CHAPTER 1

Introduction and Preliminaries

1.1 Introduction

In Medical Science and Reliability Theory studies, prevention of either disease or damage to men or machines are given very much importance as that would prevent loss of life or production failure. Diabetes, the chronic disease is taken for study in this Thesis. A study of risk factors of diabetes mellitus was discussed by Bhattacharya, Biswas, Ghosh and Banerjee in [5]. Diabetes mellitus was extensively studied by Foster et al, in [9] and they presented the Global burden of diabetes, prevalence, numerical estimates and projections of the same for the period 1995-2025. The lifestyle modification in management of diabetes mellitus was analysed in [34] by Sahay and Sahay. The Global estimates for prevalence of diabetes mellitus, impaired glucose tolerance in adults were treated by King and Rewers in [21]. A study on diabetes and Cardiovascular risk factors was presented by Kannell and McGee [17].


Many research workers [8, 11, 12, 18, 30, 31] and [39] have studied Mathematical Reliability models extensively. Gopalan and D’Souza [12] treated preventive maintenance models in 2-unit system. Ramanarayanan [31] introduced the concept of alertness of worker in the prevention of damages in reliability models.

It is natural to compare parts of the body of a diabetic person to parts of a machine or certain machines and use reliability theory to study the time to
send the person for hospitalization and the time required for the treatment of
the person after which he recovered from the disease. These are comparable
with time to failure and repair time of a machine widely studied in reliability
theory.

In this thesis we use Geometric, Poisson, Erlang and Markov processes for
the study of models and we discuss diabetes and its related diseases such as car-
bohydrate metabolic disorder, vital organs disorder and gestational diabetes.
Models with prophylactic treatment are also concentrated. Using transform
techniques expectation, variance and numerical examples and illustrations are
provided. In what follows we present a brief note on diabetes and mathematical
concepts used for our study.

1.2 Diabetes: Socio-Economic aspects

According to the World Health Organization at least 171 million people
have diabetes. This figure is likely to be doubled by 2030. Diabetes is one
of the world’s leading chronic diseases and has serious social and economic
considerations. Every 10 seconds a person dies from diabetes related causes,
mainly from cardiovascular diseases. Diabetes is a silent epidemic that claims
as many lives each year as HIV/AIDS.

A study of global prevalence of diabetes, estimates and projection for 2030
was discussed by Wild, Roglic, Green, Sicree and King [46]. World over dia-
betes is responsible for over one million amputations each year, a large per-
centage of cataract and at least five 5 percent of worldwide blindness is due to
diabetes retinal diseases.

Diabetes is the largest cause of the kidney failure in developed countries and
is responsible for huge dialysis cost. The risk of heart disease and stroke are
all significantly higher for people with diabetes. Diabetic pandemic threatens
to be a rapidly expanding burden in the future to the developing countries like
India. The direct and indirect cost involved in the treatment of chronic disease,
especially when associated with the complications are enormous. Diabetes is
one of the most significant health problems that we face in 21st century. More
than 50 percent people suffering from diabetes mellitus globally do not know
that they have the disease.
The majority of the undiagnosed or untreated people are in developing world. The disease is neglected by companies policy makers and aid funding agencies. Global prevalence of diabetes is estimated to increase from 4 percent in 1995 to 5.4 percent in the year 2025. The total number of people with diabetes is predicted to raise to about 300 million by 2025 with one third of the affected individuals in India and China. American diabetes association has been given the standards of medical care for patients with diabetes mellitus [2].

The major risk factor for high prevalence of diabetes mellitus are genetic predisposition, insulin resistance obesity, central obesity, along with urbanization and sedentary life style. Based on the available data there are about 25 million persons with diabetes in India out of which only 3.6 percent people are properly treated.

The economic implications are a matter of world wide concern because of increasing cost of diabetes care. This is reflected for e.g. in aggressive management of end stage of renal disease in some patients, while a large number of the patients with diabetes and hypertension receive inadequate attention, follow-up and education through diabetes with hypertension is a major cause of end stage renal disease. Health resources in India and developing countries are very limited with only 5 percent gross domestic product being spent on health care. A report of diabetes health economics was given by the economics of diabetes and diabetic care study group Gruber, Lander, Leese, Songer and Williams [13].

The cost of the illness can be classified in the direct, indirect and intangible costs. Direct cost is to the people with diabetes, their families and to the health care sectors, indirect cost is to the society and government which are productivity cost; and the intangible cost means adverse effects on the quality of life. The impact of socio-economic factor in diabetes care has been studied by Rayappa, Raju, Kapur, Bjork, Sylvist and Dilip Kumar [33]. The direct cost per patient per year for diabetes mellitus in Argentina was 330 US dollars, in France 675 USD and in Denmark 3535 USD.
1.2.1 Epidemiology of Diabetes

The diabetes pandemic is rapidly spreading and mostly affects developing countries like India. Indeed, India presently has the largest number of diabetic patients in the world and has been infamously dubbed as the Diabetic capital of the world. During the past 50 years, many countries in the world including India have experienced dramatic improvement life expectancy due to improved nutrition, better hygiene and control over many communicable diseases. However prevalence of non communicable diseases such as diabetes has dramatically increased, leading to increasing burden and cost to the society.

The term epidemiological transition is applied to describe these changes in disease pattern. This transition catapulted diabetes from its former status as a rare disease at the beginning of the last century, to its current position as a major global disease responsible for considerable mortality and morbidity. The prevalence of diabetes has increased by leaps and bounds in India and has already reached epidemic proportions. Noted diabetologist and epidemiologist Zimmet has studied the process leading to the epidemic of diabetes in developing countries [36].

Prevalence of diabetes mellitus, is increasing by leaps and bounds, particularly in India. Diabetes is not merely a metabolic disease but very much a vascular disease. Various macrovascular complications of diabetes are responsible for 75 percent of deaths in diabetics, 66 percent among these are due to coronary artery disease. Microvascular complications account for significant morbidity in diabetes.

1.2.2 Classification and Clinical Manifestations

Diabetes Mellitus is not a single disease but a syndrome consisting of different subtypes of diabetes with hyperglycemia due to insulin deficiency, either absolute or relative, as a common factor.

Diabetes Mellitus occurs due to auto immune or idiopathic destruction of insulin producing \( \beta \) cells in Islets of Langerhans in the pancreas resulting in inability to produce endogenous insulin which is vital for control of blood glucose and other metabolic function. For a detailed study over the diabetes and its complications see Patel [27]. Insulin is secreted by beta cells of Islets
of Langerhans in pancreas. Islets are scattered through the pancreas. Typically each islets contains about 1000 cells, 80 percent of which are beta cells. Insulin is secreted by the beta cells in response to small changes in glucose concentrations.

In diabetes there is a beta cell dysfunction leading to insufficient first phase insulin secretion and gradually diminishing overall insulin secretion. In addition to the insulin secretory beta cell defects about 85 percent of diabetics also have varying degree of insulin resistance. In these patients peripheral tissue response to available insulin is less than normal. However over the years the capacity of their beta cells gradually diminishes and a time comes when they can no longer be controlled on oral pills even if all the major classes are combined together.

Diabetics present with severe symptoms such as polyurea, polydepsia, polyphagia, weight loss and in some case added with symptoms of diabetic keto acidosis such as vomiting, deep rapid breathing characteristic of acidosis and deteriorating level of consciousness. If there is an underlying cause which has triggered metabolic deterioration, it’s symptoms are also super added, for example cough and fever in case of pneumonia or tuberculosis.

Diabetes Mellitus was called maturity onset diabetes because it is usually diagnosed in the middle age, if the affected patient may present with severe symptoms such as polyurea, polydepsia, polyphagia, weight loss weakness and itching etc. In diabetes mellitus, there is an interplay between environmental and genetic factors leading to a chain of events, ultimately leading to diabetes.

Most of the patients have varying degrees of dual defects, β cell dysfunction and insulin resistance. Both these pathogenic factors have contributions from genetic and acquired factors. Diabetics have inherited β cell defect to which acquired dysfunction of β cells due to infantile or intrauterine malnutrition and transient dysfunction due to toxic effect of severe hyperglycemia.

Insulin resistance has genetic as well as acquired components. The Diabetes Control and Complications Trial Research Group studied the effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus [38].

Obesity is associated with insulin resistance and has acquired as well as genetic components. Diabetes Mellitus is more common in obese people be-
cause of insulin resistance which is associated with obesity. Obesity in diabetes should be discussed by Bloomgarden [7]. An integrative view of obesity was studied by Wise, Kim and Schwartz [47]. There are many conditions which are associated with or which lead to diabetes. The list is given below.

1. Genetic defects of beta cell function
2. Genetic defects in insulin action
3. Diseases of exocrine pancreas
4. Endocrine disorders
5. Drug or chemical induced diabetes
6. Infections
7. Immune mediated diabetes
8. Other genetic syndromes associated with diabetes.

1.2.3 Diabetes Characterization and Complications

Diabetes is characterized by elevated glucose concentrations, the impact of diabetes on both the health of individuals and on the health care systems, resides almost entirely in the long term “complications” of diabetes affecting almost every system in the body including eyes, heart, feet and nerves. Hyperglycemia and microvascular and macrovascular diseases in diabetes are discussed by Klein [22].

The term diabetes without classification refers to diabetes mellitus, which roughly translates to excessive sweet urine. Diabetes mellitus often referred to as diabetes-a condition in which a person has high blood sugar, either because the body doesn’t produce enough insulin, or the cells doesn’t respond to the insulin produced. Diabetes related complications can be broadly classified as below.

1. Micro vascular complications:
   Micro vascular complications are specific for diabetes and are responsible for considerable morbidity and mortality, affect retina-diabetic
retinopathy, kidney-diabetic nephropathy, and peripheral nerves-diabetes neuropathy.

2. Macro vascular complications:
Which affects heart-cardiovascular disease, brain-cerebrovascular disease and peripheral arteries-peripheral vascular disease.

1.2.4 Micro Vascular Complications

People with diabetes have an increased risk of developing micro vascular complications, which if undetected or left untreated, can have a devastating impact on quality of life and place a significant burden on health care costs. The most specific complications of diabetes are micro vascular complications, of which diabetic retinopathy is considered as the hallmark of diabetes.

**Diabetic Retinopathy:** Diabetic retinopathy affects the microvasculature in retina or back portion of eye. Affliction of the capillaries in the retina(diabetic retinopathy), can ultimately lead to blindness, thus making the affected patient dependent. The onset and progression may be influenced by many systematic factors genetic and ocular factors. A systematic approach to diabetic retinopathy in clinical ophthalmology was given by Jack [15].

**Diabetic Nephropathy:** Affection of capillaries in the kidneys(Diabetic nephropathy) ultimately leads to end stage renal failure, needing either renal transplantation or permanent thrice a week hemodialysis. Both are extremely expensive and beyond the reach of an average Indian. Kidney disease in diabetic patients is clinically characterized by increasing rates of urinary albumin secretion, starting from normal albuminuria which progress to microalbuminuria, macroalbuminuria and eventually lead to end stage of renal disease.

Further, Agarwal and Dash [1] studied the spectrum of renal disease in Indian adults. National Institute of Health and National Institute of Diabetes and Kidney Diseases has given the report about the renal data system [45].

**Diabetic Neuropathy:** Diabetic neuropathy leads to unbearable pain and paraesthesia in the legs which interfere with the day to day activities and sleep and can be totally incapacitating. More over impaired sensations over the legs is one of the major underlying factors responsible for diabetic foot
lesions which can lead to gangrene and amputations.

The intensity and extent of the functional and anatomical abnormalities of diabetic neuropathy is parallel to the degree and duration of hyperglycemia. Among the individuals with diabetes it is the common cause of morbidity—painful polyneuropathy, neurophatic ulceration and mortality—autonomic neuropathy. Joshi [16] discussed about the diabetic neuropathy.

**Diabetic Foot:** The diabetic foot is one of the common complications of diabetes, often requiring prolonged hospitalization. Approximately 5 – 10 percent of all diabetics develop foot ulcers at least once in their lifetime and more than 50 percent of non-traumatic amputations of lower limbs are for foot complications in diabetic patients. The foot infections are the major cause of limb loss. One of the major consequences of non-healing foot ulcer is osteomyelitis of tarsal and metatarsal bones. Levin and O'Neal [24] discussed about the diabetic foot.

Diabetics, particularly those who have long standing and poorly controlled diabetes, are at increased risk to develop varied foot complications such as infection leading to cellulitis, non healing ulcers and gangrene as compared to the general population. Many such diabetic patients are totally divorced from their feet because of sensory deficiency due to diabetic peripheral neuropathy and visual defects due to diabetic retinopathy. The risk factors for foot infections with diabetes was discussed by Lavery, Armstrong, Wunderlich and Lipsky [23].

1.2.5 **Macro Vascular Complications**

Macro vascular disease is considered to be the deadly triangle comprising coronary artery disease, peripheral vascular disease and cerebrovascular disease.

**Cardiovascular disease:** Diabetes mellitus is an independent risk factor for cardiovascular disease. Diabetic person has higher risk factor for cardiovascular disease which is estimated to be 2 – 4 folds compared to a non diabetic person.

Hypertension is also much more common in diabetics. Hypertension is recognized as a major risk factor for cardiovascular disease so is diabetes. Hyper-
tension is twice as common in individuals with diabetes mellitus as compared to normal persons. Renal damage in diabetic nephropathy is responsible for hypertension. Hypertension and Cardiovascular disease with diabetes was discussed by Sowers and Epstein [37].

**Cerebrovascular disease:** Cerebrovascular disease leading to stroke, coronary artery disease leading to myocardial infarction and peripheral vascular disease leading to gangrene, are commonly associated with diabetes. Strokes are third commonest cause of mortality after heart disease and cancer. Patients with diabetes have higher frequency of stroke.

### 1.2.6 Gestational Diabetes

Diabetes first diagnosed during pregnancy is called gestational diabetes. It results from insulin resistance of pregnancy interacting with beta cell defects. Usually blood glucose is normalized after the delivery. Since significant insulin resistance of pregnancy develops only in third trimester, Gestational diabetes sets in only in this period.

This occurs in pregnant women who never had diabetes before, have a high glucose level only during pregnancy. Gestational diabetes usually resolves after delivery. Gestational diabetes mellitus is defined as glucose intolerance with recognition or onset during pregnancy, irrespective of the treatment with diet or insulin.

Women with a history of gestational diabetes are at increased risk of future diabetes as are their children. Gestational diabetic mellitus occurs when the mother's beta cell function is not able to overcome the antagonism created by anti insulin hormones of pregnancy and the increased fuel consumption required to provide for feto material unit. Seshiah, Balaji, Madhuri, Sanjeevi and Green [35] discussed the Gestational diabetes mellitus in India.

It is common knowledge that diabetes mellitus and infections often go together - one aggravating the other. Poorly controlled diabetes increases the risk for a variety of infections and also making them more severe; infections in turn worsen the diabetes. This leads to a self- perpetuating cycle which frequently goes out of hand contributing to a marked increase in morbidity and mortality.
1.2.7 Common Infections Associated with Diabetes

The common infections associated with diabetes are

1. Diabetic foot infections
2. Urinary tract infections
3. Respiratory tract infections
4. Skin and soft tissue infections
5. Periodontal infections

Diabetes can affect every part of the body, including the skin.

1.3 Operations Research

Since the advent of the industrial revolution, the world has seen a remarkable growth in the size and complexity of organizations. The small shops of an earlier era have evolved into the billion dollar corporations of today. An integral part of this revolutionary change has been a tremendous increase in the division of labor and segmentation of management responsibilities in these organizations. The results have been spectacular.

However, along with its blessings, this increasing specialization has created new problems. One problem is that as the complexity and specialization in an organization increase, it becomes more and more difficult to allocate its available resources to its varied activities in a way that is most effective for the organization as a whole. These kinds of problems and the need to find a better way to resolve them provided the environment for the emergence of Operations Research.

The roots of Operations Research can be traced back many decades, when early attempts were made to use a scientific approach in the management of organizations. However, the beginning of the activity called Operations Research has generally been attributed to the military services early in World War II. Because of the war effort, there was an urgent need to allocate scarce
resources to the various military operations and to the activities within each operation in an effective manner.

Therefore the British and then the American military management called upon a large number of scientists to apply a scientific approach to dealing with this and other strategic and tactical problems. In effect they were asked to do research on (military) operations. These teams of scientists were the first Operations Research teams. Spurred on by the apparent success of Operations Research in the military, industry gradually became interested in this new field.

In this way Operations Research began to creep into industry, business and civil government. Operations Research may be described as a scientific approach to decision making that involves the operations of organizational systems. Therefore, perhaps the best way of grasping the unique nature of organization is to examine its outstanding characteristics.

Operations Research is applied to problems that concern how to conduct and coordinate the operations or activities within an organization. The nature of the organization is essentially immaterial and in fact, Operations Research has been applied extensively in business, industry, military, hospitals and so forth. Therefore, the area of application is unusually wide.

The approach of Operations Research is that of the scientific method. In particular, the process begins by carefully observing and formulating the problem and then constructing a scientific (typically mathematical) model that attempts to abstract the essence of the real problem. Introduction to Operations Research has been given by Frederick, Hiller, Gerald and California [10].

The largest areas of application are production management, financial planning, inventory and reliability. In case of probabilistic models Stochastic Process is used. Stochastic Models in Operations research has been discussed by Heyman and Sobel [14].

### 1.4 Stochastic Process

Since the last century there have been marked changes in the approach to scientific enquiries. There has been greater realization that probability models are more realistic than deterministic models in many situations. Observations
taken at different time points rather than those taken at a fixed period of time began to engage the attention of probabilists. This led to a new concept of indeterminism.

Many a phenomenon occurring in physical and life sciences are studied now not only as a random phenomenon but also as one changing with time or space. The scope of applications of random variables which are functions of time or space or both has been on the increase. Families of random variables which are functions of time(say), are known as Stochastic Processes. Stochastic Processes concern sequences of events governed by probabilistic laws.

A Stochastic Process is defined to be simply an indexed collection of random variables \( \{X_t\} \), where the index \( t \) runs through a given set \( T \). These relationships are specified by giving the joint distribution function of every finite family of variables of the process. Many applications of Stochastic Processes occur in physics, engineering, biology, medicine, psychology and other disciplines, as well as in other branches of mathematical analysis. For more details one may refer the book *A First Course in Stochastic Processes*, by Karlin and Taylor [19].

### 1.4.1 Reliability theory

The qualitative concepts of reliability are somewhat old but its quantitative aspects have been developed over the past two decades or so. Reliability theory is mainly concerned with the determination of the probability that a device performs adequately over the interval \([0, t]\). Statistical Analysis of Reliability and Life-testing Models was discussed by Bain [3] and Barlow and Proschan [4]. Birolini analyzed, the Use of Stochastic Processes in modelling reliability problems [6].

In general, it is assumed that unless repair or replacement occurs, adequate performance at time \( t \) implies adequate performance during the interval \([0, t]\). The device under consideration may be an entire system, a subsystem or a component. As an example, consider an automobile. There are a large number of functional parts, wiring and joints. These may be broken into subsystems, with each subsystem having a reliability associated with it. Possible subsystems are the engine, transmission, exhaust, body, carburetor and breaks.
A mathematical model of the automobile system can be abstracted and the theory of combinatorial probability used to predict the reliability of the automobile. A study of Stochastic Models in Reliability theory was presented by Ravichandran [32]. Kapur, Yadav, Singh and Yadavalli [18] discussed the Testing Domain Dependent Software Reliability Growth Models with Power-Logistic Function.

1.4.2 The Poisson Process

A stochastic process \( \{N(t), t \geq 0\} \) is said to be a counting process if \( N(t) \) represents the total number of events that have occurred up to time \( t \). Hence, a counting process \( N(t) \) must satisfy:

1. \( N(t) \geq 0. \)
2. \( N(t) \) is integer valued.
3. If \( s < t \), then \( N(s) \leq N(t) \).
4. For \( s < t \), \( N(t) - N(s) \) equals the number of events that have occurred in the interval \( (s, t] \).

The counting process \( \{N(t), t \geq 0\} \) is said to be a Poisson process having rate \( \lambda \), \( \lambda > 0 \), if

1. \( N(0) = 0. \)
2. The number of events in any interval of length \( t \) is Poisson distributed with mean \( \lambda t \). That is, for all \( s, t \geq 0 \),

\[
P \{ N(t + s) - N(s) = n \} = e^{-\lambda t} \frac{(\lambda t)^n}{n!}, \quad n = 0, 1, \ldots
\]

1.4.3 Shock models and wear processes

Suppose that a device is subjected to shocks which occur in accordance with a Poisson process with parameter \( a \). Denote the probability that the
device survives the first $k$ shocks, $k = 0, 1, 2 \cdots$ by $q_k$. Clearly, the reliability of the device at time $t$ is

$$R(t) = Pr \{ T > t \}$$

$$= P(\text{life time of the device } T > t)$$

$$= \sum_{k=0}^{\infty} \frac{q_k e^{-at}(at)^k}{k!}, \quad t \geq 0$$

$$= 1, \quad t < 0.$$

Now, $q_k$ being the probability of surviving shocks and $p_k$, the probability of failure on the $k^{th}$ shock, is given by

$$p_k = q_{k-1} - q_k, \quad k = 1, 2, \cdots \text{ and } p_0 = 1 - \sum_{k=1}^{\infty} p_k = 1 - q_0.$$

The failure of mechanical devices such as ships, trains, and cars, is similar in many ways to the life or death of biological organisms. Statistical models appropriate for any of these topics are generically called “time-to-event” models. Death or failure is called an “event”, and the goal is to project or forecast the rate of events for a given population or the probability of an event for an individual. Shock models were described by Esary [8] for the life time of a device.

When reliability is considered from the perspective of the consumer of a technology or service, actual reliability measures may differ dramatically from perceived reliability. In research, the term reliability means “repeatability” or “consistency”. A measure is considered reliable if it would give us the result over and over again.

Economists, environmental scientists and others take keen interest in reliability and this gives rise to many publications in this field. Reliability theory is a general theory about systems failure. Ramanarayanan [30, 31] and Usha and Ramanarayanan [39] studied up and down time models in the case of system failure of a machine.

In this thesis, using Geometric Distribution, Poisson process, Renewal process, Exponential distribution, Modified Erlang with Laplace - Stieltjes transforms, the expected time to failure and time to treatment of diabetic person and their variances are calculated.
1.4.4 Renewal Process

Renewal theory is viewed as the general study of functions of independent, identically distributed, nonnegative random variables representing the successive intervals between renewals. The results are applicable in a wide variety of both theoretical and practical probability models. A natural generalization is to consider a counting process for which the inter arrival times are independent and identically distributed with an arbitrary distribution. Such a counting process is called a renewal process.

Let \( X_n, n = 1, 2, \ldots \) be a sequence of nonnegative independent random variables with a common distribution \( F \). Let

\[
\mu = E[X_n] = \int_0^\infty x dF(x)
\]

denote the mean time between successive events.

Let

\[
S_0 = 0, \quad S_n = \sum_{i=1}^{n} X_i, \quad n \geq 1,
\]

it follows that \( S_n \) is the time of the \( n^{th} \) event. And hence for the largest value of \( n \), \( N(t) = \sup \{ n : S_n \leq t \} \).

Distribution of \( N(t) \): The distribution of \( N(t) \) can be obtained in theory by noting that the important relationship that the number of renewals by time \( t \) is greater than or equal to \( n \), if and only if, the \( n^{th} \) renewal occurs before or at time \( t \). That is

\[
N(t) \geq n \Leftrightarrow S_n \leq t.
\]

Therefore,

\[
P \{ N(t) = n \} = P \{ N(t) \geq n \} - P \{ N(t) \geq n + 1 \} = P \{ S_n \leq t \} - P \{ S_{n+1} \leq t \}.
\]

Now since the random variables \( X_i, i \geq 1 \), are independent and have a common distribution \( F \), it follows that \( S_n = \sum_{i=1}^{n} X_i \) is distributed as \( F_n \), the \( n \)-fold convolution of \( F \) with itself. Here

\[
P \{ N(t) = n \} = F_n(t) - F_{n+1}(t)
\]

and \( m(t) = E[N(t)] \), is called the renewal function.
1.4.5 Markov Process

A Markov process is a process with the property that, given the value of $X_t$, the values of $X_s$, $s > t$, do not depend on the values of $X_u$, $u < t$; that is, the probability of any particular future behavior of the process, when its present state is known exactly, is not altered by additional knowledge concerning its past behavior. We should make it clear, however, that if our knowledge of the present state of the process is imprecise, then the probability of some future behavior will in general be altered by additional information relating to the past behavior of the system. In formal terms a process is said to be Markov if

$$Pr\{a < X_t \leq b | X_{t_1} = x_1, X_{t_2} = x_2, \ldots X_{t_n} = x_n\} = Pr\{a < X_t \leq b | X_{t_n} = x_n\}, \quad (1.4.1)$$

whenever $t_1 < t_2 < \cdots < t_n < t$.

Let $A$ be an interval of the real line. The function

$$P(x, s; t, A) = P\{X_t \in A | X_s = x\}, \quad t > s, \quad (1.4.2)$$

is called the transition probability function and is basic to the study of the structure of Markov processes. It is easy to observe from (1.4.1) that

$$Pr\{a < X_t \leq b | X_{t_1} = x_1, X_{t_2} = x_2, \ldots X_{t_n} = x_n\} = Pr(x_n; t_n; t, A),$$

where $A = \{\xi | a < \xi \leq b\}$. Thus the probability distribution of $(x_{t_1}, x_{t_2}, \ldots, x_{t_n})$ can be expressed in terms of (1.4.2) and the initial distribution function of $X_{t_1}$.

1.4.6 Setting the Clock Back to Zero Property

It is a natural phenomenon that the human immune system undergoes frequent changes due to the influence of the factors, which are external and internal to the system. Hence the immune capacity undergoes changes from time to time, hence it is assumed that the random variable which denotes the immune ability of an individual, which in other words called the antigenic diversity threshold, undergoes a change of parameter after a particular value of the random variable which is called the truncation point and this is called SCBZ property. This property is due to Raja Rao [28].
In this thesis, we introduce \textit{SCBZ} concept. Here damage rate changes after an exponential time from one rate to another. Raja Rao [28] introduced Setting the Clock Back to Zero property and discussed the life expectancy. Murthy and Ramanarayanan [25, 26] introduced the SCBZ concepts in Inventory models. Setting the Clock Back to Zero property of a Family of Bivariate Life Distributions was discussed by Raja Rao, Jasem.M.Alhumoud and Damaraaju [29].

Considering the truncation point $T_0$ in which the parameter $\lambda_1$ changes to $\lambda_2$, we note that the pdf of threshold is

$$
h(y) = \begin{cases} 
\lambda_1 e^{-\lambda_1 y} & \text{if } y \leq T_0 \\
\lambda_2 e^{-\lambda_2 y} e^{T_0(\lambda_2 - \lambda_1)} & \text{if } y > T_0.
\end{cases}
$$

When the truncation point $T_0$ itself is a random variable with pdf $ce^{-cT_0}$, we find

$$
h(y) = \lambda_1 e^{-\lambda_1 y}e^{-cy} + \lambda_2 e^{-\lambda_2 y} \int_0^y e^{T_0(\lambda_2 - \lambda_1)} ce^{-cT_0} dT_0,
$$

which reduces to

$$
h(y) = \frac{(\lambda_1 - \lambda_2)(c + \lambda_1)}{(c + \lambda_1 - \lambda_2)} e^{-y(\lambda_1 + c)} + \frac{c\lambda_2 e^{-\lambda_2 y}}{(c + \lambda_1 - \lambda_2)}
$$

with distribution function

$$
H(y) = 1 - pe^{-y(\lambda_1 + c)} - qe^{-\lambda_2 y}
$$

where $p = \frac{(\lambda_1 - \lambda_2)}{(c + \lambda_1 - \lambda_2)}$ and $q = \frac{c}{(c + \lambda_1 - \lambda_2)}$. Also it is clear that $p + q = 1$.

In what follows the results obtained by the author on Stochastic Models relevant to diabetes are presented.

### 1.5 Author’s Work

The first chapter deals with the introduction of the thesis with a review of relevant research articles.
Chapter II deals with the carbohydrate metabolic disorder. Diabetes mellitus is a chronic disease of pancreatic origin, characterized by insulin deficiency. Due to the secretion of less insulin in the pancreas, the glucose level exceeds the threshold level of the human body and the carbohydrate metabolic disorder takes place. In the estimation of the expected time to carbohydrate metabolic disorder, there is an important role for the inter arrival times between damages of the cells. Often expected inter damage times are in decreasing order or increasing order forming geometric processes. Under the above circumstances the expected time to carbohydrate metabolic disorder and its variance are derived with numerical example.

The content of this chapter has been published as a research paper in “International Journal of Applied Mathematics” Vol.22, No. 2,(2009)317 – 330, [40].

In chapter III, we consider the damages of two organs of the diabetic person. Heart and kidney are the vital organs of the human body. The dysfunctioning of those organs would cause death to the person. In model-1, heart is exposed to cumulative damage process and the organ kidney has a constant failure rate. In model-2, both the organs are exposed to cumulative damage process. They have exponential thresholds and exponential inter damage times. Considering treatment to all the damages of the two organs of a diabetic person, in this chapter we present the expected time to failure of the organs, variance and the joint Laplace transforms of the curing and damage times.

The content of this chapter has appeared as a research paper in “International Journal of Applied Mathematics”. Vol.23, No. 2,(2010)293 – 308, [41].

Chapter IV deals with the case of three organs failure of a diabetic person, who is liable for damages of vital organs like heart, kidneys and legs, if the person is not given proper treatment. The heart, two kidneys and legs are considered as three sub-systems of the main system. These three sub-systems are exposed to damages. The two kidneys have constant failure rate. In model-1, the organ heart has a general life time and the damages occur in the leg in accordance with Poisson process and in model-2 the heart has an exponential life time where as the leg is exposed to renewal damage processes. Considering treatment to the diabetic person, in this chapter we present the expected time to failure of the organs, variance and the joint Laplace- Stieltjes transforms of the curing and damage times with numerical examples.
Diabetes mellitus is a chronic disease of pancreatic origin which is not fully curable once a person become diabetic. Chapter V treats two models with prophylactic treatment, considering a person who is exposed to diabetes and organ failure. In model-1, time to diabetes is exponential where as organ failure process is general and in model-2 time to diabetes has general distribution where as organ failure process is Markovian. In this chapter we present the expected time to treatment and expected cure time with numerical examples.

In chapter VI- Gestational Diabetes Mellitus which is a form of diabetes, which affects pregnant women is studied. The hormones produced during pregnancy reduce a woman's receptivity to insulin, leading to high blood sugar levels. In this Chapter we consider the damages of two vital organs of the gestational diabetic person. The dysfunctioning of those organs may cause death to the person. In model-1, the organ-1 is exposed to cumulative damage process and the failure distribution of the organ-2 has SCBZ property. In model-2, the damages of the organ-1 occur in accordance with modified Erlang process and the organ-2 has SCBZ failure property. Considering treatment to all the damages of the two organs of a diabetic person, in this chapter we present the expected time to treatment and treatment time of the organs, with numerical example.