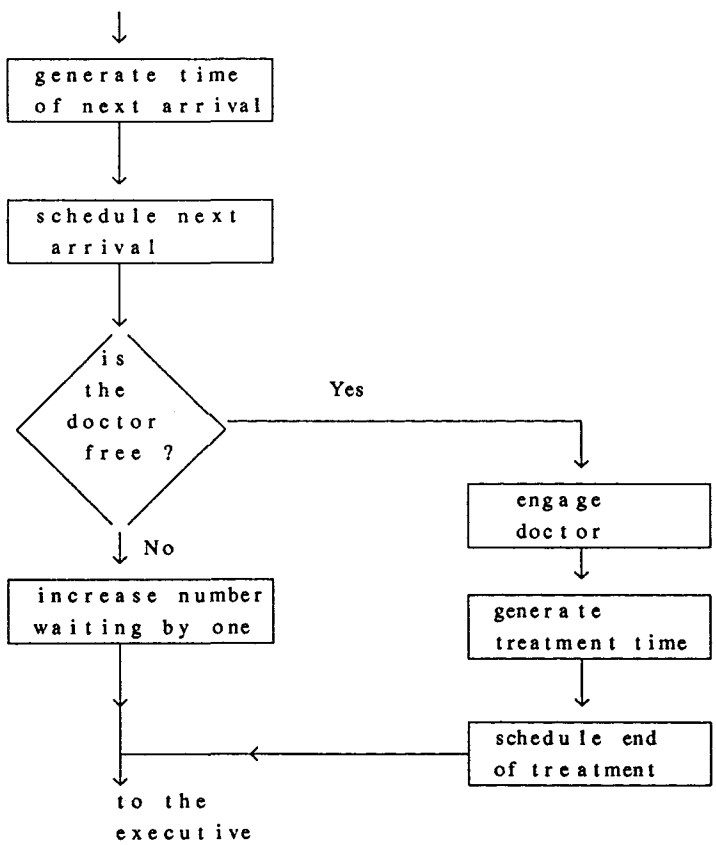


Figure 7.1. Arrival event routine for the asthma clinic.

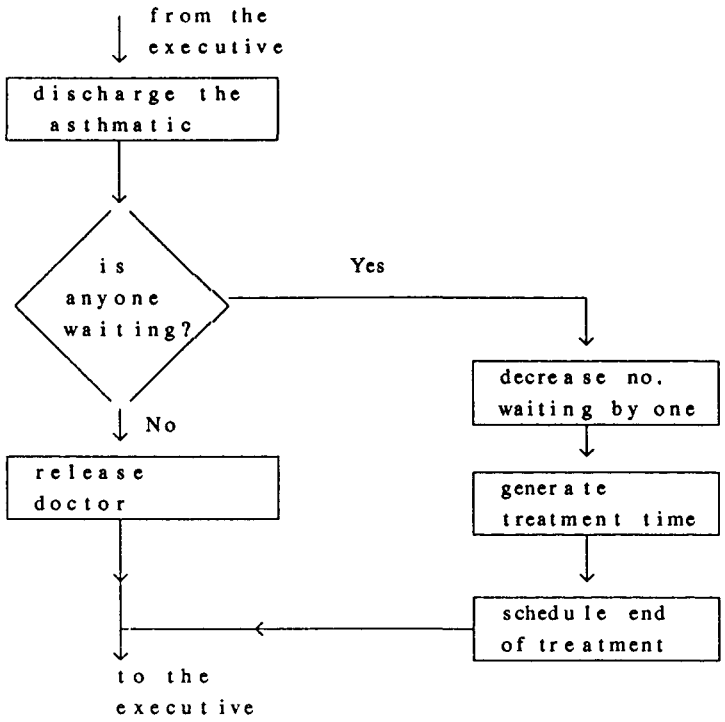


Figure 7.2. End of treatment routine for the asthma clinic.

The event based executive performs the following tasks :

(1) time scan;
(2) event identification;
(3) event execution.

These tasks are being managed by the use of an *event list,* which can be thought of as a diary into which future event notices are written. Event notices are added to and removed from this list as the simulation progresses. For instance, an arrival might cause an event notice for the end of treatment to be added to the event list in our asthma clinic system. Each event notice on the list contain two pieces of information : the time at which the event is due to occur and something to identify the event. The executive performs a two phase cycle as follows :

(1) Time scan, which involves

(i) scanning the event list to determine the time of the next event;

(ii) moving the simulation clock to that time;

(iii) producing a *current event list* of all events identified as due now;

(2) Event execution, which ensures that each event on the current event list is executed.

The cycle is repeated until the simulation is over. The event based executive is given in figure 7.3.

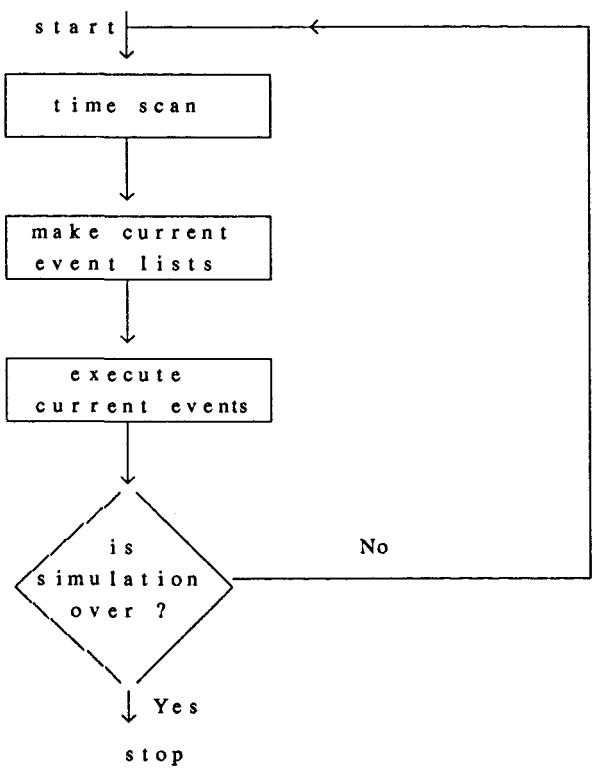


Figure 7.3. Executive for the event approach.

7.3.2. Activity Approach

Here the simulation proceeds from event to event by scanning activities. No event list is maintained. This approach is used in the design of the simulation language CSL (Buxton 1966). It has however being superseded by the three phase approach. An activity is bound by any two successive events. Each activity is associated with a condition which may be true or false depending on the simulation time and the system state. In our clinic system for instance, there are two event routines, these are represented by three activities :

(1) arrival of an asthmatic
(2) begin treatment
(3) end treatment

The beginning of treatment is a condition that occur either at (a) an arrival event (given that the doctor is idle and no one is waiting for treatment) or (b) a departure event (given that someone is waiting for treatment). The status of all the activities in the model is scanned at every time step and the activities that satisfy the necessary boolean conditions are scheduled immediately and the appropriate action segments executed . This means that the events are implicitly scheduled. Flow diagrams of these activities are shown in figures 7.4-7.6.

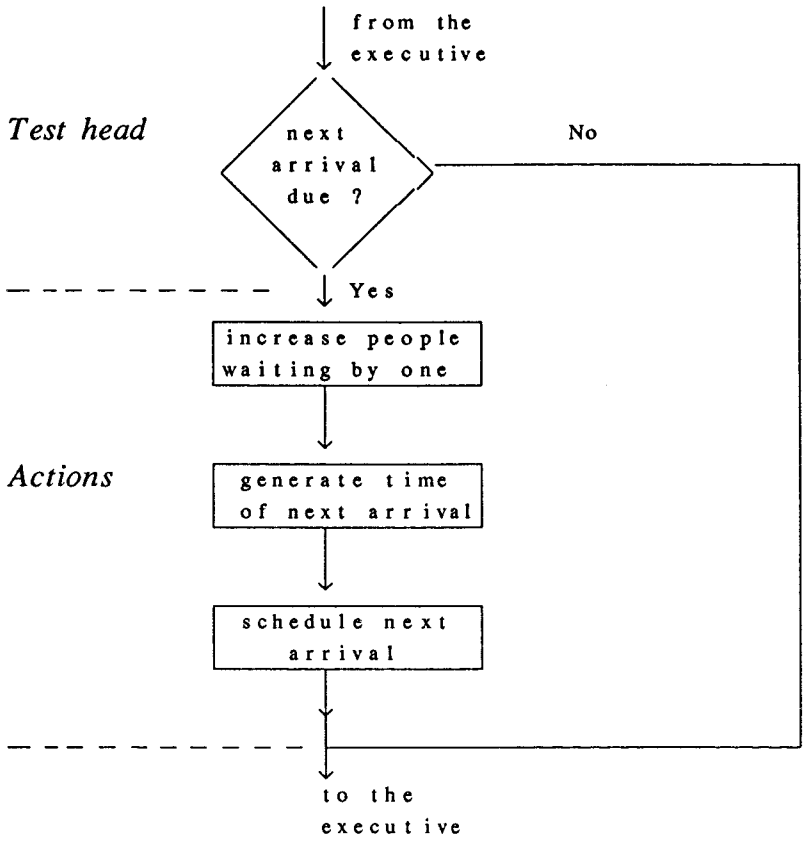


Figure 7.4. Arrival activity for the asthma clinic.

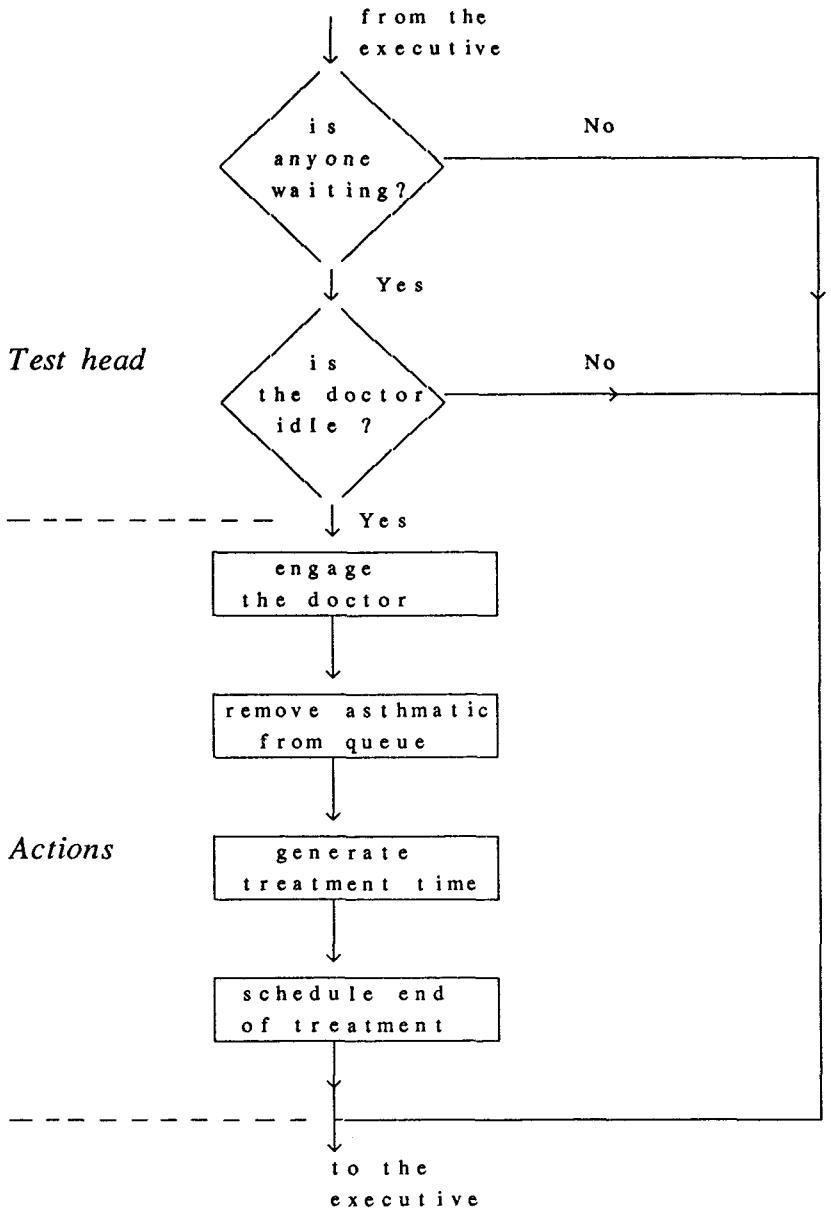


Figure 7.5. Begin treatment activity for the asthma clinic.

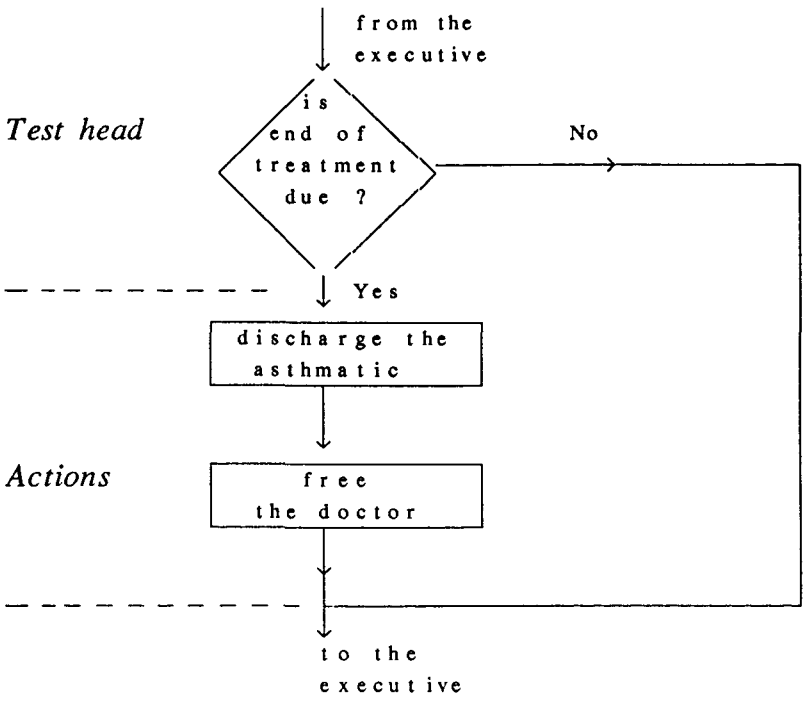


Figure 7.6. End of treatment activity for the asthma clinic.

The executive then has only one major task to perform, the *time scan*. This involves the identification of when the next event is due. In the event approach this was achieved by a dynamic event list, time cells are used in the activity approach. Time cells indicate when each entity is due to change state and is set to the time at which the entity is due to make this state change. For example, DOCTOR(TIME) = 55 indicates that a state change is due at time 55. If the current simulation time is greater than the value of the time cell, then it means that the entity is in an idle state waiting for something to happen e.g. the doctor is waiting because there are no asthmatics for treatment. After the time scan the clock is moved to the next event time and the executive makes repeated activity scans.

Thus the activity based executive has two phase structure as follows :

(1) time scan;
(2) repeat activity scan.

When phase (2) is accomplished, the executive returns to phase (1), etc., until the simulation is over (see figure 7.7).

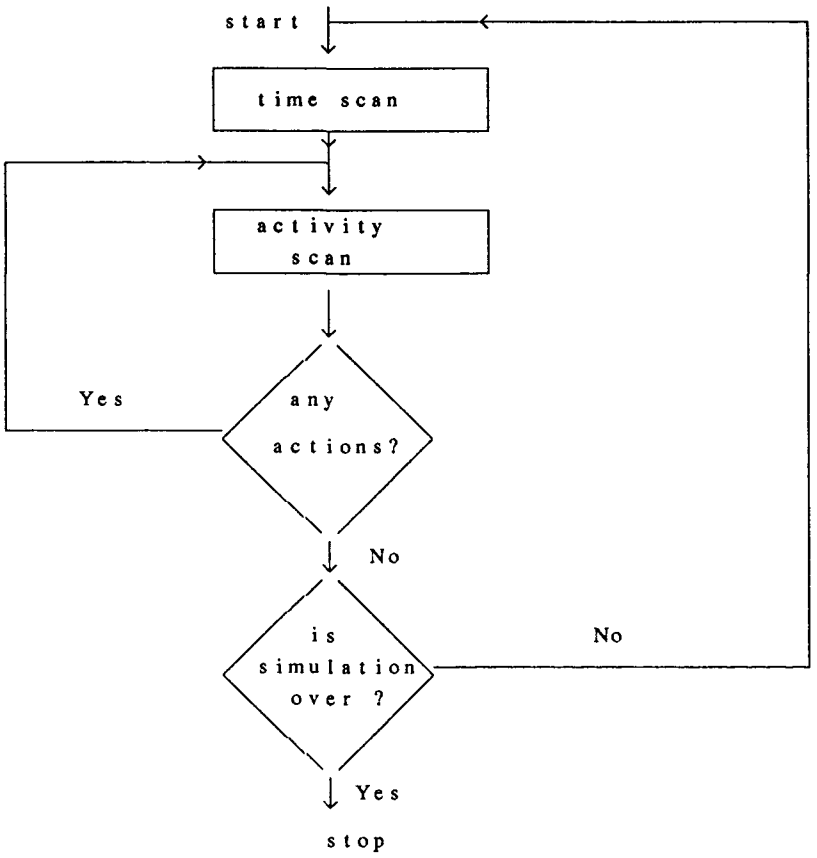


Figure 7.7. Executive for the activity approach.

7.3.3. Process Interaction Approach

This approach attempts to combine the features of both event and activity based approaches. A process is a sequence of actions experienced by an entity during its life in the model. Each separate entity (e.g. each asthmatic) has its own process which stops and starts as the simulation progresses. This approach is embodied in the two well known simulation languages, GPSS (Greenberg, 1972) and SIMULA (Hills, 1973). In the asthma clinic example, the asthmatic's process is as follows :

arrive;
wait until head of the queue;
move into the treatment room;
remain in the treatment room until treatment is complete and finally leave the clinic.

A flow diagram for this process is shown in figure 7.8.

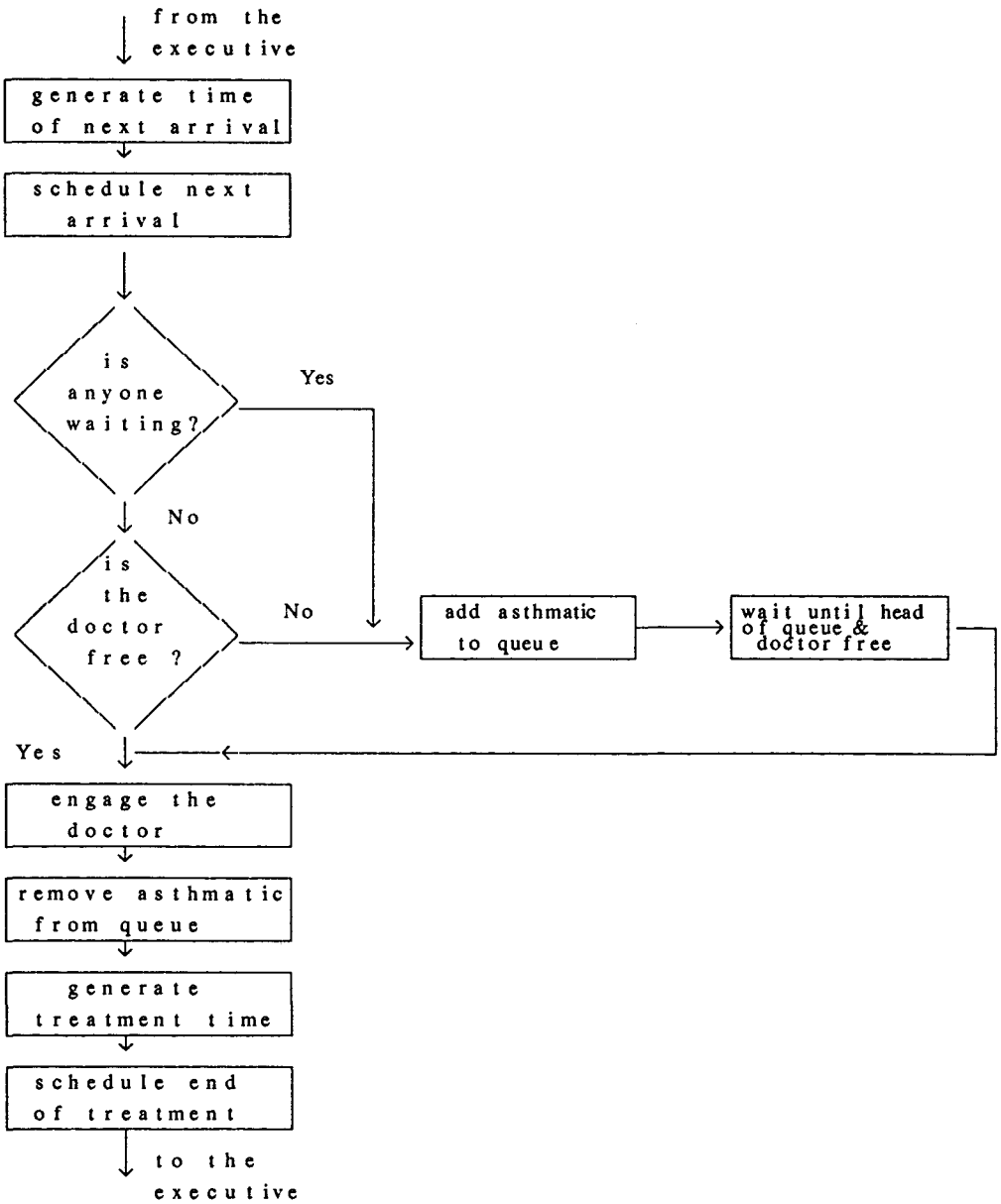


Figure 7.8. Asthmatic's process for the process approach.

The simplest way to implement a process interaction executive is to create two lists of records each identifying the entity concerned and its next re-activation point. In GPSS these two lists are called *future events list* and *current events list.* The Future Events list contains the records for those entities whose movement is delayed and those re-activation time is known. In the asthma clinic, for example, an arrival due sometime in the future or a scheduled end of treatment would be entered on this list. The Current Events list includes the records of two types of entity

(1) Those whose movement is delayed and whose re-activation is scheduled for the current clock time in the simulation;

(2) Those whose movement is delayed by conditions within the simulation.

The executive repeats the following cycle as the simulation progresses :

(a) Future Events scan. From the records on this list, pick out those entities with the earliest re-activation time and the simulation clock moved forward to that time;

(b) Move records of current entities from the Future Events list to the Current Events list;

(c) Current Events scan. Attempt to move each entity on the Current Events list through its process from its re-activation point.

This is shown in figure 7.9.

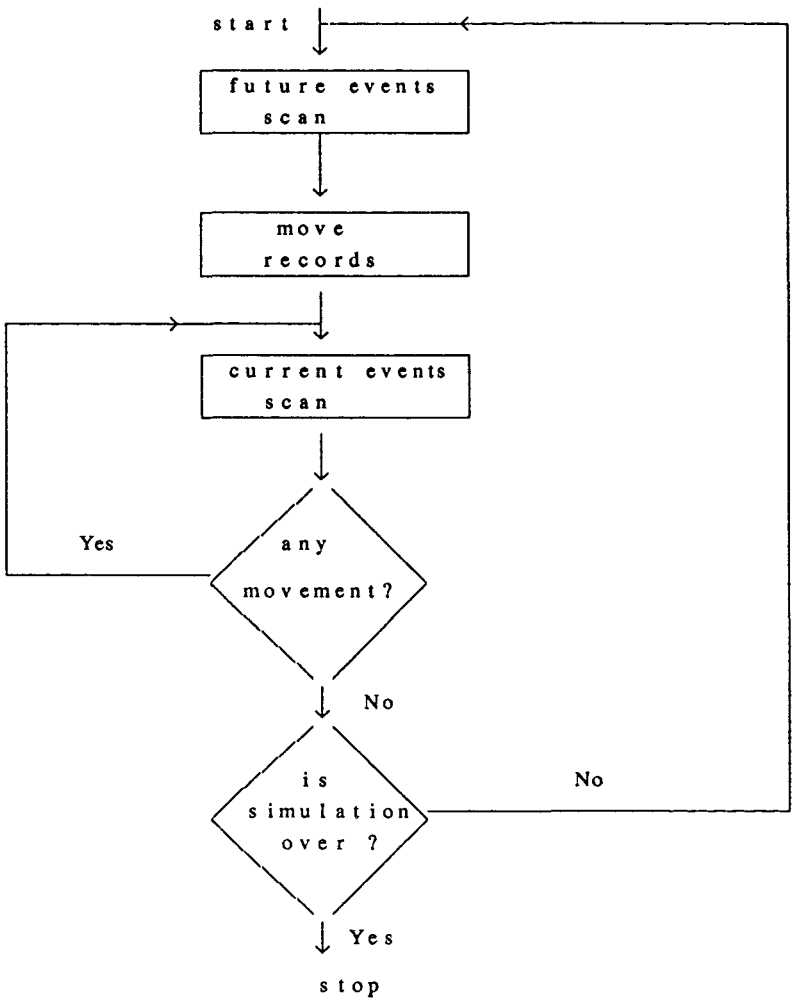


Figure 7.9. Executive for the process interaction approach.

7.3.4. The Three Phase Approach

This approach originally devised by Tocher (1963) succeeds in combining the simplicity of the activity approach with the efficient execution of the event approach. It achieves this by recognizing that there are two quite different kinds of activity in most systems, activities which can be directly scheduled, and others which cannot. The two different activity types are defined as follows, (Pidd 1992) :

"B" ACTIVITIES: (Bound or Book-keeping activities) which are executed whenever their scheduled time is reached.

"C" ACTIVITIES: (Conditional or Co-operative activities) whose execution depends on either the co-operation of different classes of entity or the satisfaction of specific conditions within the simulation.

The executive directly controls the execution of the Bs but the conditions within the simulation determine whether any Cs will follow. For example, a person who has asthma but has no attack at a given time, a state called "No attack" in the simulation models described in chapter 8, would be moved to the state called "Mild attack" by a B activity. If it was decided that an asthmatic who is upset enough would have an attack, then this test would be processed by a C activity. This activity then cause the relevant B activity to occur. The C activity makes structural changes and does not have any physical effect on the model.

The Three-phase approach takes its name from the three phases A, B, C (Tocher, 1963; Crookes et al., 1986; Pidd, 1992) which are processed as follows :-

A Phase (Time scan): Determines when the next event is due, moves the simulation clock to the time of this event, and decides which of the B activities are then due to occur.

B Phase (B calls): Executes only those B activities identified in the A phase as being due now.

C Phase (C scan): Attempts each of the C activities in turn and process those whose conditions are satisfied. Repeats the C scan until no more activity is possible.

The above process is repeated until :

1. there are no more activities to perform;
2. the time of the next activity to be performed exceeds the maximum time set for the duration of the simulation;
3. some terminating event is encountered.

Bound activities and conditional activities are thus written as separate independent modules. See figure 7.10 for the executive of the three phase approach.

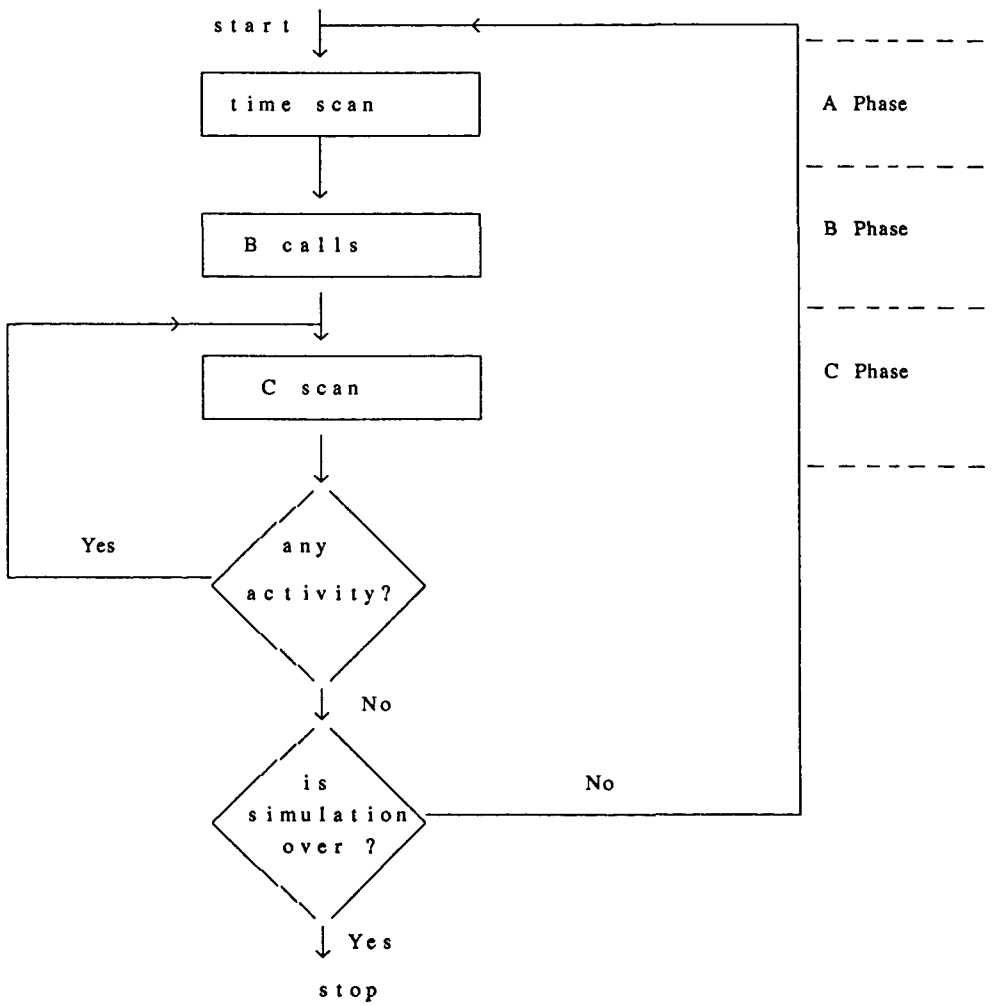


Figure 7.10. Executive for the three phase approach.

7.3.5. Comparison of the Modelling Approaches

The activity approach treats each activity independently, this obviously can lead to run-time inefficiency. This is because, at each event, the activity scan attempts each activity in turn, even if one activity is possible. The event based approach involves the execution of only those events known to be possible. An event based simulation thus runs faster than one which is activity based . It is however easier to write activity based programs. The process interaction approach requires a complex executive and more importantly the processes are more complex to program than are the comparable activities. The approach, however, has the advantage that its building block, the process, is similar to the intuitive notions of the naive analyst trying to map out the life history of each class of entity. The three phase approach uses some features of the event and activity approaches. Since the event based simulation runs faster and it is easier to write activity based programs, the three phase approach is preferable to the other approaches. This approach is embodied in the simulation shell, TOCHSIM, used in the asthma simulation discussed in chapter 8.

7.4 Sampling Methods.

In the study of systems, the underlying processes will usually be stochastic in nature. For example, in the asthma clinic system, the average arrival and treatment times can be measured but it is impossible to predict when people will arrive and how long it will take for them to be treated. Thus for a simulation to demonstrate the stochastic nature of the system, it must sample different interarrival and treatment times and the frequency distribution of the samples should look like those measured in the real system. Distribution sampling is therefore needed. These are sequences of random numbers. The generation of random numbers and random variates for use in simulations is discussed in the following sections.

7.4.1. Random Number Generation

The generation of Uniform [0,1] form the basis for the generation of random variates, as it will be shown in section 7.4.2.

Tocher (1963), discussed various methods of generating random digits. A common method of generating random numbers is by the use of the mixed congruential generator, developed by Lehmer (1951). It is of the form

$$X_n = (a\ X_{n-1} + c) \bmod m \qquad \text{for } n = 1, 2, \ldots, m.$$

where a, c, and m are integer constants. The desired sequence is $\{ X_n \}$, X_0 being the starting value called the *seed*. The above expression generates m distinct numbers. These generators repeat indefinitely, the length of the *cycle* being m. To obtain U_n, a Uniform [0,1], we have

$$U_n = X_n / m.$$

Thus certain criteria must be met in designing a congruential random number generator :-

(1) The cycle length should be very long. m is chosen to be the maximum interger available for the computer at use.

(2) The sequence of values $\{ X_n \}$ should appear random (pseudo-randomness) and independent.

(3) the sequence should be generated with efficiency and speed.

Neelamkavil (1987) discusses in detail, the methods of testing random number generators.

The random number generator used in the asthma simulation has the following form :

$$X_n = (31421\ X_{n-1} + 27181) \bmod 100000\ ,\ X_0 = 57722.$$

For more details on this subject, see the work by Knuth (1969) or Fishman (1978) or Law and Kelton (1982) or Bratley et al.(1987) or Ripley (1987) or Morgan (1984).

Once the pseudo-random numbers are generated, they are used in taking samples from distributions. This is discussed in the following.

7.4.2. Generation of Random Variates

The inverse transformation method is most commonly used in generating random variates. It is easy to use this method to generate variates from the exponential, geometric, Poisson and Bernoulli distributions. It is however not always possible to compute the inverse of a given distribution function. Other methods have been developed for use in these cases and can be classified as follows :

(i) rejection - acceptance methods
(ii) composition methods
(iii) comparison methods
(iv) special methods
(v) decomposition methods

The book by Knuth, (1973) is a comprehensive work available on the methods of generating random variates. Others include that by Brately et al., (1987), and Fishman (1978). Since the inverse tranformation method is the most popular method, it is discussed in more detail in the next section.

7.4.2.1. The Inverse Transformation Method

Let f(x) be any density function defined on the interval [a,b] and let F(x) be its distribution function. The inverse transformation method exploits the fact that F(x) ranges between 0 and 1 as x goes from a to b. Consider figure 7.11.

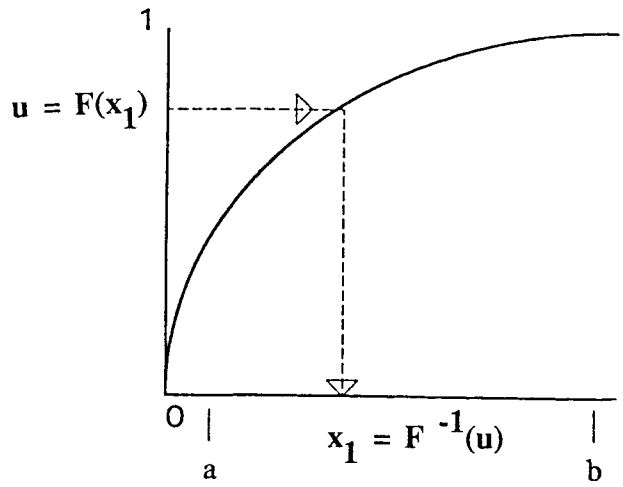


Figure 7.11. Distribution function showing the use of inverse transformation method

In the above figure we see that if we sample a random number, u, between 0 and 1, for any value of u, there is a corresponding value of F(x). Therefore if

$u = F(x)$, and the inverse exists, then

$$x = F^{-1}(u).$$

In the following sections we shall only describe the generation of random variates from distributions used in the asthma simulation.

7.4.2.2. Generating Uniform Variate

The Uniform distribution is given by the formula :

$$f(x) = \frac{1}{b - a}, \quad a \leq x \leq = b, \ a, \ b \text{ real.}$$

Since each u is generated from Uniform [0,1] (a = 0, b = 1), a sample from a general Uniform distribution can be derived from the linear transformation :

$$x = a + (b - a)\, u.$$

Algorithm

(1) Generate u from Uniform [0,1],

(2) Set $x = a + (b - a) * u$

Then x is a Uniform [a,b] variate.

7.4.2.3. Generating Negative Exponential Variate

The probability density function of the negative exponential distribution is of the form

$$f(t) = \begin{cases} \lambda \exp(-\lambda t), & t > 0, \lambda > 0 \\ 0 & \text{otherwise} \end{cases}$$

Then $F(x) = \int_0^x \lambda \exp(-\lambda t)\, dt = 1 - \exp(-\lambda x)$

mean = $E(X) = 1/\lambda$; variance = $1/\lambda^2$.

Since F(x) is continuous and strictly increasing, we have that for each value of x there is a unique value of F(x) between 0 and 1. Thus if $F(x) = u$, u is Uniform [0,1], then $x = F^{-1}(u)$.

Therefore

$$u = 1 - \exp(-\lambda x)$$

or

$$x = -1/\lambda \ln(1-u).$$

Now put $r = 1-u$, then r is also Uniform [0,1] and

$$x = -1/\lambda \ln r.$$

Algorithm

(1) Generate r from Uniform [0,1],

(2) Set $x = -\ln r * m$, where $m = E(X) = 1/\lambda$

Then x is a negative exponential variate.

7.4.2.4. Generating Normal Variate

The polar method is a fast and simple method of generating Normal variates. Developed by Box and Muller (1958), it generates two independent Normal variates x and y from Normal distribution with mean 0.0 and variance 1.0.

Algorithm

(1) Generate u_1, u_2 independent Uniform [0,1],

(2) Set $v_1 = 2 * u_1 - 1$ and $v_2 = 2 * u_2 - 1$,

(3) Set $w = v_1^2 + v_2^2$,

If w >= 1, reject u_1, u_2 and go to step 1, otherwise

return

$$z_1 = v_1 * \{ - 2 \ln(w)/w \}^{1/2}$$
$$z_2 = v_2 * \{ - 2 \ln(w)/w \}^{1/2}$$

(4) Set $x = \mu + \sigma z_1$ and $y = \mu + \sigma z_2$

Then x and y are $N(\mu,\sigma^2)$ variates and one of these values may be selected for use in simulation.

7.4.2.5. Generating LogNormal Variate

If X has a Normal distribution with mean μ and variance σ^2, then Y = exp(X) has a LogNormal distribution with probability density function

$$f(y) = \frac{1}{(2\pi)^{1/2} \sigma y} \exp\left\{ - \frac{[\ln(y) - \mu]^2}{2\sigma^2} \right\} \quad 0 < y < \infty.$$

Algorithm

(1) Generate z, a N[0,1] using the previous method,

(2) Set $x = \mu + \sigma z$,

(3) Set y = exp(x),

Then y is a LogNormal variate.

7.4.2.6. Generating Weibull Variate

The probability density function of the two parameter Weibull distribution is of the form

$$f(t) = \begin{cases} \beta/\alpha \ (t/\alpha)^{\beta-1} \exp\left\{-(t/\alpha)^{\beta}\right\}, & t \geq 0 \\ 0, & t < 0 \end{cases}$$

where α, $\beta > 0$ are referred to as the scale and shape parameters respectively.

Here $F(x) = 1 - \exp\left\{ - (t/\alpha)^{\beta} \right\}$

mean = $\alpha \ \Gamma(1 + 1/\beta)$

and variance = $\alpha^2 \left[\Gamma(1 + 2/\beta) - \Gamma(1 + 1/\beta)^2 \right]$

where Γ represents the gamma function.

Therefore

$$u = 1 - \exp\left\{ - (t/\alpha)^{\beta} \right\}$$

$$\text{or} \quad t = \alpha * \exp\left\{ \frac{\ln(-\ln(r))}{\beta} \right\}, \text{ where } r = 1 - u.$$

Algorithm

(1) Generate u from Uniform [0,1],

(2) Set $x = = \alpha * \exp\left\{ \frac{\ln(-\ln(u))}{\beta} \right\}$

Then x is a Weibull variate.

In asthma simulation model V we ask the user to give the mean, μ and one percentile value, p for transition durations. These values are then used to calculate the parameters α and β using the following :

$$\mu = \alpha\, \Gamma(1 + 1/\beta) \qquad (1)$$

and

$$p = F(t_1) = 1 - \exp\left\{ - (t_1/\alpha)^{\beta} \right\} \qquad (2)$$

where t_1 is the p percentile value.

Making α the subject in (1) and substituting this value in (2) yields

$$p = 1 - \exp\left\{ - \left[\frac{t_1 \Gamma(1+1/\beta)}{\mu} \right]^{\beta} \right\}$$

and thus

$$\left\{ \frac{t_1 \Gamma(1+1/\beta)}{\mu} \right\}^{\beta} + \log (1-p) = 0 \qquad (3)$$

A numerical algorithm is applied to expression (3) to estimate the value of β which is then substituted in (1) to yield the estimate of α. The Weibull algorithm is then used for sampling with these values of α and β.

7.5. Simulation Verification and Validation

With the advent of visual interactive simulation, the problem of constructing simulation models has become relatively easy and common place in the management setting. Checking that these models have been correctly coded (verification) and that they model reality (validation) is not straightforward (Tobias, 1991). In constructing simulation models, the modeller may make errors in syntax or consistency in the coding or even if the model is syntactically correct and consistent, it may bear little relation to the system being modelled simply because of, say, an unintended minus sign. Thus further checks are needed at this stage to establish that the model performs as would be expected theoretically.

One way of doing this is to ignore temporarily the stochastic elements altogether from the model to yield its deterministic version. No repetitions are then necessary, and the results from the computer run should not just be close but identical. Several key outputs or parameters can be checked in this fashion. Verification in this way does not prove the correctness of the model but at least demonstrates that the model is probably not wrong and the modeller builds up enough confidence in his model.

Validation is where the model builder is concerned with whether the model mirrors reality or not. This is one of the most difficult tasks of simulation. Since one of the problems of simulation is that it does not give optimal solutions, validation is very difficult in the absence of sufficient and reliable data. The philosophy of the process is discussed by, amongst others, Pidd (1992). In practice, it involves returning to the full version of the model including its stochastic features. Checking the validity of any distribution chosen to represent the stochastic input variables, usually using a goodness of fit (χ^2) test is very important at this stage. The main aim is however to compare the performance of the model against observations of the actual system.

7.6. Conclusion

The simulation shell, TOCHSIM, employed in this work uses the three phase approach. The random number generator given in section 7.4.1 and the generation of all the variates discussed are incorporated in the shell and are used in the asthma simulation. The simulation programs have been verified using the approach discussed in section 7.5 and validation of the simulation models is discussed in chapter 10.

CHAPTER 8

ASTHMA SIMULATION

The advantages of the simulation approach over mathematical modelling were discussed in chapter 2. In this chapter we construct simulation models of increasing complexity and realism for the disease asthma. The models employ the three phase approach described in chapter 7 and were greatly eased, in terms of development, by the use of the simulation shell, TOCHSIM, described in chapter 9.

8.1. Development of the Models

In the simulation models described in this chapter, we consider people who are at least 3 years old. This is because below this age the diagnosis of asthma is not very easy since wheezing may not imply asthma. Even when a diagnosis is made the response to treatment is often not satisfactory (Warner et al.,1989).

The simulation models use a day as the basic time period. A short time interval has the disadvantage that the computation time for the simulation would be very large. A long time interval will not capture the necessary disease dynamics sufficiently well. Thus, what is needed is a suitable short time period that can allow the flexibility of changing state as and when the simulated population require but to also maintain a reasonable time interval so that the computation time does not become excessive. Medical advice and the literature on asthma resulted in the choice of a day as the appropriate time unit.

8.1.1. Elements of the Models

Asthma is regarded as a process in time. A natural history model, which is a description of this process, needs a suitable set of states of the disease and

descriptions of the manner in which people move from one state to another. Treatments or some course of action are used at various states of the disease. These actions require resources, and costs are involved.

In the development of these models, the following four linked elements are considered.

Natural history of disease
Possible, or selected treatments
Resources
Costs

It will be readily appreciated that there is no unique set of states and that the progress of people through the states can be described in a variety of ways. The choice of a set of states should be governed mainly by the intended use of the model; another important consideration is the availability of data and expert opinion.

8.1.2. The Power of the Microcomputer

The development of the asthma simulation models has been on a PS/2 model 70 386, using Dos 4.0 and Turbo Pascal 5.5, which has a significant speed and storage capacity, together with a high resolution graphics screen (VGA).

A microcomputer was preferable to the mainframe for the development of the simulation model for the following reasons: firstly, microcomputer software is more user friendly than the mainframe software, because it produces more descriptive error messages and provides facilities other than just the standard ones. Turbo Pascal has powerful screen editors which are superior to the editors on the mainframes, including the IBM 3090 editor XEDIT. Furthermore, when a Turbo Pascal program breaks down, the editor is automatically loaded and the cursor is set to the location of the error in the programming code along with a meaningful error message. Secondly, a microcomputer works at the same constant speed and will perform the same operation at exactly the same rate, unlike the mainframes which can almost stop during periods of very high computer demand from other users on the

system. Thirdly, microcomputers offer colour graphics which are useful for visual output. The PS/2 is equiped with VGA high resolution colour graphics. Finally, a model on a microcomputer has a greater appeal to medical people.

8.1.3. The Choice of the Simulation Language

Writing simulations in a general purpose language could be a time consuming task because of the large amounts of code for each new application, (Shearn, 1990). The usual way of overcoming this is to use a program generator. A number of these have been reported, covering not only Pascal (Paul and Chew, 1987), but simulation languages and systems involving ECSL (Clementson, 1987), Fortran (Mathewson, 1983), GASP (Mathewson and Allen, 1977), SIMULA (Mathewson, 1976), SIMSCRIPT (Subrahmaniam and Cannon, 1981), and GPSS (Gordon, 1981). These generators all work from a model description, i.e. a specification of the model in some formal description language, invariably based on the activity cycle diagram. The model is entered into the program generator either interactively or through an editor, and a program is produced that can then be compiled and run.

The design of GPSS was influenced by block diagram and flowchart concepts which is less flexible and therefore unsuitable for certain types of applications, (Neelamkavil, 1987). The process concept plays the central role in defining a model in the SIMSCRIPT language. Compared to GPSS it is more difficult to learn, and programs tend to be larger in size.

The language choice depends on the type of application and the intended use of the simulation. The cost of acquiring the software or writing it must also be considered. If the software is acquired from elsewhere, the training costs are also important and cannot be ignored.

With the above factors in mind, we decided to write the asthma simulation programs in Pascal embodied in the simulation shell, TOCHSIM. See chapter 9 for the description of this shell.

8.2. Asthma Model I

This section reports on the first asthma model developed. The model is concerned with asthma in childhood.

8.2.1. Objectives of the Model

Good management of asthma would mean the prevention or the control of the degree of severity of the attack. When preventive treatment is given, it is expected that the time between asthma attacks would be extended by some positive factor.

The care options available in this model are:-

1. Bronchodilators and Mast-cell stabilizers for prevention of an attack
2. Corticosteroids for treatment of an attack
3. (1) and (2) combined

Each of these care options has its own effectiveness. The aim of this simulation study is to investigate the effect of these care options (taking into account their effectiveness) on the number of asthma attacks generated per person, for a given number of asthmatics. These predictions can be used to select the best possible combination of these care options.

8.2.2 Assumptions and Simplifications of the Model

The cost of an asthma attack can be defined as a combination of the cost of drugs and drug administration apparatus prescribed, the cost to individuals of any side effects suffered, the cost of hospital admissions etc. The list of costs associated with an asthma attack is endless. However, a boundary has to be drawn somewhere and so in this model, the cost of an attack has been restricted to the costs of drugs administered either as preventive treatment and/or the control of an attack. It is assumed that the cost of a unit of a particular drug includes the cost of the drug itself and the cost of the drug inhalation device.

The model assumes that there are only three prescription policies: Ventolin for the prevention of an attack; Inhaled and Oral steroids for use during an attack; and Ventolin for prevention of an attack with both Inhaled and Oral steroids for use during an attack.

In this preliminary model , death from asthma could occur only when the attack is severe. The possibility of death from other causes is not considered.

8.2.3. The Model

The model, shown in Figure 8.1 consists of 6 different states and 14 different inter-state transition routes. A computer simulation program has been constructed for this model.

The natural history of asthma can be summarised as follows :-

(i) An individual develops asthma which can be categorized as extrinsic, intrinsic, secondary or occupational. In this model these distinctions are not made.

(ii) The asthmatic stays without an attack for a period of time.

(iii) After the attack-free period, an attack is experienced for a period of time.

(iv) The attack could be classified as mild, moderate or severe depending on (among other things) the peak flow reading.

(v) Death could occur when the attack becomes very severe - the state called "status asthmaticus". The occurrence of death only when the attack is very severe is a subject of debate.

(vi) The asthmatic could grow out of asthma. About one-third of cases in early childhood grow out by adult age.

The set of states that we use are :

State I No Attack
State II Mild Attack
State III Moderate Attack
State IV Severe Attack
State V Grow out
State VI Death

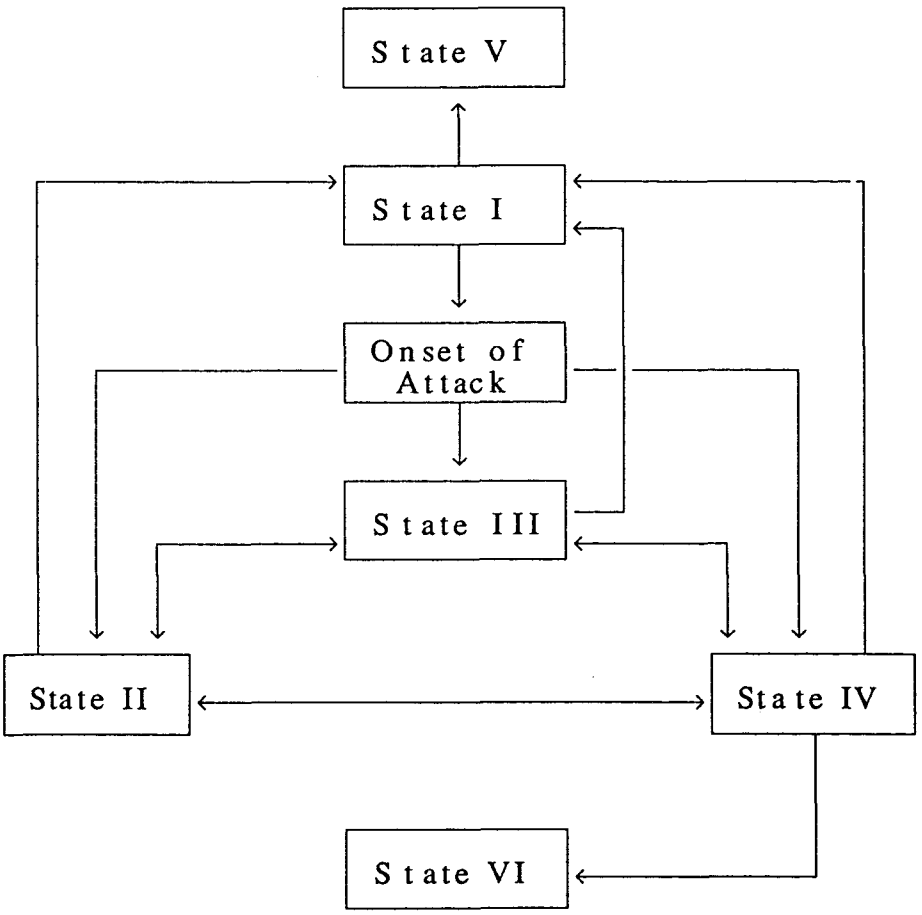


Figure 8.1. The state transition diagram for model I

8.2.4. The Disease States and State Transition Factors

The states in the model must reflect every state a real person in the real world could be found in whenever the person has an asthma attack. The six disease states (see Figure 8.1) were evolved after reading about asthma and discussion with medical people. Some of these states are as follows:-

Mild Attack - Forced Expiratory Volume for one second (FEV_1) exceeds 2 litres,
- Does not interfere with normal activities
- Controlled by bronchodilators and avoidance of known stimuli.

Moderate Attack - Forced Expiratory Volume for one second (FEV_1) is between 1 litre and 2 litres,
- Occasionally interferes with normal activities
- Requires Corticosteroids in treatment

Severe Attack - Forced Expiratory Volume for one second (FEV_1) falls below 1 litre,
- Seriously interferes with normal activities
- May lead to death

The state transition variables, which determine the way in which people move from one state to another are very important. These variables determine when someone has an asthma attack, whether the attack is mild, moderate or severe, and every other state transition. These transition variables are discussed briefly as follows:-

Average time between attacks - This causes a person to have an attack at the person's average time between attacks, specified by the user during the run. The times are then sampled from the exponential distribution using this average value.

Duration of attacks - The duration of an attack is estimated using the negative exponential distribution. The duration is dependent on the type of treatment given and the type of the attack (mild, moderate or severe).

FEV_1 - This decides the type of attack someone has. It is estimated using the log normal distribution with mean 1.47 and variance 0.54. At the moment the mean and variance are fixed, but the program could be altered to allow the user to input them at run time

Death - This decides when a person is going to die. Death could occur only from a severe attack. It is guided by the asthma mortality in the United Kingdom.

Treatment Effectiveness - This is used to decide which state a person ends up in, from a given attack. When the treatment is effective enough, the attack is then controlled and the person moves to the state "Asthma No Attack". Otherwise the person develops another attack.

Asthma Prognosis - This (dependent on age) decides whether a person would grow out of asthma or not.

A given individual who has no attack at a given point, develops an attack and the FEV_1 is used to determine the type of the attack (whether mild, moderate or severe depending on the FEV_1 reading). The individual then stays with this attack for a certain time (duration of the attack). Then, depending on the effectiveness of the treatment given, may make a transition to the state "Asthma No attack" or may develop some other attack or if the initial attack was a severe attack, may make a transition to the state "Death" depending on the asthma mortality rate.

We note here that one person may generate many attacks depending on his time between attacks.

8.2.5. The Asthma Program and the Program Input Requirements

The asthma simulation program consists of a suite of four programs running on a PS/2 and consisting of some 1,703 lines of code. A package called TECHNOJOCK (1989) was used to enhance the input screens. The first program, DECS, consists of variable declarations used in the simulation. The second program, SCREENS, is the data input program. It request, among other things, the age, the care option with its treatment effectiveness, the average time between attacks, and the average duration of an attack. The third program, ASTHRUN, uses programmed parameters on the duration of each state determined from the input screen to compute how long each individual is to remain in the present state before moving to the next destined state defined by the state transition diagram (Figure 8.1). This program moves each individual at the designated time (T Phase) to the destined state (B phase), taking account of the treatment effectiveness, FEV_1 reading and the mortality rate. The fourth program, ASTHMA1, is the main simulation program. It consists of the static display and initialises the variables. It also sets the histograms for data collection. It calls the procedure **Run** to perform the simulation.

8.2.6. Some Results from the Model

Some results obtained from the model by giving preventive treatment (Bronchodilators) to 20 asthmatics are displayed in figures 8.2, 8.3, and 8.4.

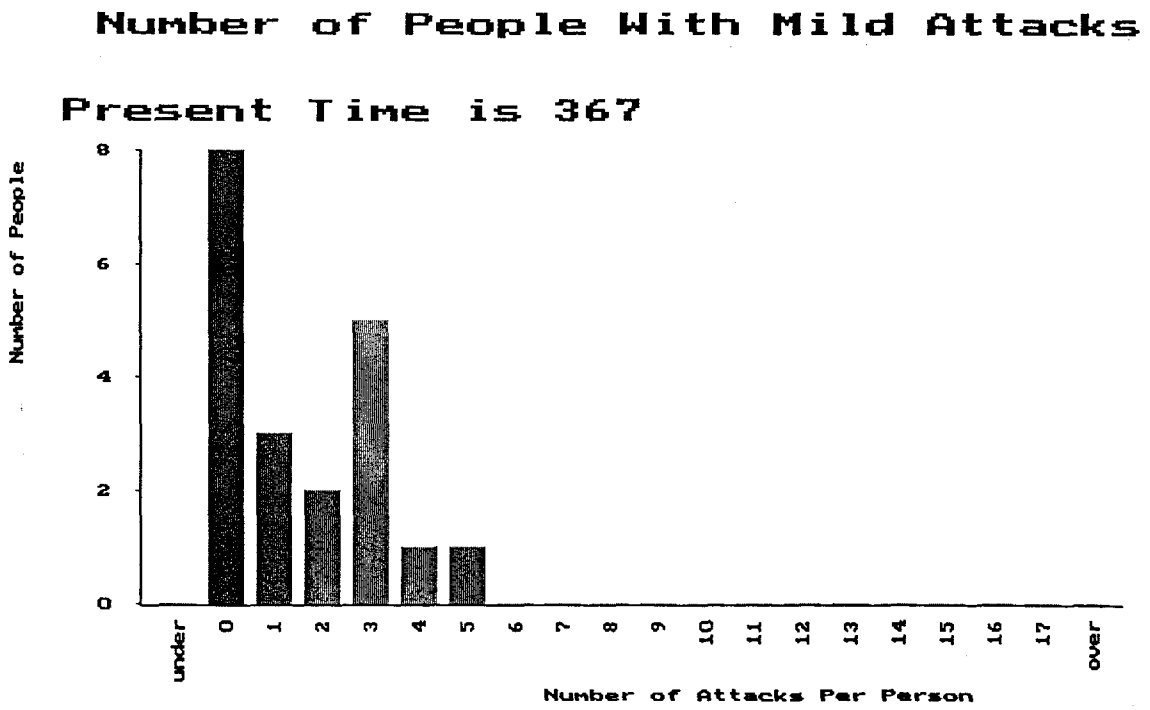


Figure 8.2. Number of people with mild attacks

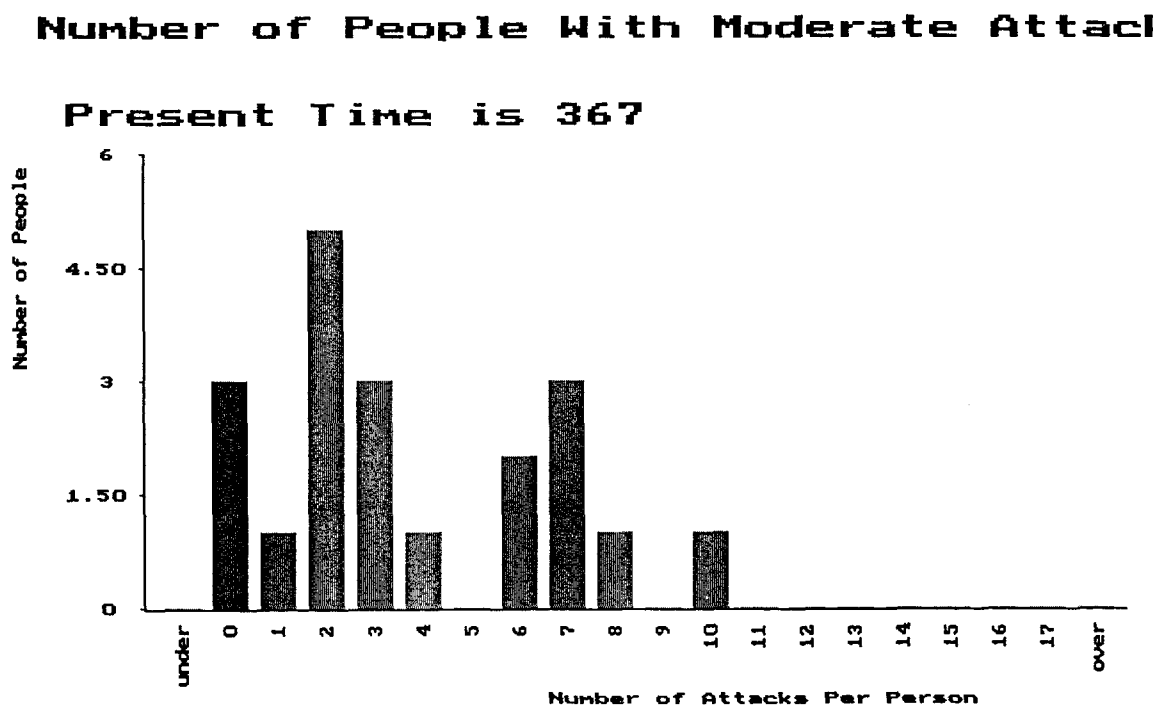


Figure 8.3. Number of people with moderate attacks

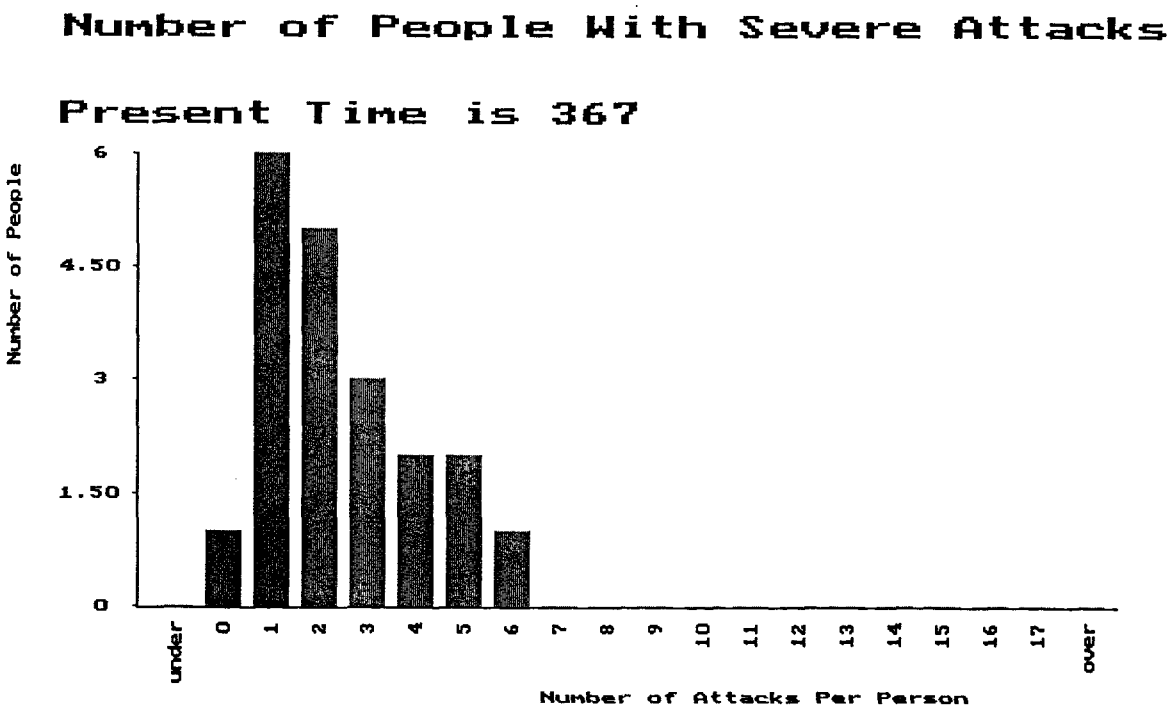


Figure 8.4. Number of people with severe attacks

The simulation was run with option 2 (treatment of attacks only) and option 3 (preventive treatment) and the results are presented in figures 8.5, 8.6, and 8.7.

Figure 8.5. Number of people with mild attacks

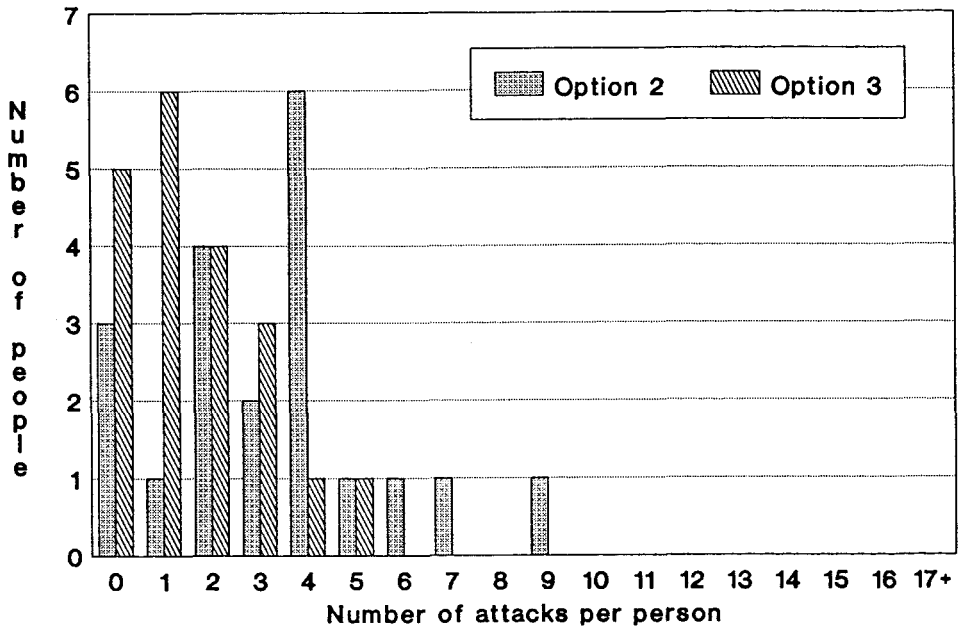


Figure 8.6. Number of people with moderate attacks

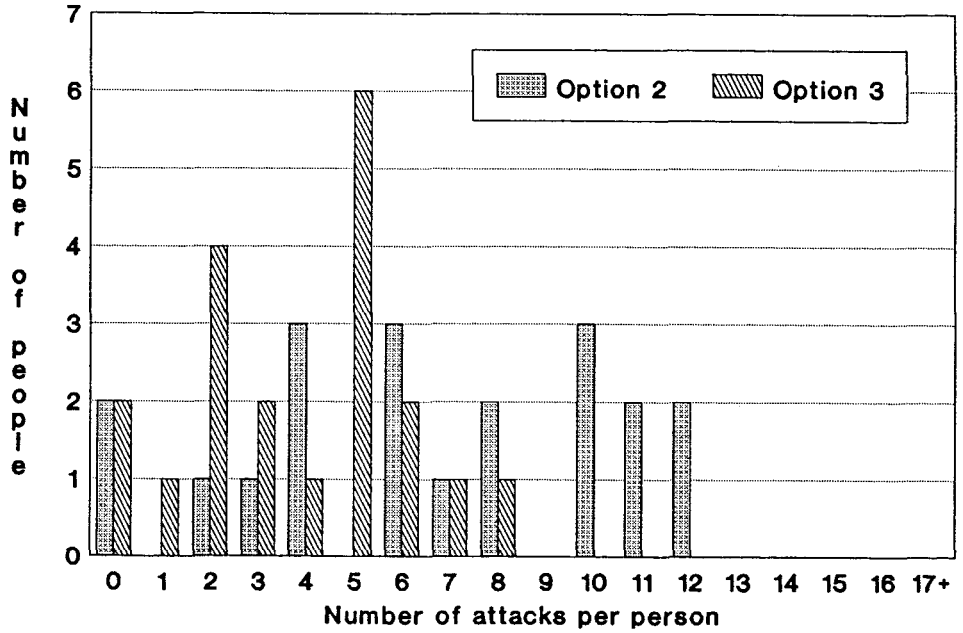
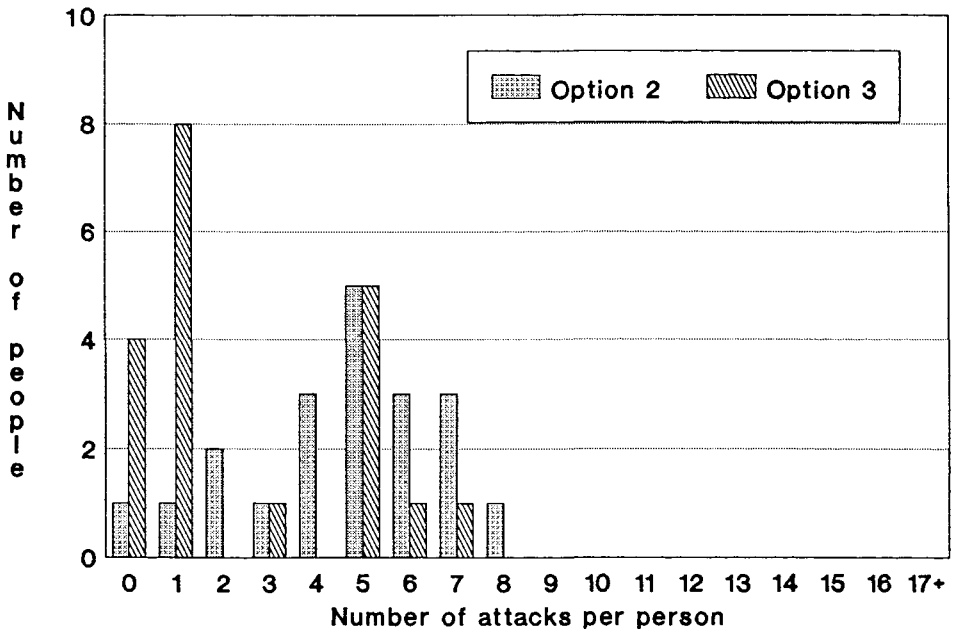


Figure 8.7. Number of people with severe attacks



8.2.7. Comments

Doubts about the practical value of computer models are sometimes expressed; these doubts usually arise when the models are not rigorously based on relevant epidemiological and an understanding of the disease. However, a model cannot, nor does it need, to capture the full complexity of real life in order to be useful. Asthma model I was a good starting point and it helped in the discussion about the necessary improvements with medical people.

8.3. Asthma Model II

This model is also concerned with childhood asthma. The set of states and state transitions are the same as described in model I. Care options are made more flexible in this model. This is because we feel that one person may be on different preventive measures and when he has an attack may be given

different combinations of treatment as time progresses. Some of the preventive measures can not even be quantified, such as avoidance of precipitating factors like cats and dogs or the house dust mite. Model II therefore allows the user to enter treatments for each of the states such that the asthmatic will now use these treatments whenever he finds himself in any of these states.

Transitions between the various states are controlled by the following :-

Duration in states - This includes the time between attacks and the duration of an attack, all taken to be negative exponential variates.

FEV_1, death, treatment effectiveness, and prognosis are taken to be the same as in model I

At this stage of development, most of the transition times were fixed since there were no data available. They could however be changed by the user during the run time.

8.3.1. Data Input

The model gets its data from four files classified under three headings

1. Natural history file,
2. Resources file, which also contains information about costs,
3. Simulation run file.

New files can be created during the simulation run. All these files can be selected for data input. Alternatively, the user can run the simulation without even seeing these files (this is not good practice). The natural history data file (known as the MAIN data file) holds information about durations in states and also the age distribution of the asthmatics. The resources option contains the available resources which can be allocated to states. Thus it is divided into two files - the available resources data file

and the allocation data file. These resources include personnel, drugs and facilities used in managing the disease. Figures 8.8, 8.9, and 8.10 show examples of the input screens. Figure 8.8 requests for the number of asthmatics by age. Figure 8.9 requests for the average time in each state of the disease and figure 8.10 are the treatments needed for a mild attack.

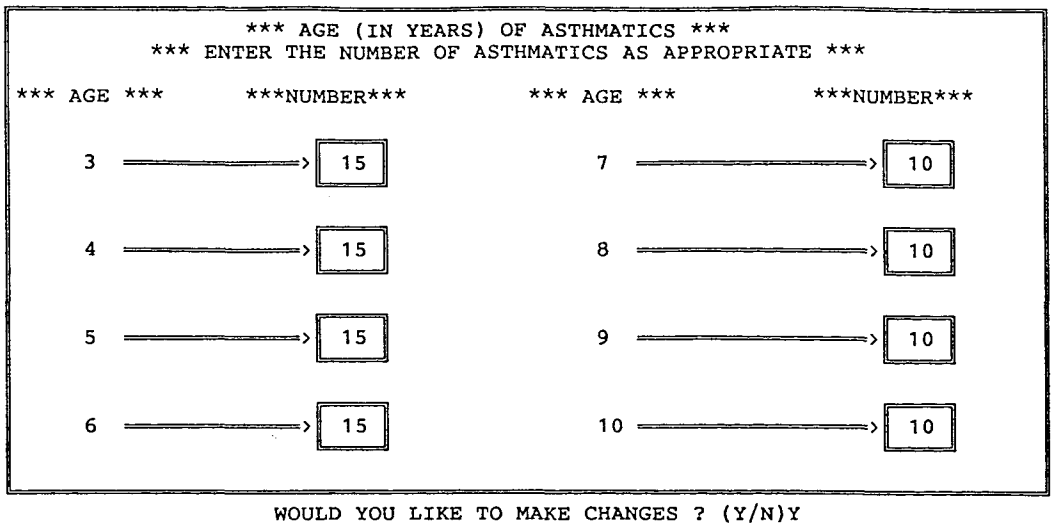


Figure 8.8 Age distribution of asthmatics

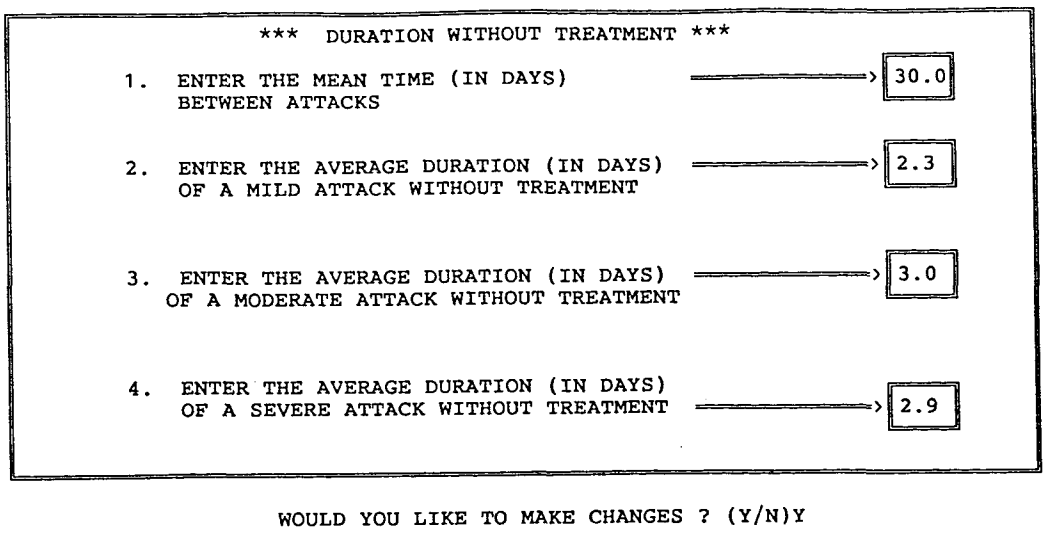


Figure 8.9 Duration in states

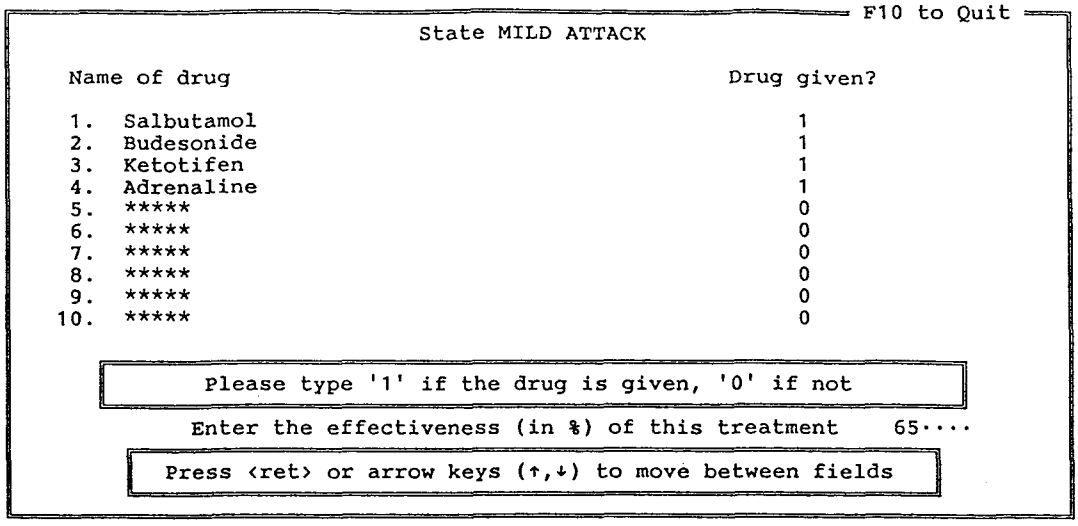


Figure 8.10 Treatments for mild attacks

The run data file contains information about the simulation run time and the reporting interval. See section 8.4 for a detailed description of this concept.

8.3.2. Results from the Model

Illustrative results from a simulation of 100 children with asthma for 180 days and a reporting interval of 10 days are displayed in figures 8.11- 8.16. Examples of the personnel we use are : senior medical officers, and nurses. Drugs such as salbutamol, budesonide, ketotifen, and adrenaline are also used. Facilities like inhalation devices, peak flow meters, and chest x-rays are also used.

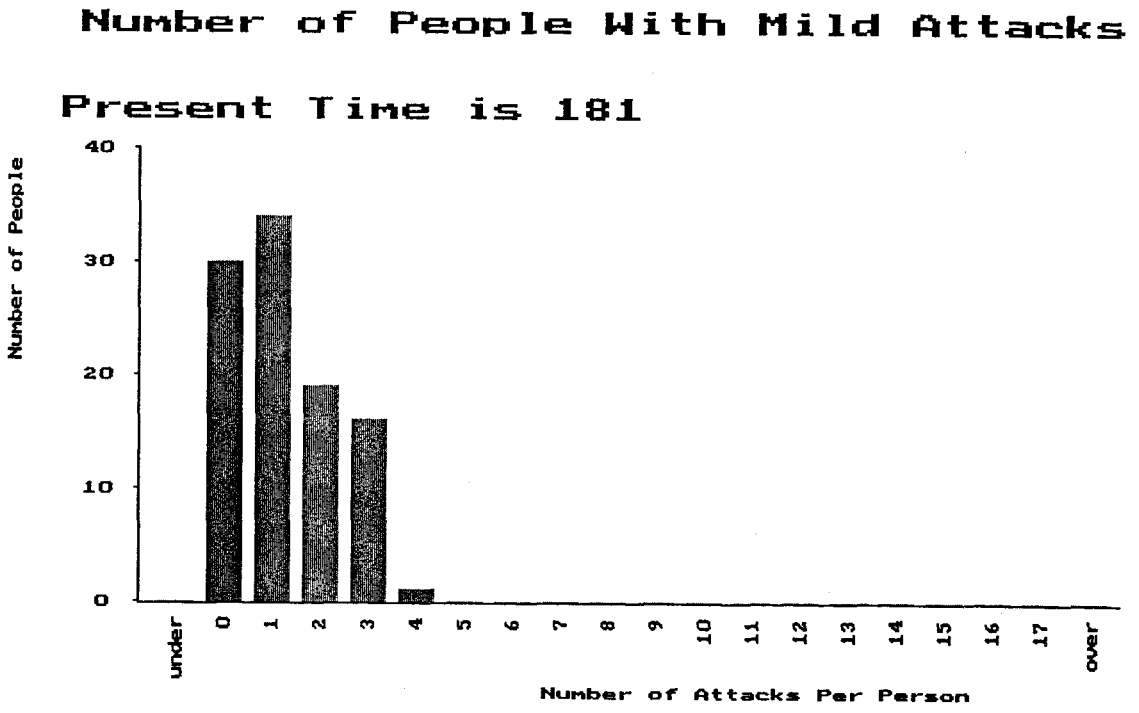


Figure 8.11. Number of people with mild attacks

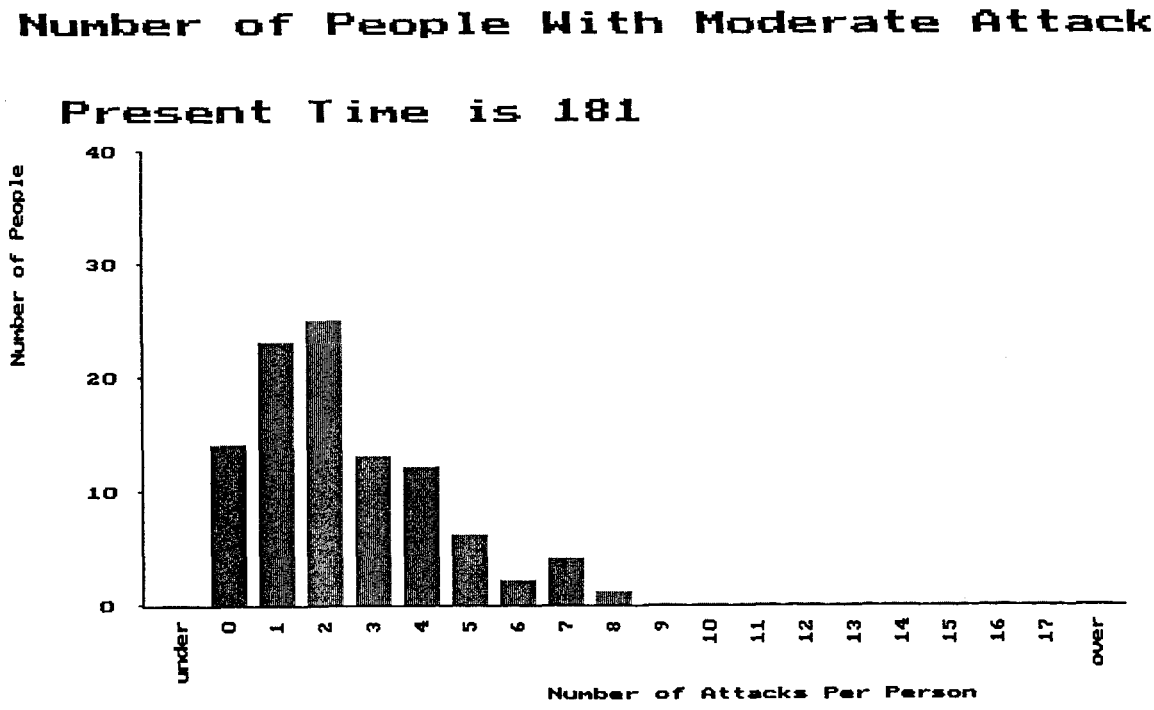


Figure 8.12. Number of people with moderate attacks

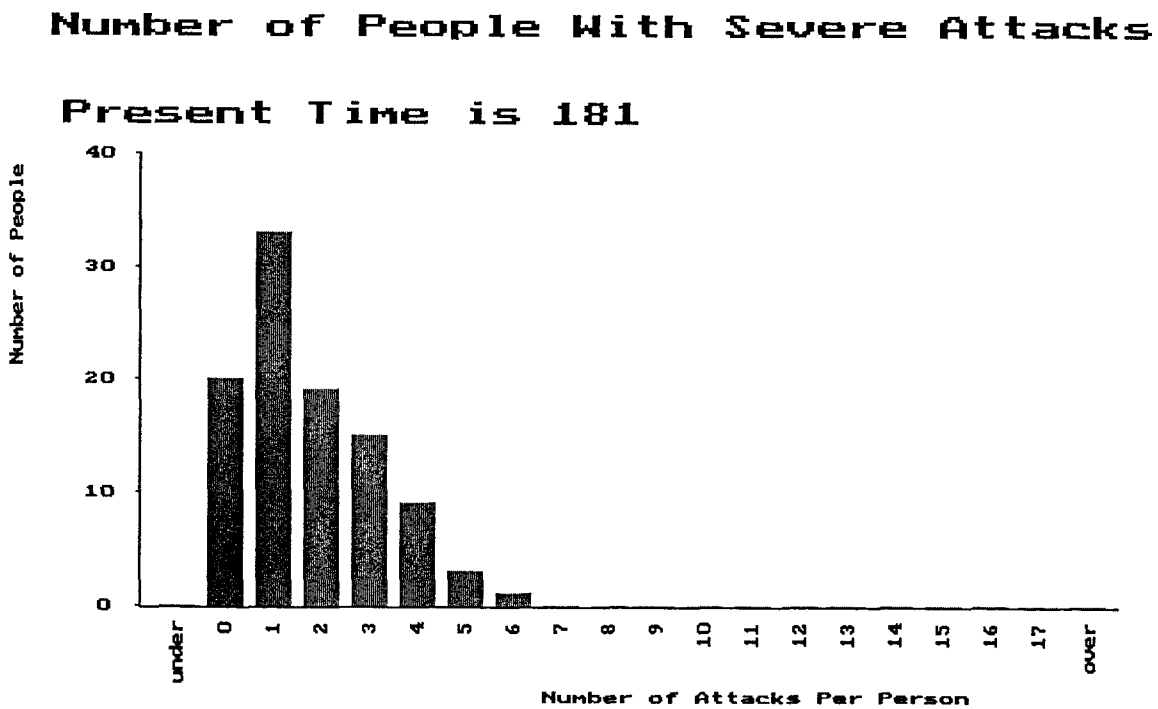


Figure 8.13. Number of people with severe attacks

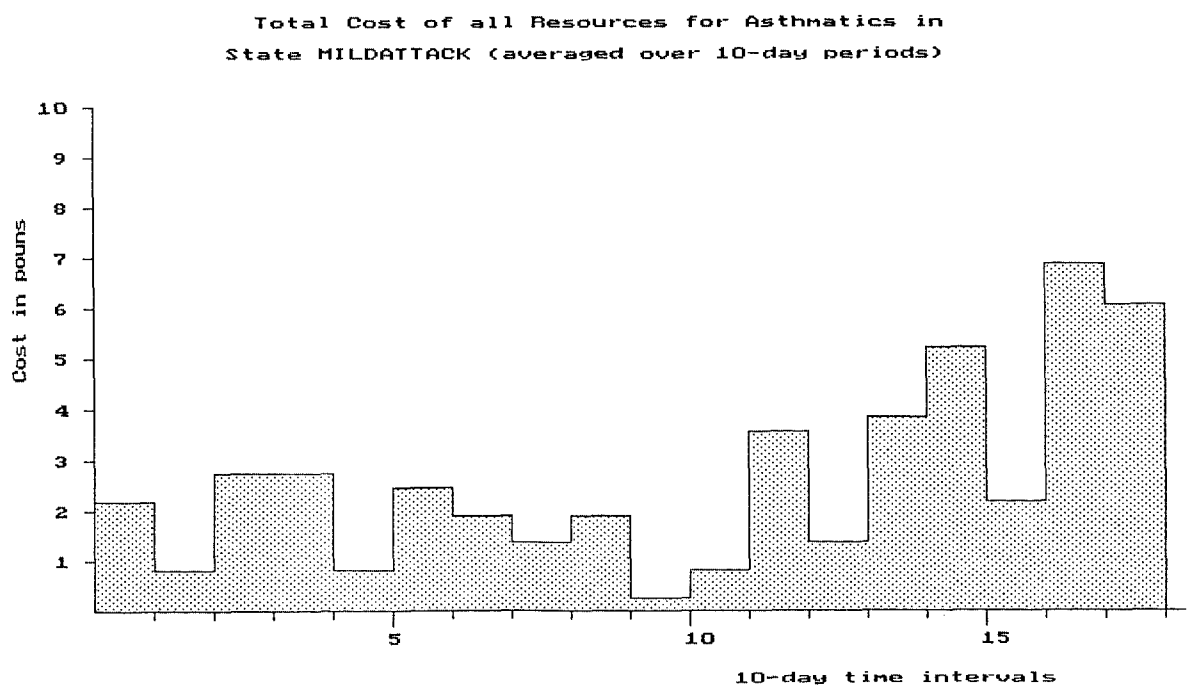


Figure 8.14. Total cost of resources for mild attacks

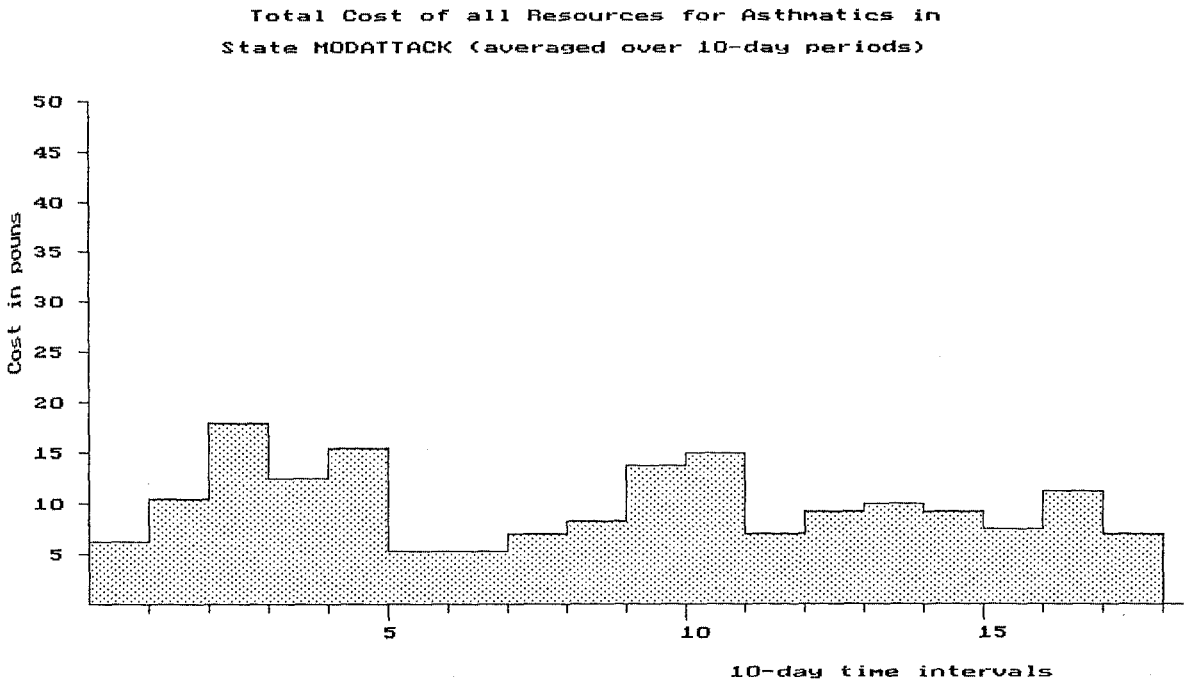


Figure 8.15. Total cost of resources for moderate attacks

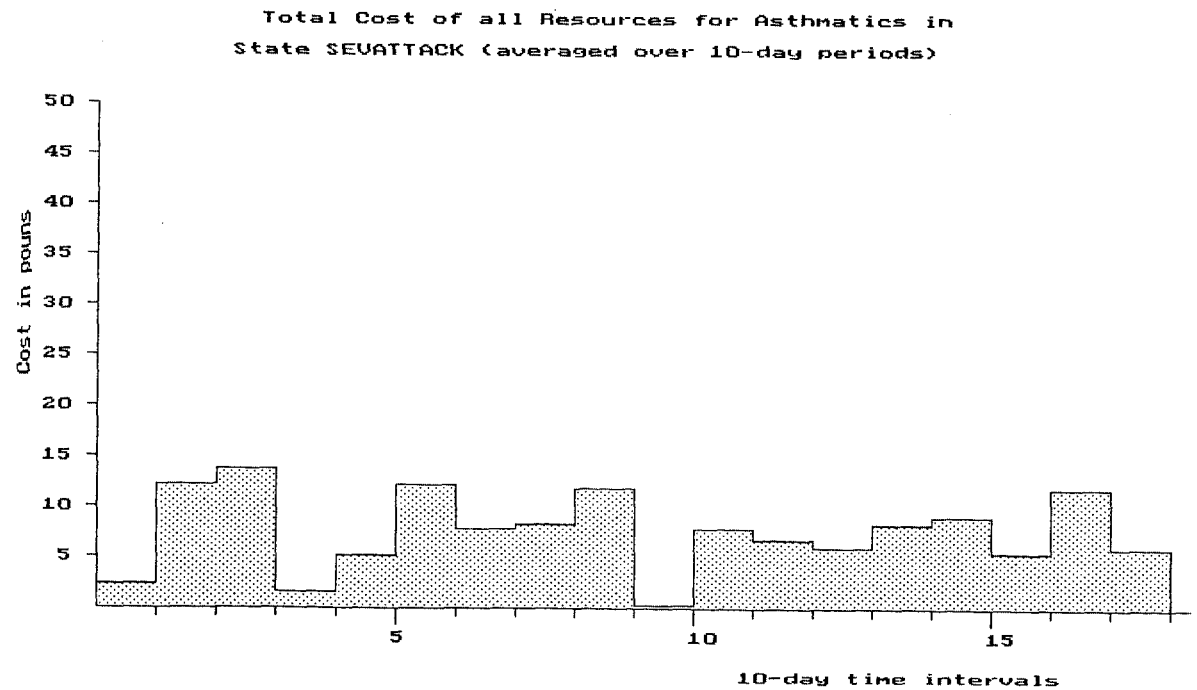


Figure 8.16. Total cost of resources for severe attacks

8.3.3. Comments

This model is still a very basic model. Its enhancement is presented as models III and IV in sections 8.4 and 8.5 respectively. The model also produces output in standard ASCII text files, which can be viewed and/or printed.

8.4. Asthma Model III

This model is an extended version of model II. It studies children and adults separately and in combination. The set of states and state transitions are as in model I.

Descriptions for transitions between the various states are also the same as those described in model I.

Note that the choice of negative exponential and lognormal distributions is somewhat arbitrary and not based on detailed data analysis. One advantage of a simulation model is that changes in the form of distributions are easy. Indeed sensitivity analysis involving different forms of distributions is a worthwhile activity.

8.4.1. Inputs for the Model

As mentioned earlier, the model has four linked structures. The natural history of asthma, a set of available resources, a set of treatment options, and a set of costs. This is reflected in the way that input data is organized into files. Thus in order to run the simulation, data is read from four distinct files :-

1. Natural history data file,
2. Treatment options file, which is for allocation of treatments,
3. Available resources file, which also contains cost information,
4. Run data file, which contains information for a particular run of the simulation model.

Within the program, the user can create new files or view and possibly edit existing ones. At the beginning of the simulation, the user selects the category of people to be simulated (children, adults or all ages). The user then selects the natural history data file which contains information about the time between attacks and the durations of attacks. It also contains information about the distribution of ages of the asthmatics to be simulated, and the proportion of asthmatics with each type of asthma. Figures 8.17, 8.18 and 8.19 show examples of the input screens.

Figure 8.17 shows the age distribution of asthmatics. It also requests for the probability of growing out of asthma. Figure 8.18 is the distribution of the asthmatics by asthma type and figure 8.19 requests for the average time in states.

To allocate treatments to the disease states, the user must first select the available resources. In the program, the available resources file is "Available" file, listing all the resources and their cost. The treatment options file is an "allocation" file which associates some of these resources with each state of the disease. See Figure 8.20 for the input screen for treatment allocation for the state "Mild Attack".

The run data file contains information about the simulation run time and the reporting interval - the time period over which the output data is averaged. The resolution of the computer screen imposes some restriction on displaying histograms. Thus the program only allows a maximum of 100 reporting intervals. However, the user could decide to run for a short period with a short reporting interval(e.g. 100 days with 1-day reporting interval) or a longer period with a longer reporting interval. Clearly more details will be lost in the averaging process if a longer reporting interval is used. Thus it is up to the user to choose appropriately, both the run time and the reporting interval to suit the situation.

The data output from the program can be saved to file in text and in graphics form and viewed and/or printed.

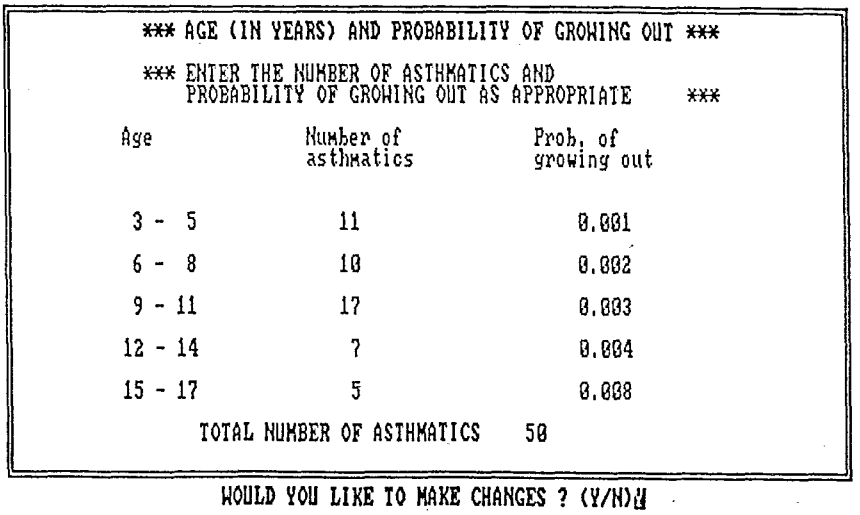


Figure 8.17. Input screen for age distribution for children.

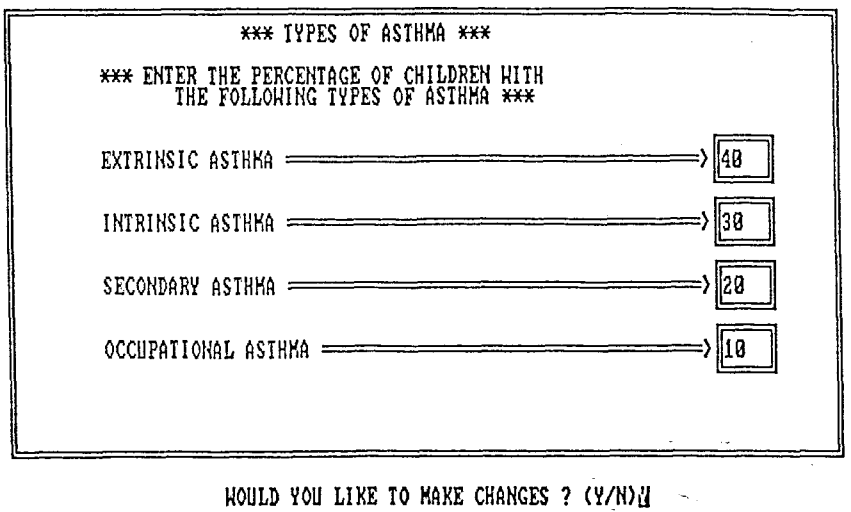


Figure 8.18. Input screen for type of asthma.

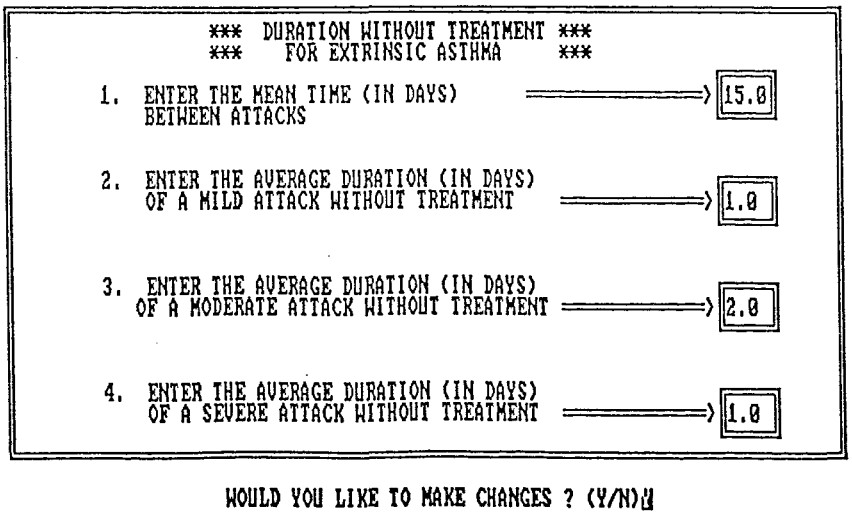


Figure 8.19. Input screen for durations for extrinsic asthma.

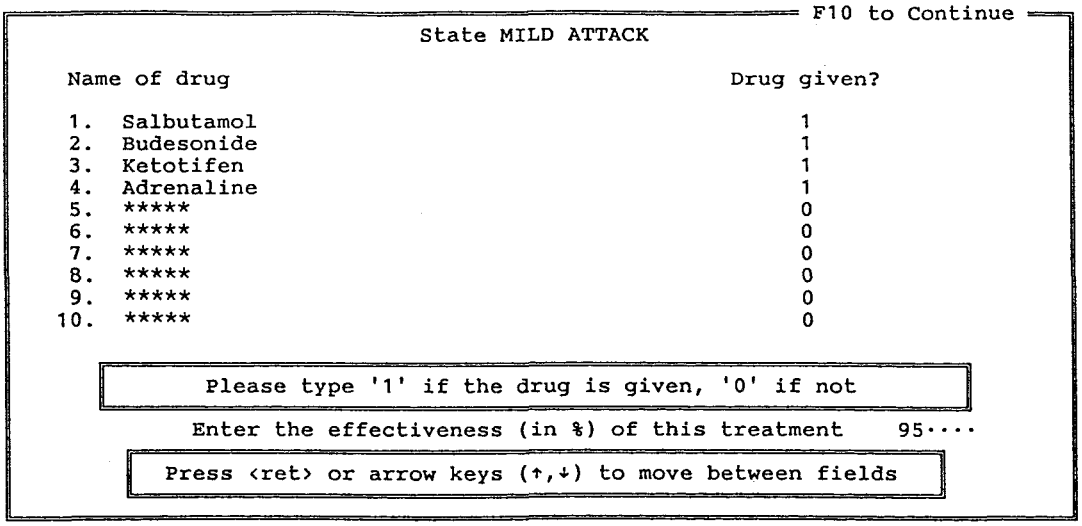


Figure 8.20. Input screen for treatments for mild attacks.

8.4.2. Some Illustrative Results from the Model

This section presents some selected results from a simulation of 50 children with asthma for 360 days and a reporting interval of 20 days.The transition probabilities and the dwelling time parameters are based on discussions with medical people and expert opinion. Some of the resources and costs given here are imaginary. These are just to illustrate the type of output produced from the model. Examples of the personnel we use are : senior medical officers, and nurses. Drugs such as salbutamol, budesonide, ketotifen, and adrenaline are also used. Facilities like inhalation devices, peak flow meters, and chest x-rays are also included. Figures 8.21, 8.22, and 8.23 give information about the number of asthma attacks, figures 8.24 and 8.25 show the total costs of resources used for a given state, and figure 8.26 shows the cost of a particular drug.

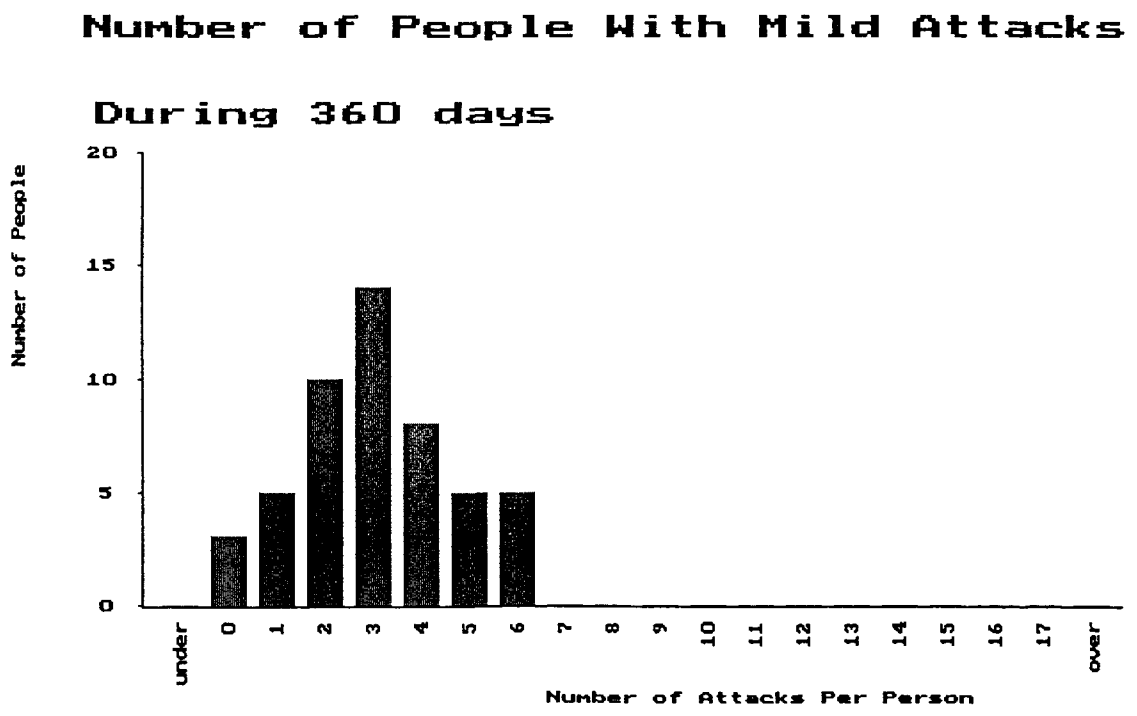


Figure 8.21. Number of people with mild attacks

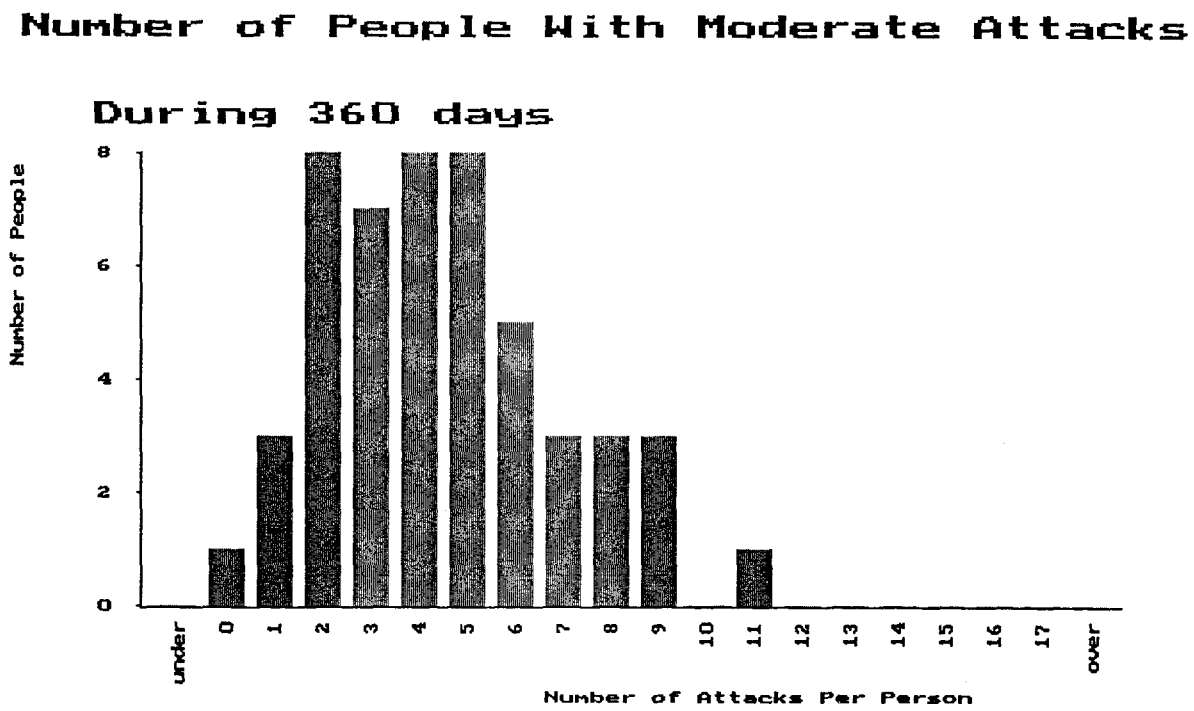


Figure 8.22. Number of people with moderate attacks

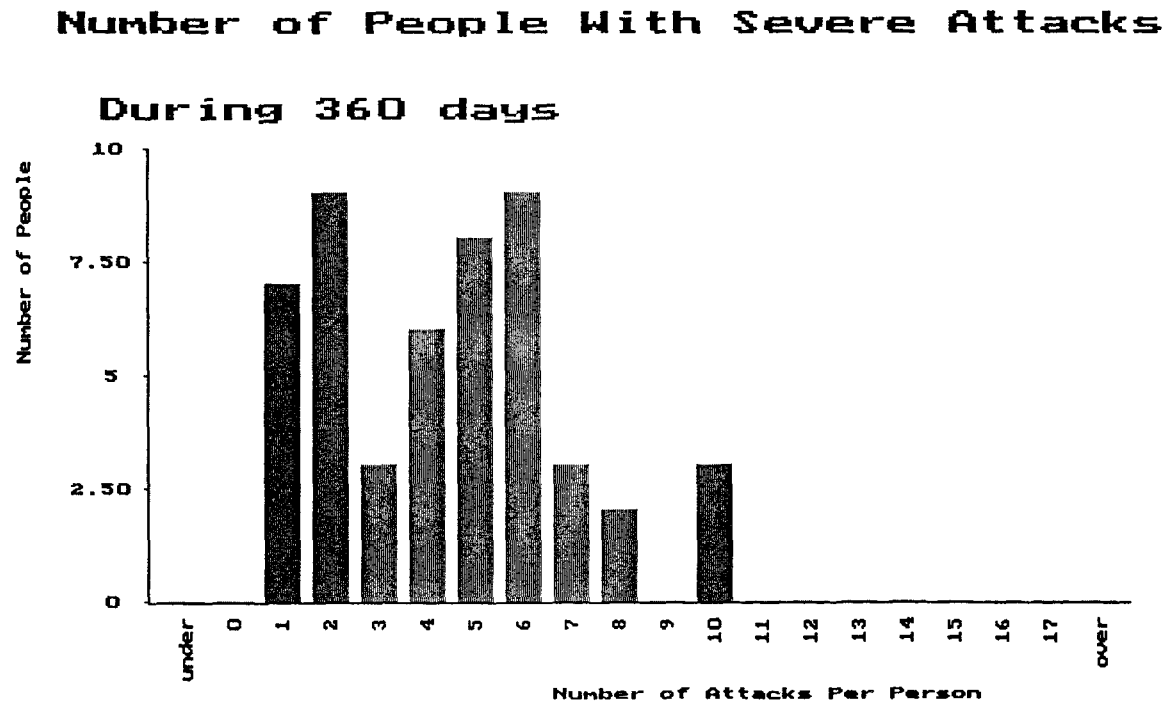


Figure 8.23. Number of people with severe attacks

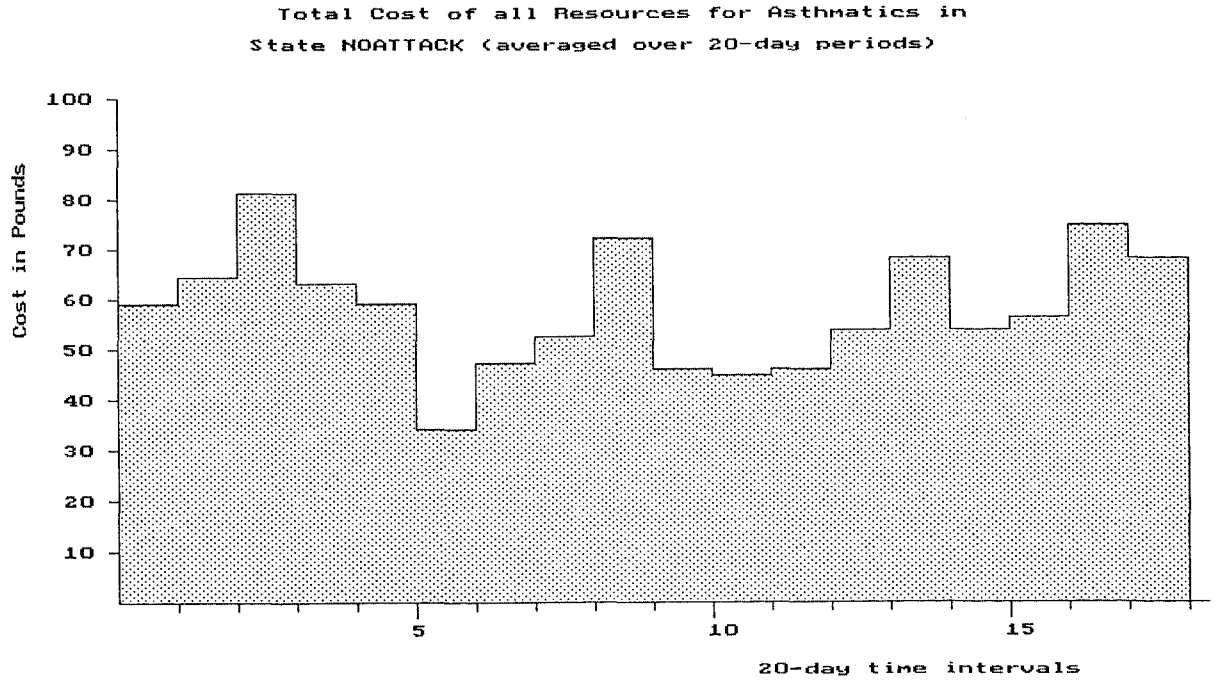


Figure 8.24. Total cost of resources for the state "No Attack"

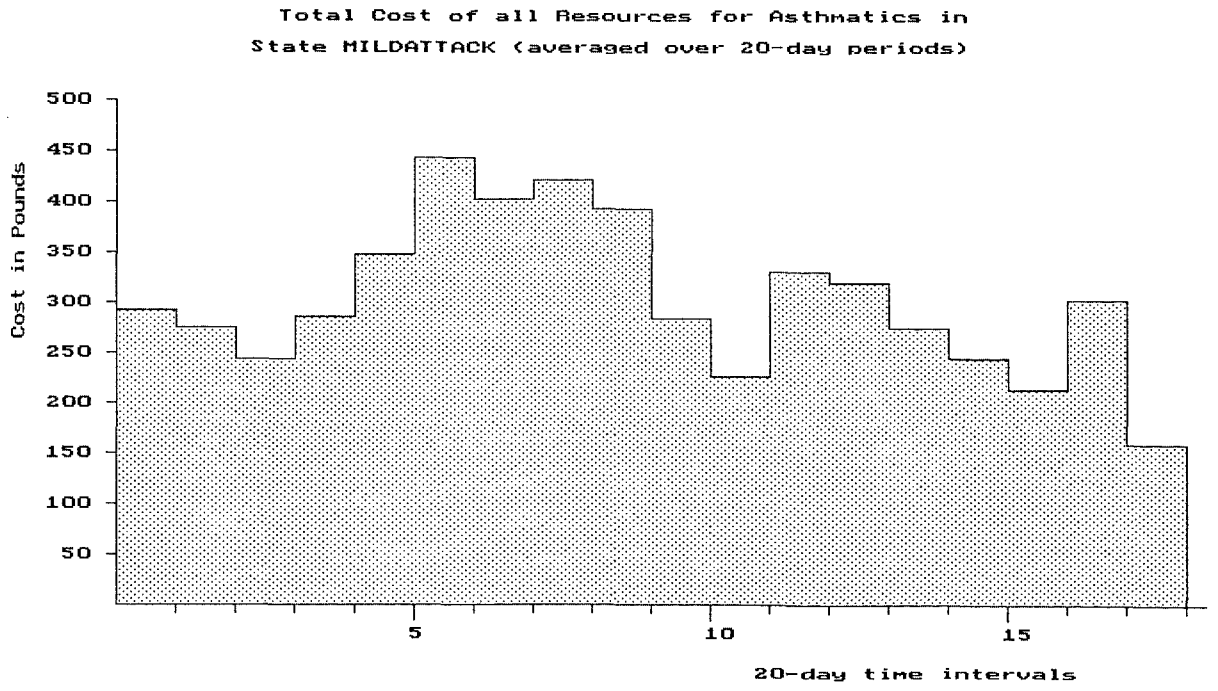


Figure 8.25. Total cost of resources for the state "Mild Attack"

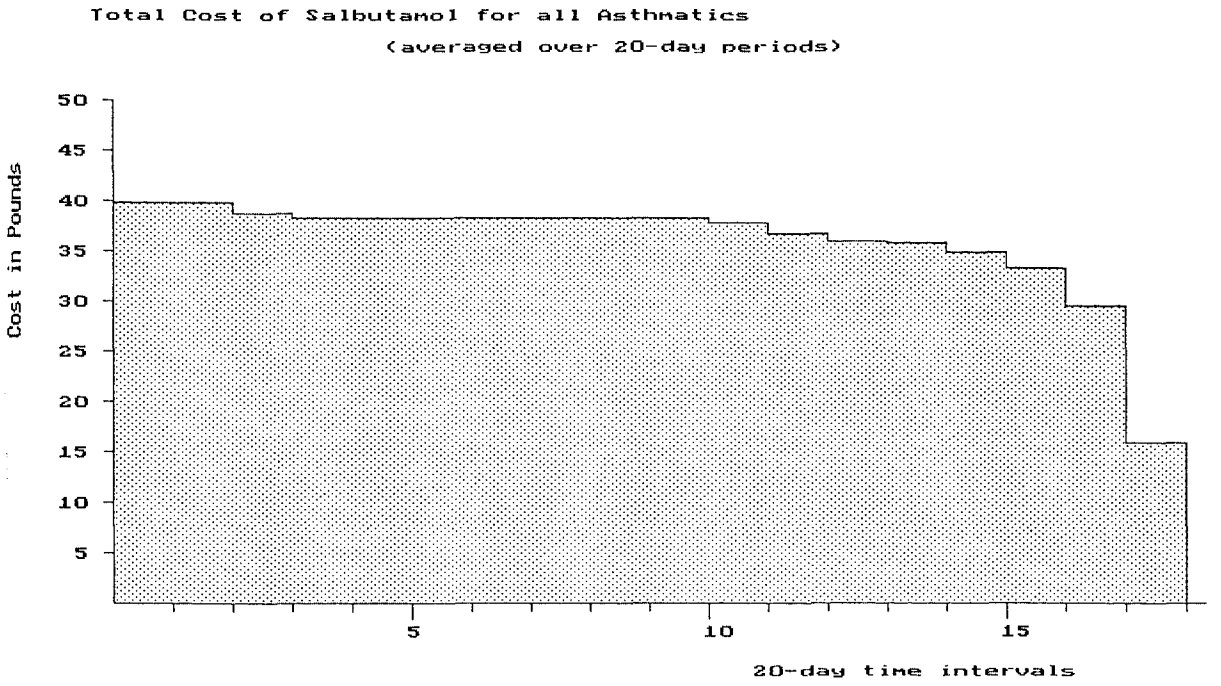


Figure 8.26. Total cost of salbutamol

8.4.3. Comments

This is still a basic model and it can be run on any IBM-compatible machine. The program produces output in standard ASCII text files, which can be viewed and/or printed on any printer, and in graphical form which can be viewed on the screen but needs a graphics printing package to be printed. This model however, illustrates the potential of the modelling approach.

8.5. Asthma Model IV

A number of further refinements were made, which would contribute further to the reality of the models. It is basically these final improvements that distinguish model IV from model III.

One of the significant refinement in model IV is the modification in the time between attacks and the durations of attacks. In model III these were taken to

be exponential variates. In model IV the Weibull distribution is also incorporated. Thus the user has the option of selecting either the exponential or the Weibull distribution for sampling the durations in states.

If the exponential distribution is selected, the user then has to enter one percentile value for this distribution, for the time between attacks, the durations of mild, moderate, and severe attacks.

After these data has been entered, graphs of the density funtion for this distribution can be seen, if desired, for all the durations in states. Figure 8.27 is the screen for the density function of the duration of mild attacks for this distribution. The 95% percentile value is 5 days.

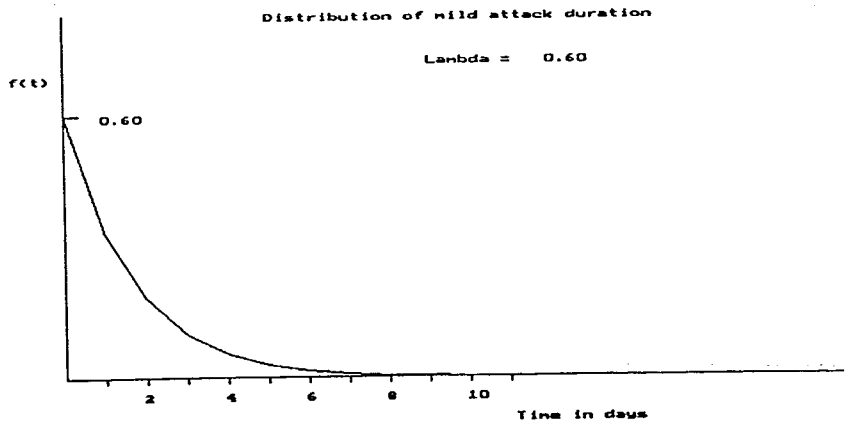


Figure 8.27. The exponential density function for duration of mild attacks

The density function for durations in other states are also shown.

When the Weibull distribution is selected, the user enters two percentile values, the 5% and the 95% percentile for the durations in states. Any two percentile values can be chosen.

Graphs of the Weibull density funtion for these data are then shown on screen

for the time between attacks, the durations of mild, moderate, and severe attacks. Figure 8.28 is the Weibull density function for the time between attacks with the 5% and 99% percentile values of 6 days and 31 days respectively.

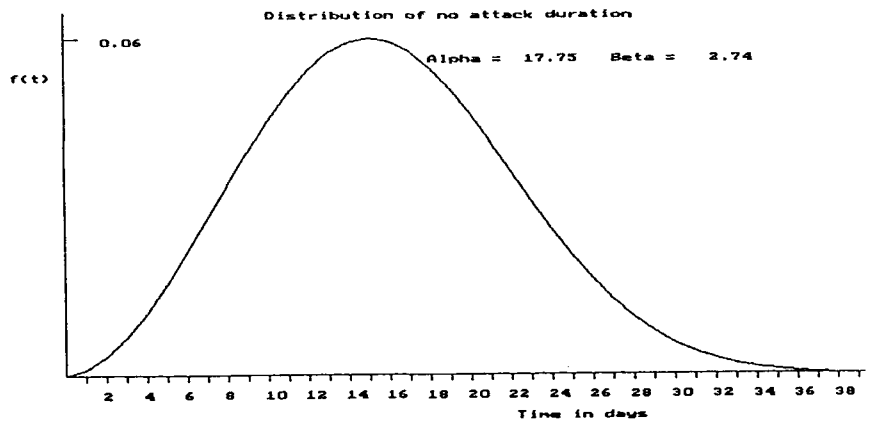


Figure 8.28. The Weibull density function for time between attacks

The density functions for other durations in states are also displayed.

There is also another major modification made in model IV. This is the idea of using the peak expiratory flow volume for one second as a measure of determining the type of attack. This change was necessary since the choice of the LogNormal distribution for determining these values in models I, II and III was arbitrary and not based on detailed analysis of data. Thus if the peak flow data does not follow the LogNormal distribution, then the results obtained from these models may not mimic reality. Another reason for this change is that it may be difficult to know the distribution of peak flow readings for asthmatics during attacks. It is therefore decided that transition probabilities be used instead of the peak flow readings. Thus in model IV the user enters the probability of moving from one state to another. The probability of a transition to the state "No attack" is however still governed by the effectiveness of the treatment given when an asthmatic is in

any one of these states. Figure 8.29 shows the state probability transition matrix for this model.

TRANSITION PROBABILITIES :

Please enter the probability of transition between states :

	Mild	Moderate	Severe
No Attack	0.600	0.350	0.050
Mild	0.500	0.420	0.080
Moderate	0.550	0.350	0.100
Severe	0.250	0.500	0.250

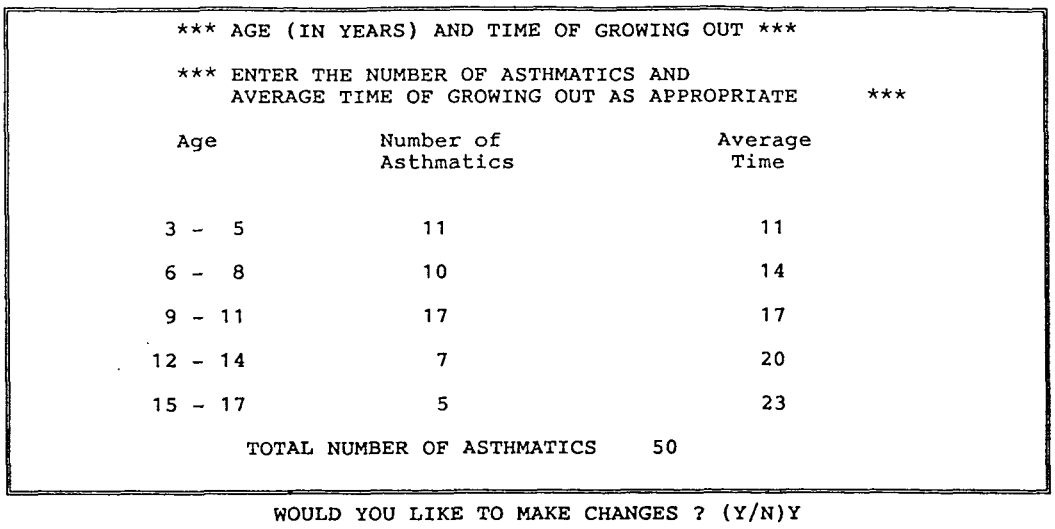
WOULD YOU LIKE TO MAKE CHANGES ? (Y/N)Y

Figure 8.29. Transition probability matrix for the states

The idea of growing out of the disease was also considered in this model. Since 1/3 of childhood asthmatics grow out by adult age, we simply let 1/3 grow out in this model. The age at which they grow out is then entered by the user during the simulation run. Figure 8.30 shows the age distribution and age of grow out for the asthmatics.

In model III, probabilities of growing out of asthma were taken to be dependent on the age of the asthmatics. These changes in model III make model IV more realistic.

The results obtained from this model are displayed in a similar form as those obtained from model III.



*** AGE (IN YEARS) AND TIME OF GROWING OUT ***

*** ENTER THE NUMBER OF ASTHMATICS AND
AVERAGE TIME OF GROWING OUT AS APPROPRIATE ***

Age	Number of Asthmatics	Average Time
3 - 5	11	11
6 - 8	10	14
9 - 11	17	17
12 - 14	7	20
15 - 17	5	23

TOTAL NUMBER OF ASTHMATICS 50

WOULD YOU LIKE TO MAKE CHANGES ? (Y/N)Y

Figure 8.30. Age distribution and time of grow out

8.6. Asthma Model V

This model is rather different in some ways from all the models discussed so far. It considers people who are currently asthmatics in a community and people who have no previous history of asthma but may become asthmatics at some point in their lives. The model is discussed in the following sections. The prevalence of asthma is taken to be 10 percent in this model.

8.6.1. An Outline of the Model

We consider a group of asthmatics in a community. We also consider a group of people who do not have a history of asthma attacks but may become asthmatics at some time in their lives. We consider two types of management. We simply refer to them as management type I and management type II. For example management type I could be a situation where the asthmatics are under preventive treatment and management type II could be when they are not under any form of preventive treatment. Whichever type of management is employed, the asthmatics experience attacks of asthma as time progresses and they go to their GP for treatment. Since the treatment of an attack is dependent on the

type of the attack, the GP then assesses the attack and classifies it as mild, moderate, or severe as defined in section 8.2.4. The asthmatic then remains with the GP for a certain period of time, called the duration of the attack, during which his attack may improve or become worse. If his attack was classified as mild, it may then become moderate or severe, if it becomes worse, or he may then be in a state of "no attack" if it improves. A mild or moderate attack may become severe, but we do not allow a transition from severe attack to mild attack or moderate attack, since in this situation we can consider the severe attack as finishing.

When the attack becomes severe, the asthmatic has some likelihood of being referred to the consultant for further treatment. Thus the GP may appropriately or inappropriately refer an asthmatic to the consultant. The referral will be inappropriate when it is discovered by the consultant that the asthmatic did not, in the first place, have a severe attack of the disease. The asthmatic stays with the consultant for another period of time, called the consultation time, irrespective of whether or not he is referred appropriately. It may however be that the consultation time for inappropriate referrals is shorter. After the consultation time, we assume that the attack is controlled and the asthmatic goes back to the community to continue with normal activities.

We have also considered the possibility of an asthmatic "outgrowing" his asthma by adolescence. The probability of death from asthma is very small, we therefore consider any death to be from natural causes. This probability was fixed in the previous models making them unrealistic.

8.6.2. The Objective of the Model

The model examines several strategies of type I management to see which ones are worthwhile. Strategies for this type of management are such that

(a) the time between attacks is extended by a factor k_1;
(b) the probability of a moderate attack is reduced by a factor p_1;
(c) the duration of a moderate attack is reduced by a factor k_2;

(d) the probability of a severe attack is reduced by a factor p_2;
(e) the duration of a severe attack is reduced by a factor k_3 .

To determine which strategy is worthwhile, the cost of type II management is calculated and compared with the cost of each type I management strategy. A type I management strategy that costs less than type II management is therefore good. For example, if we know that the cost of managing asthma when preventive treatment is not employed is , say 200 thousand pounds per year for all the asthmatics and we select a type I management strategy such that with this strategy

(1) the time between attacks is extended by 90 percent;
(2) the probability of a moderate attack is reduced by 50 percent;
(3) the duration of a moderate attack is reduced by 10 percent;
(4) the probability of a severe attack is reduced by 30 percent ; and
(5) the duration of a severe attack is reduced by 10 percent ;

then if the cost of this strategy is say, 150 thousand pounds per year then type I management strategy is better.

8.6.3. States and State Transitions

Following the discussions at the beginning of this section, we have the following set of states :-

State 1 Susceptible
State 2 New case
State 3 Asthma, no attack
State 4 Mild attack
State 5 Moderate attack
State 6 Severe attack
State 7 Severe attack, appropriately
referred to the consultant
State 8 Severe attack, inappropriately
referred to the consultant

State 9 Grow out
State 10 Death

The possible transitions between these states are shown in figure 8.31.

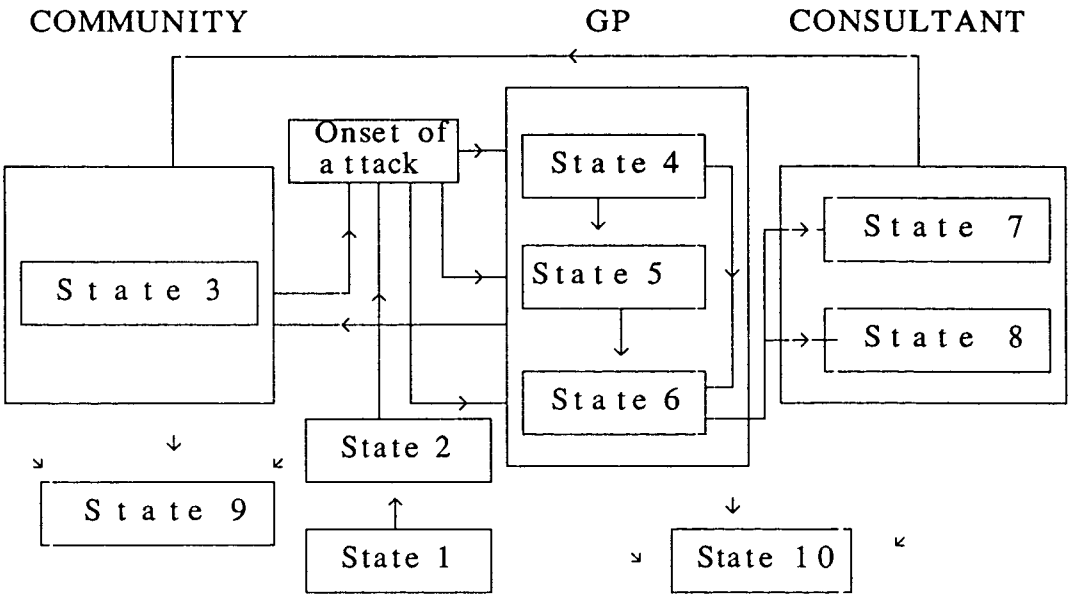


Figure 8.31. The transition diagram for model V

The transition mechanism is described as follows :

1. Duration of attacks

This determines how long an asthmatic stays under the care of a GP. The times are sampled from two well known distributions, the exponential and the Weibull, depending upon choice. When the exponential is chosen the user supplies the average occupation time in these states, while for the Weibull the user must give the average occupation time together with one percentile value. Note that the average time is used instead of another percentile value.

2. Consultation times

This factor determines how long a person is going to remain with the consultant. The times are also sampled from either the exponential or the Weibull distribution.

3. Time between attacks

This determines the attack-free periods. It is also taken from the exponential or the Weibull distribution.

4. Transition probabilities

These are used in determining the likelihood of making a transition from one state to the other. Since about 25% of the asthmatics have moderate form of asthma, while 2.5% have the severe form (Clark and Godfrey, 1983), we take the probability of having a moderate attack to be 0.25 and that of severe attack to be 0.025 and hence the probability of a mild attack is 0.725. The probabilities of appropriate and inappropriate referrals and other probabilities are arbitrary chosen. The user, however has the option of changing these values to suit his own available data or expert opinion.

5. Mortality

Anderson and Strachan (1991) concluded that there was no evidence for an increase in asthma mortality over 1979-1989. The mortality rate was obtained per million per year and the maximum value was about 17.5 which occurred in the 35-44 year age group. We emphasize that this value is small enough to be neglected when conducting short term studies.

The simulation therefore uses the general mortality in England and Wales for the year 1991, OPCS (1992), to determine whether an individual will die at the end of an event. If the individual is about to have an attack in the next, say 30 days, then the program checks to see if the individual will die before this time and, if so, when. The probability of dying is based on age, sex, and the

time interval, see table 8.1. From the table if an individual is female, 10 years old, then she has a probability 0.00016 of dying within one year. The figures in table 8.1 are used to calculate the probability of dying in one day intervals. Therefore, if an individual dies in any interval, the model determines this time of death.

In the simulation program, these values are stored in array form and the one day values are calculated before the simulation run. When the simulation is running the "Function Alive", using age, sex, and the time intervals, determines who dies during these time intervals.

6. Incidence

The asthma incidence data (Fleming et al., 1991), published by the Royal College of general Practitioners were used in the simulation. The incidence rate is given per thousand population according to age. For example the incidence per thousand population in the 5-14 year age group is 32. These figures are used in the simulation to cause this number of people in this age group to have asthma in a year. For convenience, the values are divided by 365 to obtain the daily incidence rate, the basic time interval used in the simulation. The program checks at daily intervals to see if there are any incidences of asthma in the next day. An individual is allowed to become an asthmatic only when the program checks to see that he is not going to die in the next interval. If he is going to die, then another person is selected and examined accordingly. The sex of the person is determined from the fact that before puberty, the ratio of male to female asthmatics is 2:1. After this age there is an equal sex distribution (Clark and Godfrey, 1991). We have taken the age of puberty to be 13 years.

7. Growing out of asthma

It is mentioned in chapter 3 that about one-third of asthmatics whose asthma starts in childhood grow out of their disease during adolescence. The simulation uses this figure to determine the number of asthmatics who would grow out of their disease. The age at which they grow out is however not

known. We nevertheless know that a certain proportion p grow out by a certain age t. We assume that the age of growing out has a Weibull distribution, and we therefore allow the user to supply two ages with their corresponding

Age group	probability of dying within one year	
	Male	Female
0 - 4	0.00220	0.00169
5 - 9	0.00020	0.00014
10 - 14	0.00022	0.00016
15 - 19	0.00074	0.00028
20 - 24	0.00093	0.00031
25 - 29	0.00091	0.00037
30 - 34	0.00099	0.00052
35 - 39	0.00138	0.00086
40 - 44	0.00204	0.00133
45 - 49	0.00344	0.00224
50 - 54	0.00592	0.00362
55 - 59	0.01049	0.00626
60 - 64	0.01848	0.01082
65 - 69	0.03148	0.01747
70 - 74	0.04886	0.02737
75 - 79	0.07835	0.04514
80 - 84	0.11935	0.07602
85 - 89	0.17170	0.12557
90 +	0.22807	0.22022

Table 8.1. The probability of dying in a year obtained from the annual mortality in England and Wales.

percentages : p1 grow out by age t1, and p2 grow out by age t2. The minimum age of growing out is taken to be the minimum age c of the population, which is 3 years. For instance, Douglas (1968) prospectively studied a group of children with asthma with a view to determining the frequency of remission of asthma, he found that 22% lost their disease by the age of 16. Blair (1977)

conducted a follow-up study of children affected with asthma and he found that 52% who reached the age of 20 no longer had asthma. We could therefore take t1 to be 16 and p1 to be 22%; t2 to be 20 and p2 to be 52%. These values are used to obtain α, the scale parameter, and β, the shape parameter for the Weibull distribution. In this case $\alpha = 18.35$ and $\beta = 4.04$. With α and β we then determine the age L by which an asthmatic who is going to grow out must do so. That is, L for which

$$G(L) = 0.999$$

where G(t), obtained below, is the conditional distribution function for the age of growing out. For these values of α, β, and c we have that L = 33. The age of growing out for each asthmatic whose initial age is less than or equal to L is then sampled using the following :

Let T be the age of growing out of asthma. This is assumed to have a Weibull distribution. Let f(t) be the density function of T.

$$\text{Then} \quad f(t) = \begin{cases} \beta/\alpha \ \{(t-c)/\alpha\}^{\beta-1} \exp[-\{(t-c)/\alpha\}^{\beta}] \ , \ t > c \\ 0 \qquad \text{otherwise} \end{cases}$$

Let F(t) be the distribution function of T and let g(t) be the density function of age of growing out given the initial age, h of the asthmatic, i.e.

$$g(t) = \frac{f(t)}{1-F(h)} = \beta/\alpha\{(t-c)/\alpha\}^{\beta-1}\exp[\{(h-c)/\alpha\}^{\beta} - \{(t-c)/\alpha\}^{\beta}]$$

and G(t), its distribution function is thus

$$G(t) = 1 - \exp[\{(h-c)/\alpha\}^{\beta} - \{(t-c)/\alpha\}^{\beta}]$$

The inverse transformation method is then used in sampling from this distribution. The "Function Growout", using age, determines who grows out, in a given interval of time, at the end of an event.

8.6.4. Data Input for the Model

Data entry into the model is quite similar to that described in section 8.4.1. It is read from four files :- the natural history file, the available resources file, the allocation file which is used for the allocation of these rsources to the states and also holds information about the cost of these resources; and the run file which contains information about the duration of the simulation run. The user has the option of editing the existing data files or creating new ones.

Menus are designed to ease the entry of data for this model. We have the main menu which allows the user to decide whether to create new data files, view or edit existing ones or run the simulation with the data files already created by the modeller or previous user. On this same menu the user can choose to just view the results from previous runs.

When the user decides to create new data files or edit existing ones, then he is confronted with a submenu with three options :- the natural history option, associated with the main data file, contains all information concerning the model except the resources; the resources option which holds information about the resources available for allocation including their costs; and the third option allows the user to quit and go back to the main menu.

The natural history option allows the user to input data concerning the total number of people in the community, the percentage of asthmatics on type I management, the percentage on type II management, and of course the percentage of people in the community who have not experienced asthma attacks before. With this same option the user has the opportunity to select a strategy for type I management, input the transition probabilities from one state to another, occupation time in states, the age distribution of current asthmatics, the growing out statistics, the incidence data, and the simulation run time. This is also organized in form of a submenu with the appropriate options.

The transition probabilities from the "no attack" state is shown in figure

8.32 as an illustration.

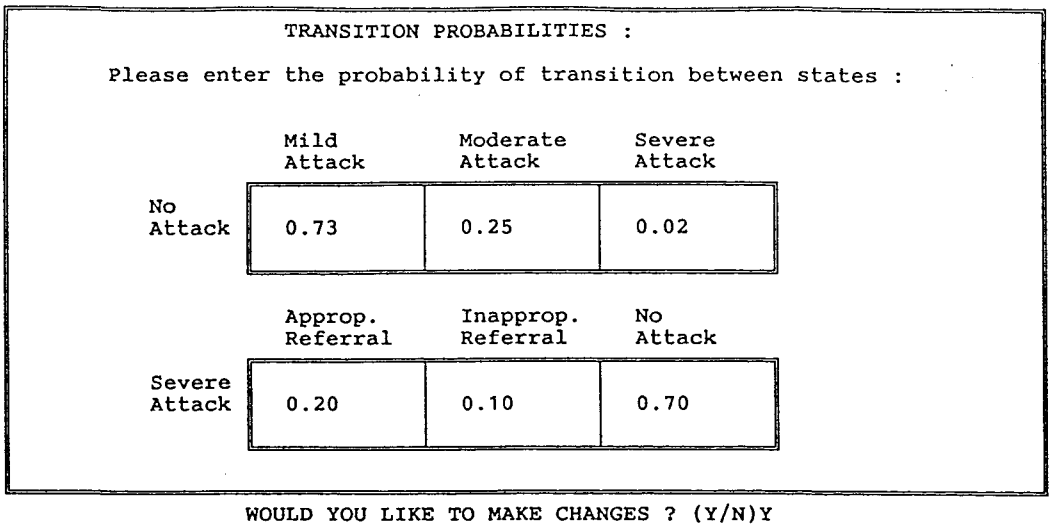


Figure 8.32. Transition probabilities

The "occupation times" option on the submenu allows the user to select one of two distrbutions, the exponential or the Weibull, from which samples are taken for use in the simulation. With the exponential distribution option the user inputs the average time in each of the states. With the Weibull distrbution option the user inputs the average occupation time and one percentile value. The screen for the Weibull distributions is shown in figure 8.33.

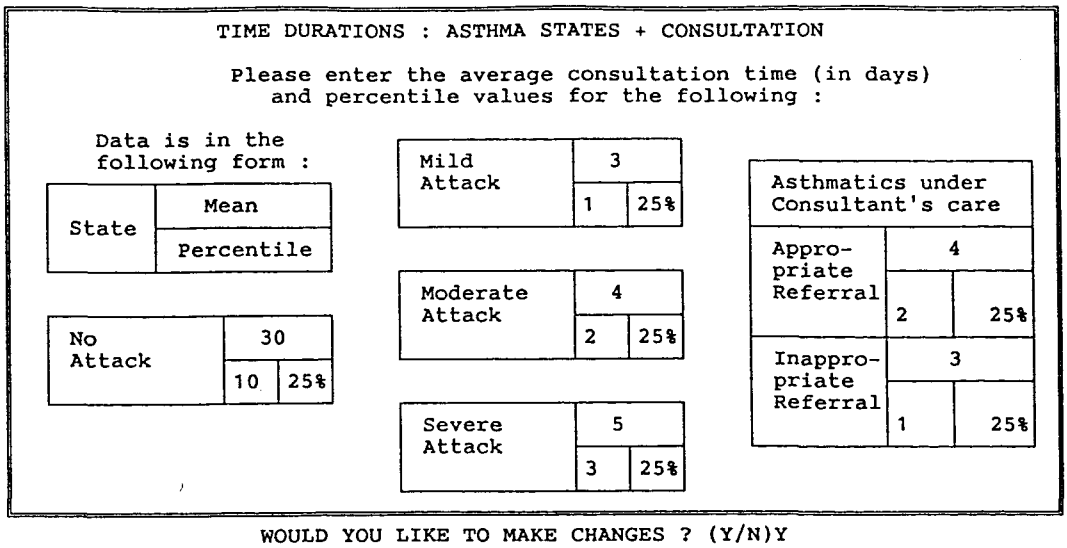


Figure 8.33. The Weibull data entry screen

After these times are entered the user then has the option of viewing all, some or none of the density functions associated with the occupation times in these states. This is also organized in form of a submenu.

The resources option produces another submenu when selected. This is to aid data entry for the available resources which will be used to allocate to the states. Thus the submenu has three options :-

Available
Allocation
Quit to submenu

The "Available" option allows the user to give the possible available resources for the management of asthma. These resources include personnel, drugs, and facilities.

The available resources are then selected for use in the appropriate states. Hence the allocation option allows the user to allocate these resources with their costs appropriately. If a resource is not used, the cost is simply given a zero value. A possible allocation of the available drugs to state 4 is shown in figure 8.34.

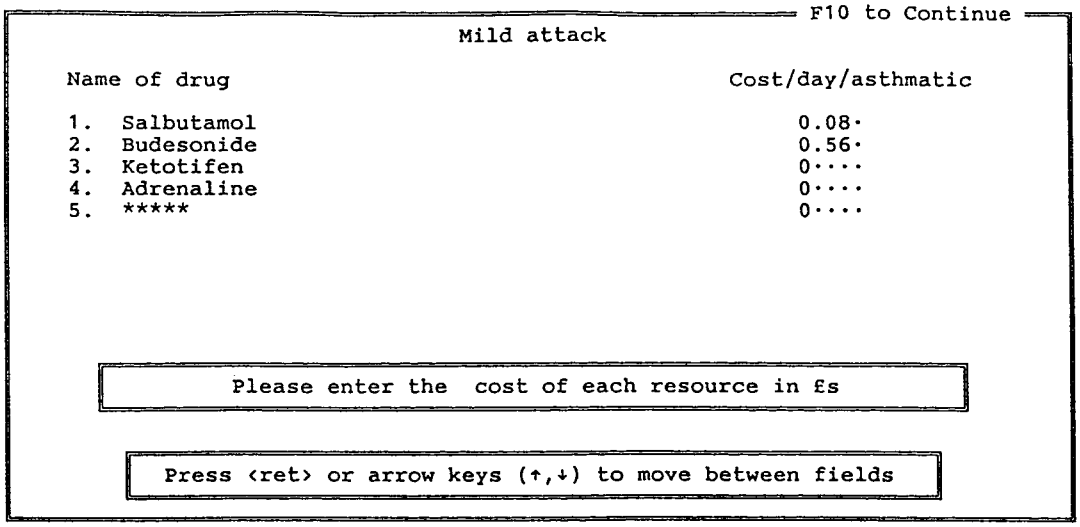


Figure 8.34. Drugs and costs for mild attack

After all these data have been entered, the user then finally decides on how long he is going to run the simulation.

We emphasize here that some of the data shown in the figures are from literature, others are based on discussions with medical people and expert opinion and some are rather arbitrary.

8.6.5. Some Results Generated from the Model

The model was run for 365 days with different strategy sets. The results are shown in the following tables. In table 8.2 the population of the community was taken to be 1,500 people with a resulting number of asthmatics of 247 at the end of the run. In table 8.3 the population considered was 2,500 with 407 asthmatics, while in tables 8.4 and 8.5, the population of the community was taken to be 2,500 people with 326 number of asthmatics at the end of the run.

Percentage reduction in

1. probability of (a) moderate attack = 90
   (b) severe attack = 90
2. duration of (a) moderate attack = 0
   (b) severe attack = 0

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	135.45
10	124.92
20	121.97
30	119.87
40	113.05
50	108.75
60	110.36
70	107.43
80	102.97
90	100.59
100	101.87
Cost of type II management	115.53

Table 8.2. Strategy set 1

We can see from table 8.2 that the type I management strategy should be such that the time between attacks is extended by at least 40%, in order for it to be beneficial.

Percentage reduction in

1. probability of (a) moderate attack = 90
   (b) severe attack = 90
2. duration of (a) moderate attack = 50
   (b) severe attack = 50

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	196.97
10	188.66
20	183.29
30	180.18
40	173.71
50	169.56
60	164.58
70	161.88
80	161.20
90	153.69
100	156.96
Cost of type II management	175.81

Table 8.3. Strategy set 2

This strategy should extend the time between attacks by at least 40%, in order for it to be cost effective.

Percentage reduction in

1. probability of (a) moderate attack = 90
   (b) severe attack = 90
2. duration of (a) moderate attack = 90
   (b) severe attack = 90

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	151.99
10	147.55
20	143.51
30	138.02
40	134.45
50	131.30
60	130.11
70	129.34
80	124.23
90	122.33
100	119.45
Cost of type II management	144.60

Table 8.4. Strategy set 3

This strategy should be such that the time between attacks is extended by at least 20%.

Percentage reduction in

1. probability of (a) moderate attack = 50
   (b) severe attack = 50
2. duration of (a) moderate attack = 50
   (b) severe attack = 50

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	155.92
10	153.14
20	147.38
30	143.98
40	138.06
50	132.19
60	133.47
70	132.71
80	127.91
90	124.33
100	122.08
Cost of type II management	144.60

Table 8.5. Strategy set 4

For this strategy to be cost effective, it needs to extend the time between attacks by at least 30%.

Results on the effect of these strategies on the number of attacks and the number of referrals were also collected. Figures 8.35 and 8.36 are recorded for strategy set 1, while figures 8.37 and 8.38; 8.39 and 8.40; and 8.41 and 8.42 are for strategy sets 2, 3 and 4 respectively.

Figure 8.35. The effect of strategy set 1 on number of attacks

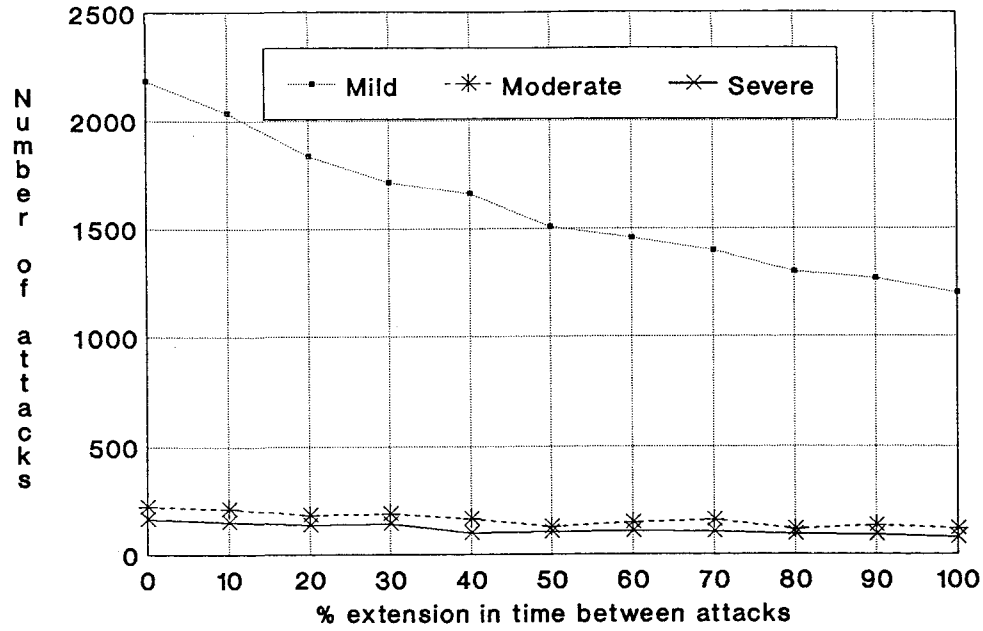


Figure 8.36. The effect of strategy set 1 on number of referrals

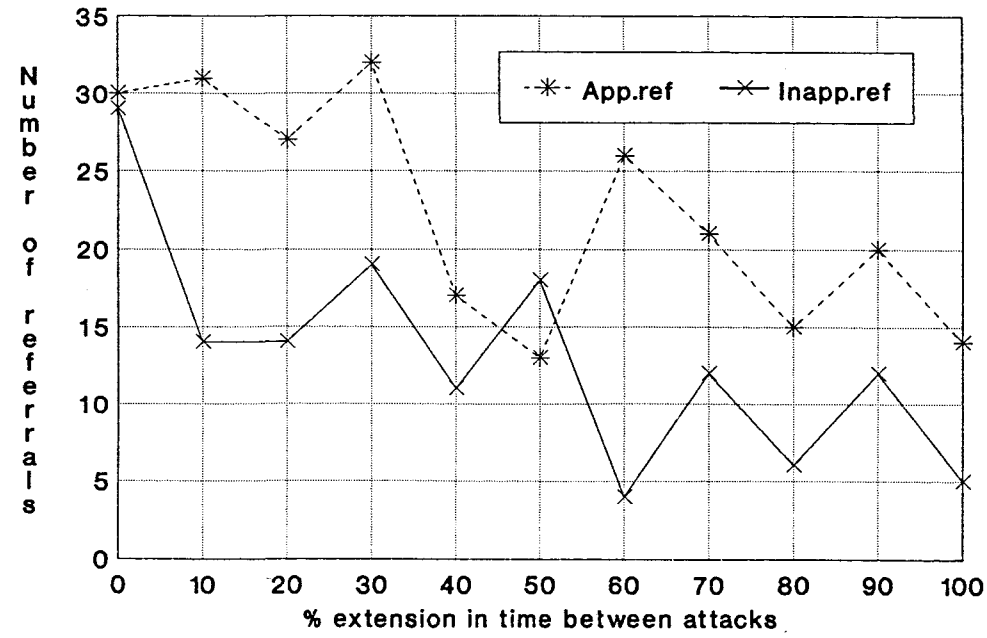


Figure 8.37. The effect of strategy set 2 on number of attacks

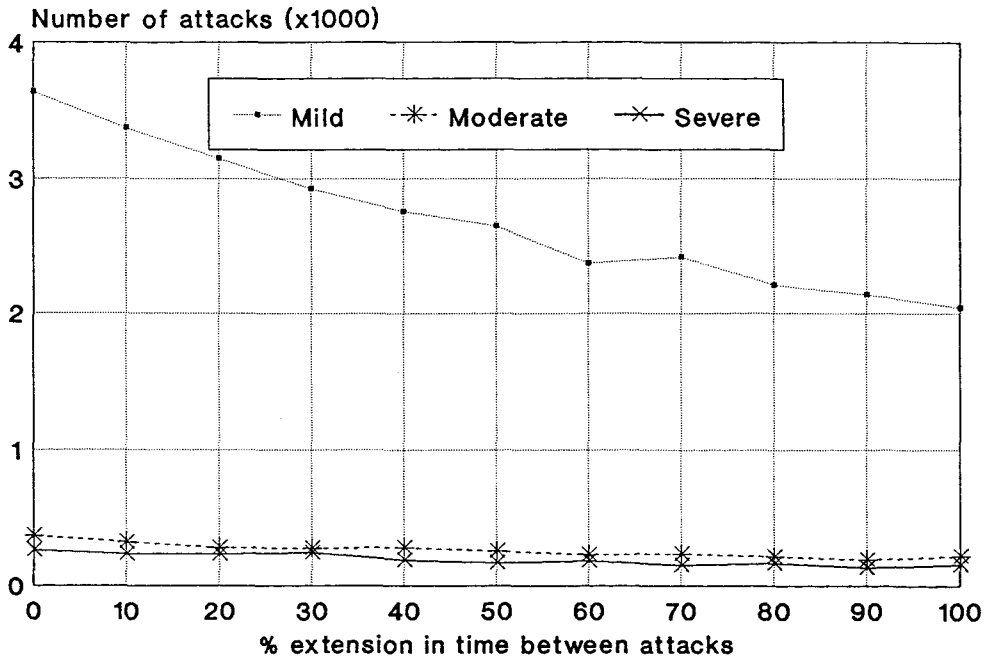


Figure 8.38. The effect of strategy set 2 on number of referrals

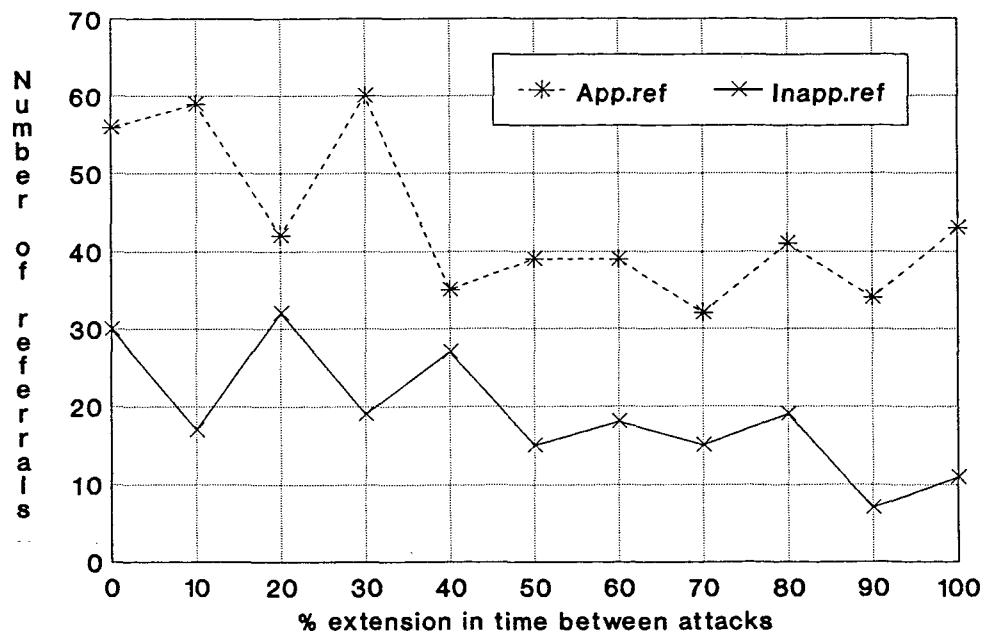


Figure 8.39. The effect of strategy set 3 on number of attacks

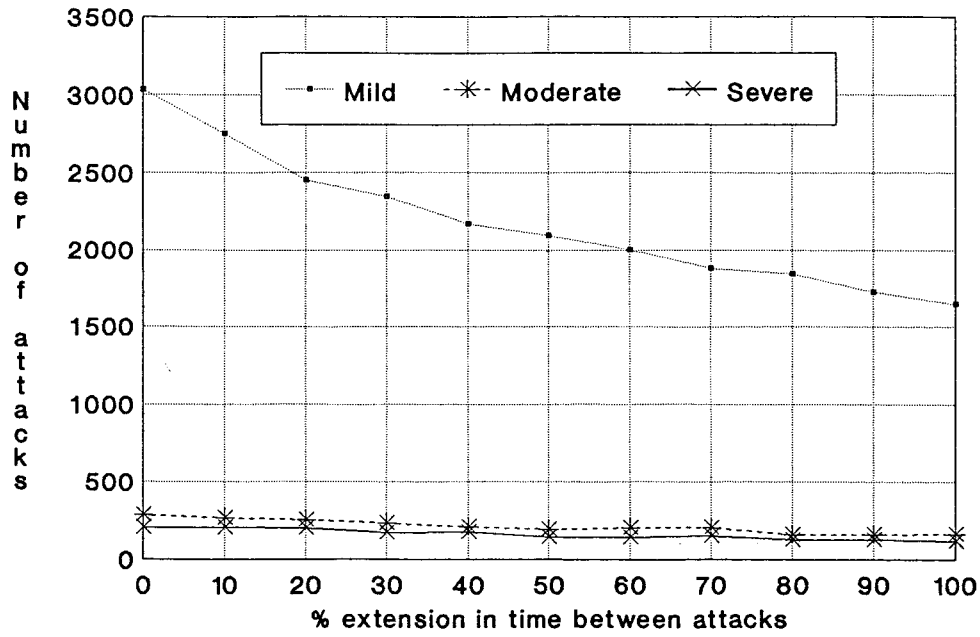


Figure 8.40. The effect of strategy set 3 on number of referrals

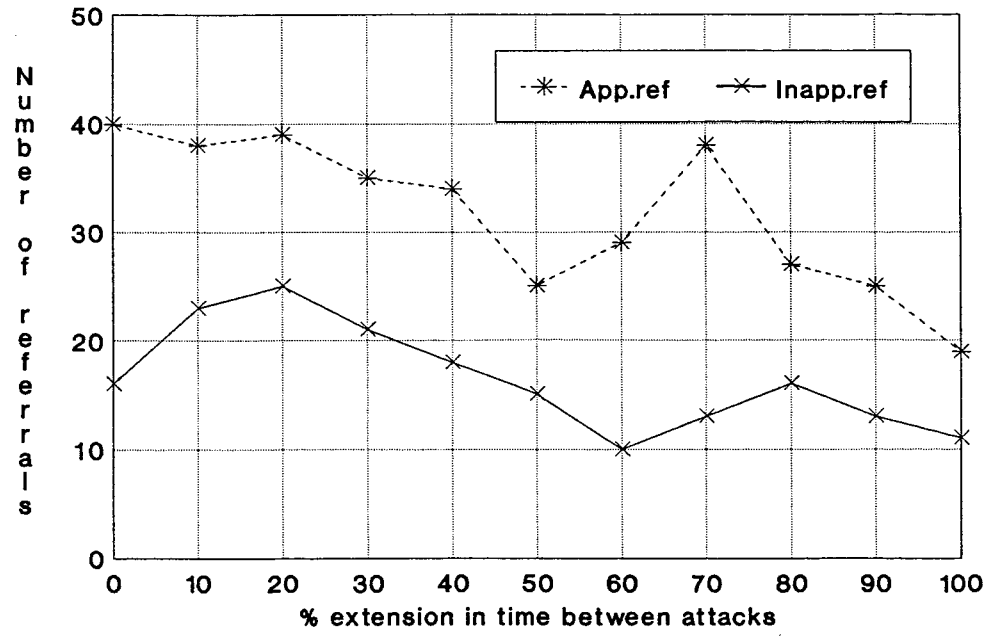


Figure 8.41. The effect of strategy set 4 on number of attacks

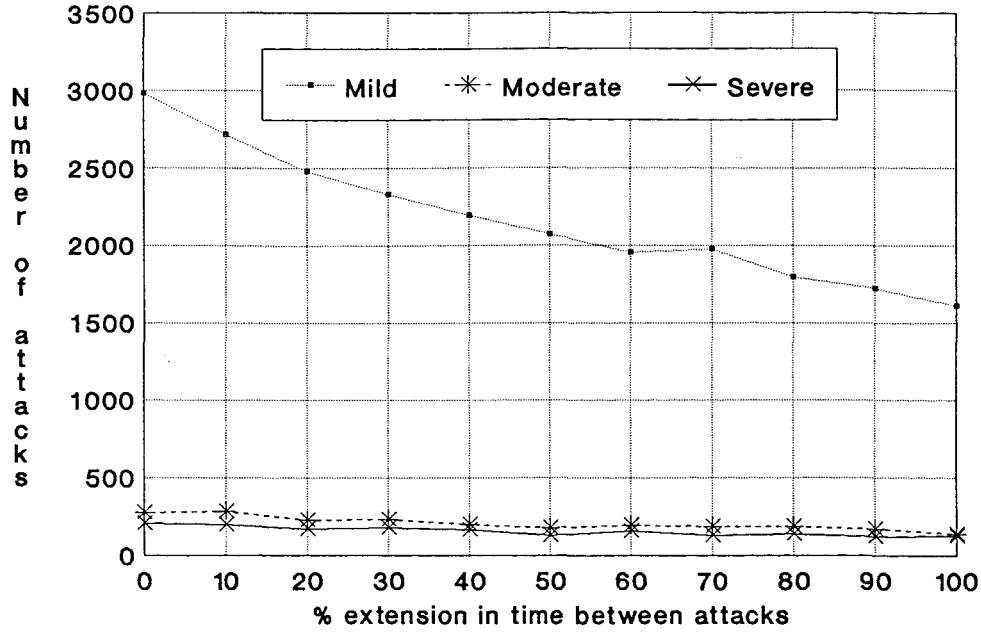
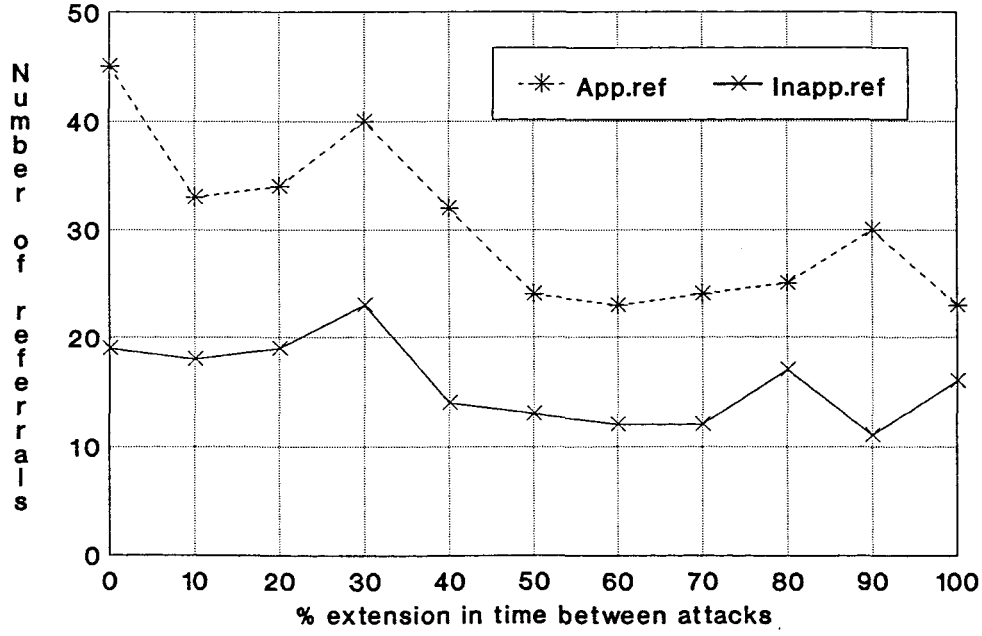


Figure 8.42. The effect of strategy set 4 on number of referrals



Other strategies were also considered. Tables 8.6-8.9 show the resulting costs while figures 8.43-8.50 give the resulting number of attacks and number of referrals.

Percentage reduction in

1. probability of (a) moderate attack = 50
   (b) severe attack = 50
2. duration of (a) moderate attack = 0
   (b) severe attack = 0

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	223.88
10	203.61
20	198.83
30	198.92
40	194.12
50	188.56
60	185.33
70	179.40
80	169.76
90	170.60
100	168.46
Cost of type II management	175.81

Table 8.6. Strategy set 5

This strategy should extend the time between attacks by at least 80%, in order for it to be cost effective.

Percentage reduction in

1. probability of (a) moderate attack = 50
   (b) severe attack = 50
2. duration of (a) moderate attack = 90
   (b) severe attack = 90

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	190.34
10	185.34
20	179.32
30	170.13
40	168.45
50	165.64
60	162.49
70	163.87
80	154.13
90	149.62
100	150.17
Cost of type II management	175.81

Table 8.7. Strategy set 6

For this strategy to be beneficial it needs to extend the time between attacks by at least 30%.

Percentage reduction in

1. probability of (a) moderate attack = 10
   (b) severe attack = 10
2. duration of (a) moderate attack = 50
   (b) severe attack = 50

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	119.23
10	112.88
20	108.57
30	101.72
40	104.75
50	99.08
60	101.31
70	96.92
80	95.71
90	94.17
100	91.36
Cost of type II management	115.53

Table 8.8. Strategy set 7

This strategy should extend the time between attacks by at least 10%.

Percentage reduction in

1. probability of (a) moderate attack = 10
   (b) severe attack = 10
2. duration of (a) moderate attack = 90
   (b) severe attack = 90

Percentage extension in time between attacks	Cost (in 1000 pounds per year) of type I management
0	153.63
10	147.58
20	143.51
30	138.03
40	134.46
50	132.69
60	130.11
70	129.40
80	124.24
90	122.41
100	119.43
Cost of type II management	144.60

Table 8.9. Strategy set 8

This strategy is worthwhile only if it extends the time between attacks by at least 20%.

Figure 8.43. The effect of strategy set 5 on number of attacks

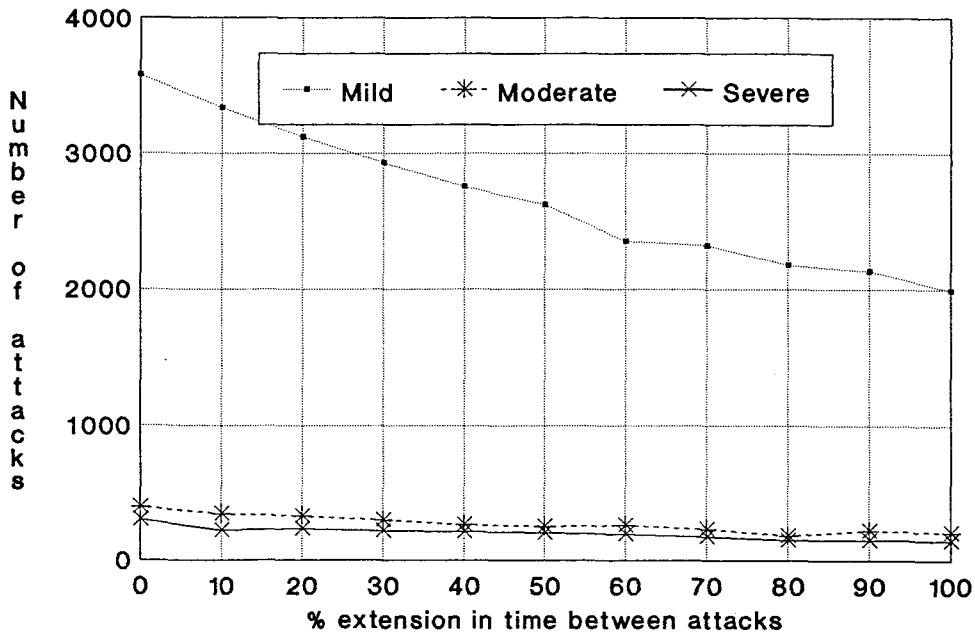


Figure 8.44. The effect of strategy set 5 on number of referrals

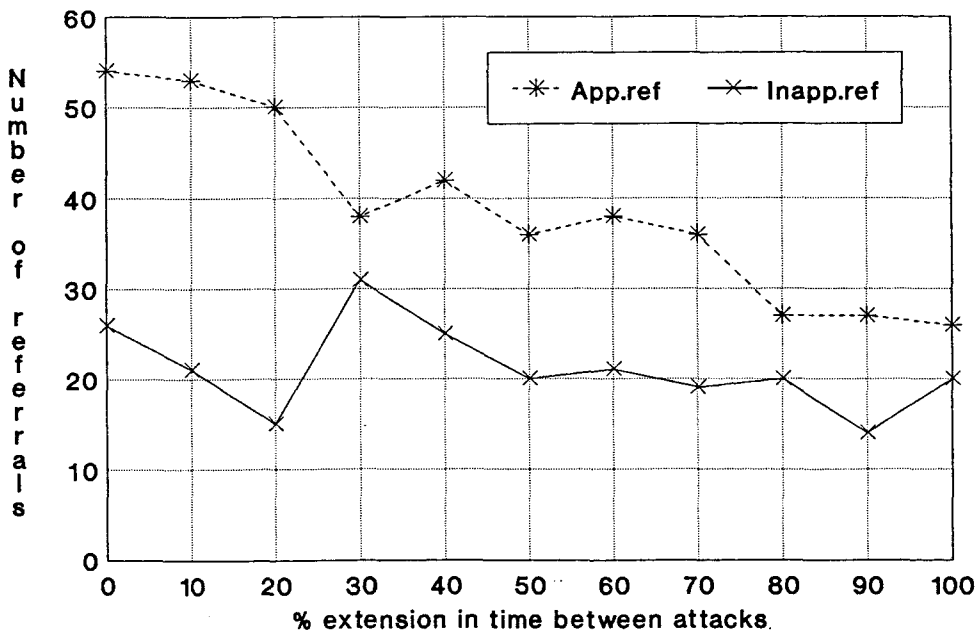


Figure 8.45. The effect of strategy set 6 on number of attacks

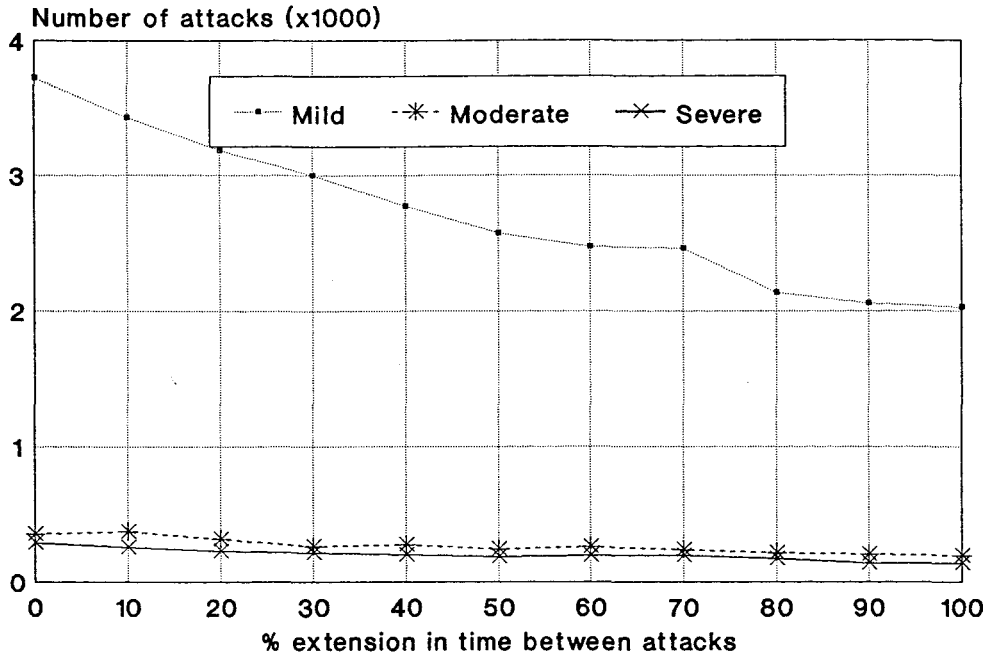


Figure 8.46. The effect of strategy set 6 on number of referrals

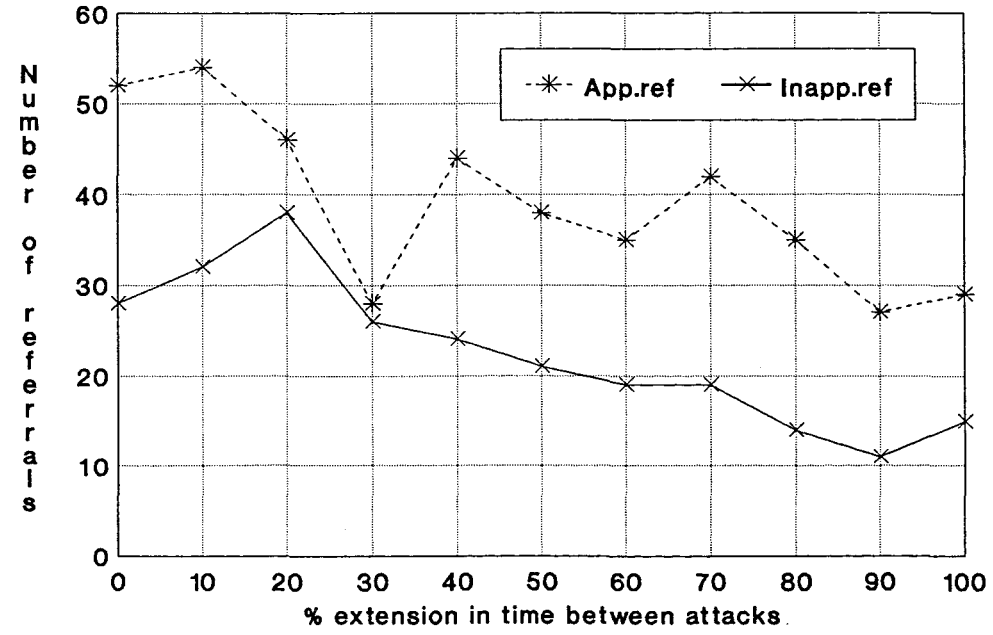


Figure 8.47. The effect of strategy set 7 on number of attacks

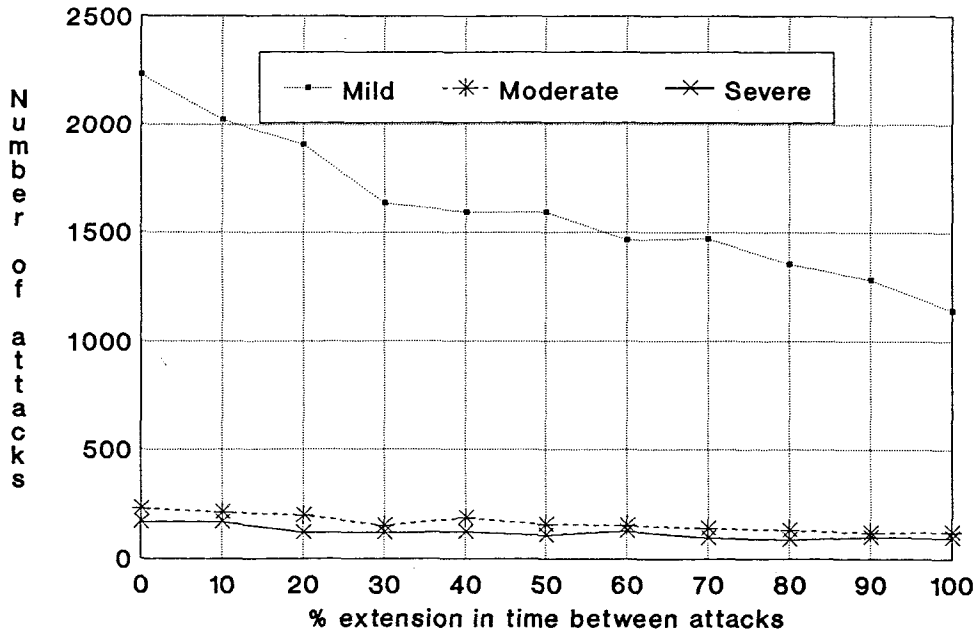


Figure 8.48. The effect of strategy set 7 on number of referrals

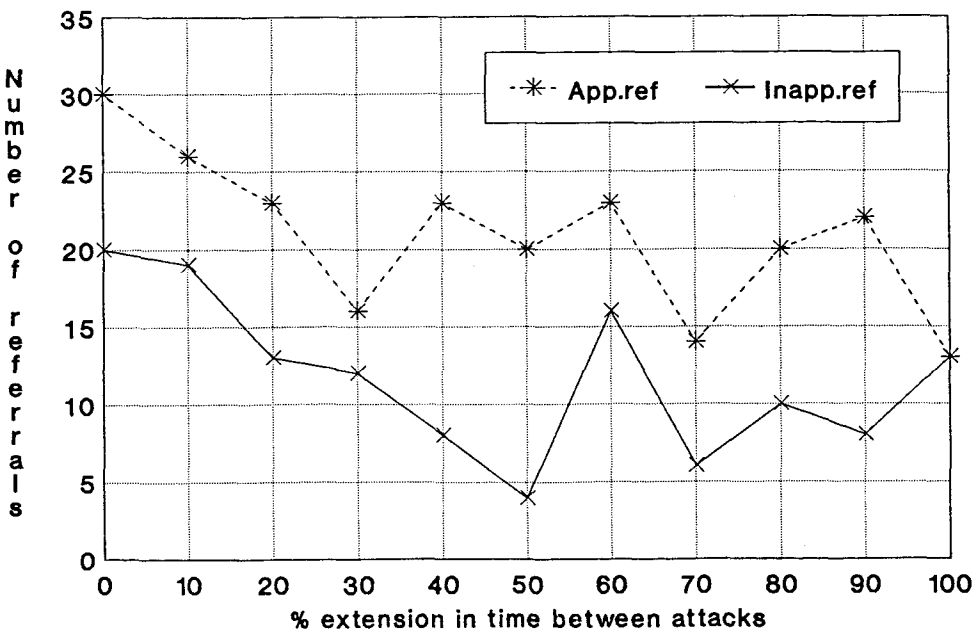


Figure 8.49. The effect of strategy set 8 on number of attacks

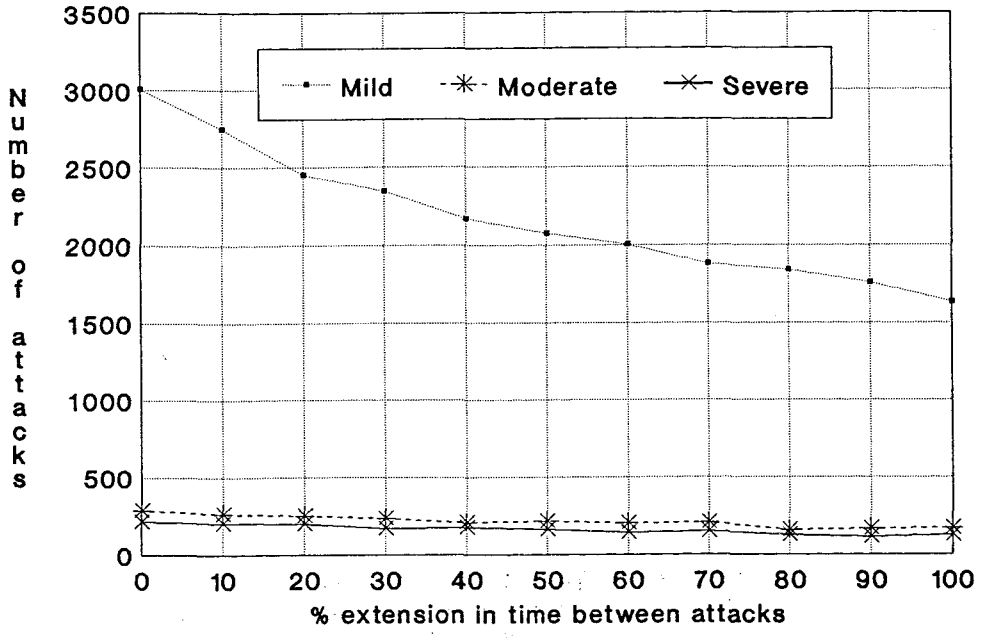
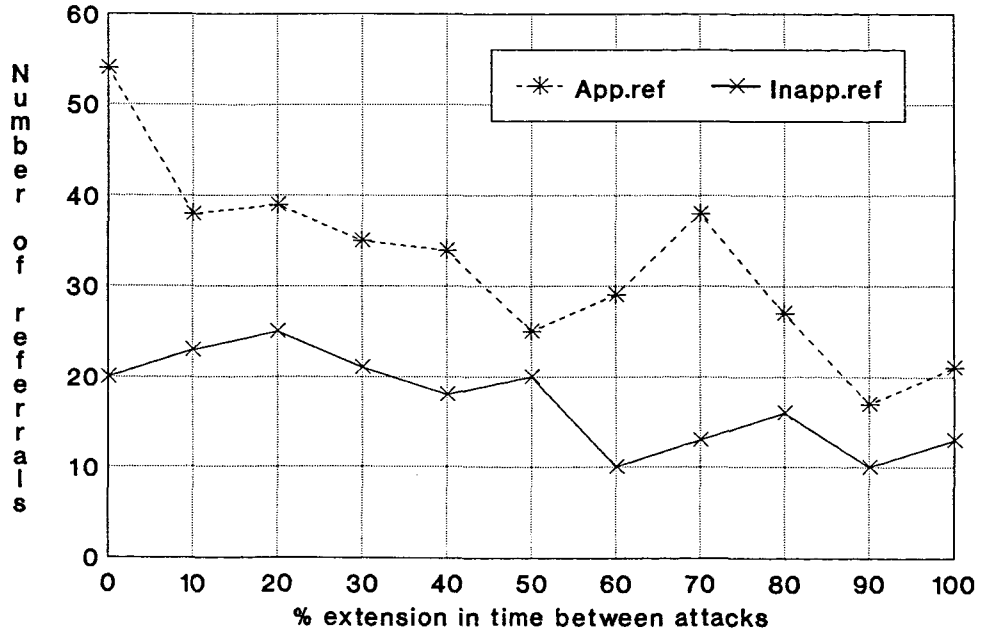


Figure 8.50. The effect of strategy set 8 on number of referrals



Results are also displayed graphically after the simulation run. The results shown in figures 8.51-8.53 are obtained from a simulation run of 2000 people with the following type I management strategy :

Percentage reduction in

1. probability of (a) moderate attack = 60
   (b) severe attack = 80

2. duration of (a) moderate attack = 50
   (b) severe attack = 90

Percentage increase in
time between attacks = 100

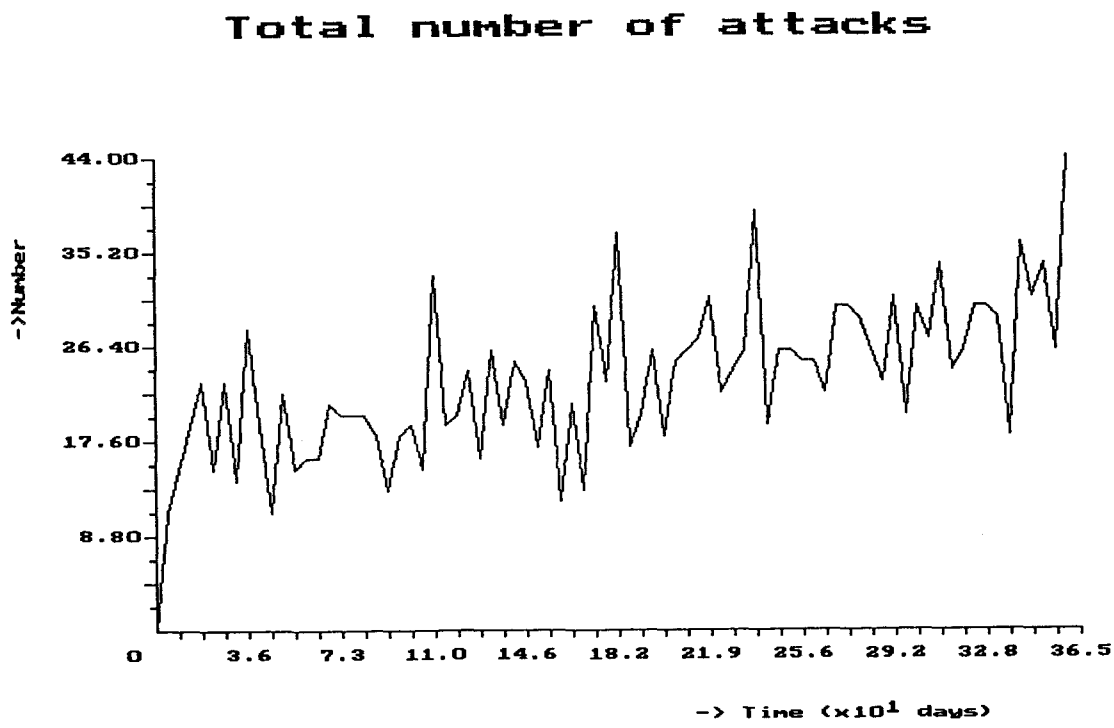


Figure 8.51. Total number of attacks

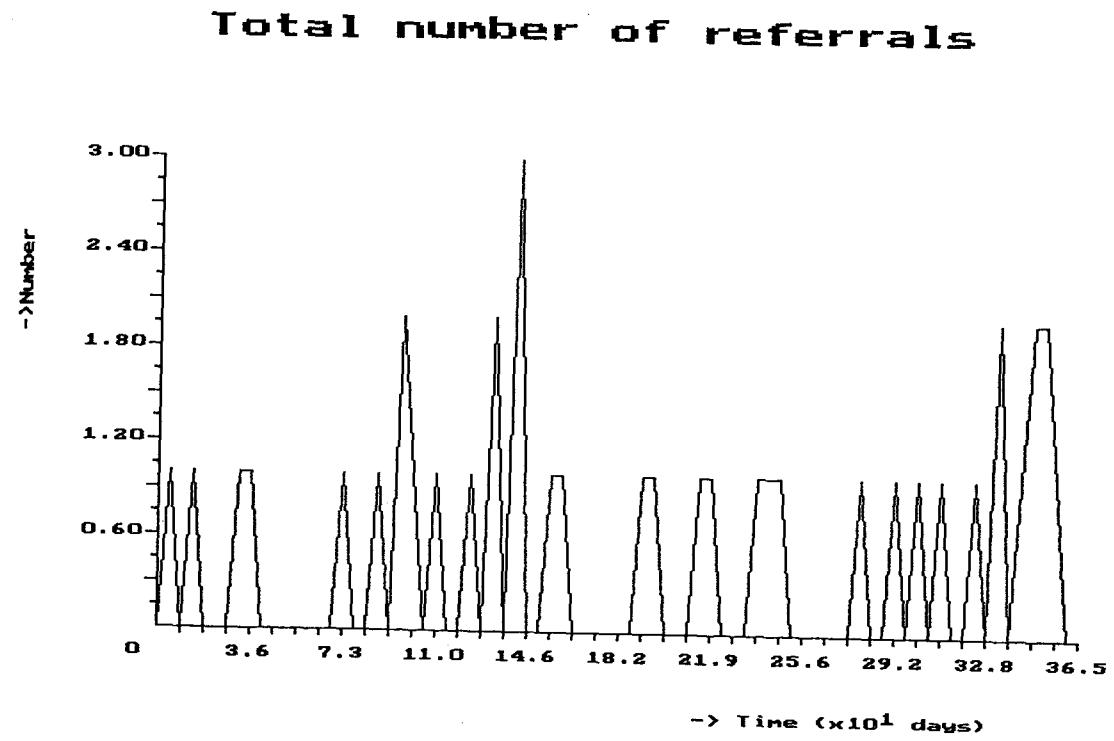


Figure 8.52. Total number of referrals

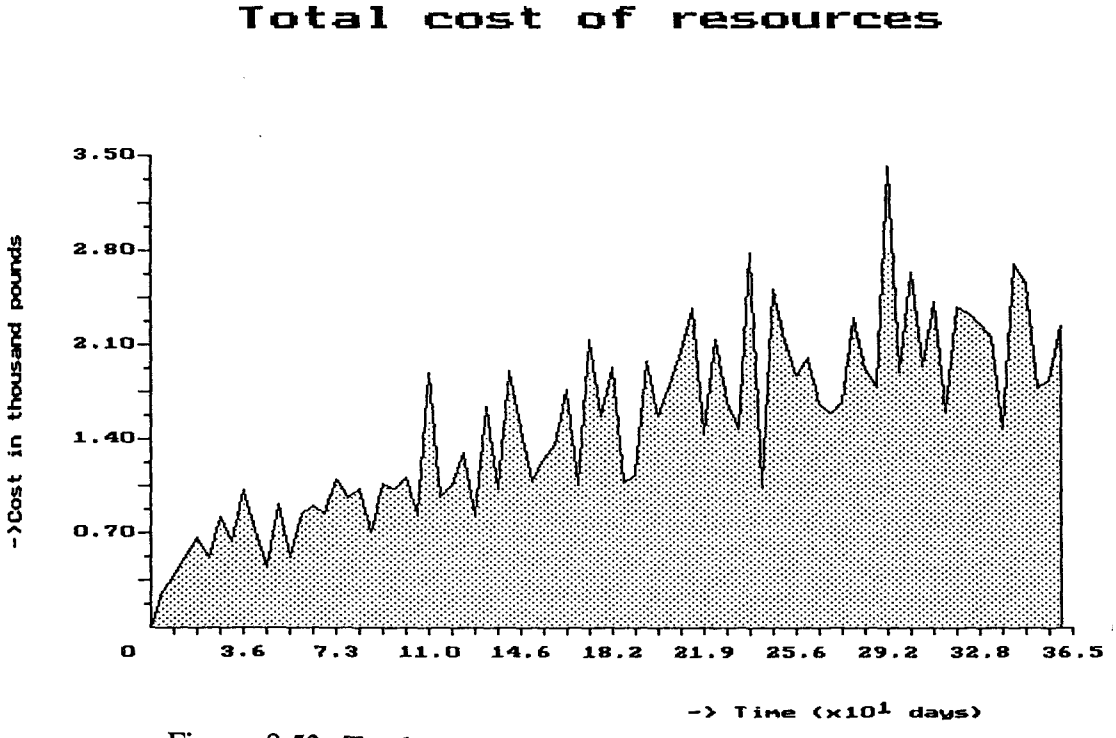


Figure 8.53. Total cost of resources

8.6.6. Comments

This model is more realistic and can be used by health policy makers to explore management strategies, under scarce resources, for a given number of asthmatics. The model can be run on any IBM-compatible machine with a VGA graphics screen mode.

The model does not take into account the consequential "costs" of an attack. These "costs" are incurred at the individual and at the community level. For an individual, attacks mean a poorer quality of life through loss of sleep, days off work, etc. For the community the "costs" are the contributions lost because the attacks prevent an asthmatic from a full participation in community life.

CHAPTER 9

TOCHSIM : THE SIMULATION SHELL USED

This chapter describes a simulation shell which is a suite of Pascal routines, used in the simulation models developed in chapter 8, which originate from the Faculty of Mathematical Studies, University of Southampton. These were written and named in honour of professor K.D. Tocher, a pioneer of the three phase method of simulation. The simulation shell, developed to aid the modelling of discrete-event simulations, is called TOCHSIM. Section 9.1. gives the rationale behind the use of Pascal for the implementation of this shell and the routines of the shell are described in section 9.2.

9.1. Pascal

Despite the availability of simulation languages such as SIMSCRIPT, GPSS and many others, many analysts implement models in general purpose, high-level languages. It has been suggested that up to 70% of all simulations are programmed in FORTRAN, see Uyeno and Vaessen (1977). A major reason is that modellers are familliar with FORTRAN and, with simulation concepts, but are unwilling to invest the time to learn a special-purpose simulation language. Unfortunately, FORTRAN does not provide built-in procedures for describing entities and events, scheduling events, and formatting and analysing results - the basic requirements of discrete-event simulation, Uyeno and Vaessen, (1977). Pascal however has some of these features. It has good list-processing facilities, it is portable, encourages good programming practices, and is

widely used. In view of these facts, a set of Pascal routines called TOCHSIM, were developed in order to help the implementation of discrete event simulation.

9.2. TOCHSIM

The shell TOCHSIM consists of a number of library units, consisting of procedures and functions, written in Turbo Pascal, concerned with some aspect of simulation programming. The units are :

1. Tochvar
2. Tochrun
3. Tochvga

and the host program TOCHSIM. We give a description of each of these in the following :-

9.2.1. Tochvar

This unit consists of the file TOCHVAR which "includes" another file called TOCHPROC. TOCHVAR is used for declarations of constants, variables and other types. It also contains procedures for the B and C activities which are called respectively by the procedures b_call and c_call.

TOCHPROC contains all procedures and functions which are used when writing the B and C activity procedures. The user can add new routines in this file. In the development of the asthma simulation programs, some graphical routines used in collecting results from a simulation run were added in this file. A description of what can be found in this file is given as follows :

An entity record in TOCHSIM has the following structure :

```
TYPE
    entity_type = Record
                    available : boolean;
                    next_b_activity : b_activity;
                    time_of_b_act : real;
                    (other user information if needed)
                  end;
```

where b_activity is of the type *byte*.

The fields of the record could be explained as follows :

available : is set to TRUE if the entity is available for a B activity, otherwise it is set to FALSE.

next_b_activity : is the number of the next B activity the entity is set to perform.

time_of_b_act : is the starting time of the B activity attached to this entity.

Entity is then declared to be of the above type. These fields are called the *attributes* of the entity. The user may include attributes of his own to distinguish between different entities. This is done in the asthma simulation. For instance, age is an attribute of the asthmatics and asthmatics are regarded as entities in the simulation. There is a global variable called CURRENT of type entity in this unit. This is a temporary name for an entity. When an entity is just taken off the CALENDAR in a B activity, it takes the name CURRENT.

Entities can be created in the simulation when needed by a procedure :

```
Procedure make_entity(e:entity);
```

This procedure also initializes the values of the attributes in the entity's

record. When the entity is no longer needed, the procedure :

Procedure dispose__entity(e:entity);

disposes of it in order to recover memory space.

A queue in TOCHSIM is represented by the following :

```
TYPE
   ptr = ^ptr_type
   ptr_type = Record
                next,pre : ptr;
                ent : entity;
              end;
```

and the queue is of type *ptr* :

queue = ptr;

Consequently, all queues the user intends to use in his program must be of type *queue*. Example, in asthma simulation, we have

```
var
  no_att_q,attack_q,
  mild_q,mod_q,sev_q : queue;
```

The procedure :

Procedure make__queue(var q:queue);

creates a queue with a previously declared name 'q' when initializing the program. Thus

Procedure make__queue(mild_q);

makes a queue of asthmatics with mild attacks.

Entities may be added to the BACK or FRONT of the queue using the procedure :

Procedure add__queue(e:entity;place:q_place;q:queue);

where

q_place = (front,back); is an enumerated type.
e : the name of the entity to be added to the queue,
place : takes values BACK or FRONT,
q : the name of the queue the entity is to be added to.

The entity can be removed from queue by the function :

function remove__from_queue(place:q_place;q:queue):entity;

The function removes an entity from the BACK or FRONT of the queue 'q'. All entities may be removed from a queue and disposed of by using

Procedure empty__queue(q:queue);

where 'q' is the name of the queue to be emptied. Alternatively, entities in a queue may be examined, but not emptied nor removed by the following :

1. *function look_queue(place:q_place;q:queue):entity;*
2. *function count_queue(q:queue):integer;*
3. *procedure list_queue(q:queue);*
4. *procedure list_b_list(q:queue);*

The first returns the pointer to the entity in the FRONT or BACK of the queue 'q'. The second gives the total number of entities in the queue 'q', and the third scans through a queue. The fourth prints all the occurrence times of the entities in the calendar.

The B activities are scheduled using the procedure :

procedure cause(b_act:byte;ent:entity;time:real);

b_act : number of B activity to be attached to the entity,
ent : the name of the entity,
time : the time from now that this B activity must happen.

The B and C activites are executed (with instructions from the executive - the RUN procedure) respectively by the two procedures

procedure b_call;
procedure c_call;

If there is no need to test any of the C activities, we can use the procedure

procedure c_off(c:byte);

c : is the integer number representing the C activity to be switched off. This procedure is used inside a C activity. The C activity number 'c' will not be performed. However, if the programmer decides that the C activity be reinstated, he can use the procedure :

procedure c_on(c:byte);

The C activity number that has been switched off in the past will now be switched on again.

Results can be displayed on screen with the use of the procedure *interact.* This procedure is called by the RUN procedure after performing a B activity and testing all the C activities.

There are other routines for resource use in this unit which we do not intend to describe here since there are not used in the asthma simulation.

Random number generation is a very important aspect in computer simulations. In TOCHSIM the procedure for setting up the random number generator is :

procedure rndset(s:seed);

Seed : is of type *longint.* Here *s* takes values from 1 to 100 inclusive. A default value of $s = 1$ is used in TOCHSIM. However a different seed can be used in the range 1 to 100.

In TOCHSIM there are procedures and functions for sampling from a few commonly used distributions. Below we shall only describe those used in the asthma simulation.

1. Sampling from Uniform[0,1] distribution
   The function :

   function rnd:real;

   returns a random number uniformly distributed in the interval (0,1).

2. Sampling from Exponential(λ) distribution
   The function :

   *function negative_exponential_deviate(***MEAN***:real):real;*

   returns a random number from the negative exponential distribution with mean **MEAN.**

For the purpose of asthma simulation we included the following distribution

4. The Weibull distribution
   We use the function *:*

   function weibull_variate(a,b:real):real*;*

   which returns Weibull variate when the scale parameter *a*, and the shape parameter *b* are specified.

There are lots of other distributions in this unit, such as

(a) the Gamma [n,σ],
(b) the poisson (μ),
(c) the Binomial (n,p).

which are not used for the asthma simulation.

9.2.2. Tochrun

This unit contains the EXECUTIVE, the procedure *run*. it also includes the procedure *initialize*. It is not altered by the programmer.

The procedure :

procedure initialize;

(a) sets the *program_abort*, a boolean variable, to FALSE. When it becomes true the program is terminated.
(b) sets the simulation time (SIMTIME) to zero.
(c) sets the random stream default value (rndset(1)).
(d) sets up the temporary CALENDAR - the b_list.

There is also the procedure :

procedure list_b_list;

This prints out the event times of all entities in the CALENDAR.

TOCHSIM makes the list of active C activities with the use of the procedure :

procedure make_c_list;

The entities are put into the CALENDAR, ordered by the time of their B activities, with the aid of the procedure :

procedure cause_b_act(ent:entity);

ent : is the entity to be put into the CALENDAR.

Finally, there is a procedure :

procedure run(runtime:real);

which is called after the programmer has set up the start conditions of the simulation. This procedure then carries out the simulation for *runtime* units of time, in the standard three phase way described in chapter 7. It finds the B activity that is to be executed next, calls the procedure *b_call* using this B activity number and passing across the entity CURRENT, which was used to call this B activity (using procedure *cause*). After each b_call, the procedure *interact* is executed and then control is passed to the procedure *c_call* which checks the C activities. This continues until one of the following occurs :

1. The simulation run time (*runtime*) is exceeded or
2. No more B activities remain to be executed or
3. *program_abort* has been set to TRUE.

9.2.3. Tochvga

This unit includes all procedures used for setting up graphical display and building histograms. Notable among them is the procedure :

procedure vga_histogram(histogram:graph_out);

where

```
graph_out = Packed record
                title,x,y:string;
                base,width:real;
                dat:array[0..20] of real;
                scale:real;
                oldtime:real;
            end;
```

This procedure draws the histogram on the screen. But before this is done, the programmer has to call the procedure :

procedure set_vga;

which sets up the screen for high resolution VGA graphics.

The procedure :

procedure set_text;

resets the screen back to normal text mode, if needed.

The histograms are created using the procedure :

procedure reset_histogram(var histogram:graph_out);

This also resets the histogram for new input.

Data is logged on to the histogram by the procedure :

procedure log_histogram(hist:graph_out,x,y:real;is_graph:boolean);

This logs the data y into cell x on the histogram. The boolean variable *is_graph* enables the collection of time dependent data e.g. queue length. If it is set to TRUE, then y takes the value of SIMTIME.

9.2.4. Tochsim

This is the host program. The initialization process is done here with the use of the procedure :

procedure init;

This procedure

(a) calls the procedure *initialize* from TOCHRUN,
(b) declares queues, resources, histograms,
(c) initializes other user defined variables,
(d) creates the first entity and puts it in the CALENDAR,
(e) decides on the run time of the simulation.

The program calls the procedure *run* to start the simulation.

9.3. Comments

We can see that Pascal allows the modeller to represent the various entities clearly and concisely. The type declaration allows the modeller to define new types that combine the structural types array and record and the simple variable types - integer, real, boolean, and char. The fields of records do not have to be of the same type. Furthermore, Pascal provides dynamic variables. TOCHSIM combines dynamic record variables and *pointers* to develop the data structures required for efficient manipulation and scanning of lists and the effective utilization of memory.

CHAPTER 10

SUMMARY, FURTHER WORK AND CONCLUSION

This chapter gives a summary of the work done together with suggestions for further work. It is concluded that the modelling approach of Operational Research is well suited for dealing with asthma and other diseases.

10.1. Summary

The thesis explores a variety of models which could be used for the understanding of asthma. In chapter 4 we considered models in discrete time. Variability and uncertainty was not considered at this stage. This kind of approach does not really reflect the nature of the disease. For example, the average time between attacks was assumed to be 30 days, hence in this discrete version every asthmatic must have an attack when this time is due. In reality this attack-free period vary from one person to another. Thus in this situation involving variability and non-linearity, the use of averages could be misleading (Shahani, 1981). With this kind of problem therefore, the deterministic model is rather inadequate.

For this reason, stochastic models were considered in chapter 5. An assumption of the Markov property was initially made and Markov chains were developed for this disease. Notably among them was a seasonality model which could be used to study the effect of changes in weather conditions on the asthmatics. This approach has proved to be quite good. It however has its own short-comings in that transitions are only considered at uniformly spaced intervals of time. With the disease asthma a lot of things might happen between these time instants which may then be unaccounted for, or it may be that nothing has happened between two consecutive time instants and hence there might be no need to stop at the next time point to see what has happened. Because of this, a semi-Markov chain model was considered in this same chapter. We can

see that as the model was made more realistic the more complicated it became and hence the mathematics involved became more difficult to comprehend.

In chapter 6 the asthma process was considered as a process in continuous time. This is because it may be necessary to have information about the asthmatics at any given time. There are limitations in developing models of this sort, since with a large number of states, the tedious task of using the Laplace transform method, although appropriate computer packages may be used, may yield round off errors.

The restriction to the Markov structure was dropped in section 6.3, but appropriate methods were suggested on how to convert non-Markovian processes to those with the Markov property. An alternative formulation was given in section 6.3.2 for situations where the conversion to a Markov process is not necessary.

Disadvantages of this kind of modelling were highlighted in chapter 2. These disadvantages are more pronounced when the model is to be used by people who have limited knowledge of mathemetical methods. For this reason simulation models of increasing realism were constructed in chapter 8. These models require a lot of data some of which are nowhere to be found at this moment. The problem of validation of the models is discussed in section 10.2.

10.2. Further Work

Further work required for this model can be summarized as follows :

(1) The models should capture the aspect of admissions to hospital and days off work or school. This could be used in justifying the high cost of preventive care (type I management).

(2) The possibility of growing out of asthma at the time of adolescence has been thought to be affected by a previous history of atopic diseases such as hayfever and eczema.

These models could be modified to include these possibilities.

(3) The time between attacks and durations of attacks which depend on the type of asthma - extrinsic or intrinsic, used in models III and IV could also be easily incorporated in model V.

(4) The treatment of an asthmatic is said to depend on age. This aspect could also be incorporated in these models in order to make them more realistic.

(5) Data is also needed on the age distribution of asthmatics, probabilities of making transitions from mild attack to moderate attack or severe attack, from moderate attack to severe attack, and from severe attack to appropriate and inappropriate referrals. Data on the effects of treatments is also needed. Without these data validation is not possible.

The major work which requires further attention is the problem of validation of the simulation models.

As suggested by Sargent, (1991) a third party has to be used as part of the validation process. The party has to make a decision that the model is valid. This is a subjective decision and is based on the results of the various tests and evaluations conducted as part of the model development process.

The following techniques are suggested for a more realistic validation of these simulation models.

(1) The result on the annual incidence of asthma obtained from the model is 76 per thousand population. It has been reported that this incidence is 84. This discrepancy may be as a result of deaths, people that have grown out of the

disease, or some other cause. It however has a close relationship with the real system. The occurence of other "events" obtained from the simulation models e.g. number of grow outs, and deaths, should be compared to those of the real system to determine if they are the same.

(2) The structure of the models and their output should be checked for any extreme and unlikely combination of levels of factors in the system. Part of this has been done e.g. in model V every asthmatic was put on type I management and the resultant cost of type II management was zero. The asthmatics were also put on type II management and the cost of type I management was zero, making the model reliable for these extreme combination of levels of this factor in the system.

(3) Specialists in the management of asthma confirmed that the models and their behaviour are reasonable. This is just a minute part of model validation.

(4) Data is needed on the cost of resources, the time between attacks, the durations of attacks, and the number of attacks experienced by the asthmatics, in order to perform some serious validation. The data should be used to determine if the models behave as the real system does. This may be done by comparing, say the number of mild, moderate, and/or severe attacks obtained from the models, against the number obtained from the actual system.

Using data to determine the validity of a simulation model is not an easy task. This is because it is time consuming, and costly to obtain sufficient, accurate and appropriate data, (Sargent, 1991). This is the major reason why the validation of the models developed here has not been possible.

10.3. Conclusion

Models considered in this reasearch can help medical personnel to evaluate the effect of management plans on the health outcome of the asthmatics and also to choose a management plan that is cost effective. The mathematical models can be used to determine the number of asthmatics in each disease state at any time point. The simulation model V is more realistic and can be used to help in decisions about which management strategy to adopt.

The simulation models use a reasonable set of default values for most of the data needed. Some parameters, such as, transition probabilities, mortality, incidence, proportion of asthmatics growing out of their disease were estimated from various sets of data. The simulation models allow the user to use their own estimates for these parameters, and other parameters such as the effectiveness of treatments for which there is no published data.

Asthma is a very complex disease, even medical doctors find it difficult to diagnose, assess the severity, and give appropriate and adequate treatment. The development of models for asthma requires time, resources and the support and cooperation of people in the medical profession.

The intensive study that was required for the development of these models has not only resulted in basic models for management of the disease but has also resulted in a better understanding of the disease dynamics. For example, there is a general belief that the cost of preventive care is higher than that of acute care, but if preventive care leads to reduced mortality and fewer number of referrals then this higher cost can be justified. The problem is determining what the optimum balance between the two should be. Simulation model V not only confirms this but also showed that at a certain stage a very good preventive care costs less than the cost of acute care, making it more effective. The models do not take the important consequential costs of asthma attacks such as days away from work, hospital costs, loss of sleep etc. into account.

Models developed in this research are very simple. This is because they are developed for use by the medical planners who have no strong background in mathematics. To make these models more realistic requires more time, resources and support and cooperation of the national or local authority in providing the necessary information. Operational Research has been very useful in health care management problems and its scope in problems related to the control of chronic and infectious diseases is very wide. This new area of developing models for dealing with disease is very challenging for Operational Research scientists.

APPENDIX 1

A DESCRIPTION OF PROGRAMS FOR MODEL V

The program for model V consists of eleven units of code. TECHNOJOCK (1989) was used extensively for the design of input screens. The following gives a description of these units and the main program.

1. VARDECS

This unit consists of variable declarations used in the simulation.

2. SCREENS

This is the data input unit. It requests for the population of people in the community including asthmatics. It also contains information for type I management strategies, the age distribution of people who are currently asthmatic, the incidence rates of the disease asthma, and the growing out statistics.

3. FIRST

This unit is used to calculate the number of attacks and the number of referrals resulting from the simulation. The time between attacks, the durations and consultation times are also recorded by this unit.

4. SECOND

This unit uses the results obtained with the unit FIRST to calculate the costs of resources.

5. SETUP

This unit allows the reading and writing of data (excluding resources) into files.

6. RESINP

This unit deals with the reading and writing of resources data into files. New data files can be created using this unit.

7. DENSITY

Information about the time between attacks, the durations and consultation times is requested by this unit. The unit also displays the density functions of the exponential or Weibull distribution of these time durations, if required.

8. OUTPUT

This unit takes care of output from the simulation model. It is used to store and/or display results from the simulation. It is also used to view results from previous runs.

9. RUNSIM

This unit initialises variables and sets the necessary parameters and queues for the simulation. It consists of the procedure **Runnit** which contains the procedure **Run**. The procedure **Runnit** is called by the main program ASTHMA5 to start the simulation.

10. TOCHVAR

This unit uses programmed parameters on the duration in each state determined from the input screens to compute how long each person is to remain in the present state before making a transition to another state. The unit moves each

person at the designated time (T phase) to the destined state (B phase), using the transition probabilities.

11. ASTHMA5

This is the main program for model V. It initialises some of the menus and calls the procedure **Runnit** to perform the simulation.

12. OVRINT

This is the overlay unit which is used for memory management.

APPENDIX 2

HOW MODELS III AND V CAN BE RUN

The following explains how the simulation programs for models III and V can be run.

1. HARDWARE REQUIREMENTS

The simulation programs for these models will run on any IBM - compatible machine with a VGA graphics screen mode. The programs will not fit on a 5 1/4" low density disk, but could however be made to fit by just deleting the files with extensions **PAS** and **BAK**.

It is highly recommended that you run the programs from the hard disk drive if there is any. Programs run from this drive will run faster, but the speed at which the program runs will depend on the particular machine it is running on. If the machine has no hard disk, then the programs can be run from a high density floppy disk. What you just need to do is to put the disk in the disk drive and type asthma3 for model III or asthma5 for model V.

To run from the hard disk, you first make a directory **DOO** then copy all the files on the floppy disk into this directory. The programs need enough memory space and a memory manager is required since they use overlays.

All the files created during the program run will be automatically saved in the directory **DOO**. Furthermore the programs will only look for input data files and output files in this directory.

2. INPUT DATA FILES

For both models you have the option of creating your own input files from scratch or editing existing files. The programs however come with their sample files. When you select a data input option, a directory will be displayed,

showing all the files of the same type which already exist. If there is more than one you can then select one by writing its name as will be requested. A new file can be created by just typing its name (without an extension). This filename should not be more than 8 characters long and must be a valid **DOS** filename. All the data input screens have been designed to make the input of data as easy as possible.

3. RUNNING THE PROGRAMS

The simulation run is initiated by selecting the **RUN** option from the main menu. Files for all the data you created or have been created will now be required for a run. You then select these files, one after the other, from directories of all the available files (if there are many of each type) before you run.

4. OUTPUT

After the run is completed you will have the option of viewing the output in text form and/or in graphical form (for model III) or just in graphical form (for model V). The results from the run can also be saved in files with their filenames entered by the user. Output from a previous run can also be viewed by selecting the appropriate option from the main menu.

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