A FORTRAN PROGRAM OF A SEMI-MARKOV MODELLING FOR THE CONTROL OF LEPROSY

BY

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CERTIFICATION

This is to certify that this project work carried out by Mallam Abubakar Usman Yusuf meets the requirement for the award of a post graduate Diploma (PGD) in computer Science of the Federal University of Technology (FUT) Minna,Niger State.

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DEDICATION

To my Son ABUBAKAR, my Late father ABUBAKAR, my wife Hajara and to my mother Hajara and of course the entire family.

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ABSTRACT

Leprosy is considered in this project as a form of Markov process. The basic concept of a Markov process is that of "state " of a system and state "transition". It is a process that runs in time. At any given point in time, the process is in a given state and could possibly make a transition to another state after a period of time.

The fundamental basis of the semi-Markov process is the 'interval transition probabilities'. This is made up of tansition probabilities of the Markov chain and the holding time in the state described by a random variable . The exponential distribution has been used to describe the holding times in the states of the disease.

We have been able to demonstrate quatitatively the application of computers to a semi-Markov modelling. The semi Markov modelling involves the calculation of the interval transition probabilities.

The determination of the interval transition probabilities including the effectiveness of treatment have been obtained by the fortran program. The computer is a useful tool in a semi- modelling. The model could be used as a predictive device for the studying of health status of leprosy cases. The predictions are useful to health polcy makers for the planning of resourses.

LIST OF FIGURES

LIST OF TABLES

TABLE OF CONTENTS

CHAPTER ONE

MARKOV & SEMI - MARKOV PROCESSES

INTRODUCTION

We shall discus the Markov and Semi- Markov processes in this chapter; the exponential distribution is also discussed in section 1.2 , programming in Fortran language in section 1.3 and leprosy and review of its' model in section 1.4.

1.1 Markov and Semi- Markov processes

Andrei Andreavich Markov (1856-1922) is recognised as the 'inventor' of markov chains. The basic concept of a markov process is that of "state" of a system and state "transition". It is a process that runs in time. A markov process in discrete time and discrete state is called markov chains. When the particular set of states have been specified it is necessary to record probability of change from one state to another during a unit of time. This information can be show in a 'directed graph' called transition diagram and recorded in transition 'matrix'.

The markov chain requires the process to change state at the appropriate time units. However, some processes may not necessarily change at these time units. Therefore, we consider a situation where transition occurs at several time units.

This leads to the general form of markov process called the semi- markov process. Simply put, a semi-markov process is that process that depends on the transition probability matrix P_{ij} and holding time matrix $h^{(t)}$ where (i,j = 1,2,3,...denoting) states . These two parameters form the input data for the interval transition probabilities $Q_{ij}(n)$where

n = 0,1,2,.....representing years.

1 . 2 TIE EXPONENTIAL DISTRIBUTION

The probability density function of the random variable T having the exponential distribution is given by

$$f(t) = \begin{cases} \lambda e^{-\lambda t} & t \geq o \\ o & \text{elsewhere} \end{cases} \qquad \text{_____ (1)}$$

Where $\lambda > 0$

The distribution has λ as a parameter. λ also determines the shape of the distribution. The mean μ of the exponential distribution is

$$\mu = E(T) = \int_{-\infty}^{\infty} t\lambda e^{-\lambda t}\, dt - \int_{o}^{\infty} t\, \lambda e^{-\lambda t}\, dt$$

Substituting w $= \lambda t$ = t = w/λ and dw = λdt in the integrand gives

$$\mu = \int_{o}^{\infty} \frac{w}{\lambda} e^{-w}\, dw = \frac{w}{\lambda} e^{-w}\Big|_{o}^{\infty} - \frac{1}{\lambda}\int_{O}^{\infty} e^{-w}\, dw$$

$$= \frac{1}{\lambda}$$

Thus μ = 1/λ

$$E(T^2) = \int_{\infty}^{\infty} t^2 \lambda e^{-\lambda t}\, dt$$

Let w = λt = t = w/λ and dw = λdt

So that $E(T^2) = \int_{\infty}^{\infty} t^2 \lambda e^{\lambda t}\, dt = \int_{o}^{\infty} \frac{w^2}{\lambda^2} e^{w}\, dw$

$$= \frac{w^2}{\lambda^2} e^{-w}\Big|_0^\infty - \frac{2}{\lambda}\int_0^\infty w e^{-w}\, dw$$

$$= -\frac{2}{\lambda} e^{-w}\Big|_0^\infty = \frac{2}{\lambda^2}$$

The variance s^2 of the exponential distribution is therefore given by

$$s^2 = E(T^2) - (E(T))^2$$

$$= 2\lambda^2 - 1\lambda^2 = 1\lambda^2$$

Thus $s^2 = 1\lambda^2$

The survivor function S(t) is given by

$$S(t) = P(T > t)$$

and it is the probability that an individual has survived up to time t.

Suppose F(t) is the cumulative distribution function of the random variable T. Then

$$S(t) = 1 - F(t)$$

For the exponential distribution

$$F(t) = P(T \le t) = \int_0^t f(s)ds$$

$$= \int_0^t \lambda e^{-\lambda s} ds$$

$$= 1 - e^{-\lambda t}$$

Therefore

$$S(t) = e^{-\lambda t}$$

The failure rate or the hazard rate, 'h' associated with the random variable T is given by

$$h(t) = f(t)/S(t)$$

For the exponential distribution, the hazard rate is given by

$$h(t) = \lambda$$

This explains that the failure rate for an exponential random variable in constant.

To interprete h(t) we consider the conditional probability $P(t < T < t + \Delta t / T > t)$. That is, the probability that the individual will die during the next Δt time units, given that he survived at time t. Using the definition of conditional probability, we have

$$P(t < T < t + \Delta t / T > t) = \frac{P(t < T < t + \Delta t)}{P(T > t)}$$

$$= \frac{\int_t^{t+\Delta t} f(s)ds}{p(T > t)}$$

$$= \frac{\Delta t f(\xi)}{s(t)}$$

Where $t < \xi < t + \Delta t$

This failure rate is a constant in the case of the exponential distribution.

1. 2 . 2 PARAMETER ESTIMATION

We have seen that the exponential distribution has a simple probability density function f(t) given in (1) that is fully specified by a single parameter λ. This parameter is estimated by specifying the mean of the distribution. Thus if the mean μ is specified then the parameter λ is estimated using

$$\lambda = 1/\mu$$

The exponential distribution is a prominent statistical measurement model. It has the advantage of been fully specified by one parameter. Most applications are based on its 'memoryless' property, when the measurement variable T has a time dimension. This property refers to the phenomenon in which the history of the past events does not influence the probability of occurrence of present or future events. The application of the exponential model arises in the theory of queues in conjunction with the Poisson and Erlang models. From the waiting time interpretation of Erlang variable T, it follows that $f(t) = \lambda e^{-\lambda t}$ is the waiting time model to the first Poisson event. But the exponential model is 'memoryless' as mentioned earlier. Consequently, the waiting time to the first Poisson event is the same random variable as the waiting time between

any two adjoining Poisson events. The exponential distribution is a special case of both the Gamma and the Weibull distributions

Despite the above advantages of the exponential distribution, it has the weakness of the measure of hazard rate which is constant (λ). Thus it does not accurately define the holding time in the states of a disease which changes with time.

1.3 THE FORTRAN PROGRAMMING LANGUAGE

One of the first high-level languages to gain wide spread acceptance was FORTRAN (FORmula TRANslation). It was developed for the IBM 704 computer by John Backus and a team of thirteen other programmers.

It is one of the most widely used programming languages for solving problems in science and Engineering, since its creation in the late 1950s, it has undergone a number of modifications that have made it very powerful yet easy- to -use language. These modifications, however, led to a proliferation of different dialects of fortran, which hindered program portability. Since some uniformity was desirable, the American National Standards Institute (ANSI) published the first fortran standard in 1966. In the years following extension to this standard version of fortran were developed, some of which came into common use. It became apparent that many of these features should be incorporated into a new standard. This updated ANSI RORTRAN standerd (ANSI x3.9-1978), popularly known as Fortran 77 is the programming language used in this project.

It reflects our view that the main reason for learning a programming language is to use the computer to solve problems. The basic steps in program development in this project includes

(1) Problem analysis and specification

(2) Algorithm development

(3) Program coding

(4) Program execution and testing

(5) Program maintenance.

ADVANTAGES OF PROGRAMMING IN FORTRAN LANGUAGE

Fortran language is recommendable for both the Novice and veteran programmers. It is suitable for compute - bound processes. This is a major characteristic of science and Engineering processes. Thus it is particularly suitable for a semi markov processes. Fortran compiler is common software available in most personal and mainframe computers.

Fortran programs are highly portable and easily maintaned.

However, Fortran programs could be difficult to debug and therehy take much time to compile, unlike some other programing languages that utilises interpreters.

1.4 LEPROSY AND A REVIEW OF ITS MODELS

1.4.1. DEFINITION OF LEPROSY

Many definitions of leprosy exist but Hunter (1966) defined leprosy as a chronic infectious disease primarily of the skin and nerves caused by Mycobacterium leprae. It is one of the least infections of all the infectious disease. The incubation period varies from less than a year to many years, but probably averages three to five years.

1.4.2. TYPES OF LEPROSY

Several variants of the disease are demonstrable, but the disease can be divided generally into two polar types; tuberculoid and lepromatous. A transitional or demorphous type may show a variable degree of similarity to the tuberculoid or the lepromatous types depending upon which pole it approximates.

The non-lepromatous cases exhibit resistance to the infections evidenced by paucity of bacilli in the lesions and their tissue response. In the lepromatous type there is obvious lack of resistance with an abundance of bacilli in the lesion.

1.4.3. TUBERCULOID

Tuberculoid and the non-lepromatous types have small number of bacilli limited to the intracellular locations and ordinarily have no means of exit from the body, Job (1981). In other words, this group of leprosy is not responsible for the spread and transmission of leprosy on a large extent.

1.4.4 LEPROMATOUS

Lepromatous types are so baccilliferous to such an extent that organisms overflow from them into the environment. The patients of lepromatous and the borderline lepromatous discharge Mycobacterium leprae into the surrounding through Nasal secretions, saliva, exudate from ulcer on the lepromatous skin and the normal secretions of the sweat, and mammary glands, Job, (1981).

The traditional and the simplest explanation of the spread of leprosy is by close and prolonged contact of the susceptible individual with infectious case. The source of infection is often not known. Susceptibility is important in the understanding of the epidemiology, natural history and clinical classification of leprosy, probably all cases go through an indeterminate phase, whether the point of entry is through the broken or unbroken skin.

1.4.5 DISTRIBUTION

Leprosy is widely distributed in the tropical and sub-tropical regions. This constitutes the top 25 countries that have nearly 94% of the world cases, Noordeen (1992). From the mid-sixties to the mid-eighties global estimates appeared to be constant at between 10 and 12 million. The introduction of multi-drug therapy (MDT) in many countries and the consequent reduction of prevalence of the disease has necessitated a re-assessment of the global estimate. Based on the available data and its interpretation, the number of leprosy in the world in 1991 had been estimated at 5.5 million. The number of individuals with deformity due to leprosy had been estimated as between 2 and 3 million. The following table summarizes the regional distribution of leprosy cases.

Table 1: The estimated and Registered cases of Leprosy in the (WHO) regions 1991 (×1,000)

REGION	ESTIMATED	REGISTERED
1. Africa	735	280
2. South East Asia	3,744	2,273
3. Amcrica	327	295
4. East Mediterranean	152	57
5. West Pacific	207	89
Total (top 25 countrics)	5,165	2,994
Total (all countries)	5.511	3,162

Source: See Noorden (1992)

The top 25 countries have the largest number of estimated leprosy cases and contributes 93.7% of the total estimated cases in the world.

1.4.6 DIAGNOSIS

The cardinal diagnostic signs are the presence of anaesthetic macular lesion or thickening and tenderness of peripheral nerve trunks and the demonstration of bacilli. Search should be made for suspicious macules or infilterations of the skin and for the thickening of ear lobes and the eye brows. The peripheral nerves should be palpated carefully. The patient should be examined in bright sunlight to appreciate fully even to find certain lesions of leprosy.

Smears should be made from several sites, skin lesion, earlobes and the nasal septum. Since bacilli are usually obtainable only from lepromatous and the demorphous lesions, many cases should be diagnosed on the basis of clinical appearance and the presence of anaesthesia in simple

macular or tuberculoid lesion. In such lesions, loss of sensitivity to light touch and absence of pain on pin prick justify the diagnosis. Test for instamine flare and for sweating afford Confirmatory evidence.

1.4.7 TREATMENT

The General treatment, including personal and environmental hygiene, a well balanced diet and the correction of concomitant conditions is important. With such measures even severe lepromatous cases may show some degree of amelioration, at least for a time, Hunter (1966).

Ideally, the most promising drugs for use in combination with dapsone or for the treatment of patients with dapsone resistant leprosy are: Rifampicin, clofazimine, ethionomide, prothionamide and thiacethazone, Ellard (1981).

DURATION OF TREATMENT

Dapsone treatment of paucibacillary leprosy is still of long duration; 2 - 5 years. Lowe recommended 24 months treatment, Wheate and Pearson suggested 2 years to 5 years and the third and fourth WHO expert Committee reports recommended that tuberculoid patients should continue treatment for 18 months after all activities has ceased and the lesions have become quiescent, which means a total of 24 - 36 months (See Warndorff, 1982).

It was observed that Rifampicin (RMP) is highly bactericidal for mycobacterium leprae, Warndorff (1982). Based on previous studies it was thought that it should be possible to cure patients with short regimen of 8 weekly doses of 900 mg Rifampicin. Nevertheless, treatment of

paucibacillary leprosy should be aimed at two objectives. The killing of bacilli and stopping the allergic reaction. Evidently, Rifampicin can realise the first objective rapidly and efficiently, since in the present series, no relapse were observed after 8 weekly doses of 900 mg of Rifampicin. The second objective will have to be taken care of by other drugs.

1.4.8 RELAPSE RATE

For a long term treatment with dapsone, several cases of relapse had been reported. A follow up study of 6 months to 4 years on 69 patients observed 11.6% relapses, Lowe (1954). Seven of the eight relapses occurred within 3 - 12 months after treatment ceased and one at 28 months. Three of the 7 patients had been treated for less than a year, 3 for between 1 and 2 years and 2 for 2 - 2.5 years.

1.4.9 NATURAL HISTORY OF LEPROSY

Leprosy is a common disease that may begin at any age but due to long incubation period of Mycobacterium leprae (2 - 5 years), its appearance during infancy and childhood is minimal. For the greater part of leprosy patients, there is a history of leprosy in members of the immediate family. Perhaps, this is the reason why some people think that leprosy is hereditary.

There is no spontaneous recovery without treatment and usually all latent cases develop overt disease except if dying in the meantime. Resistance to leprosy is not uncommon be it genetic or immunological.

It is generally accepted that Mycobacterium leprae (Hansen, 1874) is the etiological agent of leprosy. Deformities in fingers, feet (toes), eye brows, nose and earlobes is not uncommon with

leprosy patients. Death due to leprosy itself is infrequent. Pulmonary tuberculosis and nephritis are common terminal events, although the frequency of tuberculosis has greatly diminished since the advent of sulfone treatment, Hunter (1966).

1.4.10 A REVIEW OF LEPROSY MODELS

There has been a widespread use of statistical techniques in clinical trials and in attempting to determine variables which are relevant to the epidemiology of leprosy, but the application of operational Research techniques to the study of leprosy has been minimal.

Bechelli adopted the kinship coefficient in his study of the correlation between leprosy rates in villages different distances apart, Bechelli (1973). According to him, given n villages V_i (i = 1, 2, - - - - - -, n) the i^{th} village having population Wi and a gene frequency Pi for one genetic marker, the kinship coefficient between all villages at distance x from each other is estimated by

$$\psi_{(x)}P = \frac{\sum \frac{W_i W_j}{W_i W_j}(P_i - P)(P_j - P)}{P(1-P)\frac{W_i W_j}{W_i W_j}}$$

where P is the average gene frequency for all villages separated by distance x, and the summation is extended over all village pair V_i and V_j that distance apart. This indicator may be interpreted as a coefficient of intra class correlation between the gene frequencies for all the pairs of villages separated by the same distance. The kinship coefficient is expected to decrease with distance and its estimate may be fitted by a monotonically decreasing function of the type:

$$\psi(x) = \frac{ae^{-bx}}{(1+x)^c}$$

where a is the mean coefficient to kinship for local population (equivalent to the coefficient of inbreeding as a result of subdivision of a population). b is a function of the standard deviation of the distribution of distance between villages and of the systematic pressure on the genetic marker, and c is a coefficient measuring the dimensionality of migration.

Bechelli concluded that "if we consider that the biological and environmental factors and the socio economic condition in the different villages were fairly uniform, the relation between prevalence rates and the distance between villages would be primarily a function of the number of leprosy and other infectious cases. An untreated Lepromatous patient exposes those in close contact with him to a high risk of infection, and the risk decreases with a decrease in contact".

In a similar study of how the incidence of Leprosy does relate to prevalence, Lechat (1981) observed that if such a quantitative relationship can be established, it could become possible to

(1) predict future incidences under present conditions of control.

(2) simulate how changes in the control measures affect incidence.

The mathematical method employed was as follows:

$$(\text{incidence})_t = f(\text{prevalence})_{t-j}$$

where annual incidence is considered as dependent on past prevalence and j corresponding to the duration of the incubation period.

The model was run on a twenty years time period in order to achieve (1) and (2) above. Of all the control measures he used, the specific vaccination for leprosy comes out by far as the most effective measure. With a 100% vaccine coverage, incidence of new cases was predicted to reduce to zero in 11 years.

He concluded that leprosy cannot bring results overnight. Long term planning and sustained efforts are required. The message is of special importance for international agencies and non-governmental organisations which at times display a tendency to expect short term results and go discouraged when the so-called eradication is not soon materialising.

CHAPTER TWO

2.0 REVIEW OF LITERATURE

In this chapter we shall discuss the related literature. Markov and semi-markov models are discussed in section 2.1 and fortran programme is reviewed in section 2.2.

2.1 MARKOV CHAIN AND SEMI-MARKOV MODELS.

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. Marshal and Goldharmmer (1955) discussed a Markov chain model for characterizing the age distribution of mental patients. The rate of progression of disease for allergic patients induced by allergic pollen is an area which require a great deal of attention from medical point of view (Lebowitz,1977). The ammount of allergic pollen in the environment can be associated with the time of year. The severity of chronic bronchial asthma is related to the changing pattern of the season (Lebowit, 1977).

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

Jain (1986) used a similar approach to devolp 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 asthmatic patients to be modelled by a three state markov chain:- a patient in state I: 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)

Abubakar (1995) considered the process of Leprosy as a semi-markov process. Four states of the disease were specified. The states are finite, mutually exclusive and exhaustive. The first three states are transient states and the fourth state is an absorbing state and it is the state of death due to leprosy. The effectiveness of treatment on the interval transition probabilities is the major result obtained from the model. The results of this stochastic analysis could be used as a predictive device to study the health stastus of leprosy patients. This model incorporates uncertainty and veriability. This is a semi-markov model which was also used for asthma, korve (1993)

2.2 FORTRAN PROGRAM

Ondoma (1991) designed a fortran program to determine the possible roots of a chebyshev polynomial. According to him, a well documented program on computer inplementation makes easier to find the roots of the polynomial.He also observed that the roots naturally occur in the

interval [-1,1]. This method is easier and more accurate than by using the alternative geometrical construction.

CHAPTER THREE

A SEMI-MARKOV MODEL

In this chapter we consider leprosy as a disease where the transition of people from one state of the disease to another may not necessarily occur at discrete time instants. We therefore look at a situation where the time between transitions may be in several units of time interval, and where the transition time can depend on the transition being made. This leads us to a generalisation of a Markov process called the semi-Markov process (Howard, 1971). In other words we shall consider the disease leprosy as a semi-Markov process running in discrete time.

3.1 INTRODUCTION

Since leprosy is considered in this project as a form of Markov process, it is worth defining what this process entails. The basic concept of a Markov process is that of "state" of a system and state "transition". It is a process that runs in time. At any given point in time, the process is in a given state and could possibly make a transition to another state after a period of time. A Markov process in discrete time and discrete state is called a Markov chain.

We may give a mathematical definition of a Markov chain as a sequence X_0, X_1, - - - - of discrete random variables with the property that the conditional probability 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,

$$P(X_{n+1} = j / X_0 = h, \text{ - - - - -}, X_n = i) = P(X_{n+1} = j / X_n = i) = Pij \text{ . } i, j = 1, 2, 3, 4$$

The matrix P whose entries are the $P_{ij's}$ is called the transition probability matrix for the process. The above chain is a first order Markov chain. In this process, the probability of making transition to a future state does not depend on the previous state but only depend on the present state. In other words, the probability of making a transition to a future state does not depend on the past history.

The matrix P and the initial state transition probabilities completely specify the process. If the transition probabilities depend on time, then the Markov chain is non-homogeneous, otherwise, it is homogeneous. In this project we shall only consider the Markov chain that does not depend on time. Thus we have stationary transition probabilities.

The Markov process discussed above has the property that state changes can only occur at the appropriate time instants. However, given the nature of the disease leprosy, transition may not actually occur at these time instants. We therefore consider a 'situation' where the time between transition may be several of units of time and where the transition time can depend on the transition that is being made. This leads to a general form of Markov process called a semi-Markov process (Howard, 1971). We therefore use the characteristics of a semi-Markov process to develop a model for the control of leprosy.

3 . 2 THE DEVELOPMENT OF THE MODEL

In this section we shall develop a semi-Markov model for leprosy. The assumptions of the model are made in section 3.2.1, the model is formulated in section 3.2.2. Interval transition probabilities are given in section 3.2.3 and effectiveness of treatment is considered in section 3.2.4.

3.2.1 MODEL ASSUMPTIONS

Leprosy is considered as a disease that runs in time. Some suitable states of the disease are specified and the description of the manner in which the patient moves from one state to another is given. The states of the disease are finite. It should be readily observed that there is no unique set of states and the progress of the people through the states can be described in a variety of ways. The choice of states should therefore be governed by the intended use of the model and the availability of data.

The basic assumption in developing the model is that the transition from one state to a different state should not occur at time t = 0 (year 0) and that the basic unit of time is one year.

A leprosy patient that dies during treatment is assumed to die of leprosy. Natural death is not considered.

A patient that fails to recover from treatment after completing a session of treatment has developed a resistance to the drug and is consequently considered to develop a relapse from the state of treatment.

3.2.2 FORMULATION OF THE MODEL

We consider a leprosy patient. Let us assume that each year the leprosy patient is under treatment or has recovered from the disease or has relapsed or has died from the disease.

We therefore have a four state process.

State 1 - Under treatment

State 2 - Recovery

State 3 - Relapse

State 4 - Death due to leprosy.

These states are assumed to be mutually exclusive and exhaustive. The transition from one state to another is indicated in the transition diagram shown in Figure 1

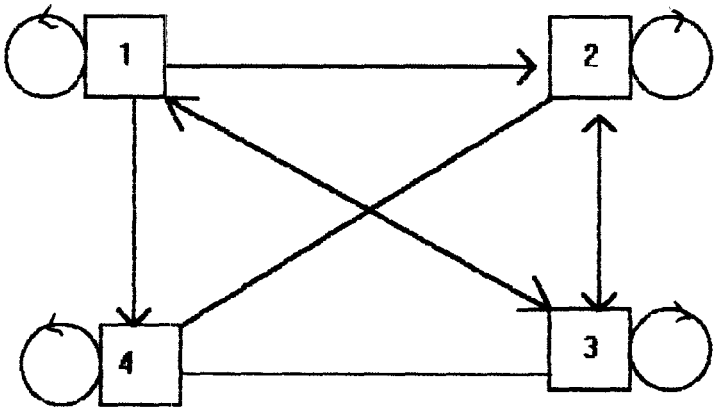


Figure 1: Transition diagram for leprosy.

We observe that states 1, 2 and 3 are transient states and state 4 is an absorbing state. In other words, all possible transitions of the process are made between states 1, 2 and 3 but once a transition is made to state 4 the process terminates. We would like a transition to occur at a time the duration of stay in a state is completed, even if the new state is the same as the old. Such a transition is called virtual transition, and are represented by loops in the transition diagram.

From the above transition diagram we can record the transition probability matrix 'P' for the process as shown in the next page.

$$P = \begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} \\ O & P_{22} & P_{23} & O \\ P_{31} & P_{32} & P_{33} & O \\ O & O & O & P_{44} \end{bmatrix}$$

We use the semi-Markov process technique to analyse the process with the above set of states. The transitions can be readily identified from the transition diagram shown in figure 5 or from the transition probability matrix P.

To study this process, we have to specify the probabilitic nature of the transition. We shall think of this process as a process whose successive state occupancies are governed by the transition probabilities of a Markov chains, but whose stay in any state is described by a random variable that depends on the state to which the next transition is made.

In precise terms, let P_{ij} be the probability that the leprosy patient who is in state 'i' on his last transition will enter state 'j' on his next transition, i, j =1, 2, 3, 4. The transition probabilities must satisfy the following

$$P_{ij} \geq 0,\ i,j = 1, 2, 3, 4.$$

$$\text{and } \sum_{j=i}^{4} P_{ij} = 1, \quad i = 1, \ 2, \ 3, \ 4.$$

whenever the patient enters state 'i' he remains there for a time T_{ij} in state i before making a transition to state 'j'. T_{ij} is called the 'holding time' in state i. The holding times are positive integer valued random variables each governed by a probability distribution function f_{ij} ( ) called the holding time distribution function for a transition from state i to state j.

$$\text{Thus } P(T_{ij} = m) = f_{ij}(m). \quad m = 1, 2, 3, \ldots$$

$$i, j = 1, 2, 3, 4.$$

We assume that the means m_{ij} of all holding time distribution are finite and that all holding times are at least one year in length. That is,

$$f_{ij}(0) = 0$$

To completely describe the semi-Markov process we must specify four holding time distribution functions in addition to the transition probabilities. For a fixed value of i T_{ij} is the same for each value of j, (i, j = 1, 2, 3, 4).

Figure 2 shows a portion of a possible trajectory for the leprosy patient.

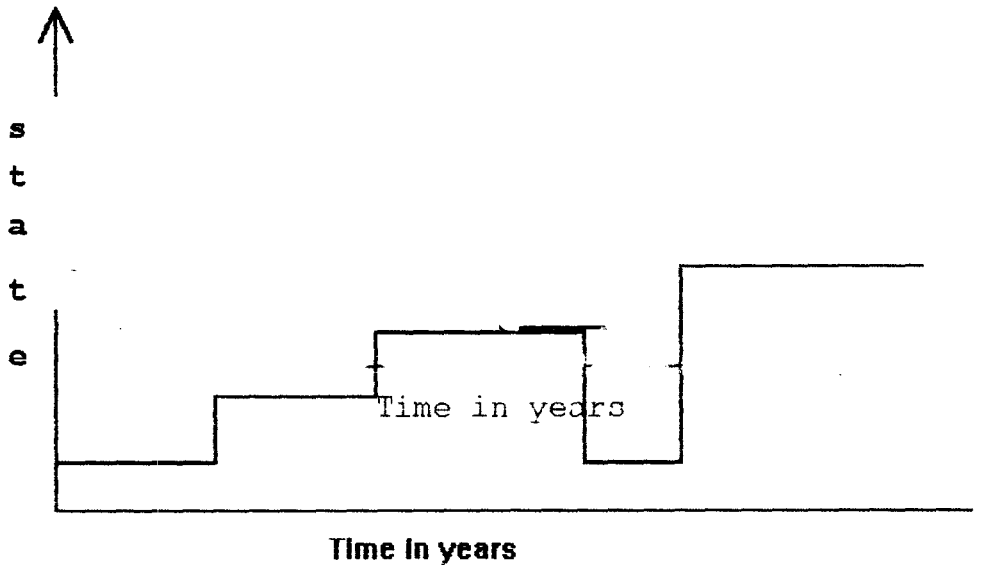


Figure 2. A possible trajectory for the process

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

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

and $\bar{F}_{ij}(\,)$ be the complementary cumulative probability distribution of T_{ij}.

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

Suppose the patient enters state i. Let Y_i be the time he spent in state i before moving out of the state i. Then Y_i is called the waiting time in state i.

We let $w_i(\,)$ be the probability distribution function of Y_i. Then

$$w_i(m) = P(Y_i = m) = \sum_{j=1}^{4} P_{ij} f_{ij}(m)$$

The cumulative probability distribution $W_i(\ )$ and the complimentary cumulative probability distribution $\overline{W}_i(\ )$ for the waiting times are given as follows

$$W_i(n) = P(Y_i \leq n) = \sum_{m=1}^{n} W_i(m)$$

$$= \sum_{m=1}^{n} \sum_{j=1}^{4} P_{ij} f_{ij}(m)$$

$$= \sum_{j=1}^{4} P_{ij} f_{ij}(n)$$

and

$$\overline{W}_i(n) = P(Y_i > n) = 1 - W_i(n) = \sum_{m=n+1}^{\infty} w_i(m)$$

$$= \sum_{m=n+1}^{\infty} \sum_{j=1}^{4} P_{ij} f_{ij}(m)$$

$$= \sum_{j=1}^{4} P_{ij} \overline{F}_{ij}(n)$$

3.3 INTERVAL TRANSITION PROBABILITIES

We define ϕ_{ij} (n) to be the probability that the patient will be in state j in year n given that he entered state i in year zero. This is called the interval transition probability from state i to state j in the interval (0, n). Then

$$\phi_{ij}(n) = \delta_{ij}\overline{W}_i(n) + \sum_{k=1}^{4} P_{ik} \sum_{m=1}^{n} f_{ik}(m)\phi_{kj}(n-m)$$

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

$$i, j = 1, 2, 3, 4, \qquad n = 1, , 3, \ldots .$$

$\overline{W}_i$ (n) is as defined in (6).

3.4 EFFECTIVENESS OF TREATMENT

When the leprosy patient undergoes treatment, it is expected that this treatment should have an effect on the disease. This effect should be noticed in the increase in probability of recovery, a decease in the probabilities of death and having a relapse. An appropriate measure of this treatment effectiveness is obtained from the following expressions.

$$E_{12} = (1 + k)P_{12}$$

$$E_{1j} = (1 - k)P_{1j}, \quad j = 3, 4$$

When k is a positive real number in the interval (0, 1). Then

$$E_{11} = 1 - \sum_{j=2}^{4} E_{1j}$$

and the transition matrix is P with the first row replaced by E_{1j}. J = 1, 2, 3, 4.

3.5 SOME ILLSTRATIVE RESULTS

Suppose the following data were collected on aleprosy patient for 24 years as shown below in the transition count.

Table2: Transition count for leprosy.

		Actual year				
		state1	state2	state3	state4	
	statc1	5	3	2	1	11
preceeding	state2	0	3	2	0	5
year	state3	4	2	1	0	7
	state4	0	0	0	1	1
						24

The results based on this transition count are provided in the next chapter as the output of the computer program.

CHAPTER FOUR

4 .0 A FORTRAN PROGRAM OF THE MODEL

We shall present the documentation of the program in this chapter. The description of the program is given in section 4.1 the program interface in section 4.2 the structure of the program in section 4.3, a listing of the program in section 4.4 and the output of the program with a short comment ends the chapter in section 4.5.

4.1 A DESCRIPTION OF THE PROGRAM

This is a program for a semi-markov model for the control of leprosy. We have seen in the previous chapter that the basis of a semi- Markov model is the internal transition probabilities'. The primary objective of the model is to determine the effectiveness of the treatment consequenthy, this program is designed to determine the interval transition probabilities and the effecveness of treatment simultaneously.

- The program accepts the transition count C_{11}, C_{12}, C_{13} and C_{14} as input data and then computes the transition probabilities, P_{11}, P_{12}, P_{13} and P_{14}, the mean holding time in the states, the effectiveness of treatment, the mean holding time distribution function for the negative exponential distribution function and finally the interval transition probabilities. It also display, the result.

- The interval transition probabilities computed are:- $Q_{12}(n)$ or A(n) which is the probabilities that the patient will recover from the disease in n years given that the patient started treatment in year 0.(2) $Q_{13}(n)$ or B(n).

This is the probability that the partient will become a relapse or develop a resistance to the disease in year n given that the patient started treatment in year 0. and (3) c(n) or $Q_{14}(n)$. The probability that the patient will die of the disease in year n given that he started treatment in year 0. The program used the data statement for input.

Limitations of the program.

The print screen on the keyboard is used to obtain a hard copy. Thus, there is no special subprogram designed to direct the output to the on-line printer. The program does not compute the other transition probabilities P_{21}, P_{22}, P_{23}, P_{24}, P_{31}, P_{32}, P_{33}, P_{34}, P_{41}, P_{42}, P_{43}, P_{44} and the corresponding interval transition probabilities. This is deliberate, because the model is esentially developed to achieve the effectiveness of treatment.

4.2. A DESCRIPTION OF THE PROGRAM INTERFACE

The program is implemented on personal computer (pc) ms Dos FORTRAN 77 compiler and the file ABUJA2.EXE was generated. The value of K is supplied as the program runs. Observe that $0 \leq K \leq 1$

In the diskette supplied with this project, we give the two files ABUJA2.FOR which needs to be compiled and the ABUJA2.EXE that has been compiled and is directly executable.

The output of the program is the interval transition probability A(n), B(n) and C(n) for a given real value of K. The print screen is used to obtain a hard copy of the output.

The compilation process takes the following procedures

c:/ FORTRAN >FOR1 a: ABUJA2.FOR ↵

PAS2 ↵

LINK ↵

To run the EXE file

c:/FORTRAN> ABUJA2.EXE ↵

supply the appropriate value for k ↵

or

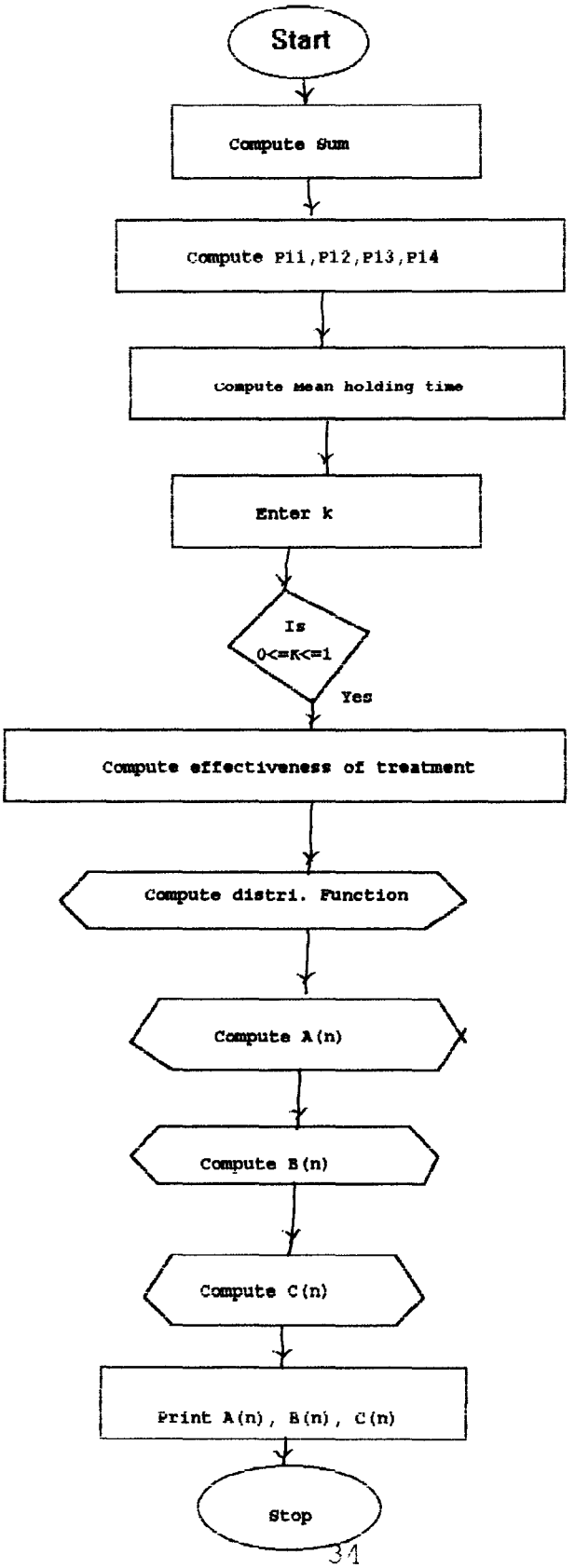
C:/ FORTRAN>a:ABUJA2.EXE ↵

supply the appropriate value for K ↵

4.3 A DESCRIPTION OF THE STRUCTURE OF THE PROGRAM

Traditionally, fortran programs have been documented by using flow charts. This is because as programs become more complex a flow chart is most helpful in planing, designing and structuring the program.

The flow chart on the next page illustrates the structure of the program.(Fig 3)


Start
Compute Sum
Compute Pi1,Pi2,Pi3,Pi4
Compute mean holding time
Enter k
Is
0<=K<=1
Yes
Compute effectiveness of treatment
Compute distri. Function
Compute A(n)
Compute B(n)
Compute C(n)
Print A(n), B(n), C(n)
Stop

4 . 4 A LISTING OF THE PROGRAM

A listing of the program is given below.

```
C   A Fortran program of a model for the control of leprosy.
C   This program accepts as input data the transition count and
C         computes the transition probabilities,
C              effectiveness of treatment, the mean holding time in the
C                   states, the mean holding time distribution
C   function and the interval transition probabilities.
      REAL K
      Dimension A(15),B(15),C(15),D(15)
C   The Transition Probabilities
      Data P,Q,R,S /5.0,3.0,2.0,1.0/
      sum = P+Q+R+S
      E = P/sum
      F = Q/sum
      G = R/sum
      H = S/sum
      rmean = sum/4.0
      L = INT(rmean)
      T=REAL(L)
```

```
      W = 1/T
C     Effectiveness of treatment
      Write(*,10)
   10 Format('Enter value -K')
      Read(*,20) K
   20 Format(F3.2)
      IF (K .GE. 0 .AND. K .LT. 1) THEN
      EF = ((1.0 + k)*F)
      EG = ((1.0 - k)*G)
      EH = ((1.0 - k)*H)
      ENDIF
C     The holding time in the states (Exponention distribution)
      Do 30 n=1,15
      o=n*w
      D(n)=(w*Exp(-o))
   30 continue
C     The Interval Transition probabilities
      Do 40 n=1,15
      A(n)=(EF*D(n))
   40 continuc
      Do 50 n=1,15
```

```
    B(n) = (EG*D(n))
 50 continue
    Do 60 n = 1,15
    C(n) = (EH*D(n))
 60 continue
    Write(*,70)
 70 Format(5X,'n',7X,'A(n)',9X,'B(n)',11X,'C(n)')
    Write(*,*)
    Do 80 n=1,15
    Write(*,90) n, A(n), B(n), C(n)
 90 Format(3X,I2,3X,F10.8,3X,F10.8,3X,F10.8)
 80 continue
    STOP
    END
```

4 . 5 OUTPUT OF THE PROGRAM

The output of the program for values of K= 0,0.50,0.90 and 1.00 is given in tables 3,4,5 and 6 below

TABLE 3: .INTERVAL TRANSITION PROBABILITIES FOR K=0

n	A(n)	B(n)	C(n)
1	0.08270873	0.0.5513915	0.02756958
2	0.05016538	0.03344359	0.01672179

3	0.03042684	0.002028456	0.01014228
4	0.01845481	0.01230321	0.00615160
5	0.1119341	0.00746227	0.00373114
6	0.00678915	0.00452610	0.00226305
7	0.00411783	0.00274522	0.00137261
8	0.00249759	0.00166506	0.00083253
9	0.001511486	0.00100991	0.00050495
10	0.00091881	0.00061254	0.00030627
11	0.00055729	0.00037152	0.00018576
12	0.00033801	0.00022534	0.00011267
13	0.00020501	0.00013668	0.00006834
14	0.00012435	0.00008290	0.00004145
15	0.00007542	0.00005028	0.00002514

Table3 presents the interval transition probabilities from state 1 to state 2, state3 and state4 rspectively when the treatment is assumed to be zero percent effective for n=1,2,3---15.

TABLE4: . INTERVAL TRANSITION PROBABILITIES FOR K=0.50

n	A(n)	B(n)	C (n)
1	0.12406310	0.02756958	0.01378479
2	0.07524808	0.01672179	0.00836090
3	0.04564026	0.01014228	0.00507114

4	0.02768222	0.00615160	0.00307580
5	0.01679011	0.00373114	0.00186557
6	0.01018372	0.00226305	0.00113152
7	0.00617674	0.00137261	0.00068631
8	0.00374638	0.00083253	0.00041626
9	0.00227229	0.00050495	0.00025248
10	0.00137822	0.00030627	0.00015314
11	0.00083593	0.00018576	0.00009288
12	0.00050702	0.00011267	0.00005634
13	0.00030752	0.00006834	0.00003417
14	0.00018652	0.00004145	0.00002072
15	0.00011313	0.00002514	0.00001257

Table4 presents the interval transitin probabilities when the treatment is assumed to be 50% effective for 15 years.

TABLE5: . INTERVAL TRANSITION PROBABILITIES FOR K=0.90

n	A(n)	B(n)	C(n)
1	0.15714660	0.00551392	0.00275696
2	0.095311422	0.00334436	0.00167218
3	0.05781100	0.00202846	0.00101423
4	0.03506414	0.00123032	0.00061516

5	0.02126748	0.00074623	0.00037311
6	0.01289938	0.00045261	0.00022630
7	0.000782387	0.00027452	0.00013726
8	0.000074542	0.00016651	0.00008325
9	0.00287824	0.00010099	0.00005050
10	0.00174574	0.00006125	0.00003063
11	0.00105885	0.00003715	0.00001858
12	0.00064222	0.00002253	0.00001127
13	0.00038953	0.00001367	0.00000683
14	0.00023626	0.00000829	0.00000414
15	0.00014330	0.00000503	0.00000251

Table5 presents the interval transition probabilities when the treatment is assumed to be 90% effective

4.6 COMMENT

The result obtained from the program confirms the earlier result obtained from manual calcilation. The values of the interval transition probabilities Q(n), j=2,3and4 denoted by A(n),B(n),and C(n) presented in the previous section show a low degree of variability in the sensitivity analysis

A(n) is the probability that a leprosy patient will be in state of recovery in year n given that the patient started treatment in year zero. B(n) is the probability that a leprosy patient will be relapsed

in year n given that the patient started treatment in year zero and C(n) is the probability that a leprosy patient will die in year n given that the patient started treatment in year zero.

A(n) increased by 4%and7% for the first year when the treatment is assumed to 50% and 90% effective respectively.Conversely, B(n) decreased by 2% and5% for the first year when the treatment is assumed to 50% and90% effective respectively. Also C(n) reduced by1% and2% for the first when the treatment is assumed to 50% and90% effective respectively. Accordingly, A(n) increases with increasing values of k. whereas B(n) and C(n) decrease with increasing values of k. Thus the effectiveness of the treatment can be determined as the probability of recovery from the disease increases and a decrease in the probabilities of relapse and death due to the disease. Simply put, more patients should recover from the disease and fewer patients should relapse or die if the treatment is effective. This can be seen clearly in the output of the program when the treatment is 0%,50%, and 90% effective respectively.The interval transition probabilties have consistent predictve power . This could be explained in terms of low degree of variability for 50% and 90% treatment effectiveness respectively. The results identify quatitatively the effective modelling of a leprosy patient. The semi-Markov model can be used as a predictive device for studying the health status of leprosy cases. The predictions are useful to the doctors, hospital administrators, policy makers and the general public.

CHAPTER FIVE

SUMMARY , CONCLUSION AND RECOMMENDATIONS

The purpose of this project is to demonstrate quatitatively the application of computers to a semi-markov modelling. This process requires very few data but a very large volume of sequential and repetitive computations. The use of scientific programming language like the fortran makes it possible and easy to translate complex algebraic expressions into simple statements that the computer can execute. In section 5.1 we present the summary the conclusion in section 5.2 and the recommendation in section 5.3.

5.1 SUMMARY

In chapter one we discussed markov processes, the negative exponential distribution and the fortran programming language and the disease leprosy and a review of its' models.

Markov process is a stochastic process that involves classification of states and recording of transition within the states. It is then possible to draw the transition graph and determine the transition probabililties. The first order markov process is the one used in this project. Thus the probability of making transition to the next state depends on the present state and it is independent of the previous states. Like the exponential distribution, the markov process is memoryless, since the probability of making transition to future state depend only on the present state and does not depend on the past state.

The markov process requires transition to occur at regular time interval. But some processes may not necessarily make transition at this time interval. Therefore, we consider a

situation where transition between the states may occur in discrete units of time interval. This leads to the generalisation of a Markov processes called the Semi- Markov. The interval transition probabilities form the basis of semi-Markov processes. It requires the transition probabilities and the mean holding time probability distribution function.

The probability distribution function used in this project is the negative exponential distribution. It has a simple probability density function. It is fully specified by one parameter. The parameter is easily estimated if the mean is specified. The exponential distribution is memoryless. It is widely used in queue theory in conjunction with the Poisson distribution.

Fortran is designed by John Backus in 1954. It is one of the earliest 'high level' computer languages used. The name means 'FORmula TRANslation'. After the revision in 1958 and the standardisation in 1966 as Fortram iv, it become the most widely used vehicle for data processing and numerical computation in science and Engineering.

Fortran programs are highly portable.It is standardised programming Language and easily available in computers. Thus Fortran 77 is a language that many people need to use.Leprosy is chronic infectious disease primarily of the skin and nerves caused by mycobacterium leprae. It is one of the least infectious of all the infectious diseases. The two major types are the tuberculiod and the lepromatous.It is widely spread in the tropical and sub-tropical regions.The disease can be treated and cured.

In chapter two we make a review of Markov chain and semi- Markov medels. We discover that stochastic models had been in use for a long time for study the progresssion of disease. Fix and Neyman (1951) were the first to use a four state Markov model to study human cancer. Jain

(1986) develop a finite Markov model with descrete time parameter for the tudy of the seasonal patterns affecting the state of health of chronic bronchial asthma patient. Abubakar (1995) developed a semi-Markov modelling for the control of leprosy. The models are useful tools for predicting the health status of patients.

Ondoma (1991) designed a fortran program to determine the possible roots of a chebyshev polynomial.

In chapter three we considered the disease Leprosy as semi- Markov process runing in descrete time units. The basic assumptions in developing the model include:- That the transition from one state to a different state should not occur in year 0 and that the basic unit of time is one year. Four distinct states were specified in the model; state 1 (under treatment), state 2 (Recovery), state 3 (Relaped) and state 4 (death due to leprosy).The states are assumed to be mutually exclusive and exhaustive.

The probability that the patient will be in state j in year n given that the patient entered state i in year 0 is called the interval transition probability from state i to state j in the interval (o,n). The effectivenesss of the treatment was also formulated so that if the treatment is effective, the probability of recovery should increase with increase in 'K'. Whereas the probabilities of relapse and death due to the disease decrease with increase in the value of K.

A Fortran program has been developed in chapter four to determine the interval transition probabilities and effectiveness of treatment. The program accepts the transition count c_{11}, c_{12}, c_{13}, and c_{14} in data statement format and then compute the transition probabilities p_{11}, p_{12}, p_{13},

and p_{14}, the effectiveness of treatment, mean holding time distribution function for the negative exponential distribution and finally the interval transition probabilities.

The output of the program is given in tabular form. The result is in harmony with the earlier result obtaind from hand held calculator. The program interface is also discussed to enable individuals to run the program and perhaps make adjustments to meet local needs and demands.Some illustrative result are provided as the output of the program for k=0 ,0.50 and 0.90. That is, when the treatment is assumed to be 0%, 50% and 90% effective respectively.

The Interval transition probabilities have consistent predictive power. Thus there is low degree of variability when the treatment is assumed to 50% and 90% effective repectively.

5.2 CONCLUSION

We have seen that a variety of highly simplified assumptions are often needed to develope mathematical models . The more releastic the models are the harder it becomes to obtain analytical solutions. The complexity of the analytical stochastic models make them more difficult for the people who are supposed to use them (usualy non-mathematicians). This communication gap could be minimsed by the use of simulation approach and simple mathematics.

We have be able to demonstrate the application of computers to semi-Markov modelling. The Fortran programming language is very useful to write programs in complex scientific and mathematical expressions. Complex algebraic expression are simply translated into Fortran statements. The computer runs the program and provides the desired solution in just few seconds. The computations that should take several days to accomplish with the use of hand held calculator is done in such a short time.

5.3 RECOMMENDATIONS

The model developed in this project could be more realistic if the following conditions were considered; The state of recovery (state2) could be an absorbing state so that the patient that does not develope a relapse gets absorbed and recovered from the disease forever since leprosy can be treated and cured. Also many leprosy patients could be studied using this model. The cost of treatment was not considered in the project.The program does not compute some other transition probabilities and the corresponding interval transition probabilities.This is deliberate because the model is essentially developed to achieve the effectiveness of treatment. This and others could be basis for further research work.

REFERENCES

ABUBAKAR U.Y "Semi-Markov modelling for the control of leprosy" MSc. Thesis, Deparptment of Mathematics University of Jos (1995).

BECHELLI. M. "Correlation between Leprosy Rate in Villages different distances Apart" Bulletin of WHO.48, 257-260 (1973).

DONALD M.M "A crash course in Fortran 77. Edward Arnold A Division of Hodder & Stoughton London (1989)

ELLARD G. A. "Drug Compliance in the Treatment of Leprosy", Leprosy Review, 201-209, (1981)

FIX E. ETAL "A simple model of recovery, Relapse and loss of patients " Human Biology, 23,205-241 (1951)

HUNTER et al "A Manual of Tropical Medcine", W.B. Saunders company London,(1966).

JAIN R. K "The use of time -varying Markov model to study the effect of weather on asthama" Biometrical J., 30, 93-97 (1988)

JAIN S. " A Markov chain and its Application", Com. Biomed. Res., 19, 374-378 (1988)

JOB C. K "Leprosy, the Source of Infection and its mode Transmition", Leprosy Review, 52 supp.,1, December, (1981)

LARRY N. et al "Fortran 77 for Engineers & scientists, Macnillam publishing company, New-York (1985)

LEBOWITZ M. D et al "The Relationship of Acute Respiratory illness History to the prevalence and incidence of obstructive Lung Disorders" American J. of Epidemiology, 105, 544- 554 (1977)

LECHAT M. F. "The Torments and Blessings of the Leprosy Epidemiometric model", Leprosy Review, 52,187- 196, (1981).

MARSHALL A. W. et al " An Application of Markov process to the study of Epidemiology of mental disease," J. American stat. ASS., 50, 99 (1955)

NOORDEEN S. K. et al "The Etimated numbers of Leprosy cases in the World", Bulletin of WHO.,1,7-10,(1992)

ONDOMA A. "Chebyshev polynomials.B. Tech Thesis Department of Mathemathics/Computer Science F.U.T. Minna (1991).

WARNDORFF J.et al "Follow up on short coures 2 months RefampicinTreatment of Paucibacillary Leprosy",Leprosy Review, 52, 9-17 , (1982)

VICTOR O.O "Today's Fortran 77 Programmmc." Times Book Ltd, Nigeria.(1996)