CHAPTER - 1

Introduction
INTRODUCTION

1.1 General introduction and aim of the study

Psychiatric disorders have emerged in the recent years as a major health problem worldwide. Although not fatal, these disorders of the mind are as important and as disabling as the physical disorders. According to the World Health Report, 2001, published by the World Health Organisation (WHO), it has been estimated that mental disorders affect around 450 million people throughout the globe and have found places among the 10 leading causes of morbidity and suffering. At this juncture, it is of prime importance that psychiatric illness should receive adequate attention not only from the medical fraternity but from researchers of other related fields as well.

It is noteworthy that of the various mental disorders, schizophrenia is rated as the third most disabling disease in the world having an ubiquitous distribution with an occurrence rate of 0.1 to 0.4 per 1000 population per year. It is also a leading public health problem which entails enormous personal and economic burden to the health care system. An estimated 300,000 episodes of acute schizophrenia occur annually in the United States, resulting in direct and indirect costs estimated at more than $33 billion (Reus, 2005). It does not respect any boundaries and cuts across gender, socio economic groups, educational status, geographical locations, caste and community (Thara et al., 2001). The complexity of the illness and its long lasting effects on the patients and the society at large makes schizophrenia a challenge to researchers the world over.
Before going into the details of schizophrenia, the focal point of this research, a brief insight about the basic concept of a mental disorder is presented as follows.

A mental disorder is an illness with psychophysical or behavioural manifestations associated with impaired functioning due to social, psychological, genetic, physical or chemical disturbances. Mental disorders are broadly classified as psychotic and neurotic which can be either organic (with presence of some physical abnormality, e.g. a tumour in the brain) or functional (where no physical abnormality is detected on examination).

Psychosis: It is a condition in which the person has delusions and hallucinations and is not attached to reality (loss of reality testing).

Neurosis: It is a condition where there is no loss of reality testing; it is based on intrapsychic conflicts of life events that cause anxiety; it appears as obsession, phobia, compulsion etc.

A psychotic illness, schizophrenia is a disorder of unknown causes. It is characterized by symptoms that significantly impair functioning and that involve disturbances in feeling, thinking and behaviour (Kaplan and Sadock, 1996). In other words, schizophrenia is a mental disorder interfering with a person's ability to recognize what is real, manage his emotions, think clearly, make judgements and communicate. People with schizophrenia usually suffer from strange
symptoms such as hearing imaginary voices and further believing that these voices are controlling their thoughts and actions. They may believe that people are plotting to harm them and may actually see those imaginary people vividly. They may also see other strange sights which are not seen by the normal person. These types of symptoms fall under the category of delusions and hallucinations. Another common manifestation of schizophrenia is behavioural change. This could take different forms such as social withdrawal, isolation, restlessness, irritability, aggressiveness and antisocial behaviour. These result in an impairment of day-to-day functioning of the individual. If treated partially or left untreated, schizophrenia can cause long-lasting impairment and disabilities, encompassing all aspects of human functioning. Apart from requiring prolonged medical care, rehabilitation and support services, the social costs and the burden on the family can also be enormous (Murray, 2002).

Even after the more obvious symptoms of this disorder have abated, some residual symptoms may remain. These include lack of interest and initiative in daily activities and work, social incompetence and inability to take interest in pleasurable activities. These can cause continued disability and poor quality of life. These symptoms can place a considerable burden on the family (Pai & Kapur, 1982). All these considerations make the study of schizophrenia very meaningful and worthwhile, more so as it usually occurs during the most productive years – between 15 and 35 years – and can affect both children and the elderly of either sex.
Schizophrenia is a chronic disorder and generally has the following three stages.

1. A prodromal phase just before the onset of a psychotic episode when the early signs of behavioural changes can be observed.
2. An active phase with delusions and hallucinations.
3. A residual phase in which the disorder may remain in remission.

The common prodromal features include reduced concentration and attention, reduced motivation, depression, anxiety, sleep disturbance, social withdrawal, suspiciousness, deterioration of role functioning and irritability (Yung and McGorry, 1996). The active phase shows all the symptoms mentioned earlier, especially, delusions and hallucinations which make it imperative for relatives to bring a schizophrenic for treatment to a psychiatrist. However, it is well known that schizophrenia cannot be cured completely. It remains under control only if medications are taken regularly. On subsequent visits to the doctor, it is expected that the number of symptoms which is concordant to the severity of the disease will reduce till all the symptoms come under control. This state is the state of complete response or complete remission. If however, a state is reached when all the psychotic symptoms are controlled and the patient shows only the behavioural changes of the disease, then the patient is said to be in the state of partial remission. This is a state when the patient is functionally normal but still has certain symptoms (Gelder et al., 1996). Nevertheless, he is still a schizophrenic. A patient once diagnosed a schizophrenic will remain to be so, but can be in states of complete or partial remission. The state of remission will
continue only on regular intake of medicines and regular follow-up with the
doctor, otherwise there is a possibility of relapse of the illness. Thus, it is of
utmost importance that a patient of schizophrenia continues medication lifelong
under proper medical supervision.

An etiologically puzzling and clinically severe disorder, schizophrenia has long
held the attention of psychiatric epidemiologists. Till date, several
epidemiological studies and clinical trials have been carried out on the course,
outcome, symptoms and treatment of schizophrenia by various researchers of
medical sciences. Computer friendly statistical modeling has also been applied in
the clinical trials involving adequate number of patients in long term follow-up
studies. However, by stochastic modeling of the disease and its characteristics in
a somewhat different direction and by subsequent statistical analysis, an
endeavour has been made, in this research work, to come up with results which
would prove beneficial in framing treatment strategies or modules, and in the
understanding of the disease from a statistical viewpoint.

With this aim in mind, this study focuses on the structure of the symptoms of
schizophrenia, the behaviour of the symptoms during the course of treatment,
the behaviour of a patient during the treatment process, the possible outcomes
of treatment and the importance of regularity in the treatment process. These
studies have been carried out in a discrete set up. The mathematics involved has
been kept simple – the conceptualization of the different aspects of
schizophrenia in terms of mathematics, or rather, the representation of the facts of schizophrenia by the statistical theories of Stochastic Processes, Markov chains, Renewal Processes, Structure Functions, Distribution Theory etc. is the strong point of this thesis. A study of the world epidemiology of schizophrenia from available literature and a subsequent study of the local epidemiological scenario of schizophrenia and symptom manifestations as observed from secondary data collected from the Gauhati Medical College Hospital (GMCH), Guwahati, Assam, India, and the primary data obtained from a three month follow-up study conducted in collaboration with a few prominent psychiatrists of Guwahati has also been undertaken.

The details of statistical methods applied in the above mentioned study has been given in the following sections.

1.2 Plan of the thesis: a summary of the work done in the different chapters

In the next section of Chapter 1, a brief survey of the work already done on schizophrenia research and on the various statistical concepts and theories which have been applied in this thesis has been presented. This is followed by the definitions and explanations of the mathematical tools used in the thesis.

Chapters 2, 3 and 4 pertain to the symptoms manifested in schizophrenia. In the first part of Chapter 2, the different terms commonly used to describe the
symptom manifestations in schizophrenia have been defined with examples. A study was conducted on the patients attending the Out Patients' Department (OPD) of the Department of Psychiatry, of the Gauhati Medical College Hospital (GMCH) to study the various aspects of schizophrenia. In all, records of 797 patients of schizophrenia attending the OPD were studied. Another 200 patients of schizophrenia were followed up in a three month study taken up in collaboration with leading psychiatrists of this region. In the 2nd part of this chapter, a few of those case studies are presented in order to give an idea about the variety of complaints reported by the schizophrenics and their attendants when they are brought to the hospital for diagnosis and treatment during an episode of psychotic illness.

In Chapter 3, an attempt has been made to mathematically structure the different categories of symptoms that may be present at the time of diagnosis of a patient of schizophrenia in terms of series and parallel structures. Having identified the structure functions, the occurrence probabilities of the different categories at the time of diagnosis have been evaluated. The modeling has been done on the basis of the Diagnostic Criteria for Research (DCR) which has been worked out by the World Health Organization (WHO) and accepted by the medical fraternity worldwide.

Chapter 4 studies the manner in which the symptoms manifested in a schizophrenic patient at the time of diagnosis either respond to or are likely to
respond to the administered treatment over time. Some important results regarding the expected number of visits to the doctor required to take a patient to the state of remission have been formulated. The possible transitions within the different symptom categories (states) of schizophrenia, as defined in Chapter 3, have been studied using Markov models and the transition probabilities have been evaluated. The remission probabilities from the states have been obtained theoretically and subsequently evaluated numerically for different values of \( w \), the probability of initial occurrence of a symptom.

In studying symptoms with respect to consecutive visits to the doctor, the concept of "Persistence score" of a symptom has been introduced and its distribution obtained as that of geometric distribution with probability of occurrence varying at every trial. Thus, the persistence scores may be looked upon as non-identical but independent geometric variables. A sampling scheme has been suggested to estimate the persistence scores of the different symptoms.

In Chapter 5, a renewal theoretic approach has been adopted to study the concept of regularity in the treatment process of schizophrenia. For a proper mathematical modeling of regularity in schizophrenia, an Adjusted Renewal Process (ARP) which is a renewal process in discrete time in a dependent and non-identical set up has been defined. Different characteristics of relevance pertaining to the ARP, viz.,
(i) the conditional probabilities of successive renewals
(ii) the expected regularity score
(iii) expectation and variance of the renewal period and
(v) the expected number of appointments required to achieve $k$ renewals
have been obtained.

A sampling scheme has been designed to obtain the estimator of the probability
of a patient visiting the doctor and the existence of the Maximum Likelihood
Estimator (M.L.E) and its large sample properties have been established for the
dependent and non-identical set up. A special case has also been considered in
which the probability of a patient visiting the doctor varies at every renewal.

In Chapter 6, a stochastic model representing the outcomes of treatment of a
schizophrenic patient has been developed. Here, the behaviour of a patient in
course of treatment is studied. Three states viz. “Non response”, “Response” and
“Loss” have been identified as outcomes of treatment under Markov chain setup
and some characteristics and properties of these states, viz.,

(i) transience and recurrence of the states under the Markov setup
(ii) the probabilities of n-step transitions
(iii) probability of first response
(iv) expected number of transitions from a particular state
(v) probability of absorption or loss at the $n^{th}$ visit
have been studied.
A sampling scheme has been designed to estimate the expected probabilities of non-response, response and loss under multinomial set up and under a nonparametric approach (Kaplan-Meier estimators). The variances of these estimators have been obtained by using

(i) Multinomial distribution and (ii) Greenwood’s formula.

A numerical study has been done by taking follow-up data from the GMCH to corroborate the above results.

As mentioned above, Chapters 2, 3 and 4 are devoted to the study of the behaviour of symptoms of schizophrenia. In Chapters 5 and 6, there has been a shift from the behaviour of the symptoms to that of the patient. While Chapter 5 considers the case of the individual patient subsequently generalized for all patients, Chapter 6 considers the case of all patients of schizophrenia in general.

Having studied the different aspects of schizophrenia from diagnosis to outcomes, the next endeavour would be examine the present scenario of the disease. A study of the world epidemiology of some aspects of schizophrenia from available literature and a subsequent study of the local epidemiological scenario of schizophrenia as observed from data collected from the sources already mentioned has been presented in Chapter 7. The persistence scores of symptoms, as conceptualized in Chapter 4 have also been evaluated. Further,
the pattern of remission / exacerbation has been studied for some of the important symptoms with respect to regular and irregular patients.

In Chapter 8, a summary of the aims of the study, the efforts made in the mathematical conceptualizations of the different aspects of schizophrenia and the possible consequences of this work, has been presented. Directions for possible future research work in this area have also been suggested. It is hoped that the study will be of considerable help to doctors and researchers in giving a new direction to the study of schizophrenia and in framing treatment strategies for schizophrenic patients.

1.3 Review of literature

The initial realms of research pertaining to schizophrenia were on the diagnostic criteria of the illness. In the early nineteenth century, all mental disorders were clubbed together as one. It was the works of Emil Kraeplin (1855 – 1926), Eugen Bleuler (1857 – 1959) and Kurt Schneider (1887 – 1967) that gave a distinct identity to schizophrenia, and the criteria for the diagnosis of the disease. Kraeplin used the term “dementia praecox” to describe the cluster of symptoms and later in 1911 the term “schizophrenia” was coined by Bleuler for these symptoms. The landmark “Schneider’s first rank symptoms” of schizophrenia were further modified by Mellor (1982) and these were later included in two major international disease classification systems, namely, the Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD).
This has been discussed in detail in Chapter 7. Sub-groupings or classifications within schizophrenia were introduced by Karl Kleist (1928, 1930), Leohard (1957), Langfeldt (1961) and later modified by Faergeman (1963), Ban (1982), Hamilton (1984), Cooper (1986) and Bergen et al. (1990). [Oxford Textbook of Psychiatry, 1986]

The fine line of difference between various forms of psychosis and mood disorders, and the difference in manifestations shown in countries throughout the globe has led to many international follow-up studies. The International Pilot Study of Schizophrenia (IPSS) sponsored by WHO was the first large scale multinational cross-cultural study of psychiatric disorders carried out to understand the international epidemiology of schizophrenia in 1973. This was followed up by another multinational collaborative study DOSMeD (Determinants of Outcomes of Severe Mental Disorders), sponsored by WHO, involving 13 research sites including two in India (details given in Chapter 7). This led to the birth of several psychiatric epidemiologists who have conducted extensive dedicated research on various aspects of schizophrenia and contributed enormously to the understanding of the disease.

Multinational long term follow-up studies on the course and outcome as also on other demographic factors of schizophrenia require mention of Cooper (1978), Eaton (1985), Sartorius et al. (1986), Stevens and Wyatt (1987), Karno and
Norquist (1989) and Jablensky et al. (1992). However, the singular credit for conducting research in the area of acute psychosis in India goes to Prof. N.N.Wig in 1967. Similar regional epidemiologic studies have been carried out by Robins and Regier (1991) in America, Nakane et al. (1992) in Japan, Hezel and Wylie (2001) in Micronesia, to name a few.

The finding that schizophrenia has a more favourable course and outcome in developing countries than in developed countries, which was upheld by the IPSS was corroborated with follow-up studies by Murphy and Raman (1971) in Mauritius, Kulhara and Wig (1978), Kulhara and Chandiramani (1988) and Kulhara et al. (1989) in India. The same result was obtained in the WHO sponsored DOSMeD and other multinational studies as reported by Sartorius et al. (1987) and Jablensky et al. (1992). A follow-up study for 13 to 14 years carried out by Dube et al. (1984) showed that in the long term, Indian patients also had a more favourable outcome.

Thara and Rajkumar (1992), Thara and Eaton (1996) and Eaton et al. (1998) studied conditions for favourable outcome and remission of schizophrenia. The fact that delays in initiation of treatment result in poorer outcome was discovered by Thara et al. (1994) and later by McGorry (2000). The effect of sustained remission of schizophrenia has been studied by Liberman and Kopelowicz (2005). Thara and Srinivasan (1997) commented on the outcome of
marriage and occupational outcome in schizophrenia. Caldwell & Gottensman (1990) and Radomsky et al. (1999) studied the risk of suicide in schizophrenia.

The association between stressful life events (loss of job, divorce, etc.) and the etiology and course of schizophrenia has been studied, among others, by Jacob et al. (1974), Gureje and Adewunmi (1988) and Kuipers and Bebbington (1990). On the contrary, family therapy, when added to antipsychotic medication, has been shown to be more efficacious than medication alone in preventing relapse in schizophrenia by Pharaoh et al. (2000) who conducted Meta analysis on long term data. The importance of family support has also been reported by Mc Gorry (2000) and Thara et al. (2001).

The important aspect of childhood onset schizophrenia has always been a subject of research and has been addressed recently by Schothorst et al. (2006) who have studied the course and prognosis of early onset psychosis in a group of 12 to 18 year olds, and by Greenstein et al. (2006), who have focused on the brain structures of child schizophrenics.

Schizophrenia research, in another direction, includes higher level studies on brain functioning and the structure of brain cells in schizophrenics as seen through MRI (Magnetic Resonance Imaging) scans. Such studies include those by Nopoulos et al. (1999), Shenton et al. (2001), Lewis (2002) and Nyman.
(2002), Rassovsky et al. (2005), to name a few. Examples of the use of specific statistical procedures in such ‘cerebral’ studies include Harris et al. (1999) who have used Discriminant analysis and Wright et al. (2000) who have done Meta analysis of regional brain volumes in schizophrenics and Jonsson et al (2003) who have also carried out Meta analysis and association study on the effect of a particular drug on schizophrenics. Follow-up studies for testing and comparing the efficacies of various antipsychotic drugs in different situations have also been the focus of schizophrenia research. Such studies are done by applying Analysis of Variance and Covariance available in software packages as observed in the works of Simpson et al. (2005) and Sawamura et al. (2005). Ciudad et al. (2005) applied Multivariate Analysis to study the effectiveness and safety of olanzapine, currently, the most commonly administered drug in schizophrenia. There have been many other similar studies conducted all over the world.

The study of cognitive functioning has been another area in schizophrenia research which has been very fertile. Busemeyer and Townsend (1993) used Decision Theory in the study of cognitive functions. Neufeld et al. (2002) have applied Stochastic Modeling to the assessment of group and individual differences in cognitive functioning. Several other studies have been conducted in this aspect.
Breakspear (2006), while studying the non-linear theory of schizophrenia, makes use of statistical concepts of Time Series, Stochastic Process, Bootstrapping technique and the like. Application of other statistical concepts like Distribution theory, Multivariate analysis, Regression models, Decision theory and Bayesian analysis to study different aspects of schizophrenia has been amply cited in literature.

However, all the studies mentioned above have been long term follow-up studies involving considerable expenditure, technical expertise and manpower. Such studies are feasible only in technically superior medical institutions in collaboration with psychiatrists and under substantial sponsorship from financing agencies. In fact, all the mentioned studies have made use of computer algorithm and software packages while carrying out the analysis of the data. Such studies are beyond the scope of an individual researcher in the field of statistics here. Hence, the direction of work in this thesis is somewhat different.

This work employs the concepts of Stochastic Processes and its properties, Discrete Renewal Process, Distribution theory, Statistical inference, Nonparametric methods and Structure functions, modified to suit the complicacies of schizophrenia. The conceptualization of the different aspects of schizophrenia in terms of the mentioned statistical theories, and to come up with ideas which would prove beneficial to the medical researcher and practitioner, is
the main focus of this work. Endeavour has also been made to make some contribution to the subject matter of statistics by way of a deviation in the usual renewal process and a theorem on consistency of maximum likelihood estimators.

The problem of consistency of the Maximum Likelihood Estimator (M.L.E.) has been addressed by several statisticians as observed in literature. Wald (1949) has given a relatively simple proof of the consistency of the M.L.E., on the lines of that given by Doob (1934) but by employing the strong law of large numbers on independent and identically distributed chance variables. Wolfowitz (1949) uses Wald's lemmas to give a proof of consistency of the M.L.E. employing only the weak law of large numbers, which can be extended to a larger class of dependent chance variables. A proof of the consistency of the M.L.E has been presented in this thesis. The proof consists in identifying the regularity conditions defined by Kulldorff (1957) and Serfling (2001) and verifying them for the dependent and non-identical set up defined in Chapter 5.

The theory of Markov chains and transition probability matrices has been elaborately addressed by Feller (1968), Ross (1989), Medhi (1994), Biswas (1993) and Bhat (2000), to name a few. Nonparametric estimates of transition probabilities in Markov Chains and a test for the order of a Markov Chain have
been suggested by Anderson and Goodman (1957). These concepts have been extensively used in this research.

The theory of renewal processes has been considered quite elaborately for the case of continuous variables in Feller (1968), Ross (1989) and Medhi (1994). Some renewal theorems in discrete time have been suggested by Heyde (1967) for a sequence of independent and identically distributed random variables. Smith (1964) studied on the elementary renewal theorem for non-identically distributed random variables and Chow and Robbins (1963) have suggested a renewal theorem for dependent and non-identically distributed random variables but they too have considered the case of continuous time. In this thesis, a renewal process in discrete time in a dependent and non-identical set up has been considered.

In the context of dependent binary outcomes which have been dealt with in Chapter 5, Bonney (1987) suggests the use of Logistic regression. Eshima et al. (1996) suggest the use of a developmental path model and causal analysis. Although this work is not in any way similar, the concept of varying probabilities employed by Bonney has been incorporated as a special case.

As already mentioned, some nonparametric methods have been applied for estimation of the parameters in this thesis. Kaplan and Meier (1958) initiated the nonparametric estimation for right censored observations. An analogue of the
Kaplan-Meier Product Limit estimator of distribution function under random censoring has been used by Lynden-Bell (1971) in the study of truncated data from an application in astronomy. Thomas and Grunkemeier (1975) have applied the classical Greenwood's formula for variances of Product Limit estimators in cases of both uncensored and randomly censored data. This formula has been used in Chapter 6. Applications of Kaplan-Meier estimates and Greenwood's formula, Hazard functions and Nonparametric tests in the study of death times of a group of psychiatric patients have been demonstrated by Klein and Moeschberger (1997).

1.4 Mathematical tools used in the thesis

Structure Functions:
Let $x_i$ denote an indicator function defined to indicate whether or not the $i^{th}$ component, in a system consisting of $n$ components, is functioning or not, i.e.,

\[
    x_i = 1, \quad \text{if the } i^{th} \text{ component is functioning}
\]

\[
    = 0, \quad \text{if the } i^{th} \text{ component has failed}
\]

The vector $\mathbf{x} = (x_1, x_2, ..., x_n)$, called the state vector indicates which of the components are functioning and which have failed. It also determines whether the system as a whole is functioning or not.

Define,

\[
    \phi(\mathbf{x}) = 1, \quad \text{if the system is functioning when the state vector is } \mathbf{x}
\]

\[
    = 0, \quad \text{if the system has failed when the state vector is } \mathbf{x}
\]

The function $\phi(\mathbf{x})$ is called the structure function of the system.
Series Structure:
A series structure, also called chain model, is a configuration of components such that the system is said to function if and only if all the components in the configuration functions. The relevant diagram representing a series structure is as follows.

\[ \Phi(x) = \min(x_1, x_2, ..., x_n) = \prod_{i=1}^{n} x_i \] ........(1.1)

Parallel Structure:
A parallel structure, also called rope model, is a configuration of components such that the system is said to function if and only if at least one of the components in the configuration functions. The relevant diagram representing a parallel structure is as follows.

\[ \Phi(x) = \max(x_1, x_2, ..., x_n) = 1 - \prod_{i=1}^{n} (1 - x_i) \] ........(1.2)
The k-out-of-n Structure:

A k-out-of-n structure is a configuration of components such that the system is said to function if and only if at least k components out of n components in the configuration functions.

The structure function is given by

\[
\phi(x) = 1, \quad \text{if } \sum_{i=1}^{n} x_i \geq k \\
= 0, \quad \text{if } \sum_{i=1}^{n} x_i < k
\]  ........(1.3)

Series and parallel structures are respectively n-out-of-n and 1-out-of-n systems.

[Reference: Ross (1989)]

Stochastic Process:

Families of random variables which are functions of say, time or space, are known as stochastic processes. (Medhi, 1994)

A stochastic process \( \{X(t), t \in T\} \) is a collection of random variables \( X(t) \) defined for each \( t \) belonging to the parameter set or index set \( T \). The index \( t \) is often interpreted as time and thus, \( X(t) \) is the state of the process at time \( t \).

When \( T \) is a countable set, the stochastic process is said to be a discrete-time process and denoted by \( \{X_n, n=0, 1, 2,\ldots\} \).

When \( T \) is an interval of the real line, the stochastic process is said to be a continuous-time process and denoted by \( \{X(t), t \geq 0\} \).
The state space of a stochastic process is the set of all possible values that the random variables $X(t)$ can assume.

**Markov Chain:**

The stochastic process $\{X_n, n = 0, 1, 2, \ldots\}$ is called a Markov chain if, for all states $i_0, i_1, i_2, \ldots, i_{n-1}, i, j$,

$$P\{X_{n+1} = j | X_n = i, X_{n-1} = i_{n-1}, \ldots, X_1 = i_1, X_0 = i_0\} = P\{X_{n+1} = j | X_n = i\} = p_{ij} \text{ ........(1.4)}$$

whenever the first member is defined.

The outcomes are called the states of the Markov chain i.e., if $X_n = j$, then the process is said to be at state $j$ at the $n^{th}$ trial.

**Transition probability:**

In (1.4), the value $p_{ij}$ which represents the probability that the process which is in state $i$ at the $n^{th}$ trial will move to the state $j$ at the $(n+1)^{th}$ trial is called the transition probability. The transition probabilities $p_{ij}$ satisfy

$$p_{ij} \geq 0, \quad i,j \geq 0; \quad \text{and} \quad \sum_j p_{ij} = 1 \text{ for all } i \text{ ........(1.5)}$$

If the transition probability $p_{ij}$ is independent of $n$, the Markov chain is said to be homogeneous or, to have stationary transition probabilities.

If the transition probability $p_{ij}$ is dependent on $n$, the Markov chain is said to be non-homogeneous.

This study is confined to homogeneous chains.
Transition probability matrix (t.p.m.):

The transition probability \( p_{ij} \) refers to the states \((i,j)\) at two successive trials i.e., the transition is one-step and \( p_{ij} \) is called the one-step transition probability. The transition probabilities \( p_{ij} \) for different values of \( i \) and \( j \) may be written in the matrix form as follows:

\[
\begin{bmatrix}
  p_{11} & p_{12} & p_{13} & \cdots \\
  p_{21} & p_{22} & p_{23} & \cdots \\
  p_{31} & \cdots & \cdots & \cdots \\
  \cdots & \cdots & \cdots & \cdots \\
\end{bmatrix}
\]

This is called the transition probability matrix (t.p.m.) of the Markov chain. \( P \) is a stochastic matrix, i.e., a square matrix with non-negative elements and unit row sums.

Consider a pair of states \((j,k)\) at two non-successive trials, say, state \( j \) at the \( n^{th} \) trial and state \( k \) at the \((n+m)^{th}\) trial. The corresponding transition probability is then called \( m \)-step transition probability and is denoted by \( p_{jk}^{(m)} \), i.e.,

\[
p_{jk}^{(m)} = P(X_{n+m} = k \mid X_n = j), \quad m > 0; j, k = 0, 1, 2, \ldots \ldots\ldots\ldots\ldots\ldots\ldots\ldots(1.7)
\]

The transition probability matrix of \( m \)-step transitions is denoted by \( P^{(m)} \) and can be obtained using Chapman-Kolmogorov equations which define

\[
P^{(m+n)} = P^m \cdot P^n = P^n \cdot P^m \quad \text{(the dot represents matrix multiplication)}
\]

In particular,

\[
P^{(2)} = P^{(1+1)} = P \cdot P = P^2
\]

Similarly,

\[
P^{(m+1)} = P^m \cdot P = P \cdot P^m \quad \text{.........(1.8)}
\]
Finite Markov Chain:
A Markov chain \( \{ X_n, n \geq 0 \} \) with \( k \) states, where \( k \) is finite, is said to be a finite Markov chain.

Order of a Markov Chain:
A Markov chain \( \{ X_n \} \) is said to be of order \( s \) \((s = 1, 2, 3, \ldots)\), if, for all \( n \),
\[
P \left\{ X_n = j \mid X_{n-1} = i, X_{n-2} = i_1, \ldots, X_{n-s} = i_{s-1}, \ldots \right\}
= P \left\{ X_n = j \mid X_{n-1} = i, X_{n-2} = i_1, \ldots, X_{n-s} = i_{s-1} \right\}
\]

whenever the left hand side is defined.
The Markov chain defined in (1.4) is said to be of order 1.

Transition graph:
When the states of a Markov chain are denoted diagrammatically by nodes or vertices and the one-step transitions between states by directed arcs joining the corresponding nodes, the diagram thus obtained gives a visual explanation of the Markov chain and is called a transition graph, an example of which is given below.
**States of a Markov Chain used in this thesis:**

**(i) Accessible states:** If \( p_{jk}^{(m)} > 0 \) for some \( m \geq 1 \), then state \( k \) can be reached or, state \( k \) is said to be accessible from state \( j \), the relation being denoted by \( j \rightarrow k \).

Conversely, if, for all \( m \), \( p_{jk}^{(m)} = 0 \), then state \( k \) is not accessible from state \( j \) and it is denoted by \( j \nmid k \). .......(1.10)

**(ii) Communicating states:** If two states \( j \) and \( k \) are such that each is accessible from the other, then it is said that the two states communicate and it is denoted by \( j \leftrightarrow k \). In this case, there exist integers \( m \) and \( n \) such that

\[
p_{jk}^{(m)} > 0 \quad \text{and} \quad p_{kj}^{(n)} > 0 \quad \text{........(1.11)}
\]

**(iii) Absorbing state:** A state \( j \) is said to be absorbing if

\[
p_j = 1 \quad \text{and} \quad p_{jk} = 0, \; k \neq j. \quad \text{........(1.12)}
\]

**(vii) Persistent and Transient states:** For any state \( j \) let \( f_j \) denote the probability that, starting in state \( j \), the process will ever revisit state \( j \) again.

If \( f_j = 1 \), state \( j \) is said to be persistent or recurrent.

If \( f_j < 1 \), state \( j \) is said to be transient. \quad \text{........(1.13)}
Fundamental Matrix of an absorbing Markov Chain:

Let $P$ be the transition probability matrix of a Markov chain with at least one absorbing state and remaining states communicating with each other. Then $P$ may be written in the form

$$P = \begin{bmatrix} I & 0 \\ R & Q \end{bmatrix} = \begin{bmatrix} Q & R \\ O & I \end{bmatrix} \tag{1.14}$$

Where $I$ is an identity matrix, $O$ is a matrix with all elements zero, $R$ has at least one non-zero element and $Q$ is a sub-stochastic matrix with at least one row sum less than unity.

To find the expected number of transitions required for the Markov chain to ultimately get absorbed at $O$, Kemeny and Snell (1983) have suggested the Fundamental Matrix given by

$$N = (I - Q)^{-1} \tag{1.15}$$

If $e$ is a column vector of unities, $Ne$ is the vector denoting the expected total number of transitions before absorption.

If $N_j$ denotes the number of times state $j$ occurs before absorption, the variance of $N_j$ given that the process starts at state $I$ is given by

$$N (2 N_{dg} - I) - N_{sq} \tag{1.16}$$

where $N_{dg}$ is the diagonal matrix with elements the same as that of $N$ and $N_{sq}$ is the matrix with elements the squares of the elements of $N$. 
Test of hypothesis for the order of a Markov Chain:

To test the null hypothesis that the considered Markov chain is of order 0, i.e.,

\[ H_0 : p_{ij} = p_i \quad \text{for all } i, \]

against the alternative hypothesis that the chain is of order 1, the following test statistic has been suggested by Anderson and Goodman (1957)

\[
-2 \log \lambda = 2 \sum_{i=1}^{m} \sum_{j=1}^{m} n_{ij} \log \left( \frac{N n_{ij}}{(n_i)(n_j)} \right) 
\]

where

- \( p_{ij} \) = probability of going from state \( i \) to state \( j \)
- \( n_{ij} \) = number of transitions from state \( i \) to state \( j \)
- \( N = \sum_i \sum_j n_{ij} \) = total number of transitions.

Under the null hypothesis, this statistic follows asymptotic \( \chi^2 \) (chi-square) distribution with \((m-1)^2\) d.f. (degrees of freedom), where \( m \) is the number of states of the Markov chain. It is to be noted that one d.f. is lost for every \( p_{ij} = 0 \), if any.

In fact, this test provides a rationale for using a Markov model.

Random Walk:

A Markov Chain whose state space is given by the integers \( i = 0, \pm 1, \pm 2, \ldots \) is said to be a random walk if, for some number \( 0 < p < 1 \),

\[ p_{i,i+1} = p = 1 - p_{i,i-1} \quad \text{for } i = 0, 1, \ldots \quad \text{(1.18)} \]
The above Markov chain is called a random walk as it can be thought of as a model for an individual walking on a straight line who at each point of time either takes one step to the right with probability $p$ or one step to the left with probability $1-p$.

**Renewal Process in discrete time:**

Consider a sequence of repeated trials, not necessarily independent, with possible outcomes $E_j$, $j = 1, 2, \ldots$. Let $E^*$ denote the outcome of interest in a series of trials. If $E^*$ occurs in the $n$th trial, then it is said that a renewal has occurred at trial number $n$. Once a trial occurs, trials are counted thenceforth from scratch.

The interval between two successive renewal is called a **renewal period** of the process.

Denote 

\[ f_n = \Pr \{ E^* \text{ occurs for the 1st time at the nth trial} \} \quad \ldots(1.19) \]

\[ p_n = \Pr \{ E^* \text{ occurs at the nth trial (not necessarily for the 1st time)} \} \]

\[ \ldots\ldots\ldots\ldots\ldots(1.20) \]

Define,

\[ f_0 = 0, \quad p_0 = 1 \quad \ldots\ldots\ldots\ldots\ldots(1.21) \]

\[ F(s) = \sum_{n=0}^{\infty} f_n s^n, \quad P(s) = \sum_{n=0}^{\infty} p_n s^n \]

\[ \ldots\ldots\ldots\ldots\ldots(1.22) \]

Now,

\[ f^* = \sum f_n \quad \ldots\ldots\ldots\ldots\ldots(1.23) \]

is the probability that the renewal $E^*$ occurs at some trial in a long sequence of trials. Thus $f^* \leq 1$.

When $f^* = 1$, the renewal event is termed as persistent (recurrent).
When $f^* < 1$, the renewal event is termed as transient.
When $f^* = 1$, then \{f_n\} is a proper probability distribution representing the
distribution of the length of a renewal period $T$, i.e., $P\{T = n\} = f_n$ ........(1.24)

and Biswas (1993)]

**Standard Probability Distributions used**

(i) **Binomial Distribution:**

A random variable $X$ is said to follow Binomial distribution with parameters $(n, p)$
if its p.m.f. is given by

$$b(x; \ n, p) = P(X = x) = \binom{n}{x} p^x (1-p)^{n-x}, \ x = 0, 1, 2, ..., n$$

where $n$ is a positive integer and $0 < p < 1$ ............(1.25)

The mean and variance of this distribution are respectively $np$ and $np(1-p)$.

(ii) **Multinomial Distribution:**

The random variables $X_1, X_2, ..., X_k$ are said to follow Multinomial distribution
with parameters $(n; p_1, p_2, ..., p_k)$ if their joint p.m.f. is given by

$$f(x_1, x_2, ..., x_k; n, p_1, p_2, ..., p_k) = P(X_1 = x_1, ..., X_k = x_k)$$

$$= \frac{n!}{x_1! x_2! ... x_k!} p_1^{x_1} p_2^{x_2} ... p_k^{x_k}$$

...........(1.26)

For $x_i = 0, 1, ..., n$ subject to $\sum_{i=1}^{k} x_i = n$, $p_i \geq 0$ and $\sum_{i=1}^{k} p_i = 1$.

The mean and variance of this distribution are respectively $np_i$ and $np_i(1-p_i)$. 29
(iii) Geometric Distribution:

A random variable $X$ is said to follow Geometric distribution with parameter $p$, if its p.m.f. is given by

$$P(X = x) = p (1-p)^{x-1}, \quad x = 1, 2, 3, ..., \text{ and } 0 < p < 1$$

The mean and variance of this distribution are respectively $\frac{1}{p}$ and $\frac{(1-p)}{p^2}$.

...........(1.27)

(iv) Negative Binomial Distribution:

A random variable $X$ is said to follow Negative binomial distribution with parameters $(r, p)$, where $r$ is a positive integer and $0 < p < 1$, if its p.m.f. is given by

$$f(x; r,p) = P(X = x) = \binom{x-1}{r-1} p^r (1 - p)^{x-r}, \quad x = r, r+1, r+2, ....$$

The mean and variance of this distribution are respectively $\frac{r}{p}$ and $\frac{r(1-p)}{p^2}$.

...........(1.28)

Likelihood Function:

If $x_1, x_2, ..., x_n$ are the values of a random sample from a population with the parameter $\theta$, the likelihood function of the sample is given by

$$L(\theta) = f(x_1, x_2, ..., x_n; \theta) \quad .........(1.29)$$

for values of $\theta$ within a domain. Here, $f(x_1, x_2, ..., x_n; \theta)$ is the value of the joint probability distribution or the joint probability density of the random variables $X_1, X_2, ..., X_n$ at $X_1 = x_1, X_2 = x_2, ......., X_n = x_n$. 

Maximum Likelihood Estimator and its properties:
The estimator of the parameter \( \theta \) obtained by maximizing the likelihood function 
\( L(\theta) \), defined in (1.29), i.e., by solving the likelihood equation \( \frac{\partial \log L}{\partial \theta} = 0 \), is called the Maximum Likelihood Estimator (M.L.E.) .......(1.30)

M.L.E.s are unique and sufficient, whenever they exist, and not necessarily unbiased. They also have the invariance property which states that if \( \hat{\theta} \) is the M.L.E. of \( \theta \), then \( u(\hat{\theta}) \) is the M.L.E. of \( u(\theta) \), provided \( u(\theta) \) is some single-valued function of \( \theta \).

Large sample properties or asymptotically optimum properties:
Under certain regularity conditions,

(i) the likelihood equation has a solution which converges in probability to the true value of the parameter \( \theta_0 \) (Kullhorf, 1957);

(ii) a consistent solution of the likelihood equation corresponds to the maximum of the likelihood;

(iii) a consistent solution of the likelihood equation is asymptotically normally distributed about the true value \( \theta_0 \) and is asymptotically most efficient (Kullhorf, 1957);

(iv) the likelihood equation has one and only one consistent solution (Huzurbazar, 1948);
(v) the solution of the likelihood equation which corresponds to the absolute maximum of the likelihood is necessarily consistent (Wald, 1949).

**Property of Completeness:**

A family of probability distributions $f(x, \theta)$ is said to be complete or, the random variable $X$ is said to be complete for $\theta$, if

$$E_\theta(\psi(x)) = 0 \ \forall \ \theta \quad \Rightarrow \quad \psi(x) = 0 \ \forall \ x \quad \ldots \ldots \quad (1.31)$$


**Product Limit (Kaplan-Meier) Estimator and its variance:**

Let the considered time period $t$ be partitioned into a fixed sequence of intervals $I_1, I_2, \ldots, I_k$, not necessarily of equal lengths, such that $I_i \cap I_{i+1} = 0$.

Let $n_i =$ number of events taking place at the beginning of the interval $I_i$

$d_i =$ number of events taking place in the interval $I_i$

$p_i = P (\text{event taking place through the interval } I_i \mid \text{the event started initially at the beginning of } I_i)$

$q_i = 1 - p_i$

The Product Limit (PL) estimate of the probability of occurrence of the considered event during time $t$, when no ties are present, is given by
The estimated variance of the above PL estimator is given by Greenwood's formula as follows:

$$\text{Var} (\hat{\Psi}(t)) = \hat{\Psi}^2(t) \sum_{i=1}^{k} \frac{d_i}{n_i(n_i - d_i)} \quad \text{.........(1.33)}$$

[Reference: Miller (1981), Klein and Moeschberger (1997)]