Study of Some Mathematical Models in Population Dynamics and Epidemiology

THESIS

Submitted in partial fulfilment of the
requirements for the degree of
Doctor of Philosophy

By

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Under the supervision of

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Birla Institute of Technology and Science
Pilani, Rajasthan
2008

Acknowledgements

I express my sincere gratitude and indebtedness to my teacher and guide, Prof. Rajiv Kumar, Associate Professor, Mathematics Group, BITS, Pilani, for his constant guidance and support, and for giving me a wonderful opportunity to work on this topic. He had been a constant source of inspiration right from the day I started my M.Phil course work as a research scholar. His encouragement and inspiring words motivated me to pursue this doctoral research. The enthusiasm, moral support and advice that he has been giving me will stimulate me to the best in all my future endeavours. I sincerely acknowledge the help rendered by him at all times.

I am thankful to Prof. L.K. Maheshwari, Vice Chancellor, BITS, Pilani for giving me the opportunity to carry out my doctoral research work. I would like to thank Prof K. E. Raman, Deputy Director, Administration, Prof. G. Raghurama, Deputy Director, Academics and Prof. R.N.Saha, Dean Faculty Division III and Educational Development Division for extending support during my research work. I express my sincere gratitude to Prof. Ravi Prakash, Dean, Research and Consultancy Division for his timely help and support throughout my research work.

I am thankful to members of Doctoral Advisory Committee, Dr. Balram Dubey, Group Leader, Mathematics and Prof. R.S. Parihar for their valuable suggestions. I would like to thank all the faculty members of Mathematics Group for their cooperation during my research activities and academic responsibilities. I express my sincere thanks to Dr. Ishwar Bhat for helping me borrow journal articles and books from different libraries across the country. I am grateful to Dr. Srinivasa

Regalla, Dr. Hemant Jadhav, Mr. Dinesh Kumar, Mr. Sharad Srivastava, Raghuvirji, Mahipalji and Soniji of Research and Consultancy Division for their help at various stages of my doctoral research. I express my thanks to all my dear friends and well wishers for their help and moral support.

I express my hearty gratitude to my parents, parents in-laws, sister and brother-in-law for their love, encouragement and moral support. This work would not have been possible but for my dear daughter Dhanya Mahalakshmi who had been very patient during the long hours I spent in pursuing my research. My special thanks are due to my beloved husband, Murali who had been indispensable right from the day I started my doctoral research and encouraging me throughout.

I am grateful to the Almighty, without whose blessings, this thesis would not have been possible.

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Introduction

1.1 Population Dynamics

Mathematical biology or biological mathematical modeling is an interdisciplinary field of academic study which aims at modeling natural, biological processes using applied mathematical techniques and tools. It has both practical and theoretical applications in biological research. Ecology, which is a branch of mathematical biology is a study of the inter relationship between species and their environment such areas as predator-prey and competition interactions, renewable resource management, evolution of pesticide resistant strains, ecological and genetically engineered control of pests, multi species societies, plant-herbivore systems and so on is now an enormous field. The continually expanding list of application is extensive on various aspects of the field [1].

Population dynamics has traditionally been the dominant branch of ecology, which has a history of more than 210 years, although more recently, it's scope has greatly expanded [2]. Population dynamics is the study of marginal and long-term changes in the numbers, individual weights and age composition of individuals in one or several populations, and biological and environmental processes influencing those changes [3]. Work in population dynamics dates back to the nineteenth century and the Lotka-Volterra predator-prey equations are a famous example [4].

The increasing study of realistic and practically useful mathematical models in population dynamics, whether we are dealing with a human population with or without its age distribution, population of an endangered species, bacterial or viral growth and so on, is a reflection of their use in helping to understand the dynamic processes involved and in making practical predictions. The study of population change has a very long history [5]. In the year 1202, an exercise in an arithmetic book written by Leonardo of Pisa involved building a mathematical model for a growing rabbit population [6]. Mathematical and computational approaches provide powerful tools in the study of problems in population biology and ecosystems science. The subject has a rich history intertwined with the development of statis-

tics and dynamical systems theory [7, 8]. These mathematical and computational approaches are now considered as some of the most powerful tools in learning about nature. Such approaches have led to extensive work and have provided a framework for synthesis and analysis of such biological models [9].

Since the early nineteenth century, there has been growing interest in the study of mathematical ecology. Ecology studies the conditions of existence and the interaction of living organisms with each other and with their environment [10]. Population dynamics, which studies population growth, mortality, competition and predator-prey relations, is perhaps the most mathematically developed area of ecology.

A great deal of research has been done in sophisticated models in population ecology, for example, models in both discrete and continuous time with and without delays along with stochastic models with the effects of spatially non-uniform environments and with diffusive spread of populations [11, 12]. The increasing study of realistic mathematical models in ecology is a reflection of their use in helping to understand the dynamic processes involved in such areas as predator-prey and competition interactions, renewable resource management, evolution of pesticide resistant strains, ecological control of pests, multi-species societies, plant-herbivore systems and so on. The continually expanding list of applications is extensive. There are also interesting and useful applications in the bio-medical sciences and in physiology [6].

Mathematical models give an important contribution to ecological studies. They propose quantities that can be measured, define concepts enabling to quantify biological interactions, and even propose different modeling strategies with different assumptions to describe particular features of the populations.

In population dynamics, from the mathematical point of view, there are essentially two main modeling techniques:

1. The continuous time approach using ordinary and partial differential equa-

tions and

2. The discrete time approach which is more closely related with the structure of the census of a population.

Both approaches extensively use the methods of the qualitative theory of dynamical systems [13].

In the continuous time approach, the number of individuals of a population varies continuously in time and the most common modeling framework applies to the description of the types of biotic inter-specific interactions and to the interactions of the species with environment.

In the discrete time approach, models are built in order to describe the census data of populations. They are discontinuous in time, and are closer to the way population growth data are obtained [10].

The first significant work in the theory of population dynamics was by Malthus in the year 1798. The Malthusian growth model, sometimes called the simple exponential growth model, is essentially exponential growth based on a constant rate of compound interest. The model is named after the Reverend Thomas Malthus, who authored "An Essay on the Principle of Population", one of the earliest and most influential books on population. He proposed a single species model where the rate of population growth was proportional to the size of the population [14]. The malthusian model is given by

$$\begin{aligned} \frac{du(t)}{dt} &= ru(t), \quad t > 0 \\ u(0) &= u_0 \end{aligned}$$

where $u(t)$ is the total population size at time t and r is the growth rate of the given population, also called as the malthusian parameter.

A malthusian population makes no allowance for the effects of crowding or the limitations of resources. This model is often referred to as "The Exponential Law"

and is widely regarded in the field of population ecology as the first principle of population dynamics.

A more realistic model of population growth, which allows the growth rate to depend upon the size of the total population was introduced by Verhulst in the year 1838 and is known as the logistic equation given by

$$\begin{aligned} \frac{du(t)}{dt} &= ru(t)\left(1-\frac{u(t)}{K}\right), \quad t>0 \\ u(0) &= u_0 \end{aligned}$$

where r is the intrinsic growth constant and K is the environmental carrying capacity [6]. In this model, the initial stage of growth is approximately exponential; then, as saturation begins, the growth slows, and at maturity, growth stops. The logistic equation was first used in the models for human population and it follows a principle that the resistance to growth should be quadratic. The motivation for the quadratic term was the analogy with motion, in a resisting medium where, the resistance term may be modeled as quadratic in the velocity. A typical application of the logistic equation is a common model of population growth, which states that:

1. the rate of reproduction is proportional to the existing population, all else being equal

2. the rate of reproduction is proportional to the amount of available resources, all else being equal. Thus the second term models the competition for available resources, which tends to limit the population growth.

One of the deficiencies of the above two models is that the birth rate is considered to act instantaneously where as there may be a time delay to take account of the time to reach maturity, the finite gestation period and so on. We can incorporate such delays by considering delay differential equation models. Thus an improvement of the logistic equation is the Hutchinson equation where a delay

was introduced to describe the age-structure [15].

$$\begin{aligned} \frac{du(t)}{dt} &= ru(t)\left(1-\frac{u(t-\tau)}{K}\right), \quad t>0, \quad \tau>0 \\ u(t) &= \phi(t) \end{aligned}$$

where $\phi(t)$ is defined in the interval $(-\tau, 0]$.

Here, τ is the time delay that is introduced and is a known parameter. The above equation implies that the regulatory effect depends on the population at an earlier time $t-\tau$, rather than at t. This equation is itself a model for a delay effect which should really be an average over past populations and which results in an integrodifferential equation [15].

Thus, a more accurate model than the Hutchinson equation is, the convolution type,

$$\frac{du(t)}{dt} = ru(t)\left(1-\frac{1}{K}\int_{-\infty}^{t} w(t-s)u(s)ds\right),$$

where $w(t)$ is a weighting factor which says how much emphasis should be given to the size of the population at earlier times to determine the present effect on resource availability.

The models discussed above are all examples of single species models. In the year 1926, the Italian mathematician Volterra constructed a two-species model describing a predator-prey community [11]. He assumed that the growth rate of the prey population, in the absence of predators, is given by some constant, but decreases linearly as a function of the density of predators. At the same time, an American ecologist and mathematician Lotka produced the same model independent of Volterra [6, 14]. This is the now famous Lotka-Volterra model. The prey-predator model is given by

$$\frac{du}{dt} = \alpha u - \beta uv$$

$$\frac{dv}{dt} = -\gamma v + \delta uv$$

where

$u = u(t)$ denotes the prey population

$v = v(t)$ denotes the predator population.

The parameters $\alpha, \beta, \gamma, \delta$ are all positive constants.

α denotes the growth rate of the prey.

βuv is the reduction in the prey population due to the presence of the predators.

γ denotes the death rate of the predators.

δuv is the increase in the predator population due to the presence of the prey.

The other assumptions made by the Lotka-Volterra model are:

1. The prey in the absence of any predation grows unboundedly in a Malthusian way.

2. The effect of the predation is to reduce the prey's per capita growth rate by a term proportional to the prey and predator populations.

3. In the absence of any prey for sustenance, the predator's death rate results in exponential decay.

4. The predator's growth rate is proportional to the available prey as well as to the predator population [6, 11].

Some of the other, two species models are the competition and the co-operation models. Competition models denote two species competing with each other for the same resources like food, water etc. In co-operation model or the symbiosis model, the species in a common habitat co-exist in harmony. Several of these models called the Lotka-Volterra models have been extensively studied by many

mathematicians [16].

The models of Malthus, Verhulst, Lotka and Volterra are examples of continuous or deterministic population models. Mathematical demographers and population biologists have extensively developed the theory of continuous population dynamics. One of the most important theories in this development has been for models that allow for the effects of age structure. For many populations, consideration of the age distribution within the population leads to a more realistic and useful mathematical model [17].

Sharpe and Lotka in the year 1911 and McKendrick in the year 1926 first proposed the continuous time age dependent model. It is known as the classical model of linear age-dependent population and is also called the Sharpe-Lotka-McKendrick model [18]. In the classical linear model, the birth and mortality rates are linear functions of the age a.

$$\begin{aligned} \frac{\partial u(a,t)}{\partial t} + \frac{\partial u(a,t)}{\partial a} &= -\mu(a)u(a,t), \quad t>0, \quad a>0 \\ u(0,t) &= \int_0^\infty \beta(a)u(a,t)da, \\ u(a,0) &= \phi(a), \end{aligned}$$

where $u(a,t)$ is the population density with respect to age a and time t,

$\mu(a)$ is the age specific mortality rate that is a non-negative function of age,

$\beta(a)$ is the birth rate that is a non-negative function of the age a,

$\phi(a)$, where $a \geq 0$, is the initial age distribution of the population and is a non-negative function of the age a.

The non-linear age-structured population model was first introduced by Gurtin and McCamy in the year 1974 [18]. The model is given by

$$\begin{aligned} \frac{\partial u(a,t)}{\partial t} + \frac{\partial u(a,t)}{\partial a} &= -\mu(a,N)u(a,t), \quad t>0, \quad a>0 \\ u(0,t) &= \int_0^\infty \beta(a,N)u(a,t)da, \end{aligned}$$

$$u(a,0) = \phi(a),$$

where $u(a,t)$ is the population density with respect to age a and time t ,

$$\begin{aligned} N(t) &= \int_0^\infty u(a,t)da \\ &= \text{the total population at time } t, \end{aligned}$$

$\mu(a,N)$ is the age specific mortality rate that is a non-negative function of age

$\beta(a,N)$ is the birth rate that is a non-negative function of the age a,

$\phi(a)$, where $a \geq 0$, is the initial age distribution of the population and is a non-negative function of the age a.

Another important extension of the basic classical linear model is the mitosis model involving organisms that reproduce by binary fission [10, 17].

The model equations are given by

$$\begin{aligned} \frac{\partial u(a,t)}{\partial t} + \frac{\partial u(a,t)}{\partial a} &= -(\mu(a)+\beta(a))u(a,t), \quad t>0, \quad a>0 \\ u(0,t) &= 2\int_0^\infty \beta(a)u(a,t)da, \\ u(a,0) &= \phi(a), \end{aligned}$$

where $u(a,t)$ is the population density with respect to age a and time t,

$\mu(a)$ is the age specific mortality rate that is a non-negative function of age

$\beta(a)$ is the birth rate that is a non-negative function of the age a,

$\phi(a)$, where $a \geq 0$, is the initial age distribution of the population and is a non-negative function of the age a.

In the above models, the birth rate and the mortality rates depended on the age of the individual. Other than age dependence, there are models where the size or mass of the individual is taken into consideration. Thus, in these models, the birth rate and the mortality rates are positive bounded functions of the size variable x [19]. Also, there are models where the population depended on the age as

well as the size of the individual [17]. Age and density dependent continuous time models in a variable environment, where the birth and the death rates depended, other than age and population density on the external environment have been studied [17] and the special case where density dependence is restricted to the birth rate has also been studied [20].

Early population studies concentrated on models where the populations were considered only in time. However, it is not enough that populations of organisms are considered in only time, many ecological processes that are distributed over some space should be considered. For example, dispersion of animals, the spreading of invading species, the spreading of a plant disease etc. This is the process of biological diffusion. For a more detailed description of diffusion models, we refer to the book by Akira [12]. A generalization of age dependent diffusion models have also been studied in [21, 22, 23, 24].

Population dynamics overlaps with another active area of research in mathematical biology: mathematical epidemiology, the study of infectious diseases affecting populations. Epidemiology is an important area wherein significant work is being done. Various models of microbial spread are being proposed and analysed, and provide important results that may be applied to health policy decisions.

1.2 Epidemiology

Epidemiology is the study of factors affecting the health and illness of populations, and serves as the foundation and logic of interventions made in the interest of public health and preventive medicine. It is considered a cornerstone methodology of public health research, and is highly regarded in evidence-based medicine for identifying risk factors for disease and determining optimal treatment approaches to clinical practice [25].

Epidemiology is the study of the distribution and determinants of disease preva-

lence in humans. Epidemiologists study both infectious diseases and chronic diseases such as cancer and cardiovascular disease. Epidemiology describes the distribution of the disease. It identifies the causes or risk factors for diseases. It helps to build and test theories and plans, implements and evaluates detection, control and prevention programs. Here, epidemiological modeling refers to dynamic modeling where the population is divided into compartments based on their epidemiological status, for example, susceptible, infectious, recovered and the movements between compartments by becoming infected, progressing, recovering or migrating and are specified by differential or difference equations [25, 26].

Even though vaccines are available for many infectious diseases, these diseases still cause suffering and mortality in the world, especially in developing countries. In developed countries, chronic diseases such as cancer and heart disease have received more attention than infectious diseases, but infectious diseases are still a more common cause of death in the world. Recently, emerging and reemerging diseases have led to a revived interest in infectious diseases. The transmission mechanism from an infective to susceptibles is understood for nearly all infectious diseases and the spread of diseases through a chain of infections is known. However, the transmission interactions in a population are very complex, so that it is difficult to comprehend the large scale dynamics of disease spread without the formal structure of a mathematical model [27].

An epidemiological model uses a microscopic description (i.e.) the role of an infectious individual to predict the macroscopic behavior of disease spread through a population. Mathematical models have become important tools in analysing the spread and control of infectious diseases. The model formulation process clarifies assumptions, variables, and parameters. Moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing quantitative

conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data [28].

Understanding the transmission characteristics of infectious diseases in communities, regions and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are used in comparing, planning, implementing, evaluating, and optimising various detection, prevention, therapy and control programs. Epidemiology modeling can contribute to the design and analysis of epidemiological surveys, suggest crucial data that should be collected, identify trends, make general forecasts, and estimate the uncertainty in forecasts [29, 30].

The following are some uses of epidemiological modeling [31] :

1. The model formulation process clarifies assumptions, variables and parameters.

2. The behaviour of precise mathematical models can be analysed using mathematical methods and computer simulations.

3. Modeling allows explorations of the effect of different assumptions and formulations.

4. Modeling provides concepts such as a threshold, reproduction number, etc.

5. Modeling is an experimental tool for testing theories and assessing quantitative conjectures.

6. Models with appropriate complexity can be constructed to answer specific questions.

7. Modeling can be used to estimate key parameters by fitting data.

8. Models provide structures for organizing, coalescing and cross checking diverse pieces of information.

9. Models can be used in comparing diseases of different types or at different times or in different populations.

10. Models can be used to theoretically evaluate, compare or optimize various detection, prevention, therapy and control programs.

11. Models can be used to assess the sensitivity of results to changes in parameter values.

12. Modeling can suggest crucial data which needs to be collected.

13. Modeling can contribute to the design and analysis of epidemiological surveys.

14. Models can be used to identify trends, make general forecasts, or estimate the uncertainty in forecasts.

15. The validity and robustness of modeling results can be assessed by using ranges of parameter values in many different models.

Epidemiological modeling cannot solve or model all situations. There are limitations to this modeling. Some limitations are:

1. An epidemiological model is not reality; it is an extreme simplification of reality.

2. Deterministic models do not reflect the role of chance in disease spread and do not provide confidence intervals on results.

3. Stochastic models incorporate chance, but are usually harder to analyse than the corresponding deterministic model.

Despite the importance of diseases in human communities, there was little work on mathematical models for them until the beginning of the last century. An interesting exception is a paper by Daniel Bernoulli, written in the year 1760 and

published in 1766, which analyses deaths from smallpox. It was aimed at influencing public policy towards variolation, a technique of injecting a mild strain of the small pox to induce immunity against the full disease.

More systematic work on modeling disease was done in the early twentieth century by Hamer [32], who was interested in the regular recurrence of measles epidemics, and Ross, who obtained a Nobel prize in the year 1902 for showing that malaria was transmitted by mosquitoes [33]. They put forward hypotheses about transmission of infectious disease and investigated their consequences through mathematical modeling.

Based on their work, Kermack and McKendrick published a classic paper in 1927 that discovered a threshold condition for the spread of a disease and gave a means of predicting the ultimate size of an epidemic [34]. Kermack and McKendrick and other early authors assumed that the population mixed homogeneously, and much has been done since their paper was published to investigate the effect of removing this unrealistic assumption. Their threshold theory has been extended to more complex models. Mechanisms of spatial spread have been analysed, and control theory has been applied to optimise public health policies. The mechanisms of recurrent epidemics have been elucidated. There has also been the development of a number of important stochastic mathematical models [35].

In modeling an epidemic process, one needs to make assumptions about the population affected, the way the disease is spread, and the mechanism of recovery from the disease or removal from the population. With regard to the population and modeling of population dynamics: whether the population is closed, so that immigration, emigration, and birth and disease unrelated death can be neglected, or open. Also, the disease status structure of the population is modeled: a mutually exclusive and exhaustive classification of individuals according to their disease status. In epidemiology, with respect to the diseased condition, an individual is in one of the following classes.

- **Susceptible** One who can catch the disease
- **Latent or Exposed** Infected by the disease, but not yet infectious
- **Infective or Infectious** One who has the disease and can transmit it
- **Removed** One who is no longer infectious i.e. had the disease earlier, recovered, immune, isolated until recovered or dead
- **Carrier** In some diseases there may be individuals who remain infectious for long periods, may be for life, but do not show any symptoms of the disease themselves. They may be important for the progress of the disease

The infective class may be split up further depending on whether the diseases is microparasitic or macroparasitic.

- **Microparasitic** diseases are caused by a virus, for example measles, or a bacterium, for example tuberculosis, or a protozoan, for example malaria where an individual either has a disease or he does not have it.
- **Macroparasitic** diseases are caused by a helminth, for example a tape worm, or an arthropod, for example a tick, when the degree of infestation may be important.

Also the diseases may be distinguished as epidemic diseases and endemic diseases.

- **Epidemic** diseases are one which are prevalent in a population only at particular times or under particular circumstances, for example measles, chickenpox, avian flu etc.
- **Endemic** diseases are one which are habitually prevalent, for example, Hepatitis B is endemic in China and various other parts of Asia .

In epidemiology, we have what is called the threshold phenomenon. The threshold for many epidemiology models is the basic reproduction number R_0, which is

defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible [36]. For many deterministic epidemiology models, an infection can get started in a fully susceptible population if and only if $R_0 > 1$. Thus the basic reproduction number R_0 is often considered as the threshold quantity that determines when an infection can invade and persist in a new host population. R_0 is also called the basic reproduction ratio [37] or basic reproductive rate [38]. It is implicitly assumed that the infected outsider is in the host population for the entire infectious period and mixes with the host population in exactly the same way that a population native would mix.

The contact number σ is defined as the average number of adequate contacts of a typical infective during the infectious period [39, 40]. An adequate contact is one that is sufficient for transmission, if the individual contacted by the susceptible is an infective. The replacement number R is defined to be the average number of secondary infections produced by a typical infective during the entire period of infectiousness [41]. These three quantities R_0, σ, and R are all equal at the beginning of the spread of an infectious disease when the entire population (except the infective invader) is susceptible. In recent epidemiological modeling literature, the basic reproduction number R_0 is often used as the threshold quantity that determines whether a disease can invade a population [37]. Although R_0 is only defined at the time of invasion, σ and R are defined at all times. For most models, the contact number σ remains constant as the infection spreads, so it is always equal to the basic reproduction number R_0. In these models, σ and R_0 can be used interchangeably and invasion theorems can be stated in terms of either quantity. But for the pertussis models, the contact number σ becomes less than the basic reproduction number R_0 after the invasion, because new classes of infectives with lower infectivity appear when the disease has entered the population [31, 42]. The replacement number R is the actual number of secondary cases from a typical

infective, so that after the infection has invaded a population and everyone is no longer susceptible, R is always less than the basic reproduction number R_0. Also, after the invasion, the susceptible fraction is less than 1, so that not all adequate contacts result in a new case. Thus the replacement number R is always less than the contact number σ after the invasion. Combining these results leads to $R_0 \geq \sigma \geq R$, with equality of the three quantities at the time of invasion. Also, $R_0 = \sigma$ for most models, and $\sigma > R$ after the invasion for all models.

As an introduction to the basic methods in mathematical epidemiology, models without incorporating age effects and those with age dependence have been shown to play a unifying role in population mathematics and in the study of contagious phenomena such as epidemic diseases. Study of epidemic models has a long history with a vast variety of models and explanations for the spread and cause of epidemic outbreaks. Researchers working in this field have proposed several models.

The basic mechanism for driving a contagious phenomenon is the interaction between susceptibles and infectives. Therefore, the way this interaction is described is very important. Most of the models studied model this interaction in the same way that certain chemical reactions are modeled by the law of mass action. The rate at which effective contacts occur is taken to be proportional to the number of susceptibles and the number of infectives. Among other things, it is implicit in this assumption that the population is homogeneously mixing. That is every pair of individuals in the population has equal probability of meeting. The mass action law is the continuous analogue of the deterministic Reed-Frost model [43]. The first significant development in the deterministic theory is the classic SIR model by Kermack and McKendrick. Kermack and McKendrick first proposed the study of epidemic models in the year 1927 [6, 34]. They developed an epidemic model, an ordinary differential equation model, called the SIR model where

the total population is taken to be a constant. The SIR model is given by

$$\begin{aligned}
\frac{dS}{dt} &= -rSI \\
\frac{dI}{dt} &= rSI - aI \\
\frac{dR}{dt} &= aI \\
S(0) &= S_0 > 0 \\
I(0) &= I_0 > 0 \\
R(0) &= 0
\end{aligned}$$

where $S(t)$ denotes the number of susceptibles at time t, $I(t)$ denotes the number of infectives at time t and $R(t)$ denotes the number of infectives removed at time t. The model is represented as $S \rightarrow I \rightarrow R$. r denotes the contact rate of the infection and a is the quarantine rate of the infectives. The susceptibles are removed due to the presence of the infectives and exposed susceptibles become immediately infective. Infectives are lost through quarantine at a rate proportional to their numbers. The population is assumed to be closed in that there is no mechanism for gaining or losing individuals.

A more realistic model was proposed by Soper in 1929 and it was developed by Wilson in 1942 and was called the Measles model [44]. This model is of the SEIR type and is given by

$$\begin{aligned}
\frac{dS}{dt} &= A - rSI \\
E(t) &= \int_{t-\tau}^{t} rS(x)I(x)H(x)dx \\
I(t) &= I_0(t) + \int_{t-\tau-\sigma}^{t-\tau} rS(x)I(x)H(x)dx \\
R(t) &= R(0) + \int_{0}^{t-\tau-\sigma} rS(x)I(x)H(x)dx + I_0(0) - I_0(t)
\end{aligned}$$

where the incubation time and the fixed period of time of the infection is given by τ and σ respectively. Here, $E(t)$ denotes the number of susceptibles exposed at time t. The new features here are that there is a fixed period between exposure and becoming infected, called the incubation period, and there is a fixed period of infectiousness. Thus, rather than an exposed susceptible becoming immediately infectious, it enters the class E, remaining there a fixed period of time. This can be interpreted as a period where the infection incubates in the exposed individual until a sufficient level of infection is acquired. Then, after a fixed period of infectiousness, the individual is removed, in this case through the onset of permanent immunity. The model is described by

$\rightarrow S \rightarrow E^{\tau} \rightarrow I^{\sigma} \rightarrow R$

This model is an open system model.

Many phenomenon have the property that after a period of infection, individuals eventually become susceptible again. This is a relapse recovery model, also called the SEIRS model and proposed by Hoppensteadt and Waltman in the year 1971 [44].

The model equations are given by

$$\begin{aligned}
S(t) &= S(0) - \int_{t-\tau-\sigma-\omega}^{t} rS(x)I(x)H(x)dx + [I_0(0) - I_0(t-\omega)]H(t-\omega) \\
E(t) &= \int_{t-\tau}^{t} rS(x)I(x)H(x)dx \\
I(t) &= I_0(t) + \int_{t-\tau-\sigma}^{t-\tau} rS(x)I(x)H(x)dx \\
R(t) &= \int_{t-\tau-\sigma-\omega}^{t-\tau-\sigma} rS(x)I(x)H(x)dx + I_0(0) - I_0(t) - [I_0(0) - I_0(t-\omega)]H(t-\omega)
\end{aligned}$$

where ω denotes the time period for which the person is immune to the disease.

The models discussed above have focussed on epidemics which take place at a point. They are based on an assumption that all candidates in various classes have an equal probability of meeting (i.e.) there are no individuals in a given class which are distinguished from their colleagues. When this occurs, the population

is said to be homogeneously mixing. One way of getting around this restriction is to break the population down into subpopulations in which there is homogeneous mixing, and then consider the interactions between these subpopulations. The total population can then be broken into a finite number of homogeneously mixing groups. It is useful to extend this idea by introducing a continuous decomposition of the population. This idea is illustrated through a model for spatial spread of an infection. The population is considered to be dispersed over a planar region $\Omega \subset \Re^2$. In 1974, Noble used a simple model with diffusion to study the geographic spread of plague which is an SI model with the diffusion term [6]. More such diffusion models have been discussed in the book by Akira [12].

In many diseases, the chronological age of the individual is an important factor in assessing their vulnerability and infectiousness. For example, the interesting data quoted by Bernoulli in 1760 on the incidence and severity of smallpox with age is a vivid illustration. Vulnerability and mortality go down markedly with age. A variety of age dependent models have been discussed in [44]. Dietz 1982 proposed such a model for river blindness (onchocersiasis) and used it to compare various possible control strategies. Age may also be interpreted as the time from entry into a particular population class such as the susceptibles, infectives or the removed group in a basic SIR model. The two interpretations of age are often the same. The age dependent epidemic model was first proposed by Hoppensteadt [44] in the year 1975. The model is an age dependent one of type S $\rightarrow$ I $\rightarrow$ [6, 44]. We consider a population that is divided into two classes: Susceptibles S and Infectives I. Susceptibles are individuals of the population, who can catch the disease. Infectives are people who already have the disease and can infect others. $u(t)$ denotes the number of susceptibles and $v(a,t)$ denotes the number of infectives. The assumption is that the number of susceptibles depend only on time t whereas the number of infectives depend on a as well as t. Here, a is the time that has lapsed after susceptibles have entered the infective class.(i.e) it is the age from

exposure to the disease. In this epidemic model, we start with an initial number of susceptibles and an initial number of infectives. The assumption is that, once infected, individuals from susceptible class move on to the infective class. A is a positive constant and is the inflow of individuals per time into the population due to births or immigration. μ_o is a positive constant and denotes the death rate due to natural causes and not due to infection.

$k(a)$ denotes the measure of infectiousness of the infectives and $\mu(a)$ denotes the death rate due to infection. $v(0,t)$ is the number of new individuals who enter the infective class, The functions $k(a),\ \mu(a)$ are nonnegative, bounded functions and depend on the age of infection a.

Thus, the model is given by

$$\begin{aligned}
\tfrac{du}{dt} &= A - \mu_o u - u\int_0^\infty k(a)v(a,t)da \\
\tfrac{\partial v}{\partial t} &+ \tfrac{\partial v}{\partial a} = -\mu(a)v(a,t) \\
v(0,t) &= u\int_0^\infty k(a)v(a,t)da \\
u(0) &= u_0 \\
v(a,0) &= v_0(a)
\end{aligned}$$

1.3 Plan of the thesis

The aim of this work is to study mathematical models arising in population dynamics and epidemiology and thereby provide solutions such as control, eradication of the disease, designing of vaccination strategies etc. This research identifies existing and new biological situations, which need to be modeled through differential equations. In particular, we propose and study some new as well as existing population dynamics models and epidemiological models. The emphasis of this work is to model biological situations and in particular perform numerical simulations on the models so as to conclude about the practical and real life significance of such models. In this work, we model biological systems such as prion proliferation in the presence of a chaperone, spread of the SARS virus, the transmission dynamics

of *Neospora caninum* infection in cattle, age dependent epidemic, microbial growth in a chemostat. Also, we study the dynamical system behaviour of the solutions of such systems. Since, numerical studies provide a much better picture in certain situations, we perform numerical simulations using MATLAB software for some of the models based on the data available in literature.

This thesis is organised as follows: In chapter 2, we collect some basic mathematical definitions and results that would be required for studying the different models. Some standard and preliminary definitions from stability theory and the results on linear stability analysis for two dimensional systems are illustrated. Also, the Routh-Hurwitz criterion is given which helps us to learn about the nature of the roots of the characteristic polynomials. We conclude this section with some definitions and theorems from functional analysis and the theory of semigroups.

In chapter 3, the replication of prions by nucleated polymerization under the effects of a chaperone are modeled. Prions are infectious agents and are polymers called PrP^{Sc}Prion protein scrapies, of a normal protein, a monomer called PrP^{c} Prion protein cellular. These $PrP^{Sc}s$ cause TSEstransmissible spongiform encephalopathies such as bovine spongiform encephalopathy (BSE) in cattle, scrapies in sheep, Kuru and CreutzfeldJacob diseases in humans. Cellular molecular chaperones, which are ubiquitous, stress-induced proteins, and newly found chemical and pharmacological chaperones have been found to be effective in preventing misfolding of different disease-causing proteins, essentially reducing the severity of several neurodegenerative disorders and many other protein- misfolding diseases. According to this model, the biological processes of coagulation, splitting and the inhibitory effects of the chaperone can be described by a coupled system consisting of ordinary differential equations and a partial differential equation. The model is converted into a system of ordinary differential equations and the stability of the steady states are studied. Numerical simulations on the model are performed and conditions for the threshold of the disease are drawn.

In chapter 4, the propagation of the SARS epidemic is modeled. Severe acute respiratory syndrome (SARS) is a respiratory disease, which was first identified in China's southern province of Guangdong. Infection with a novel corona virus has been implicated as a possible cause of SARS. Here, we model the SARS epidemic using the double epidemic hypothesis wherein there are two epidemics in a population and one mild infection confers immunity to the other major disease. One epidemic is SARS caused by a coronavirus , which we denote as virus A. Another epidemic, which is conjectured to have occurred before SARS, is caused by a mutant coronavirus and is denoted by virus B. The assumption is that people infected with virus B become immune to the SARS coronavirus. We propose a new model, a system of ordinary differential equations which is studied and the conditions for the stability of the disease free state and the one disease state are drawn. Numerical simulations on the model are performed and the solutions are studied in different regions of the parameter space. The stability of the three steady states in certain regions of the parameter space are found. The conditions for the control of the infection caused by virus A which is the SARS virus are determined from the model.

In chapter 5, the transmission of *Neospora caninum* infection among cattle is studied. *Neospora caninum* is a protozoal parasite that is considered a leading cause of foetal deaths in some dairy and beef herds. It is morphologically similar to other apicomplexa protozoal parasites of importance to veterinary medicine like Toxoplasma gondii and Sarcocystis spp. *Neospora caninum* is a pathogenic protozoan that was first identified in 1988 as a new genus of Toxoplasma-like apicomplexan. The dynamics of the *Neospora caninum* infection are modeled through a system of ordinary differential equations. The conditions for the stability of the steady states are drawn. The threshold of the disease is found using the basic reproduction number. Also, we perform numerical simulations on the model.

In chapter 6, we study a general nonlinear evolution equation in a Banach space.

The nonlinear model is studied in an abstract space and the space $L^1 \times \Re$ is chosen as the tractable mathematical setting for this model. The existence, uniqueness, continuous dependence of the solutions on the initial data and the semigroup property of the solutions of the general model are studied. Also, we give two examples, an age dependent epidemic model and an age dependent chemostat model as particular cases of the general model.

In many epidemic models, the chronological age of the individual is an important factor in assessing their vulnerability and infectiousness. Vulnerability and mortality go down markedly with age. In this example, we study the wellposedness of an age dependent SI model.

As a second example, we propose a new model for growth of microorganisms in a chemostat. A chemostat is a continuous culture device used in microbiology for growing and harvesting microbes. The chemostat model is a system consisting of an integro differential equation and a partial differential equation. The existence, uniqueness, continuous dependence of the solutions on the initial age distributions and the semigroup property of the solutions of the chemostat model are studied. In chapter 7, the conclusions of our work and scope for future studies are presented.

Chapter 2

Mathematical Preliminaries

2.1 Stability theory

The mathematical models or equations that describe physical phenomena are in many cases ordinary differential equations of the form

$$x\prime = F(x,t) \tag{2.1}$$

with the initial data $x(t_0) = x_0$. Since, the initial data, which often results from all types of measurements, may have errors, it is important to know the extent to which small disturbances in the initial data effect the desired behaviour of the solutions of equation (2.1). If, by making a sufficiently small change in the initial data, a substantial deviation is observed in the corresponding solution, then the solution obtained from the given initial data is unacceptable because it does not describe the required phenomenon even approximately. The problem of investigating the conditions that will not allow the solutions to remarkably deviate from the desired behaviour is therefore vital [45].

Stable: The solution $x(t)$ of (1) is said to be stable if, for each $\varepsilon > 0$, there exists a $\delta = \delta(\varepsilon) > 0$ such that, for any solution $\overline{x(t)} = x(t, t_0, \overline{x_0})$ of (1), the inequality $\| \overline{x_0} - x_0 \| \leq \delta$ implies $\| \overline{x(t)} - x(t) \| < \varepsilon$ for all $t \geq t_0$.

Asymptotically Stable: The solution $x(t)$ of (1) is said to be asymptotically stable if it is stable and if there exists a $\delta_0 > 0$, such that $\| \overline{x_0} - x_0 \| \leq \delta_0$ implies $\| \overline{x(t)} - x(t) \| \to 0$ as $t \to \infty$.

Unstable: The solution $x(t)$ of (1) is said to be unstable if it is not stable.

Phase plane analysis: Consider the general autonomous second order differential equations of the form [14]

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \\ \frac{dy}{dt} &= g(x,y) \end{aligned} \tag{2.2}$$

Phase curves or phase trajectories of equations (2.2) are solutions of

$$\frac{dx}{dy} = \frac{f(x,y)}{g(x,y)}$$

Critical Points(Equilibrium Points): The points (x_0, y_0) at which both $f(x,y)$ and $g(x,y)$ vanish simultaneously are called critical points or equilibrium points. Through any point (x,y), there is a unique curve except at the critical points (x_0, y_0).

Set $x = x - x_0$ and $y = y - y_0$. Then, $(0,0)$ is a critical point of the transformed equation. Thus, we can conclude that system (2.2) has a critical point at the origin. If f and g are analytic near $(0,0)$, we can expand f and g in a Taylor series and retaining only the linear terms, we get

$$\frac{dx}{dy} = \frac{ax+by}{cx+dy},$$

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix} = \begin{pmatrix} f_x & f_y \\ g_x & g_y \end{pmatrix}_{(0,0)}$$

which defines the matrix A and the constants a, b, c, d. Matrix A is also called the Jacobian matrix about the critical point. The linear form is equivalent to the system

$$\begin{aligned} \frac{dx}{dt} &= ax + by \\ \frac{dy}{dt} &= cx + dy \end{aligned} \tag{2.3}$$

Solutions of the system (2.3) give the parametric forms of the phase curves, where t is the parameter.

Let λ_1 and λ_2 be the eigen values of the above matrix A.

$| A - \lambda I | = 0$

$\Rightarrow \lambda_1, \lambda_2 = \frac{1}{2}(a + d \pm [(a+d)^2 - 4\ detA]^{\frac{1}{2}})$

Solutions of the system (2.3) are now

$$\begin{pmatrix} x \\ y \end{pmatrix} = c_1\mathbf{v_1}\ exp[\lambda_1 t] + c_2\mathbf{v_2}\ exp[\lambda_2 t]$$

where c_1 and c_2 are arbitrary constants and $\mathbf{v_1}, \mathbf{v_2}$ are the eigen vectors of A corresponding to λ_1 and λ_2 respectively. They are given by

$$\mathbf{v_i} = (1 + p_i^2)^{-1/2} \begin{pmatrix} 1 \\ p_i \end{pmatrix}$$

where

$$p_i = \frac{\lambda_i - a}{b},\ b \neq 0,\ i = 1, 2$$

Elimination of t in solutions of the system (2.3) gives the phase curves in the (x, y) plane. The solution form of system (2.3) is for distinct eigen values. If the eigen values are equal, the solutions are proportional to $(c_1 + c_2 t)\ exp[\lambda t]$.

We now examine the various cases:

Case : 1 λ_1 and λ_2 are real and distinct.

(a) λ_1 and λ_2 have the same sign.

Eigen vectors $\mathbf{v_1}$ and $\mathbf{v_2}$ are illustrated in Figure 2.1 Suppose $\lambda_2 < \lambda_1 < 0$. Then, from

$$\begin{pmatrix} x \\ y \end{pmatrix} = c_1\mathbf{v_1}\ exp[\lambda_1 t] + c_2\mathbf{v_2}\ exp[\lambda_2 t],$$

for example, for $c_2 = 0, c_1 \neq 0$,

$$\begin{pmatrix} x \\ y \end{pmatrix} = c_1\mathbf{v_1}\ exp[\lambda_1 t],$$

so the solution in the phase plane simply moves along $\mathbf{v_1}$ towards the origin as $t \to \infty$ in the direction shown in Figure 2.1 (i.e.) along PO if $c_1 > 0$ and along QO if $c_1 < 0$.

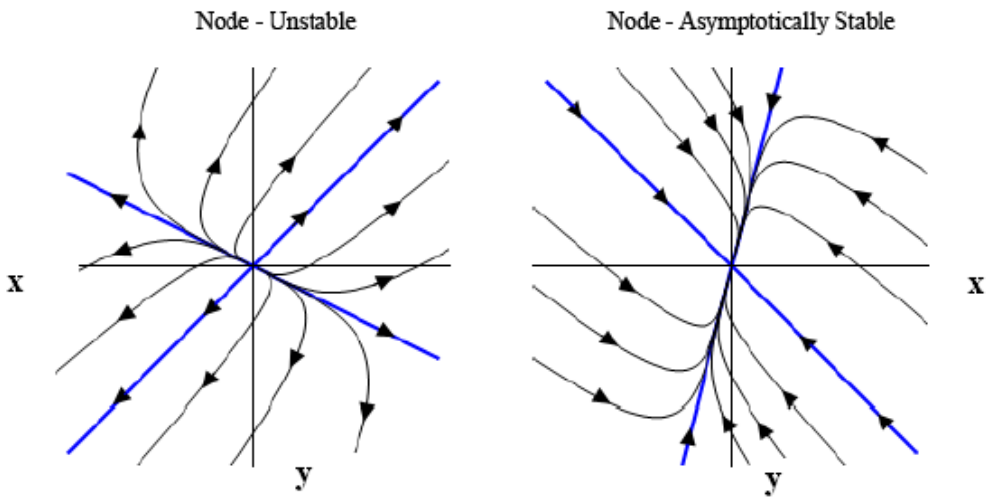

Figure 2.1: **Unstable node and asymptotically stable node- eigen values are real and distinct**

From above, every solution tends to $(0,0)$ as $t \to \infty$ when $\lambda_2 < \lambda_1 < 0$.

Thus, close enough to the origin all solutions tend to zero along $\mathbf{v_1}$ as shown in Figure 2.1 This is called a node.

With $\lambda_1 < \lambda_2 < 0$, it is a stable node since all trajectories tend to $(0,0)$.

If $\lambda_1 > \lambda_2 > 0$, it is an unstable node; here $(x,y) \to (0,0)$ as $t \to -\infty$.

The phase trajectories are shown in Figure 2.1

(b) λ_1 and λ_2 have different signs. Suppose, for example, $\lambda_1 < 0 < \lambda_2$, then $\mathbf{v_1}\ exp[\lambda_1 t] \to 0$ along $\mathbf{v_1}$ as $t \to \infty$ while $\mathbf{v_2}\ exp[\lambda_2 t] \to 0$ along $\mathbf{v_2}$ as $t \to -\infty$.

Thus, there are different directions on $\mathbf{v_1}$ and $\mathbf{v_2}$.

This is a saddle point and it is always unstable. This is illustrated in Figure 2.2

Case : 2 λ_1 and λ_2 are complex conjugates: (i.e.) $\lambda_1, \lambda_2 = \alpha \pm i\beta, \beta \neq 0$. Here, the solutions involve $exp[\lambda t], exp[\pm i\beta t]$ which implies an oscillatory approach to $(0,0)$.

(a) $\alpha \neq 0$. Here, we have a spiral, which is asymptotically stable if $\alpha < 0$ and unstable if $\alpha > 0$. In such a case, the critical point is called a focus. In such a case, the trajectories form a spiral. Figure 2.3 illustrates an unstable and an asymptotically stable spiral.

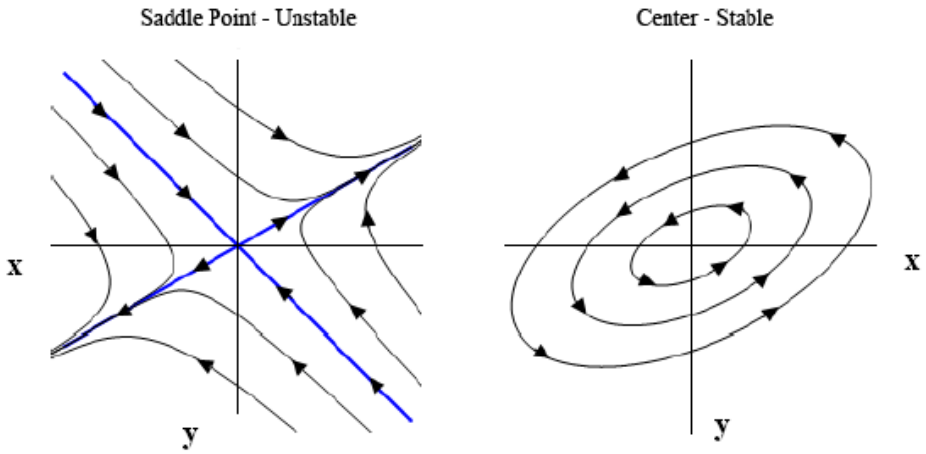

Figure 2.2: **Saddle point and centre**

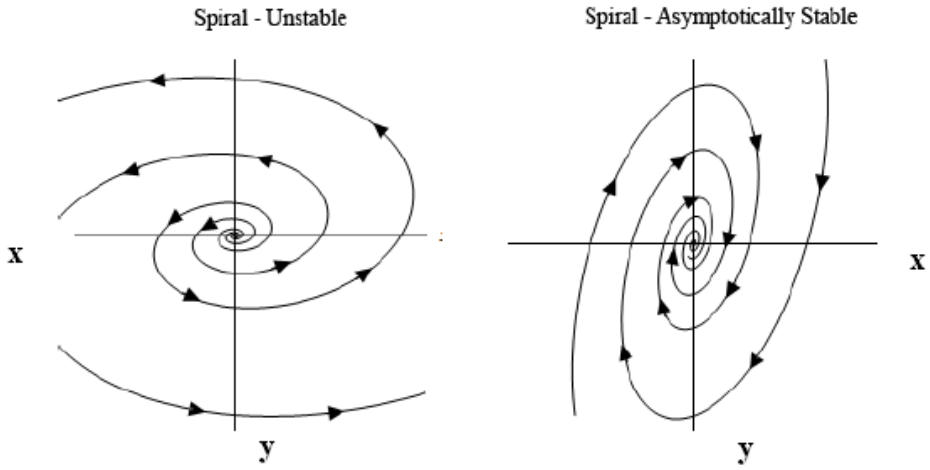

Figure 2.3: **Unstable spiral and asymptotically stable spiral -eigen values are complex conjugates**

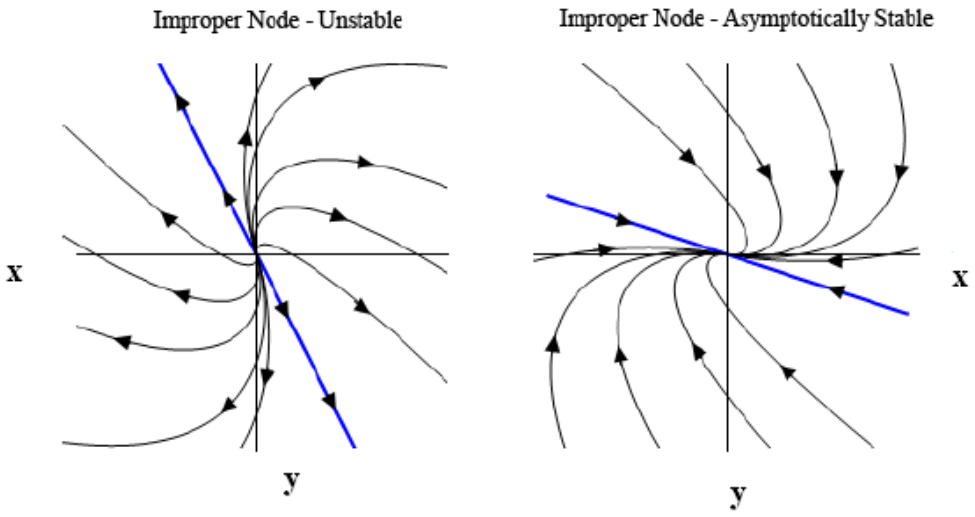

Figure 2.4: **Unstable node and asymptotically stable node - eigen values are real and equal**

(b) $\alpha = 0$. In this case, the phase curves are ellipses. Then, the critical point is called a centre and is stable, but not asymptotically stable. This is illustrated in Figure 2.2

Case : 3 $\lambda_1 = \lambda_2 = \lambda$. Here, the eigen values are not distinct.

(a) In general, solutions now involve terms like $t\ exp[\lambda t]$ and there is only one eigen vector $\mathbf{v}$ along which the solutions tend to $(0, 0)$. The t in $t\ exp[\lambda t]$ modifies the solution away from $(0, 0)$. It is called a node, an illustration of which is given in Figure 2.4

(b) If the solutions do not contain the $t\ exp[\lambda t]$ term, we have phase curves resembling a star. These may be stable or unstable, depending on the sign of λ.

Thus, the above cases can be summarised in the following theorem.

Theorem 2.1.1 *The critical point* $(0, 0)$ *of system (2.2) is stable, asymptotically stable or unstable if all the characteristic roots of A have zero or negative or positive real parts, respectively.*

2.2 Routh-Hurwitz Criteria

Linear stability of the systems of ordinary differential equations arising in interacting population models and reaction kinetics system, for example is determined by the roots of a polynomial [14]. The stability analysis, we are concerned with, involves linear systems of the vector form

$$\frac{dx}{dt} = Ax,$$

where A is the matrix of the linearised non linear interaction/reaction terms: it is the Jacobian matrix about the steady state - the community matrix in ecological terms. Solutions are obtained by setting

$$x = x_0 e^{\lambda t},$$

in the above equation where x_0 is a constant vector and the eigen values λ are the roots of the characteristic polynomial

$$\mid A - \lambda I \mid$$

where I is the identity matrix. The solution $x = 0$ is stable if all the roots λ of the characteristic polynomial lie in the left-hand complex plane; that is Re $\lambda < 0$ for all roots λ. If this holds, then $x \to 0$ exponentially as $t \to \infty$ and hence $x = 0$ is stable to small linear perturbations.

If the system is of n^{th} order, the characteristic polynomial can be taken in the general form

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_n = 0,$$

where the coefficients $a_i,\ i = 0, 1, 2...n$ are all real. We assume that $a_n \neq 0$ since otherwise $\lambda = 0$ is a solution, and the polynomial is then of order $n-1$. We require conditions on the $a_i,\ i = 0, 1, 2...n$ such that the zeros of $P(\lambda)$ have Re $\lambda < 0$. The necessary and sufficient conditions for this to hold are the Routh-Hurwitz conditions. There are various equivalent forms of these, one of which is, together with $a_n > 0$,

$$D_1 = a_1 > 0,$$

$$D_2 = det \begin{pmatrix} a_1 & a_3 \\ 1 & a_2 \end{pmatrix} > 0$$

$$D_3 = det \begin{pmatrix} a_1 & a_3 & a_5 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{pmatrix} > 0$$

$$D_k = det \begin{pmatrix} a_1 & a_3 & . & . & . & . \\ 1 & a_2 & a_4 & . & . & . \\ 0 & a_1 & a_3 & . & . & . \\ 0 & 1 & a_2 & . & . & . \\ . & . & . & . & . & . \\ 0 & 0 & . & . & . & a_k \end{pmatrix} > 0, k = 1, 2, 3....n$$

The derivations for these conditions are given in [45, 14]. As an example, for the cubic equation

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

the conditions for Re $\lambda < 0$ are

$$a_1 > 0, a_2 > 0, a_3 > 0, a_1a_2 - a_3 > 0.$$

Although, the above are the necessary and sufficient conditions, we need the usual algebraic relations between the roots and the polynomial coefficients can often be very useful. If $\lambda_1, \lambda_2, ...\lambda_n$ are the distinct non zero roots of the polynomial $P(\lambda)$, these are

$$\sum_{i=1}^{n} \lambda_i = -a_1,$$

$$\sum_{i,j}^{n} \lambda_i \lambda_j = a_2, i \neq j$$

$$.$$

$$.$$

$$.$$

$$.$$

$$.$$

$$\lambda_1 \lambda_2 .... \lambda_n = (-1)^n a_n$$

2.3 Basic definitions and results from functional analysis.

Let X be a vector space over a field F of the set of real numbers or the set of complex numbers.

Norm: A norm on X is a mapping $\| \ \|$: $X \mapsto \Re$ such that

1. $\| x \| \geq 0 \, \forall \, x \in X$
2. $\| x \| = 0$ iff $x = 0$ (the zero vector in X)
3. $\| \lambda x \| = | \lambda | \, \| x \| \ \forall \, x \in X, \, \lambda \in F$

4. $\| x + y \| \leq \| x \| + \| y \| \ \forall\, x, y \ \in \ X$ (the triangle inequality) [46]

Normed Vector Space: A vector space with a norm defined on it is called a normed vector space or a normed linear space.

Convergent Sequence: Let $(X, \ \| \ \|)$ be a normed vector space. A sequence $\{x_n\}_{n=1}^{\infty} \subseteq X$ converges to $x \in X$ if $\| x_n - x \| \rightarrow 0$ as $n \rightarrow \infty$, (i.e) for each $\varepsilon > 0$, there exists $N = N(\varepsilon)$ such that $\| x_n - x \| < \varepsilon \ \forall \ n \geq N$.

Cauchy Sequence: A sequence $\{x_n\}_{n=1}^{\infty} \subseteq X$ is a Cauchy sequence if for each $\varepsilon > 0$, there exists $N = N(\varepsilon)$ such that $\| x_m - x_n \| < \varepsilon \ \forall \ m, \ n \geq N$.

Lipschitz Continuity: A function $f : [a, b] \mapsto \Re$ is said to be Lipschitz continuous if there exists a constant $M > 0$ such that $\mid f(x) - f(y) \mid \leq M \mid x - y \mid$ for all $x, y \in [a, b]$.

Theorem 2.3.1 *In any normed vector space, every convergent sequence has a unique limit and is a Cauchy sequence.*

Note: However, in a normed vector space, every Cauchy sequence is not necessarily convergent.

Banach Space: A normed vector space $(X, \ \| \ \|)$ is complete if every Cauchy sequence converges to a unique limit in X. Then, $(X, \ \| \ \|)$ is called a Banach space [47].

Linear Operator: A linear operator T is an operator such that

(i)the domain of T, *D(T)* is a vector space and the range, *R(T)* lies in a vector space over the same field

(ii)for all $x, y \in$ *D(T)* and scalars α,

$T(x + y) = T(x) + T(y)$

$T(\alpha x) = \alpha T(x)$.

Bounded Operator: Let $T : X \mapsto X$ be a linear operator where X is a Banach space.

T is bounded if there is a constant $C \geq 0$ such that $\| Tx \| \leq C \| x \| \ \forall\, x \in X$.

Continuous Operator: T is continuous at $x \in X$ if, whenever $\{x_n\}_{n=1}^{\infty} \subseteq X$ is a

sequence converging to x with respect to the norm in X, then $\{Tx_n\}_{n=1}^{\infty}$ converges to Tx.

T is continuous on X if T is continuous at x for all $x \in X$.

Theorem 2.3.2 *Let $T : X \mapsto X$ be a linear operator. Then, the following statements are equivalent.*

(i) T is bounded.

(ii)T is continuous on X.

(iii)T is continuous at 0.

Closed Operator: Let X be a Banach space and $T : D(T) \subseteq X \mapsto X$ be a linear operator. Then, T is closed if

$x_n \in D(T)$ $(n = 1, 2, 3....)$ $x_n \to x \ \in X$, $Tx_n \to y$

$\Rightarrow x \in D(T)$ and $Tx = y$.

Dense Set: A subset A of X is dense in X if $\overline{A} = X$, i.e. if the closure of A with respect to $\| \ \|$ is X. This means that any element $x \in X$ can be approximated by a sequence of elements of A with respect to $\| \ \|$.

Space $C[a, b]$: Let $C[a, b]$ denote the set of all real valued functions which are continuous on $[a, b], -\infty < a < b < \infty$. Then, for $f \in C[a, b]$, the norm, $\| \ \|_\infty$ is defined as

$\| f \|_\infty = sup_{x\in[a,b]} \mid f(x) \mid$

$(C[a, b], \| \ \|_\infty)$ is a Banach space.

Define $\| \ \|_p$ on $C[a, b]$ by

$\| f \|_p = \{\int_a^b \mid f(x) \mid^p dx\}^{1/p}$. Then, $(C[a, b], \| \ \|_p)$ is not a Banach space.

Space $L^p[a, b]$: For $1 \leq p < \infty$, we define $L^p[a, b]$ by

$L^p[a, b] = \{[a, b] \mapsto \Re : \| f \|_p < \infty\}$ where

$\| f \|_p = \{\int_a^b \mid f(x) \mid^p dx\}^{1/p}$.

$(L^p[a, b], \| \ \|_p)$ is a Banach space. It is the completion of the space of the continuous real valued functions with the p-norm, $\| \ \|_p$.

Fixed Point: A fixed point of a mapping $T : X \mapsto X$ of a set X into itself is an

$x \in X$ which is mapped onto itself i.e. $Tx = x$, the image Tx coincides with x.

Contraction:: Let $(X, \| \|)$ be a Banach space. A mapping $T : X \mapsto X$ is called a contraction on X if there is a positive real number $\alpha < 1$ such that for all $x, y \in X$ $\| Tx - Ty \| \leq \alpha \| \text{x- y} \|$.

Theorem 2.3.3 *Banach Fixed Point Theorem (Contraction Theorem):*
Let $(X, \| \|)$ be a Banach space and let $T : X \mapsto X$ be a contraction on X. Then T has precisely one fixed point.

2.4 Theory of Semigroups

Before defining what a semigroup is, one needs to recognise their global importance. Of course their importance cannot be fully realized until we have a clear definition and developed theory [48]. However, in general, semigroups can be used to solve a large class of problems commonly known as evolution equations. These types of equations appear in many disciplines including physics, chemistry, biology, engineering, and economics. They are usually described by an initial value problem (IVP) for a differential equation which can be ordinary or partial. When the evolution of a system in the context of semigroups is viewed, it is broken down into transitional steps (i.e.) the system evolves from state A to state B, and then from state B to state C. When it is recognised that there is a semigroup, instead of studying the IVP directly, it can studied via the semigroup and its applicable theory. The theory of linear and nonlinear semigroups is very well developed [49]. For example, semigroup theory actually provides necessary and sufficient conditions to determine the well-posedness of a problem [50].

Consider the physical state of a system which is evolving with time according to some physical law as given by the following IVP (or abstract Cauchy problem ACP)

$$\frac{du}{dt} = Au(t), t \geq 0$$

$$u(0) \;=\; f$$

where u(t) describes the state at time t which changes in time at a rate given by the function A. The solution of the ACP is given by

$$u(t) = e^{At} f$$

One is interested in the wellposededness of the IVP. A well posed problem is one whose solution exists and is unique. Semigroup theory can determine when a problem is well posed and in order to use the theory, we need to know that we have a semigroup. So to continue with the solution of the IVP, let T operate on u as follows:

$$T(t) : u(s) \rightarrow u(t+s)$$

If it is assumed that, A does not depend on time, then T(t) is independent of s [51]. The solution, u(t + s) at time t + s, can be computed as T(t + s) acting on f. Likewise, if the process is broken down into two steps, then :

$$\begin{aligned} Step: 1\; T(s)(f) &= u(s) \\ Step: 2\; T(t)(u(s)) &= T(t)(T(s)(f)) = u(t+s) = T(t+s)(f). \end{aligned}$$

Semigroup Property:

By transitionally breaking down the process of evolution, it is evident that the state of the system at time $t + s$ can be reached by either going directly from the initial condition to the state at time $t + s$ or by allowing the state to evolve over s time units, and then allowing it to evolve t more time units. Here the $T(\cdot)$ is acting like a transition operator [52]. The uniqueness of the solution reveals the

semigroup property which is given by

$$T(t+s) = T(t)T(s)(t, s > 0)$$

The semigroup property of the family of functions, $\{T(t); t \geq 0\}$, is a composition and not a multiplication. Notice that $T(0)$ is the identity operator I (i.e.) there is no transition at time zero and the initial data exists [51].

More Properties:

Now, to find out how A and T relate to each other. It is observed that

$$T(t)(f) = T(t)(u(0)) = u(t) = e^{At}f$$
$$\frac{dT(t)(f)}{dt} = A(T(t)(f)).$$

Now, $u(t) = T(t)(f)$ is a solution of the IVP and suggests that: $T(t)(f) = e^{At}f$ where A is the derivative of $T(t)$. In addition, each $T(t) : f \to e^{At}f$ is a continuous operator on a Banach space X, which indicates the continuous dependence of $u(t)$ on f [51]. The initial data f should belong to the domain of A. Upon inspection of $T(t)(f) = e^{At}f$, we have the following results:

(i) $T(t)$ exhibits the semigroup property.

(ii) $T(t)$ is a continuous function

(iii) $T(0)f = f$

(iv) T(t) is linear or nonlinear according to whether A is linear or nonlinear. These observations bring forth the notion of C_0 semigroups.

Strongly Continuous Semigroup: A C_0-semigroup or strongly continuous semigroup of bounded linear operators $B(X)$ on a Banach space X is a family $\{T(t)\}_{t\geq 0} \subseteq B(x)$ such that

- $T(0) = I$, the identity operator on X
- $T(s)T(t) = T(s+t)$ for all $s, t \geq 0$

- for each fixed $f \in X, T(t)f \to f$ as t $\to 0+$ with respect to the norm on X.

The continuity condition given by the third condition above arises naturally as we do not want our physical system to breakdown in time due to small measurement errors in the initial state.

Generator of a semigroup:

Let T be a semigroup. The infinitesimal generator of T, denoted by A, is given by the equation

$$Af = lim\ t \to 0 + A_t f = lim\ t \to 0 + \frac{T(t)f - f}{t}$$

where the limit is evaluated in terms of the norm on X and f is in the domain of A if and only if this limit exists [1]. So, according to the above, the generator A is obtained by differentiating the semigroup T. From this we see that $u(\cdot) = T(\cdot)f$ solves the IVP.

Theorem 2.4.1 *A semigroup is uniquely determined by its generator.*

Theorem 2.4.2 *Well Posed Theorem: The IVP is well posed if and only if A is the generator of a semigroup T. In this case the unique solution of the IVP is given by $u(t) = T(t)(f)$ for f in $D(A)$, the domain of A [48, 49].*

This turns out to be quite important as it provides both necessary and sufficient conditions to determine if a problem is well-posed.

Chapter 3

Prion Proliferation in the Presence of a Chaperone.

3.1 Introduction

Prions are infectious agents and are polymers called PrP^{Sc} - Prion protein scrapies, of a normal protein, a monomer called PrP^{c}- Prion protein cellular. These $PrP^{Sc}s$ cause TSEs - Transmissible Spongiform Encephalopathies such as bovine spongiform encephalopathy (BSE) in cattle, scrapies in sheep, Kuru and Creutzfeld-Jacob diseases in humans. Prions are pathogens responsible for a variety of animal and human neurodegenerative diseases, such as bovine spongiform encephalopathy (BSE), scrapie of sheep, Creutzfeldt- Jacob and Gerstmann-Straussler-Scheinker diseases of humans. Bewilderingly, all these diseases can be sporadic, genetic and infectious, thus making the identification of the disease mechanism a challenging task. For many years, the prion diseases were thought to be caused by slow-acting viruses. These diseases were often referred to as slow virus diseases, transmissible spongiform encephalopathies, or unconventional viral diseases. Considerable effort was expended searching for the scrapie virus; yet none was found either with respect to the discovery of a virus-like particle or a genome composed of RNA or DNA [53].

The unusual properties of the infectious agent became the focus of attention beginning in the 1960s, and in the early 1980s Stanley Prusiner, building upon earlier suggestions proposed the prion hypothesis [54]. This stated that the infectious agent in human and animal spongiform encephalopathies was composed exclusively of a single kind of protein molecule designated PrP^{Sc} without any encoding nucleic acid. Based on foregoing findings, the term prion was introduced to distinguish the proteinaceous infectious particles that cause scrapie from both viroids and viruses . Perhaps, the best current working definition of a prion is a proteinaceous infectious particle that lacks nucleic acid [55].

This protein can appear in two forms that differ only in their conformation. One form is the mainly α-helical form, called cellular prion protein (orPrP^{c}). This is the native form of the protein which naturally appears in many tissues, however

with a notable abundance in the brain, where it is mainly located at synaptic areas. It is commonly believed that the agent causing prion diseases is composed of the second form, called scrapie prion protein (or PrP^{Sc}). It differs from PrP^{c} only by its secondary structure which is dominated by beta-sheet. The structural differences cause differences in physical and chemical properties, for instance a high resistance of PrP^{Sc} to proteases and a tendency of PrP^{Sc} to aggregate and form polymers and even large amyloid plaques. Furthermore, interaction of the two forms leads to a conversion of PrP^{c} into PrP^{Sc}. In this way, PrP^{Sc} multiplies and acts as an infective agent [56].

Prions proliferate by a process called nucleated polymerization. The infective agent, PrP^{Sc} is not a single protein, but a polymer or short oligomer. The PrP^{Sc} increases its length by attaching units of PrP^{c} in a string like fashion. Then, the PrP^{c} which is attached to the PrP^{Sc} is converted to the infectious form. Once the PrP^{Sc} is long enough to wrap into a helical shape called the nucleus, it forms stabilising bonds and thus becomes stable. $PrP^{Sc}s$ can consist of thousands of monomer units. PrP^{Sc} polymers may split into two smaller infectious polymers which can lengthen further. If the split PrP^{Sc} falls below a critical length, it degrades immediately into normal PrP^{c} monomers. Thus, the instability of short polymers is a barrier to the formation of PrP^{Sc} polymers. Since, the formation of the nuclei is believed to be a very slow process, this model accounts for the long incubation periods of the TSEs [57].

In this study, we model the replication of prions by nucleated polymerization under the effects of a chaperone. Cellular molecular chaperones, which are ubiquitous, stress-induced proteins, and newly found chemical and pharmacological chaperones have been found to be effective in preventing misfolding of different disease-causing proteins, essentially reducing the severity of several neurodegenerative disorders and many other protein-misfolding diseases. Chaperones are known to inhibit PrP^{Sc} production and they can be molecular chaperones, chem-

ical chaperones or pharmacological chaperones. Molecular chaperones are proteins that facilitate the folding of polypeptides during their biosynthesis and transport into organelles and that help prevent protein aggregation during conditions of cellular stress [58]. These cellular chaperones along with some chemical and pharmacological chaperones have been found to be effective in preventing misfolding of different disease-causing proteins, essentially reducing the severity of several neurodegenerative disorders and many other protein-misfolding diseases like the prion diseases. The role of molecular, chemical and pharmacological chaperones in suppressing the production of $PrP^{Sc}s$ have resulted in them being potential therapeutic agents against different types of degenerative diseases, including neurodegenerative disorders like the TSEs [59].

3.2 The model

In this section, we describe the model of prion proliferation under the inhibitory effects of a chaperone. The assumption is that the prions replicate by nucleated polymerization [60]. According to this model, the biological processes of coagulation, splitting and the inhibitory effects of the chaperone can be described by a coupled system consisting of ordinary differential equations and a partial differential equation. Let $V(t)$ denote the population of PrP^c monomers at time t, $u(x,t)$ be the population of PrP^{Sc} polymers of length x at time t and $C(t)$ denotes the amount of chaperone in the system at time t. Let λ denote the constant rate of production of PrP^c in the system and γ be the constant rate of degradation of the PrP^c due to metabolic processes. τ is the conversion rate of monomers PrP^c to polymers PrP^{Sc} and they are converted at a rate proportional to the population of the total number of polymers $\int_{x_0}^{\infty} u(x,t)dx$. $\beta(x)$ is the binary splitting rate of the PrP^{Sc} polymers of length x and $\kappa(x,y)$ is the probability density function that a polymer of length y splits into one of length x and another of length $y-x$.

x_0 is the critical length of the polymer below which the polymer degrades into normal PrP^c monomers. Thus, the rate of change of the monomer population is given by

$$\frac{dV(t)}{dt} = \lambda - \gamma V(t) - \tau V(t) \int_{x_0}^{\infty} u(x,t)dx + 2\int_0^{x_0} x \int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(y,t)dydx$$

where the last term on the right hand size represents the monomers gained when a PrP^{Sc} polymer splits with at least one polymer shorter than the minimum length x_0. We assume that such a polymer piece degrades immediately into PrP^c monomers.

The 2 in the expression accounts for the fact that a polymer of length x greater than x_0 splits into two PrP^{Sc} polymers.

The polymer lengths have been shown to range over thousands of monomer units [61]. In [61], polymer lengths x were assumed to be integer values, but we assume continuous values for mathematical tractability. $\mu(x)$ is the rate of degradation of the $PrP^{Sc}s$ due to metabolism. δ_2 denotes the rate at which the PrP^{Sc} population gets reduced due to the presence of the chaperone. $-\tau V(t)\frac{\partial u(x,t)}{\partial x}$ accounts for the loss of polymers of length x due to lengthening. $2\int_x^{\infty} \beta(y)\kappa(x,y)u(y,t)dy$ denotes the number of $PrP^{Sc}s$ which are added to the population when longer polymers split into polymers of length x.

Therefore, the rate of change of $PrP^{Sc}s$ is given by

$$\frac{\partial u(x,t)}{\partial t} = -\tau V(t)\frac{\partial u(x,t)}{\partial x} - (\mu(x) + \beta(x) + \delta_2 C(t))u(x,t) + 2\int_x^{\infty} \beta(y)\kappa(x,y)u(y,t)dy$$

Let δ_0 be the rate at which the chaperone is degraded from the system due to metabolic processes and δ_1, the rate at which the chaperone is getting increased in the system.

Table 3.1: **Parameters of the prion proliferation model.**

Parameters	Description
λ	Constant rate of production of PrP^c in the system
γ	Constant rate of degradation of the PrP^c due to metabolic processes
τ	Conversion rate of monomers PrP^c to polymers PrP^{Sc}
$\beta(x)$	Binary splitting rate of the PrP^{Sc} polymers of length x
$\kappa(x,y)$	Probability density function that a polymer of length y splits into one of length x and another of length $y-x$
x_0	Critical length of the polymer below which the polymer degrades into normal PrP^c monomers
$\mu(x)$	Rate of degradation of the $PrP^{Sc}s$ due to metabolism
δ_2	Constant rate at which the PrP^{Sc} population gets reduced due to the presence of the chaperone
δ_0	Constant rate at which the chaperone is degraded from the system due to metabolic processes
δ_1	Constant rate at which the chaperone is getting increased in the system

Therefore, the rate of change of chaperone in the system is given by

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t) \int_{x_0}^{\infty} u(x,t)dx$$

Now, in the above model we make the following assumptions:

Let $\mu(x) = \mu$, $\beta(x) = \beta x$,

For every $y > x_0$, $\kappa(x,y) = 1/y$ *for* $x \in (0,y)$ *and* 0 *otherwise.*

Substituting the above in our model, the model transforms into the following:

$$\begin{aligned}
\frac{dV(t)}{dt} &= \lambda - \gamma V(t) - \tau V(t)\int_{x_0}^{\infty} u(x,t)dx + \beta x_0^2 \int_{x_0}^{\infty} u(x,t)dx && (3.1)\\
\frac{\partial u(x,t)}{\partial t} &= -\tau V(t)\frac{\partial u(x,t)}{\partial x} - (\mu + \beta x + \delta_2 C(t))u(x,t) \\
&\quad +2\beta \int_{x}^{\infty} u(y,t)dy && (3.2)\\
\frac{dC(t)}{dt} &= -\delta_0 C(t) + \delta_1 C(t)\int_{x_0}^{\infty} u(x,t)dx && (3.3)\\
V(0) &= V_0 && (3.4)\\
C(0) &= C_0 && (3.5)\\
u(x,0) &= u_0(x), \;\; x_0 < x < \infty && (3.6)\\
u(x_0,t) &= 0, \;\; t \geq 0 && (3.7)
\end{aligned}$$

where the constants $\lambda,\ \gamma,\ \tau,\ \beta,\ \delta_0,\ \delta_1,\ \delta_2$ are all positive.

3.3 The steady states of the system

In this section, we convert the model into a system of ordinary differential equations and compute the steady states of the system [62].

Introduce the functions $U(t) = \int_{x_0}^{\infty} u(x,t)dx$ which denotes the total number of PrP^{Sc} polymers and $P(t) = \int_{x_0}^{\infty} xu(x,t)dx$ which is the total number of monomers in the polymers. Now, substituting these functions in equations (3.1) and (3.3), we get

$$\begin{aligned}
\dot{V(t)} &= \lambda - \gamma V(t) - \tau V(t)U(t) + \beta x_0^2 U(t). && (3.8)\\
\dot{C(t)} &= -\delta_0 C(t) + \delta_1 C(t)U(t). && (3.9)
\end{aligned}$$

Now integrating equation (3.2) for $u(x,t)$ between x_0 *and* ∞, we get

$$\frac{dU(t)}{dt} = -\tau V(t)[u(x,t)]_{x_0}^{\infty} - \mu U(t) - \beta P(t) - \delta_2 C(t)U(t) + 2\beta \int_{x_0}^{\infty}\int_{x}^{\infty} u(y,t)dy,$$

$$
\begin{aligned}
&= -\mu U(t) - \beta P(t) - \delta_2 C(t)U(t) + 2\beta \int_{x_0}^{\infty} (y - x_0)u(y,t)dy, \\
&= -\mu U(t) - \beta P(t) - \delta_2 C(t)U(t) + 2\beta P(t) - 2\beta x_0 U(t),
\end{aligned}
$$

Thus simplifying further, we get

$$
\dot{U(t)} = -\mu U(t) - \delta_2 C(t)U(t) - 2\beta x_0 U(t) + \beta P(t). \tag{3.10}
$$

Now multiplying equation (3.2) with x and integrating for $u(x,t)$ between x_0 *and* ∞, we get

$$
\begin{aligned}
\frac{dP(t)}{dt} &= -\tau V(t)[[xu(x,t)]_{x_0}^{\infty} - \int_{x_0}^{\infty} u(y,t)dy] - \mu P(t) - \beta \int_{x_0}^{\infty} x^2 u(x,t)dx - \delta_2 C(t)P(t) \\
&+ 2\beta \int_{x_0}^{\infty} x \int_{x}^{\infty} u(y,t)dydx, \\
&= \tau V(t)U(t) - \mu P(t) - \beta \int_{x_0}^{\infty} x^2 u(x,t)dx - \delta_2 C(t)P(t) \\
&\quad +\beta \int_{x_0}^{\infty} (y^2 - x_0^2)u(y,t)dy.
\end{aligned}
$$

Thus, we get

$$
\dot{P(t)} = \tau V(t)U(t) - \mu P(t) - \delta_2 C(t)P(t) - \beta x_0^2 U(t). \tag{3.11}
$$

Combining equations (3.8) - (3.11), we get the transformed system of ODES for our model given by

$$
\begin{aligned}
\dot{V(t)} &= \lambda - \gamma V(t) - \tau V(t)U(t) + \beta x_0^2 U(t), \\
\dot{U(t)} &= -\mu U(t) - \delta_2 C(t)U(t) - 2\beta x_0 U(t) + \beta P(t), \\
\dot{P(t)} &= \tau V(t)U(t) - \mu P(t) - \delta_2 C(t)P(t) - \beta x_0^2 U(t), \\
\dot{C(t)} &= -\delta_0 C(t) + \delta_1 C(t)U(t), \\
V(0) &= V_0 \geq 0, \\
C(0) &= C_0 \geq 0,
\end{aligned}
$$

$$\begin{aligned} U(0) &= U_0 \geq 0, \\ P(0) &= P_0 \geq x_0 U_0. \end{aligned}$$

For the system of ODEs, we now compute the steady state solutions.

Set $\dot{V(t)} = 0 = \dot{U(t)} = \dot{P(t)} = \dot{C(t)}$

Now, solving $\dot{C(t)} = 0$,

we get

$$\begin{aligned} -\delta_0 C + \delta_1 CU &= 0 \\ \Rightarrow (-\delta_0 + \delta_1 U)C &= 0 \\ \Rightarrow \ \textit{either}\ C &= 0 \ \textit{or}\ (-\delta_0 + \delta_1 U) = 0 \end{aligned}$$

Case 1: When $C = 0$, the system $\dot{V(t)} = 0 = \dot{U(t)} = \dot{P(t)}$ reduces to the following:

$$\begin{aligned} \lambda - \gamma V(t) - \tau V(t)U(t) + \beta x_0^2 U(t) &= 0 \\ -\mu U(t) - 2\beta x_0 U(t) + \beta P(t) &= 0 \\ \tau V(t)U(t) - \mu P(t) - \beta x_0^2 U(t) &= 0 \end{aligned}$$

Now solving the above, we get the disease free equilibrium point as $E_1 = (\lambda/\gamma, 0, 0, 0) = (\tilde{V}, \tilde{U}, \tilde{P}, \tilde{C})$

The disease state equilibrium point is given by $E_2 = (\acute{V}, \acute{U}, \acute{P}, \acute{C})$ where

$$\begin{aligned} \acute{V} &= \frac{(\beta x_0 + \mu)^2}{\beta\tau} \\ \acute{U} &= \frac{\beta\lambda\tau - \gamma(\beta x_0 + \mu)^2}{\mu\tau(2\beta x_0 + \mu)} \\ \acute{P} &= \frac{\beta\lambda\tau - \gamma(\beta x_0 + \mu)^2}{\beta\mu\tau} \\ \acute{C} &= 0 \\ \textit{where}\ \sqrt{\frac{\beta\lambda\tau}{\gamma}} &> \beta x_0 + \mu \end{aligned}$$

Case : 2 When $-\delta_0 + \delta_1 U = 0$, we get the equilibrium to be $E_3 = (V^*, U^*, P^*, C^*)$ where

$$\begin{aligned} V^* &= \frac{\lambda + \beta x_0^2 U^*}{\gamma + \tau U^*} \\ U^* &= \frac{\delta_0}{\delta_1} \\ P^* &= \frac{\tau V^* U^* - \beta x_0^2 U^*}{\mu + \delta_2 C^*} \ \ where \ \ \tau V^* > \beta x_0^2 \\ C^* &= \frac{\sqrt{\beta \tau V^*} - (\mu + \beta x_0)}{\delta_2} \ \ where \ \ \sqrt{\beta \tau V^*} > (\mu + \beta x_0) \end{aligned}$$

3.4 Stability of the equilibrium points

In this section, we give some results on the stability of the equilibrium points.

Theorem 3.4.1 *The disease free equilibrium* $E_1 = (\lambda/\gamma, 0, 0, 0) = (\tilde{V}, \tilde{U}, \tilde{P}, \tilde{C})$ *is locally asymptotically stable if and only if* $\sqrt{\frac{\beta\lambda\tau}{\gamma}} < (\mu + \beta x_0)$.

Proof We compute the jacobian matrix of the system about the equilibrium point E_1. The jacobian matrix is given by

$$\begin{pmatrix} -\gamma & -\lambda\tau/\gamma + \beta x_0^2 & 0 & 0 \\ 0 & -\mu - 2\beta x_0 & \beta & 0 \\ 0 & \lambda\tau/\gamma - \beta x_0^2 & -\mu & 0 \\ 0 & 0 & 0 & -\delta_0 \end{pmatrix}$$

The eigen values of the above matrix are

$$-\delta_0, \ -\gamma, \ -\sqrt{\tfrac{\beta\lambda\tau}{\gamma}} - (\mu + \beta x_0), \ \sqrt{\tfrac{\beta\lambda\tau}{\gamma}} - (\mu + \beta x_0) \ .$$

Now, the equilibrium E_1 is locally asymptotically stable iff all the eigen values of the jacobian matrix have negative real parts. But, all the eigen values will have negative real parts iff the condition $\sqrt{\frac{\beta\lambda\tau}{\gamma}} < (\mu + \beta x_0)$ is satisfied. This proves the theorem.

Theorem 3.4.2 *The disease state equilibrium* $E_2 = (\acute{V}, \acute{U}, \acute{P}, \acute{C})$ *is locally asymptotically stable if and only if* $\sqrt{\frac{\beta\lambda\tau}{\gamma}} > (\mu + \beta x_0)$ *and* $\acute{U} < \frac{\delta_0}{\delta_1}$

.

Proof The jacobian matrix is given by

$$\begin{pmatrix} -\gamma - \tau\acute{U} & -\tau\acute{V} + \beta x_0^2 & 0 & 0 \\ 0 & -\mu - 2\beta x_0 & \beta & -\delta_2\acute{U} \\ \tau\acute{U} & \tau\acute{V} - \beta x_0^2 & -\mu & -\delta_2\acute{P} \\ 0 & 0 & 0 & -\delta_0 + \delta_1\acute{U} \end{pmatrix}$$

The characteristic equation of the jacobian matrix is given by

$$(-\delta_0 + \delta_1\acute{U} - A)(A^3 + a_1A^2 + a_2A + a_3) = 0$$

where the coefficients

$$\begin{aligned} a_1 &= \frac{-x_0^2\beta^2(\gamma - 4\mu) + 6\beta x_0\mu^2 + 2\mu^3 + \beta\lambda\tau}{\mu(2x_0\beta + \mu)} \\ a_2 &= \frac{-2\beta(\mu + \beta x_0)(\beta x_0^2\gamma - \lambda\tau)}{\mu(2x_0\beta + \mu)} \\ a_3 &= -\gamma(\mu + \beta x_0)^2 + \beta\lambda\tau \end{aligned}$$

One eigen value is $A = -\delta_0 + \delta_1\acute{U}$ and this eigen value will have negative real part when $\acute{U} < \frac{\delta_0}{\delta_1}$.

To conclude about the other eigen values, we apply the Routh-Hurwitz criterion to the polynomial [14, 45]

$$A^3 + a_1A^2 + a_2A + a_3.$$

Therefore, the other eigen values of the matrix will have negative real parts if and only if

$$a_1, a_2, a_3 > 0 \text{ and } a_1a_2 - a_3 > 0.$$

This condition is satisfied when

$$\sqrt{\frac{\beta\lambda\tau}{\gamma}} \; > \; (\mu + \beta x_0) \; .$$

Hence, the proof.

Theorem 3.4.3 *Let*

$$\begin{aligned}
a_1 &= \gamma + \tau U^* + 2\mu + 2\delta_2 C^* + 2\beta x_0 \\
B &= \delta_1\delta_2 C^{*2} + 2\mu\gamma + 2\gamma\delta_2 C^* + 2\beta x_0\gamma + 2\mu\tau U^* + 2\delta_2 C^*\tau U^* + 2\beta x_0\tau U^* + \mu^2 + \\
&\quad 2\mu\delta_2 C^* + \delta_2^2 C^{*2} + 2\mu\beta x_0 + 2\beta\delta_2 x_0 C^* \\
Q &= \beta\tau V^* - \beta^2 x_0^2 \\
D &= \gamma\delta_1\delta_2 C^{*2} + \tau\delta_1\delta_2 U^* C^{*2} + \delta_1\delta_2\beta C^* P^* + \mu\delta_1\delta_2 C^{*2} + \delta_1\delta_2^2 C^{*3} + \mu^2\gamma \\
&\quad + 2\mu\gamma\delta_2 C^* + \gamma\delta_2^2 C^{*2} + 2\mu\gamma\beta x_0 + 2\beta\gamma\delta_2 x_0 C^* + \tau U^*\mu^2 + 2\tau\mu\delta_2 U^* C^* \\
&\quad + \delta_2^2 C^{*2}\tau U^* + 2\mu\beta x_0\tau U^* + 2\beta x_0\delta_2 C^*\tau U^* \\
E &= \delta_1\delta_2\beta\gamma C^* P^* + \gamma\mu\delta_1\delta_2 C^{*2} + \gamma\delta_1\delta_2^2 C^{*3} + \tau\delta_1\delta_2\beta U^* C^* P^* + \tau\mu\delta_1\delta_2 U^* C^{*2} + \tau\delta_1\delta_2^2 C^{*3} U^*
\end{aligned}$$

Then, the equilibrium $E_3 = (V^*, U^*, P^*, C^*)$ is locally asymptotically stable if and only if

$$\begin{aligned}
\sqrt{\beta\tau V^*} &> (\mu + \beta x_0), && (3.12)\\
\tau V^* &> \beta x_0^2, && (3.13)\\
B &> Q, && (3.14)\\
D &> Q(\gamma + \tau U^*), && (3.15)\\
E &> Q(\tau U^*) \ \textit{and} && (3.16)\\
a_1 BD + a_1 Q^2(\gamma + \tau U^*) + a_1^2\tau U^* Q + 2QD(\gamma + \tau U^*) &> a_1 QD + a_1 BQ(\gamma + \tau U^*) + D^2 \\
&+ Q^2(\gamma + \tau U^*)^2 + a_1^2 E && (3.17)
\end{aligned}$$

Proof The jacobian matrix about the equilibrium point E_3 is given by

$$\begin{pmatrix} -\gamma - \tau U^* & -\tau V^* + \beta x_0^2 & 0 & 0 \\ 0 & -\mu - \delta_2 C^* - 2\beta x_0 & \beta & -\delta_2 C^* \\ \tau U^* & \tau V^* - \beta x_0^2 & -\mu - \delta_2 C^* & -\delta_2 P^* \\ 0 & \delta_1 C^* & 0 & 0 \end{pmatrix}$$

The characteristic equation of the jacobian matrix is

$$A^4 + a_1 A^3 + a_2 A^2 + a_3 A + a_4 = 0$$

where

$$\begin{aligned}
a_1 &= \gamma + \tau U^* + 2\mu + 2\delta_2 C^* + 2\beta x_0 \\
a_2 &= \delta_1\delta_2 C^{*2} + 2\mu\gamma + 2\gamma\delta_2 C^* + 2\beta x_0\gamma + 2\mu\tau U^* + 2\delta_2 C^*\tau U^* + 2\beta x_0\tau U^* + \mu^2 + \\
&\quad 2\mu\delta_2 C^* + \delta_2^2 C^{*2} + 2\mu\beta x_0 + 2\beta\delta_2 x_0 C^* - (\beta\tau V^* - \beta^2 x_0^2) \\
&\stackrel{\text{def}}{=} B - Q \\
a_3 &= \gamma\delta_1\delta_2 C^{*2} + \tau\delta_1\delta_2 U^* C^{*2} + \delta_1\delta_2\beta C^* P^* + \mu\delta_1\delta_2 C^{*2} + \delta_1\delta_2^2 C^{*3} + \mu^2\gamma + 2\mu\gamma\delta_2 C^* \\
&\quad +\gamma\delta_2^2 C^{*2} + 2\mu\gamma\beta x_0 + 2\beta\gamma\delta_2 x_0 C^* + \tau U^*\mu^2 + 2\tau\mu\delta_2 U^* C^* + \delta_2^2 C^{*2}\tau U^* \\
&\quad +2\mu\beta x_0\tau U^* + 2\beta x_0\delta_2 C^*\tau U^* - (\gamma + \tau U^*)(\beta\tau V^* - \beta^2 x_0^2) \\
&\stackrel{\text{def}}{=} D - Q(\gamma + \tau U^*) \\
a_4 &= \delta_1\delta_2\beta\gamma C^* P^* + \gamma\mu\delta_1\delta_2 C^{*2} + \gamma\delta_1\delta_2^2 C^{*3} + \tau\delta_1\delta_2\beta U^* C^* P^* \\
&+ \tau\mu\delta_1\delta_2 U^* C^{*2} + \tau\delta_1\delta_2^2 C^{*3} U^* - \tau U^*(\beta\tau V^* - \beta^2 x_0^2) \\
&\stackrel{\text{def}}{=} E - Q(\tau U^*)
\end{aligned}$$

Since, the equilibrium point is required to be positive, equations (3.13) and (3.14) follow from that. Now, we apply the Routh-Hurwitz condition to the characteristic polynomial of the jacobian matrix about E_3. By Routh-Hurwitz criterion, the eigen values of the matrix will have negative real parts if and only if

$$\begin{aligned}
a_1, a_2, a_3, a_4 &> 0 \ \textit{and} \\
a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 &> 0
\end{aligned}$$

Now, since all the constants are positive in the model,this $\Rightarrow a_1 > 0$.

Now, equation (3.14) $\Rightarrow a_2 > 0$,

equation (3.15) $\Rightarrow a_3 > 0$,

equation (3.16) $\Rightarrow a_4 > 0$,

equation (3.17) $\Rightarrow a_1a_2a_3$ - a_3^2 - $a_1^2a_4 > 0$

Therefore, the Routh-Hurwitz condition is satisfied and hence all the eigen values of the Jacobian matrix have negative real parts. The negativity of all the eigen values implies that the equilibrium point E_3 is locally asymptotically stable. Hence, the proof.

3.5 Numerical Illustration

Our model can be used for simulations based on experimental data for prion proliferation. The model has nine parameters: λ, τ, γ, β, μ, x_0, δ_0, δ_1 *and* δ_2. The minimum stable polymer x_0 is estimated as 6 - 30 in [61]. The model parameters are as follows. The parameter values were taken from [61]. λ= 4400 day^{-1}, $\tau = 0.3$ (Scrapie-Associated Fibrils (SAF)/sq. unit)$^{-1}$ day^{-1}, $\gamma = 5$ day^{-1}, $\beta = 0.0001$ (SAF/sq.)$^{-1}$.day^{-1}, $\mu = 0.04$ day^{-1}, $x_0 = 6$, $\delta_0 = 0.1$ day^{-1}, $\delta_1 = 0.0004$ day^{-1} and $\delta_2 = 0.002$ day^{-1}. MATLAB software has been used to simulate our model.

Figures 3.1 - 3.3 show the graphs of V, U and P versus time. All the graphs show the population reaching the steady state U*, V*, and P* respectively. The simulations assume an initial PrP^c population $V_0 = 880$ along with $U_0 = 5$, $P_0 = 1000$ and $C_0 = 1000$. A biologically more useful result is obtained when we study the population of polymers along with chaperone concentration. The change in U(t) and C(t) for different values of chaperone dose with time is plotted in Figure 3.4. From figure 3.1, we find that the population of monomers increases and is at a high level and at steady concentration as long as the chaperone is present in the system. As the amount of chaperone reduces in the system, the monomers start

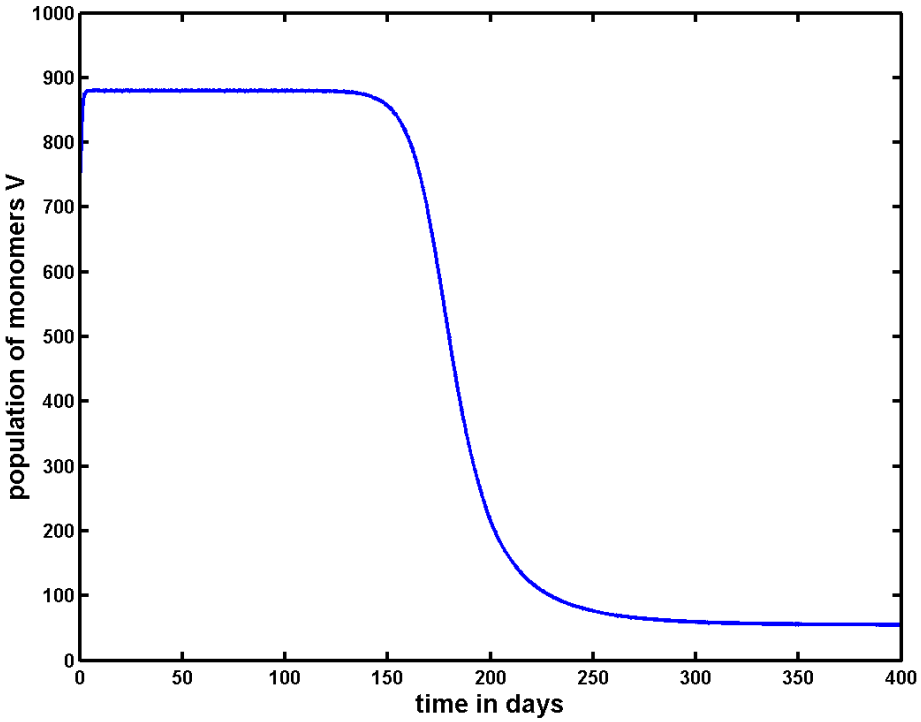

Figure 3.1: **Population of monomers V vs time**

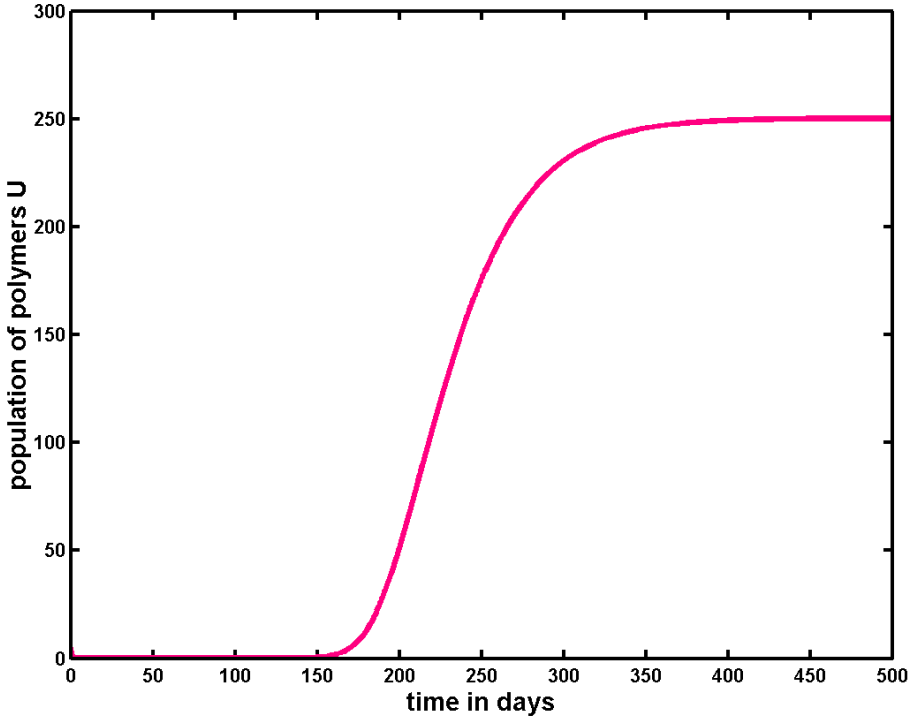

Figure 3.2: **Population of polymers U vs time**

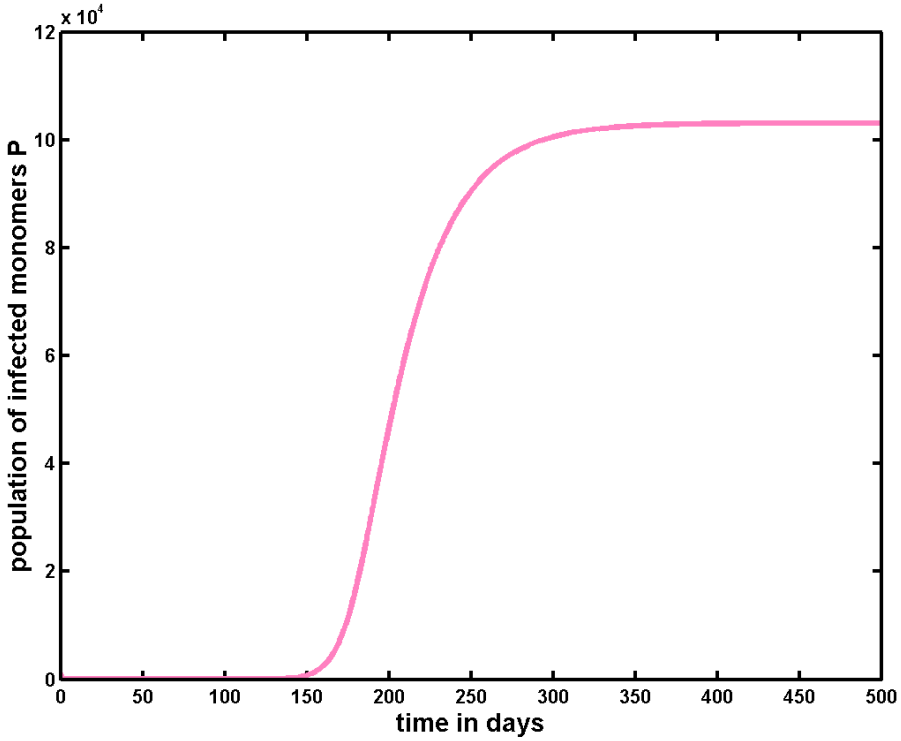

Figure 3.3: **Population of infected monomers P vs time**

decreasing and settles down at the equilibrium level. Similarly in figure 3.2, the population of $PrP^{Sc}s$ is under control in the presence of chaperone and as the chaperone concentration declines, the population of polymers is seen to increase. The same is also observed in figure 3.3. From figure 3.4, we see that the infection is curbed in the presence of chaperone in the system. We found that, with increasing levels of chaperone, the disease was under control for longer periods of time. The disease free state was achieved for a period of 170 days when a dose of 1000 units of chaperone was administered.

3.6 Conclusions

In this work, we have proposed a model of prion proliferation with the effects of a chaperone. Our model provides an extension to the model of Webb et. al [18]. We have studied the stability of the equilibrium points of the model and have

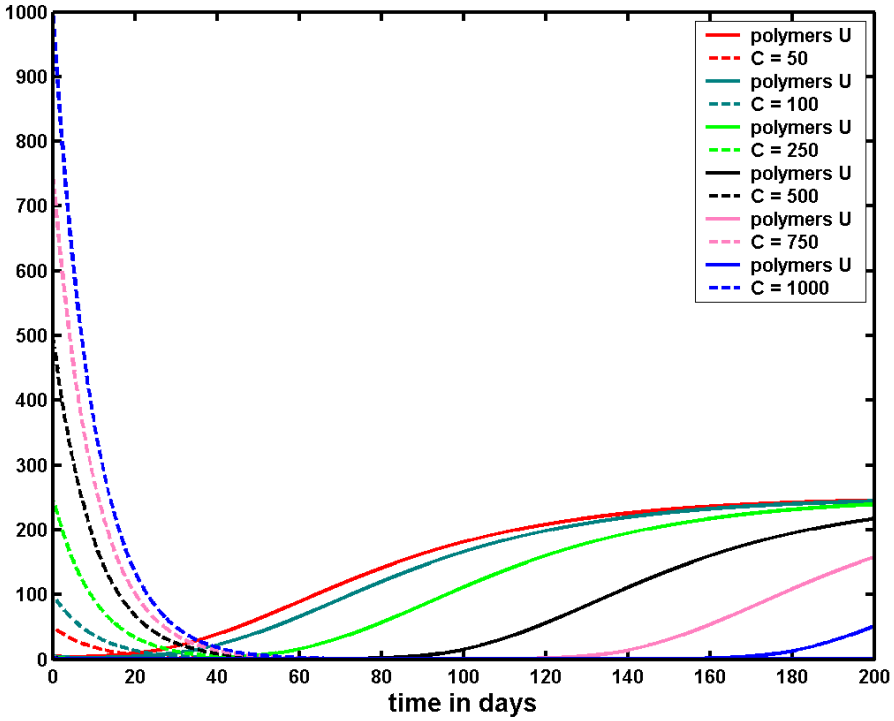

Figure 3.4: **Dose response curve of population of polymers U for varying amounts of chaperone C (50, 100, 250, 500, 750 and 1000 units of chaperone)**

proved that the steady state solutions of the model are locally asymptotically stable. From the analysis of the model and the results proved in section 3.4, we conclude the following:

Let $R_0 = \frac{\lambda\beta\tau}{\gamma(\mu+\beta x_0)^2}$ denote the number of secondary infections produced on average by one infectious prion.

If $R_0 < 1$, then the disease dies out and the disease free equilibrium E_1 is locally asymptotically stable. If $R_0 > 1$, then the disease persists and the disease state equilibrium E_2 is locally asymptotically stable. The above two conclusions are drawn by analysing the equilibrium points, when the amount of chaperone is zero. From the numerical illustration in section 3.5, we find that a disease free state can be achieved in the presence of a chaperone. The duration of the disease free state is found to increase with the amount of chaperone and this amount of chaperone can be computed from the model.

Chapter 4

Spread of the SARS Epidemic

4.1 Introduction

In recent times, newly emerging infectious diseases and their causative agents have become the focus of intense attention and investigations by medical researchers and scientists. One such disease which has created fear, world wide, is severe acute respiratory syndrome. Severe acute respiratory syndrome (SARS) is a respiratory disease, which was first identified in China's southern province of Guangdong [63]. Infection with a novel corona virus has been implicated as a possible cause of SARS. The Severe Acute Respiratory Syndrome epidemic has attacked the human society worldwide, since November 2002. It has lead to a big catastrophic threat, in terms of abrupt deaths, tour-industry disruption, economy depression, etc [63]. SARS poses a serious risk to the medical community and is a threat to international travelers. It has a substantial negative economic impact in parts of East Asia and is spreading world-wide. The serious danger SARS poses to the medical community is illustrated by the numerous cases of transmission to health-care workers. The most striking feature of SARS, however, has proven to be its ability to rapidly spread on a global scale. An individual exposed to SARS may become infectious after an incubation period of 2-7 days with 3-5 days being most common. Most infected individuals either recover after 7-10 days or suffer seven to ten percent mortality. SARS appears to be most serious in people over 40 years of age especially those who have other medical problems such as heart or liver disease. Its symptoms are similar to pneumonia or other respiratory ailments and include high fever, shortness of breath, dry cough, headache, stiff or achy muscles, fatigue and diarrhoea. These symptoms, however, are not uniform. In the US, for example, the disease seems to be a milder one than in Asia [64]. The mode of transmission of the virus is not yet very clear. SARS appears to be transmitted mainly by person-to-person contact. However, it could also be transmitted by contaminated objects, air etc. At present, there is no effective drug to cure the disease and the vaccine against the disease has yet to be developed. Hence, SARS

poses a great threat to the global public health of human beings and may lead to a possible devastating impact to worlds economy and development. Therefore, it is very significant and important to study the transmission dynamics using qualitative and quantitative mathematical models and consequently predict and control the contagious disease in time. Several models both deterministic and stochastic focusing on the spread of SARS and it's control measures have been reported in [64, 65, 66, 67, 68, 69, 70, 71, 72, 73]. Here, we model the SARS epidemic using the double epidemic hypothesis wherein there are two epidemics in a population and one mild infection confers immunity to the other major disease. It was observed that, in the SARS outbreak, there remained a more or less constant background infection level, that remained present for a long time and witnessed a slow decline, on which superimposed sudden local outbreaks. This is difficult to explain by the standard SIR epidemic model. The pattern observed in the SARS epidemic, is very similar to the coronavirus mediated epidemics, that affected pigs in $1983 - 1985$ [74]. We assume that, in the SARS epidemic, there is high mutation and recombination rate of coronaviruses [75], and that tissue tropism can be changed by simple mutations [76]. There are two epidemics, one epidemic is SARS caused by a coronavirus , which we denote as virus A. Another epidemic, which is conjectured to have occurred before SARS, and which is assumed to be extremely contagious because of the nature of the virus and of its relative innocuousness, is propagated by contaminated food and soiled surfaces. It is noted, to have been caused by some coronavirus, which we denote as virus B which causes gastroenteritis. This is assumed from the observation that diarrhoea was reported in the population for about one day just before the SARS outbreak. The most likely origin of virus A, is a mutation or recombination event from virus B [77, 78]. Also, it has been observed by scientists about possibilities, where viruses A and B, are of different origins, but would cause an overlapping immune response of the host. Both epidemics spread in parallel, and the epidemic caused

by virus B which is rather innocuous, protects against SARS so that regions, not protected by the epidemic B can get large SARS outbreaks.

4.2 The model

In this section, we model the transmission of SARS using the double epidemic hypothesis. The assumption is that, in the outbreak of the SARS epidemic, which we call as virus A, there is yet another epidemic which is spreading in parallel [71]. This virus is denoted as virus B in the model. We assume that a person once infected with virus B becomes immune to the SARS virus (i.e) virus A. Since, SARS is highly dangerous and mostly fatal, therefore, the effect of virus B on the people infected with SARS virus is negligible. Thus, the model is a model with cross immunity. We assume that the population is divided into three distinct classes: susceptibles, infectives with virus A and infectives with virus B. Let $S(t)$ denote the total population of susceptibles at time t, I_A be the total population of infectives with virus A at time t and I_B be the total population of infectives with virus B at time t. Let λ denote the constant rate of inflow of individuals into the susceptible class due to immigration or births and γ be the constant rate of removal of the susceptibles due to deaths by natural causes and not due to the infection. α is the transmission rate of virus A and αSI_A denotes the total number of susceptibles who are lost to the infective class I_A due to virus A and β is the transmission rate of virus B and βSI_B denotes the total number of susceptibles who are lost to the infective class I_B due to virus B. Thus, the rate of change of the susceptible population is given by

$$\frac{dS(t)}{dt} = \lambda - \gamma S(t) - \alpha SI_A - \beta SI_B$$

Let μ be the constant removal rate of infectives with virus A. Since, the loss in the susceptible class is the gain in the infective class, the rate of change of infectives

with virus A is given by

$$\frac{dI_A(t)}{dt} = -\mu I_A + \alpha S I_A$$

Let τ be the constant removal rate of infectives with virus B. Since, the loss in the susceptible class is the gain in the infective class, the rate of change of infectives with virus B is given by

$$\frac{dI_B(t)}{dt} = -\tau I_B + \beta S I_B$$

Combining the three equations along with the initial conditions, the model of the double epidemic is given by

$$\begin{aligned}
\frac{dS(t)}{dt} &= \lambda - \gamma S(t) - \alpha S I_A - \beta S I_B \\
\frac{dI_A(t)}{dt} &= -\mu I_A + \alpha S I_A \\
\frac{dI_B(t)}{dt} &= -\tau I_B + \beta S I_B \\
S(0) &= S_0 \\
I_A(0) &= I_{A0} \\
I_B(0) &= I_{B0}
\end{aligned}$$

where $\lambda, \gamma, \alpha, \beta, \mu, \tau$ are positive constants.

4.3 The steady states of the system

In this section, we compute the steady states of the model. The system has several steady states: when both diseases are absent (uninfected equilibrium), and when a disease (one or both simultaneously) is present.

Table 4.1: **Parameters of the SARS epidemic model**

Parameters	Description
λ	Constant rate of inflow of individuals into the susceptible class due to immigration or births
γ	Constant rate of removal of the susceptibles due to deaths by natural causes and not due to the infection
α	Transmission rate of virus A
β	Transmission rate of virus B
μ	Constant removal rate of infectives with virus A
τ	Constant removal rate of infectives with virus B

Set $\frac{dS(t)}{dt} = 0 = \frac{dI_B(t)}{dt} = \frac{dI_B(t)}{dt}$, we get

$$\begin{aligned} \lambda - \gamma S - \alpha S I_A - \beta S I_B &= 0 \\ -\mu I_A + \alpha S I_A &= 0 \\ -\tau I_B + \beta S I_B &= 0 \end{aligned}$$

Now solving the above, we get the disease free equilibrium point as $E_1 = (\lambda/\gamma, 0, 0) = (\tilde{S}, \tilde{I_A}, \tilde{I_B})$

When $I_B = 0$, the one disease state equilibrium point is given by $E_2 = (\acute{S}, \acute{I_A}, \acute{I_B})$ where

$$\begin{aligned} \acute{S} &= \frac{\mu}{\alpha} \\ \acute{I_A} &= \frac{\lambda\alpha - \gamma\mu}{\mu\alpha} \\ \acute{I_B} &= 0 \end{aligned}$$

where $\frac{\lambda\alpha}{\gamma} > \mu$

When $I_A = 0$, the one disease state equilibrium point is given by $E_3 = (S^*, I_A^*, I_B^*)$

where

$$\begin{aligned} S^* &= \frac{\tau}{\beta} \\ I_A^* &= 0 \\ I_B^* &= \frac{\lambda\beta - \gamma\tau}{\tau\beta} \end{aligned}$$

where $\lambda\beta > \gamma\tau$

4.4 Stability of the equilibrium points

In this section, we give some results on the stability of the equilibrium points.

Theorem 4.4.1 *The disease free equilibrium* $E_1 = (\lambda/\gamma, 0, 0) = (\tilde{S}, \tilde{I_A}, \tilde{I_B})$ *is locally asymptotically stable if and only if* $\frac{\lambda\alpha}{\gamma} < \mu$ *and* $\frac{\lambda\beta}{\gamma} < \tau$.

Proof We compute the jacobian matrix of the system about the equilibrium point E_1. The jacobian matrix is given by

$$\begin{pmatrix} -\gamma & \frac{-\lambda\alpha}{\gamma} & \frac{-\lambda\beta}{\gamma} \\ 0 & -\mu + \frac{\lambda\alpha}{\gamma} & 0 \\ 0 & 0 & -\tau + \frac{\lambda\beta}{\gamma} \end{pmatrix}$$

The eigen values of the above matrix are

$$-\gamma,\ -\mu + \tfrac{\lambda\alpha}{\gamma},\ -\tau + \tfrac{\lambda\beta}{\gamma}\ .$$

Now, the equilibrium E_1 is locally asymptotically stable if and only if all the eigen values of the jacobian matrix have negative real parts. But, all the eigen values will have negative real parts if and only if the condition $\frac{\lambda\alpha}{\gamma} < \mu$ and $\frac{\lambda\beta}{\gamma} < \tau$ is satisfied. This proves the theorem.

Theorem 4.4.2 *The disease state equilibrium* $E_2 = (\acute{S}, \acute{I_A}, \acute{I_B})$ *is locally asymptotically stable if and only if* $\frac{\lambda\alpha}{\gamma} > \mu$ *and* $\frac{\mu}{\alpha} < \frac{\tau}{\beta}$.

Proof We compute the jacobian matrix of the system about the equilibrium point E_2. The jacobian matrix is given by

$$\begin{pmatrix} \frac{-\lambda\alpha}{\mu} & -\mu & \frac{-\mu\beta}{\alpha} \\ \frac{\lambda\alpha-\gamma\mu}{\mu} & 0 & 0 \\ 0 & 0 & -\tau+\frac{\mu\beta}{\alpha} \end{pmatrix}$$

The characteristic equation of the jacobian matrix is given by

$$(-\tau+\tfrac{\mu\beta}{\alpha}-x)(x^2+\tfrac{\lambda\alpha}{\mu}x+\lambda\alpha-\gamma\mu)=0$$

One eigen value is $x=-\tau+\frac{\mu\beta}{\alpha}$ and this eigen value will have negative real part when

$$\frac{\mu}{\alpha}<\frac{\tau}{\beta} \tag{4.1}$$

To conclude about the other eigen values, we apply the Routh-Hurwitz criterion to the polynomial [14, 45]

$$x^2+\tfrac{\lambda\alpha}{\mu}x+\lambda\alpha-\gamma\mu$$

Therefore, the other eigen values of the matrix will have negative real parts if and only if

$$\frac{\lambda\alpha}{\gamma}>\mu \tag{4.2}$$

Hence, from equations (4.1) and (4.2), the theorem is proved.

Theorem 4.4.3 *The disease state equilibrium $E_3=(S^*,I_A^*,I_B^*)$ is locally asymptotically stable if and only if $\frac{\lambda\beta}{\gamma}>\tau$ and $\frac{\tau}{\beta}<\frac{\mu}{\alpha}$.*

Proof We compute the jacobian matrix of the system about the equilibrium point E_3. The jacobian matrix is given by

$$\begin{pmatrix} \frac{-\lambda\beta}{\tau} & \frac{-\alpha\tau}{\beta} & -\tau \\ 0 & -\mu+\frac{\alpha\tau}{\beta} & 0 \\ \frac{\lambda\beta-\gamma\tau}{\tau} & 0 & 0 \end{pmatrix}$$

The characteristic equation of the jacobian matrix is given by

$$(-\mu + \tfrac{\alpha\tau}{\beta} - x)(x^2 + \tfrac{\lambda\beta}{\tau}x + \lambda\beta - \gamma\tau) = 0$$

One eigen value is $x = -\mu + \frac{\alpha\tau}{\beta}$ and this eigen value will have negative real part when

$$\frac{\tau}{\beta} < \frac{\mu}{\alpha} \tag{4.3}$$

To conclude about the other eigen values, we apply the Routh-Hurwitz criterion to the polynomial [10,11]

$$x^2 + \tfrac{\lambda\beta}{\tau}x + \lambda\beta - \gamma\tau$$

Therefore, the other eigen values of the matrix will have negative real parts if and only if

$$\frac{\lambda\beta}{\gamma} > \tau \tag{4.4}$$

Hence, from equations (4.3) and (4.4), the theorem is proved.

4.5 Conclusions

In this work, we have studied a simple model of SARS propagation using the double epidemic hypothesis. We have found out three steady states of the model: disease free state, one disease state with infectives with virus B absent and another one disease state where the infectives with virus A is zero. We use the linear stability analysis to draw the conditions for the local asymptotic stability of the three steady states. We find that infection caused by virus A which is the SARS virus can be controlled when $\frac{\lambda\beta}{\gamma} > \tau$ and $\frac{\tau}{\beta} < \frac{\mu}{\alpha}$. Thus, the milder infection caused by virus B acts like a vaccine against the SARS virus. Hence, with the help of this study, there is a possibility in the future to develop a vaccination strategy to fight the SARS epidemic.

Chapter 5

Neospora caninum Infection in Cattle

5.1 Introduction

Infectious organisms can cause significant losses in farm ruminant production as a result of foetal deaths, embryonic damage or maternal infertility. One of the principal agents causing abortion or still-births in cattle is *Neospora caninum* . *Neospora caninum* is a protozoal parasite that is considered a leading cause of foetal deaths in some dairy and beef herds [79]. It is morphologically similar to other apicomplexa protozoal parasites of importance to veterinary medicine like Toxoplasma gondii and Sarcocystis spp. [80, 81]. *Neospora caninum* is a pathogenic protozoan that was first identified in 1988 as a new genus of Toxoplasma-like apicomplexan [82]. This parasite was first recognised as a neuromuscular disease in dogs in 1984 and was first reported as a cause of abortion in cattle in the U.S. in 1989. The occurrence of *N.caninum* infection in beef and dairy cattle has been reported worldwide, and in United States alone, the loss to the dairy industry, due to *N.caninum* is 35 billion dollars. In the bovine, transplacental transmission of N. caninum from dam to foetus is considered the most important mode of infection and can occur in consecutive pregnancies [83]. However, post natal N. caninum infection has also been observed in cattle herds [84, 85, 86, 87]. The dog, a definitive host of the parasite, has been suggested as a source of such a transmission [88]. The oocysts are excreted through dog feces and then, after they are consumed by an intermediary host (ruminants, horses, and wild animals), the sporozoites are liberated and infect the small intestine. The most frequently infected intermediary host is cattle, in which abortion is the most common clinical sign [89]. The risk of abortion is generally higher in cows congenitally infected with *N. caninum* than in non-infected animals [90]. However, abortion outbreaks have also been associated with recently acquired N. caninum infection [91]. The presence of antibodies to *N.caninum* in the serum of an individual indicates that it is, or has previously been, infected with the parasite. Also, putative infection via pooled colostrum denotes transmission from within the herd. The occurrence of

N.caninum infection in beef and dairy cattle has been reported worldwide, and in United States alone, the loss to the dairy industry, due to *N.caninum* is 35 billion dollars [80, 92]. *N.caninum* infection in cattle herds is potentially economically devastating and prevention must be emphasised. Currently, there is no effective means for treatment or control of this disease, particularly in dairies where bovine neosporosis is a major disease problem . Implementation of effective control procedures would be facilitated by the identification of the definitive host(s) for *N.caninum*. One study suggested that, as for Toxoplasma gondii, cats might also be the definitive host for *N.caninum* . However, this proposal has not been supported by other investigators. Results of laboratory and field studies looking at dogs, cats, rats, and mice have all proved negative, suggesting that the definitive host may be some other wildlife species. If so, finding this definitive host will be extremely difficult without some methodology to screen various wildlife species for evidence of exposure to the *N.caninum* protozoan [82]. Thus, it has become very important to find some effective methods so as to control this disease.

5.2 The model

In this work, we model the spread of *N.caninum* infection among cattle through a system of ordinary differential equations. The assumption is that the infection is transmitted by either

1. maternal vertical transmission (i.e) from the infected animal to it's calf
2. horizontal transmission from infected cattle within the herd (i.e)putative infection via pooled colostrum, or/and
3. horizontal transmission from an independent external source, which in this case are dogs [89].

We assume that the cattle population is divided into two distinct classes: The non infected cattle or the susceptibles and the infected cattle or the infectives.

We denote the non infected cattle by S and the infected cattle by I. Thus, $S(t)$ gives the count of the non infected population at time t and $I(t)$ gives the count of infective animals at time t. Let A denote the constant number of births in the non-infective cattle population and μ_0 denote the removal rate of the non-infective cattle population due to natural causes. Let r denote the contact rate of the infection due to horizontal transmission from infected cattle with in the herd and d be the contact rate of the infection due to horizontal transmission due to an external independent source (i.e. dogs). Thus the rate of change of the susceptible population is given by

$$\frac{dS}{dt} = A - \mu_0 S - rSI - dSI$$

Let μ be the removal rate of the infected cattle and β denote the rate at which the disease is vertically transmitted from mother to calf. The rate of change of infected population is given by

$$\frac{dI}{dt} = -\mu I + \beta I + rSI + dSI$$

The schematic representation of the model is given in figure 5.1 and the model

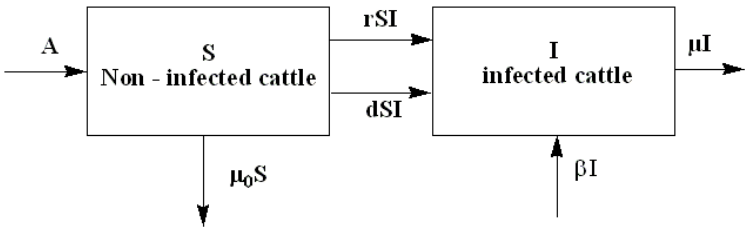

Figure 5.1: **Schematic representation of the model**

equations are

$$\begin{aligned} \frac{dS}{dt} &= A - \mu_0 S - rSI - dSI \\ \frac{dI}{dt} &= -\mu I + \beta I + rSI + dSI \end{aligned}$$

Table 5.1: **Parameters of the *Neospora Caninum* infection model**

Parameters	Description
A	Constant number of births in the non-infective cattle population
μ_0	Removal rate of the non-infective cattle population due to natural causes
r	Contact rate of the infection due to horizontal transmission from infected cattle with in the herd
d	Contact rate of the infection due to horizontal transmission due to an external independent source (i.e. dogs)
μ	Removal rate of the infected cattle
β	Constant rate at which the disease is vertically transmitted from mother to calf

$$\begin{aligned} S(0) &= S_0 > 0 \\ I(0) &= I_0 > 0 \text{ are the initial conditions} \\ \text{and} \quad & A,\ \mu_0,\ r,\ d,\ \beta,\ \mu, \text{are all positive.} \end{aligned}$$

5.3 The steady states of the system

In this section, we compute the steady states of the model and analyse the stability of the equilibrium points [14]. We compute the steady states of the model by setting

$$\frac{dS}{dt} = 0 \text{ and } \frac{dI}{dt} = 0$$

Therefore, by solving

$$\begin{aligned} A - \mu_0 S - rSI - dSI &= 0 \text{ and} \\ -\mu I + \beta I + rSI + dSI &= 0 \end{aligned}$$

we get two steady states, E_1 and E_2 for the system.

$$E_1 = (\tilde{S}, \tilde{I}) = \left(\frac{A}{\mu_0}, 0\right) \text{ is the disease free steady state}$$
$$E_2 = (S^*, I^*) = \left(\frac{\mu - \beta}{r + d}, \frac{A(r+d) + \mu_0\beta - \mu_0\mu}{(\mu - \beta)(r+d)}\right)$$

is the disease state positive equilibrium where $0 < \mu_0(\mu - \beta) < A(r + d)$.

5.4 Stability of the equilibrium points

Theorem 5.4.1 *(i) If the disease state equilibrium $E_2 = (S^*, I^*)$ does not exist, then the disease free equilibrium $E_1 = (\tilde{S}, \tilde{I}) = \left(\frac{A}{\mu_0}, 0\right)$ is locally asymptotically stable.*

(ii) If the disease state equilibrium $E_2 = (S^*, I^*)$ exists, then the disease free equilibrium $E_1 = (\tilde{S}, \tilde{I}) = \left(\frac{A}{\mu_0}, 0\right)$ is a saddle point with stable manifold locally in the S-direction and with unstable manifold locally in the I-direction.

Proof: (i) Given that the disease state equilibrium $E_2 = (S^*, I^*)$ does not exist. Computing the jacobian matrix of the system about the equilibrium point E_1, we get

$$\begin{pmatrix} -\mu_0 & -A\frac{(r+d)}{\mu_0} \\ 0 & \beta - \mu + A\frac{(r+d)}{\mu_0} \end{pmatrix}$$

The eigen values of the above matrix are

$$-\mu_0, \text{ and } \beta - \mu + A\frac{(r+d)}{\mu_0} .$$

Since $E_2 = (S^*, I^*)$ does not exist it implies that $\frac{A(r+d)}{\mu_0} < \mu - \beta$. This, therefore implies that the eigen values of the Jacobian matrix have negative real parts.

Hence the disease free equilibrium $E_1 = (\tilde{S}, \tilde{I}) = \left(\frac{A}{\mu_0}, 0\right)$ is locally asymptotically stable.

(ii) Given that the disease state equilibrium $E_2 = (S^*, I^*)$ exists. Then the eigen values of the jacobian matrix of the system about the equilibrium point E_1 will be given by

$$-\mu_0, \ and \ \beta - \mu + A\frac{(r+d)}{\mu_0} \ .$$

Since $E_2 = (S^*, I^*)$ exists, it implies that the eigen value $\frac{A(r+d)}{\mu_0} - (\mu - \beta) > 0$. Hence $E_1 = (\tilde{S}, \tilde{I}) = \left(\frac{A}{\mu_0}, 0\right)$ is a saddle point with stable manifold locally in the S-direction and with unstable manifold locally in the I-direction. This proves the theorem.

Theorem 5.4.2 *The disease state equilibrium* $E_2 = (S^*, I^*) = (\frac{\mu-\beta}{r+d}, \frac{A(r+d)+\mu_0\beta-\mu_0\mu}{(\mu-\beta)(r+d)})$, *whenever it exists, is locally asymptotically stable.*

Proof: The jacobian matrix is given by

$$\begin{pmatrix} -\mu_0 - (r+d)I^* & -(r+d)S^* \\ (r+d)I^* & \beta - \mu + (r+d)S^* \end{pmatrix}$$

The characteristic equation of the jacobian matrix is given by

$$[-\mu_0 - (r+d)I^* - \lambda][\beta - \mu + (r+d)S^* - \lambda] + (r+d)^2 S^* I^* = 0$$

Simplifying, the characteristic equation becomes

$\lambda^2 + \lambda(\mu_0 + \frac{A(r+d)+\mu_0\beta-\mu_0\mu}{\mu-\beta}) + A(r+d) + \mu_0\beta - \mu_0\mu = 0$

Since E_2 exists, we have $0 < \mu_0(\mu - \beta) < A(r+d)$. Now, by applying Routh-Hurwitz criterion [14, 45] we see that the coefficients of the characteristic polynomial are positive. Hence, the Jacobian matrix has eigen values with negative real parts. Therefore, the disease state equilibrium $E_2 = (S^*, I^*) = (\frac{\mu-\beta}{r+d}, \frac{A(r+d)+\mu_0\beta-\mu_0\mu}{(\mu-\beta)(r+d)})$, whenever it exists, is locally asymptotically stable. Hence, the proof.

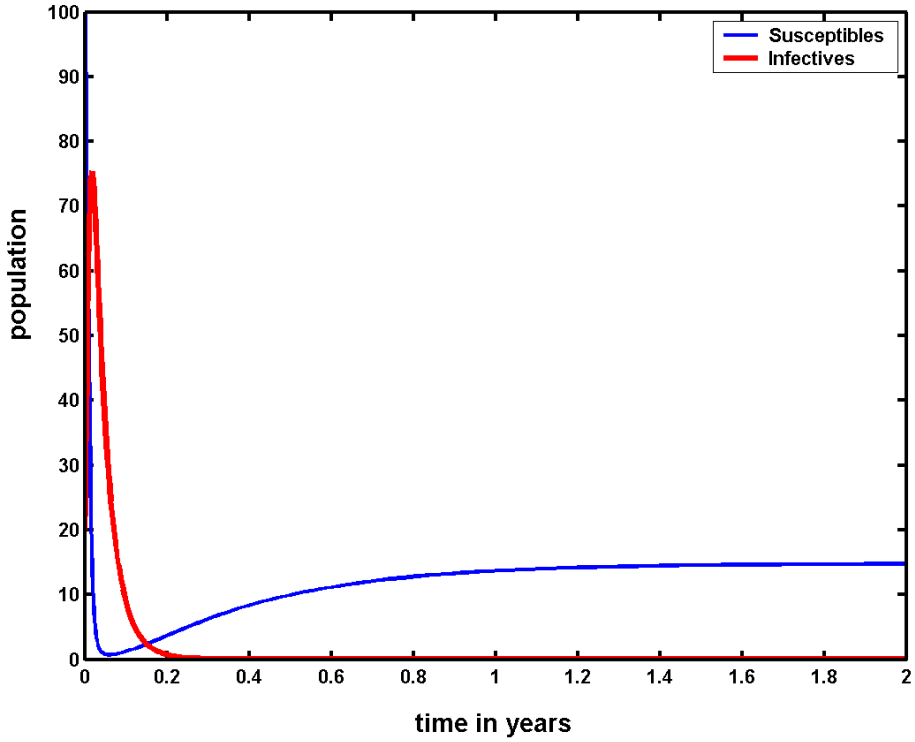

Figure 5.2: **Population approaching the disease free state**

5.5 Numerical Illustration

Our model can be used for simulations based on field data for transmission of *Neospora caninum*. The model has six parameters: A, μ_0, r, d, β, μ.

Figure 5.2 shows the population approaching the disease free state for parameter values A= 43 per year, $\mu_0 = 2.9$ per year, $r = 1.4$ year^{-1}, $d = 0.6$ year^{-1}, $\beta = 4.3$ year^{-1}, $\mu = 34$ year^{-1} [80, 81]. Figure 5.3 shows the population approaching the disease state for parameter values A= 43 per year, $\mu_0 = 2.9$ per year, $r = 1.4$ year^{-1}, $d = 0.6$ year^{-1}, $\beta = 4.3$ year^{-1}, $\mu = 10$ year^{-1} [80, 81]. Figure 5.4 gives the susceptible population for varying values of the parameter μ. We see that, as the μ value is increased, the susceptible population increases and the infection is controlled. Thus, for $\mu = 34$, the disease free state is reached. Figure 5.5 gives the infective population for varying values of the parameter μ. We see that, as the μ value is increased, the infectives decreases and the infection is controlled. For $\mu = 34$, the disease free state is reached. Thus, the parameter μ is varied which

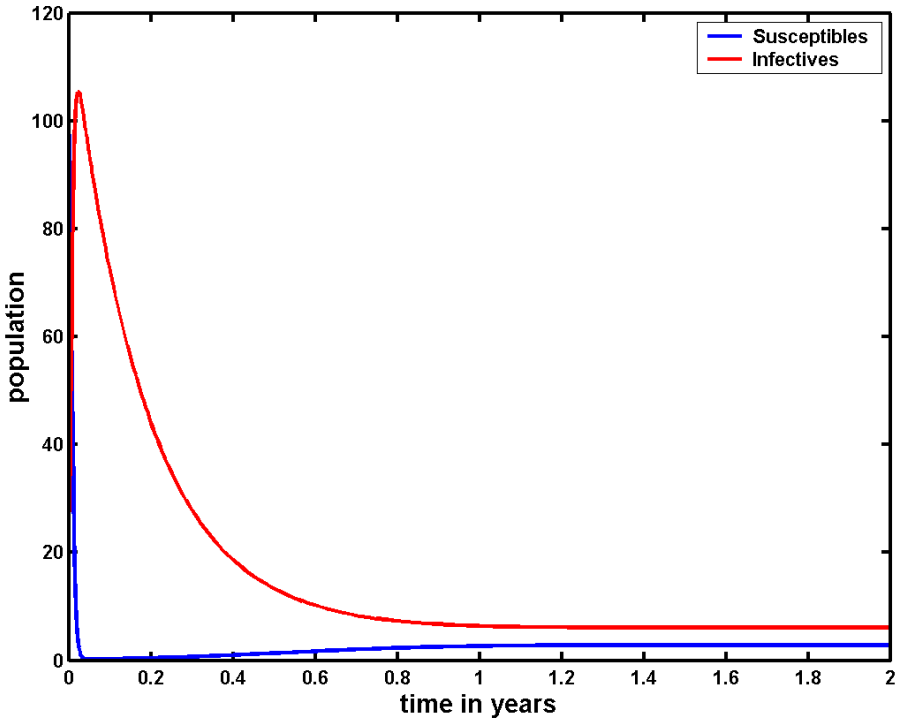

Figure 5.3: **Population approaching the disease state**

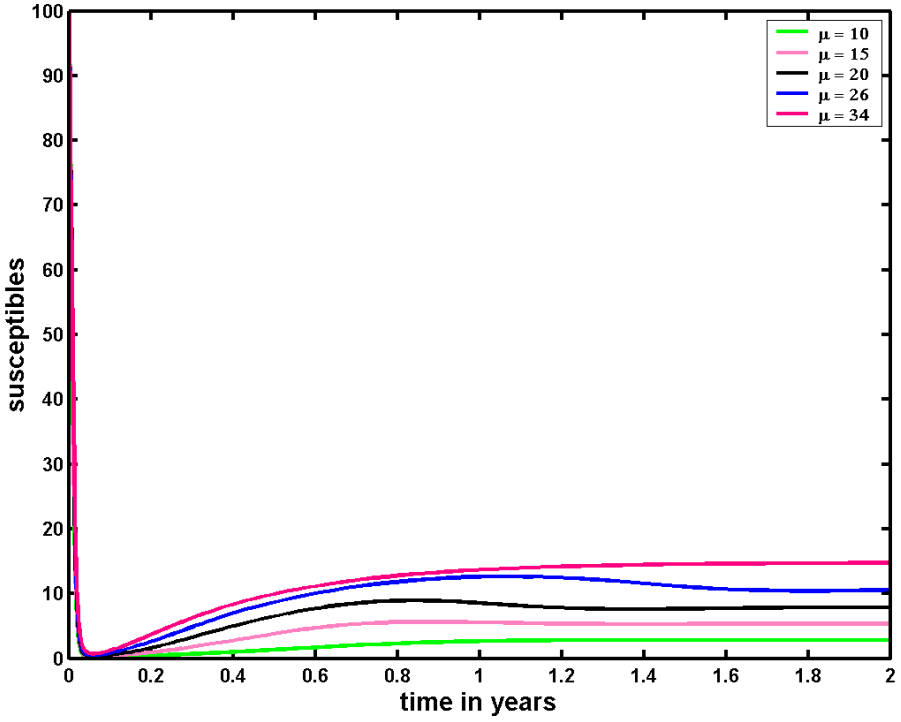

Figure 5.4: **Susceptibles for varying values of removal rate**

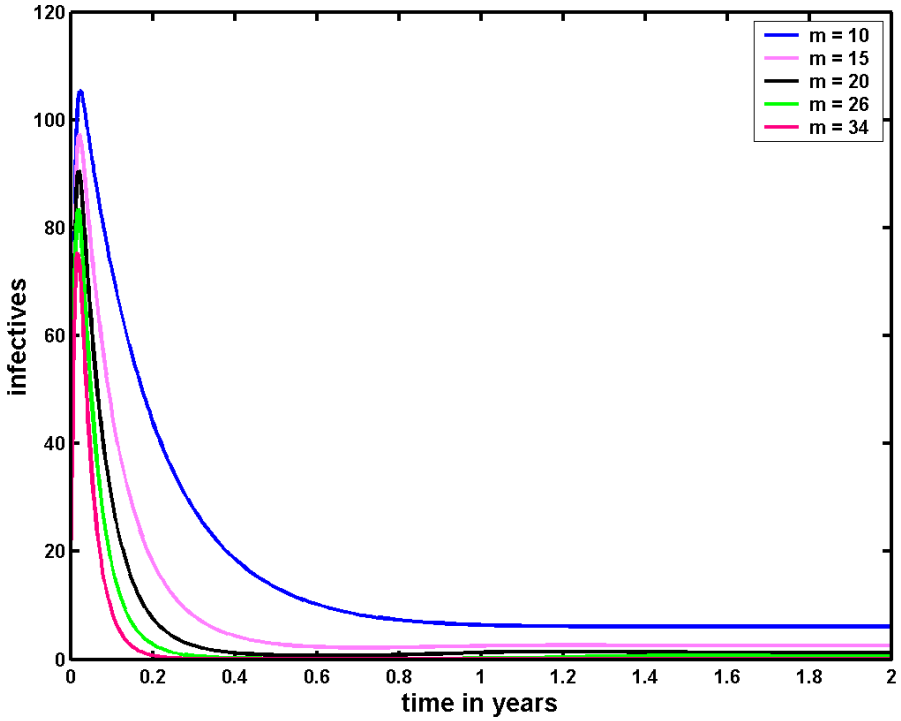

Figure 5.5: **Infectives for varying values of removal rate**

denotes the removal rate of the infected cattle. Here, it accounts for culling of the infected cattle.

5.6 Conclusions

From the numerical simulations, we find that, as the value of μ increases, the number of infectives are reduced and for $\mu = 34$, we find that the infection is curbed and the population reaches the disease free state.

The reasons for this behaviour is explained with the help of the threshold of the epidemic.:

Let $R_0 = \frac{A(r+d)}{\mu_0(\mu-\beta)}$ be defined as the threshold of the epidemic.

Case 1: $R_0 < 1$

When $R_0 < 1$ (i.e.) $\frac{A(r+d)}{\mu_0(\mu-\beta)} < 1$ or $\frac{A(r+d)}{\mu_0} < \mu - \beta$, we find from theorem 5.4.1, that the cattle population approaches the disease free state $E_1 = (\tilde{S}, \tilde{I}) = (\frac{A}{\mu_0}, 0)$.

Hence, there is no epidemic.

Case 2: $R_0 > 1$

When $R_0 > 1$ i.e. $\frac{A(r+d)}{\mu_0(\mu-\beta)} > 1$ or $\frac{A(r+d)}{\mu_0} > \mu - \beta$, we find from theorem 5.4.2, that the cattle population approaches the disease state

$$E_2 = (S^*, I^*) = (\frac{\mu - \beta}{r + d}, \frac{A(r + d) + \mu_0\beta - \mu_0\mu}{(\mu - \beta)(r + d)})$$

Thus, an epidemic breaks out.

From the above results, we conclude that, to reach a disease free state, we need to have $\mu - \beta > \frac{A(r+d)}{\mu_0}$. To achieve this, we have to increase the removal rate of the infected cattle μ. This is attained by culling of infected cattle. Thus, we see that culling the infective population helps in controlling and eradication of the disease and the same is supported by our simulation presented in Figures 5.4 and 5.5.

Chapter 6

A Nonlinear Evolution Equation in a Banach Space

6.1 Introduction

In this work, we propose to study and analyse a general age dependent population dynamics model,

$$Dl(a,t) = G(l(a,t),Q(t)) \tag{6.1}$$

$$l(0,t) = F(l(\cdot,t),Q(t)) \tag{6.2}$$

$$D(Q(t)) = g(l(a,t),Q(t)) \tag{6.3}$$

$$l(a,0) = \phi(a) \tag{6.4}$$

$$Q(0) = Q_0. \tag{6.5}$$

Our model is a generalisation of the Webb's model [18],

$$\begin{aligned} Dl(a,t) &= G(l(a,t)) \\ l(0,t) &= F(l(\cdot,t)) \\ l(a,0) &= \phi(a). \end{aligned}$$

where G is called the aging function and F is called the birth function. $l(a,t)$ is the density of the population of age a at time t and ϕ is the initial age distribution. Webb's model is a generalisation of the Gurtin-McCamy nonlinear age dependent population dynamics model [17]. For a detailed study of Webb's model, we refer the book by Webb [18]. An excellent reference for the study of early age dependent population dynamics models is the book by Hoppensteadt [44]. The book by Akira [12] is yet another good reference for models of population dynamics which take effects of spatial diffusion into account.

In this work, we consider a nonlinear evolution equation arising in the study of an age dependent population. The existence and uniqueness of the solutions of this abstract model are proved and the semigroup property and the continuous dependence of the solutions on the initial data are obtained. Also examples of

an epidemic model and a chemostat model which are particular situations of the general model are presented.

We choose $L^1 \times \Re$ as the tractable mathematical setting for our general model. Since, for population dynamics problems, $L^1 \times \Re$ is the natural choice for a mathematical setting in that the physical interpretation of the density function requires that it should be integrable and the mathematical treatment of the problem requires that the density function belong to a complete normed linear space. Our choice of $L^1 \times \Re$ is also influenced by our intention to view age dependent population dynamics from the vantage point of view of theory of semigroup of operators in a Banach space [93]. We refer to [21, 22, 23] where the semigroup theory has been used to study general age dependent models with diffusion.

6.2 Existence and Uniqueness of Solutions

In this section, we give propositions to prove the existence and uniqueness of the solutions of our general model. To prove the above, we convert the model into an equivalent integral system of equations, thereby study the properties of the solutions for this integral system of equations.

Our general model (6.1) to (6.5) can be written as

$$\lim_{h\to 0^+} \int_0^\infty \mid h^{-1}[l(a+h,t+h) - l(a,t)] - G(l(\cdot,t),Q(t))(a) \mid da$$
$$= 0, 0 \leq t \leq T, \tag{6.6}$$

$$\lim_{h\to 0^+} h^{-1} \int_0^h \mid l(a,t+h) - F(l(\cdot,t),Q(t)) \mid da \;=\; 0, 0 \leq t \leq T, \tag{6.7}$$

$$Q'(t) \;=\; g(l(a,t),Q(t)), \tag{6.8}$$

$$l(a,0) \;=\; \phi(a), \tag{6.9}$$

$$Q(0) \;=\; Q_0. \tag{6.10}$$

The equivalent integral system of equations [18] for our general model (6.6) to (6.10) is given by

$$l(a,t) = F(l(\cdot, t-a), Q(t-a)) + \int_{t-a}^{t} G(l(\cdot,s), Q(s))(s+a-t)ds$$
$$a.e\ a \in (0,t), \tag{6.11}$$
$$l(a,t) = \phi(a-t) + \int_{0}^{t} G(l(\cdot,s), Q(s))(s+a-t)ds\ a.e\ a \in (t,\infty), \tag{6.12}$$
$$Q(t) = Q_0 + \int_{0}^{t} g(l(a,s), Q(s))ds. \tag{6.13}$$

The following are the assumptions that we have on the functions F, G *and* g.

1. F, G, g are defined as follows

$$F : L^1 \times \Re \to \Re$$
$$G : L^1 \times \Re \to L^1$$
$$g : L^1 \times \Re \to \Re$$

2. F, G, g are Lipschitz continuous functions such that the following hold:
   (i) $\exists$ an increasing function $c_1 : [0,\infty) \to [0,\infty)$ such that

$$\begin{aligned} \mid F(\Phi_1, x_1) - F(\Phi_2, x_2) \mid &\leq c_1(r) \parallel (\Phi_1, x_1) - (\Phi_2, x_2) \parallel_{L^1 \times \Re} \\ &= c_1(r)[\parallel \Phi_1 - \Phi_2 \parallel_{L^1} + \mid x_1 - x_2 \mid] \end{aligned} \tag{6.14}$$

   (ii) Similarly $\exists$ an increasing function $c_2 : [0,\infty) \to [0,\infty)$ such that

$$\begin{aligned} \parallel G(\Phi_1, x_1) - G(\Phi_2, x_2) \parallel_{L^1} &\leq c_2(r) \parallel (\Phi_1, x_1) - (\Phi_2, x_2) \parallel_{L^1 \times \Re} \\ &= c_2(r)[\parallel \Phi_1 - \Phi_2 \parallel_{L^1} + \mid x_1 - x_2 \mid] \end{aligned} \tag{6.15}$$

   (iii) Similarly $\exists$ an increasing function $c_3 : [0,\infty) \to [0,\infty)$ such that

$$\mid g(\Phi_1, x_1) - g(\Phi_2, x_2) \mid \leq c_3(r) \parallel (\Phi_1, x_1) - (\Phi_2, x_2) \parallel_{L^1 \times \Re} \tag{6.16}$$

$$= \quad c_3(r)[\ \|\ \Phi_1 - \Phi_2\ \|_{L^1} + |\ x_1 - x_2\ |\ ]$$

The following proposition proves that a solution of the integral equation (6.11) to (6.13) is also a solution of the general model (6.6) to (6.10).

Proposition 6.2.1 *Let equations (6.14) to (6.16) hold, let* $T > 0$, *let* $\phi \in L^1, Q_0 \in \Re$ *and let* $(l, Q) \in L_T$. *If* (l, Q) *is a solution of the integral equation (6.11) to (6.13) on* $[0, T]$, *then* (l, Q) *is a solution of the general model (6.6) to (6.10) on* $[0, T]$.

Proof Given that $(l, Q) \in L_T$ is a solution of the integral equation (6.11) to (6.13) on $[0, T]$ where

$$L_T = \mathcal{C}([0, T]; L^1 \times \Re)$$

and the norm on L_T is given by

$$\|\ (l, Q)\ \|_{L_T} = \sup_{0 \le t \le T} [\ \|\ (l(\cdot, t)\ \|_{L^1} + |\ Q(t)\ |\ ]$$

We have to prove that (l, Q) is a solution of the general model (6.6) to (6.10) on $[0, T]$.

We now prove (l, Q) is a solution of equation (6.6) of the general model.

Let $0 \le t < T$ and let $0 < h < T - t$

In the following equation,

$$\int_0^\infty |\ h^{-1}[l(a + h, t + h) - l(a, t)] - G(l(\cdot, t), Q(t))(a)\ |\ da$$

Substitute for $l(a + h, t + h)$ and $l(a, t)$ using equations (6.11) and (6.12).

We have $l(a+h, t+h) \ = \ F(l(\cdot, t-a), Q(t+h)) + \int_{t-a}^{t+h} G(l(\cdot, s), Q(s))(s+a-t)ds$

a.e $a \in (0, t + h)$

Similarly $l(a+h,t+h) = \phi(a-t) + \int_0^{t+h} G(l(\cdot,s),Q(s))(s+a-t)ds$

$a.e\ a \in (t+h,\infty)$

Therefore $l(a+h,t+h) - l(a,t)$ for $a \in (0,t+h)$ is

$= F(l(\cdot,t-a),Q(t+h)) + \int_{t-a}^{t+h} G(l(\cdot,s),Q(s))(s+a-t)ds$

$- F(l(\cdot,t-a),Q(t)) - \int_{t-a}^{t} G(l(\cdot,s),Q(s))(s+a-t)ds$

$= \int_t^{t+h} G(l(\cdot,s),Q(s))(s+a-t)ds\ a.e\ a \in (0,t+h)$

Similarly $l(a+h,t+h) - l(a,t)$ for $a \in (t,\infty)$ is

$= \phi(a-t) + \int_0^{t+h} G(l(\cdot,s),Q(s))(s+a-t)ds -$

$\phi(a-t) - \int_0^{t} G(l(\cdot,s),Q(s))(s+a-t)ds$

$= \int_t^{t+h} G(l(\cdot,s),Q(s))(s+a-t)ds$

Therefore

$$\begin{aligned} l(a+h,t+h) - l(a,t) &= \int_t^{t+h} G(l(\cdot,s),Q(s))(s+a-t)ds \\ &\quad a.e\ a \in (0,\infty) \end{aligned} \tag{6.17}$$

Therefore equation (6.17) becomes

$$\int_0^{\infty} \mid h^{-1} \int_t^{t+h} (G(l(\cdot,s),Q(s))(s+a-t) - G(l(\cdot,t),Q(t))(a))ds \mid da$$
$$\leq h^{-1} \int_t^{t+h} \int_0^{\infty} \mid G(l(\cdot,s),Q(s))(s+a-t) - G(l(\cdot,t),Q(t))(a) \mid da\ ds$$

Adding and subtracting $G(l(\cdot,t),Q(t))(s+a-t)$ the above becomes

$= h^{-1} \int_t^{t+h} [\int_0^{\infty} \mid G(l(\cdot,s),Q(s))(s+a-t) - G(l(\cdot,t),Q(t))(s+a-t)$

$+ G(l(\cdot,t),Q(t))(s+a-t) - G(l(\cdot,t),Q(t))(a) \mid da\ ]ds$

By triangle inequality, we get

$l(a+h,t+h) - l(a,t)$

$$\leq h^{-1}\int_t^{t+h}[\int_0^\infty \mid G(l(\cdot,s),Q(s))(s+a-t)-G(l(\cdot,t),Q(t))(s+a-t)\mid da$$
$$+\int_0^\infty \mid G(l(\cdot,t),Q(t))(s+a-t)-G(l(\cdot,t),Q(t))(a)\mid da\,]ds$$
$$\leq h^{-1}\int_t^{t+h}[\int_0^\infty c_2(r)\parallel (l(\cdot,s),Q(s))-(l(\cdot,t),Q(t))\parallel_{L^1\times\Re} da\,ds+$$
$$h^{-1}\int_t^{t+h}\int_0^\infty \mid G(l(\cdot,t),Q(t))(s+a-t)-G(l(\cdot,t),Q(t))(a)\mid da\,ds$$
$$=\ h^{-1}\int_t^{t+h}\int_0^\infty c_2(r)[\parallel l(\cdot,s)-l(\cdot,t)\parallel_{L^1}+\mid Q(s)-Q(t)\mid]da\,ds+$$

$$h^{-1}\int_t^{t+h}\int_0^\infty \mid G(l(\cdot,t),Q(t))(s+a-t)-G(l(\cdot,t),Q(t))(a)\mid da\,ds$$
$$\leq \sup_{t\leq s\leq t+h} c_2(r)(\parallel l(\cdot,s)-l(\cdot,t)\parallel_{L^1}+\mid Q(s)-Q(t)\mid)$$
$$+\sup_{t\leq s\leq t+h}\int_0^\infty \mid G(l(\cdot,t),Q(t))(s+a-t)-G(l(\cdot,t),Q(t))(a)\mid da$$

For the above expression,

as $h\to 0$, $s\to t^+$.

Thus the above expression approaches 0 by the continuity of the function

$G: L^1\times\Re\to L^1$. Therefore

$$\lim_{h\to 0^+}\int_0^\infty \mid h^{-1}[l(a+h,t+h)-l(a,t)]-G(l(\cdot,t),Q(t))(a)\mid da\ =\ 0$$

Hence we have proved that (l,Q) is a solution of equation (6.6) of the general model.

We now prove (l,Q) is a solution of equation (6.7) of the general model.

Let $0\leq t<T$ and let $0<h<T-t$

In the following,

$$h^{-1}\int_0^h \mid l(a,t+h)-F(l(\cdot,t),Q(t))\mid da,$$

substituting for $l(a,t+h)$ by replacing t with $t+h$ in (6.11) of the integral equation,

we have

$$\lim_{h\to 0^+}\int_0^\infty \mid h^{-1}[l(a+h,t+h)-l(a,t)]-G(l(\cdot,t),Q(t))(a)\mid da$$
$$= h^{-1}[\int_0^h [\mid F(l(\cdot,t+h-a),Q(t+h-a))$$
$$+\int_{t+h-a}^{t+h} G(l(\cdot,s),Q(s))(s+a-t-h)ds - F(l(\cdot,t),Q(t))\mid]da]$$

Using triangle inequality, the above becomes

$$\begin{aligned}
&\leq h^{-1}\int_0^h \mid F(l(\cdot,t+h-a),Q(t+h-a))-F(l(\cdot,t),Q(t))\mid da\\
&\quad + h^{-1}\int_0^h\int_{t+h-a}^{t+h} \mid G(l(\cdot,s),Q(s))(s+a-t-h)\mid ds\,da\\
&\stackrel{\text{def}}{=} K_1+K_2
\end{aligned}$$

Now, as $h\to 0$, $K_1\to 0$ by the continuity of the function $F: L^1\times\Re\to\Re$. Changing the order of integration in case of K_2, we get

$$K_2 = h^{-1}\int_t^{t+h}[\int_{t+h-s}^h \mid G(l(\cdot,s),Q(s))(s+a-t-h)\mid da]ds$$

Putting $s-t=h$ the above becomes

$$K_2 = h^{-1}\int_t^{t+h}[\int_0^{s-t} \mid G(l(\cdot,s),Q(s))(a)\mid da]ds$$

As $h\to 0$, and by adding and subtracting $G(l(\cdot,t),Q(t))(a)$ we get

$$\lim_{s\to t^+}\int_0^{s-t} \mid G(l(\cdot,s),Q(s))(a)\mid da$$
$$= \lim_{s\to t^+}\int_0^{s-t} \mid G(l(\cdot,s),Q(s))(a)-G(l(\cdot,t),Q(t))(a)+G(l(\cdot,t),Q(t))(a)\mid da$$

By triangle inequality,the above eq. becomes

$$\leq \lim_{s\to t^+}\int_0^{s-t} \mid G(l(\cdot,s),Q(s))(a)-G(l(\cdot,t),Q(t))(a)\mid da+$$

$$\lim_{s\to t^+}\int_0^{s-t} \mid G(l(\cdot,t),Q(t))(a) \mid da$$

$$\leq \lim_{s\to t^+} c_2(r)\int_0^{s-t} \parallel (l(\cdot,s),Q(s)) - (l(\cdot,t),Q(t)) \parallel_{L^1\times\Re} da +$$

$$\lim_{s\to t^+} c_2(r)\int_0^{s-t} \parallel (l(\cdot,t),Q(t)) \parallel_{L^1\times\Re} da$$

$$= \lim_{s\to t^+} c_2(r)\int_0^{s-t} [\parallel l(\cdot,s) - l(\cdot,t) \parallel_{L^1} + \mid Q(s) - Q(t) \mid]da +$$

$$\lim_{s\to t^+} c_2(r)\int_0^{s-t} [\parallel l(\cdot,t) \parallel_{L^1} + \mid Q(t) \mid]da$$

Now as $s \to t^+$, the above equation $\to 0$.

Therefore $K_2 \to 0$ as $h \to 0$

Hence,

$$\lim_{h\to 0^+} h^{-1}\int_0^h \mid l(a,t+h) - F(l(\cdot,t),Q(t)) \mid da \;=\; 0$$

Hence, we have proved (l,Q) is a solution of equation (6.7) of the general model.

We now prove (l,Q) is a solution of equation (6.8) of the general model.

Equation (6.13) of the integral equation is given by

$$Q(t) \;=\; Q_0 + \int_0^t g(l(a,s),Q(s))ds$$

Differentiating the above equation with respect to t, we get

$Q'(t) \;=\; g(l(a,t),Q(t))$

Hence, proved that (l,Q) is a solution of equation (6.8) of the general model.

We now prove (l,Q) is a solution of equation (6.9) of the general model.

Substitute t=0 in equation (6.13) of the integral equation .

Then,

$$Q(0) \quad = \quad Q_0 + \int_0^0 g(l(a,s),Q(s))ds$$

$$\begin{aligned} &= Q_0 + 0 \\ \Rightarrow\ Q(0) &= Q_0 \end{aligned}$$

Hence , proved that (l, Q) is a solution of equation (6.9) of the general model.

We now prove (l, Q) is a solution of equation (6.10) of the general model.
Substitute $t = 0$ in equation (6.12) of the integral equation .
Then,

$$\begin{aligned} l(a,0) &= \phi(a-0) + \int_0^0 G(l(\cdot,s), Q(s))(s+a-t)ds \\ &= \phi(a) \\ \Rightarrow l(a,0) &= \phi(a) \end{aligned}$$

Hence, proved that (l, Q) is a solution of equation (6.10) of the general model.

Thus we have proved that a solution of the integral equation (6.11) to (6.13) is also a solution of the general model (6.6) to (6.10).
In the following proposition, we prove that a unique solution to the integral equation (6.11) to (6.13) exists.

Proposition 6.2.2 *Let equations (6.14) to (6.16) hold, let $r > 0$. There exists $T > 0$ such that if $\phi \in L^1, Q_0 \in \Re$ and $\| \phi \|_{L_1} \leq r$, then there is a unique function $(l, Q) \in L_T$ such that (l, Q) is a solution of the integral equation (6.11) to (6.13) on [0,T].*

Proof Choose $T > 0$ such that
$\frac{T[c_1(2r)+c_2(2r)+2c_3(2r)+|F(0,0)|+\|G(0,0)\|_{L^1}+2|g(0,0)|]+(c_1(2r)+c_2(2r)+2c_3(2r))R+2|Q_0|}{2r} + 1/2 \leq 1$
where as t ranges from 0 *to* T, $\int_0^t \mid Q(s) \mid ds$ will be bounded by a constant R.

Let $\phi \in L^1$, such that $\| \phi \|_{L^1} \leq r$.Define

$M \stackrel{\text{def}}{=} \{(l,Q) \in L_T : l(\cdot,0) = \phi, Q(0) = Q_0 \; and \; \| (l,Q) \|_{L_T} \leq 2r\}$

Define a mapping K on M as follows:

For $(l,Q) \in M, t \in [0,T]$,

$K(l(a,t),Q(t))$

$$\stackrel{\text{def}}{=} \begin{cases} (F(l(\cdot,t-a),Q(t-a)) + \int_{t-a}^{t} G(l(\cdot,s),Q(s))(s+a-t)ds, Q_0 + \int_0^t g(l(a,s),Q(s))ds) \\ a.e \; a \in (0,t). \\ (\phi(a-t) + \int_0^t G(l(\cdot,s),Q(s))(s+a-t)ds, Q_0 + \int_0^t g(l(a,s),Q(s))ds) \\ a.e \; a \in (t,\infty). \end{cases}$$

To prove this proposition, we need to prove the following:

(i) M is a closed subset of L_T.

(ii) K maps M into M.

(iii) K is a strict contraction in M.

(i) To prove M is a closed subset of L_T.

Now, M is closed iff for a sequence $(l_n,Q_n) \in M, (l_n,Q_n) \to (l,Q) \Rightarrow (l,Q) \in M$.

Now, $(l_n,Q_n) \in M$

$\Rightarrow \; (l_n,Q_n) \in L_T \; and \; l_n(\cdot,0) = \phi \; and \; \| (l_n,Q_n) \|_{L_T} \leq 2r$

Now given that$(l_n,Q_n) \to$(l,Q)

$\Rightarrow l_n \to l \; and \; Q_n \to Q$

$\Rightarrow l_n(\cdot,0) \to l(\cdot,0)$

But $l_n(\cdot,0) = \phi$

$\Rightarrow l(\cdot,0) = \phi$

Also as, $(l_n,Q_n) \to (l,Q)$

$\Rightarrow \| (l_n,Q_n) \|_{L_T} \to \| (l,Q) \|_{L_T}$

But $\| (l_n,Q_n) \|_{L_T} \leq 2r$

$\Rightarrow \| (l,Q) \|_{L_T} \leq 2r$

Therefore we have$(l, Q) \in L_T, l(\cdot, 0) = \phi, \| (l, Q) \|_{L_T} \leq 2r$

$\Rightarrow (l, Q) \in M.$

Therefore, M is a closed subset of L_T.

(ii) To prove K maps M into M. For that, we first prove

$$\| K(l(a,t), Q(t)) \|_{L_T} \leq 2r$$

$$(i.e) \sup_{0 \leq t \leq T} [\| K' + K'' \|] \leq 2r$$

$$(i.e) \sup_{0 \leq t \leq T} [\| K' \|_{L^1} + | K'' |] \leq 2r$$

$$where\ K(l(a,t), Q(t)) = (K', K'')$$

Let $(l, Q) \in M, t \in [0, T]$. By using equations (6.14) to (6.16) and by interchanging the order of integration, we get

$$\begin{aligned}
& \int_0^\infty | K(l(a,t), Q(t)) | da \\
= & \int_0^\infty | K' | da + | K'' | \\
= & \int_0^t [| F(l(\cdot, t-a), Q(t-a)) + \int_{t-a}^t G(l(\cdot, s), Q(s))(s+a-t) ds |] da \\
& + | Q_0 + \int_0^t g(l(a,s), Q(s)) ds | + \int_t^\infty [| \phi(a-t) + \int_0^t G(l(\cdot, s), Q(s))(s+a-t) ds |] da \\
\leq & \int_0^t [| F(l(\cdot, t-a), Q(t-a)) | + \int_{t-a}^t | G(l(\cdot, s), Q(s))(s+a-t) | ds] da \\
& + \int_t^\infty [| \phi(a-t) | + \int_0^t G(l(\cdot, s), Q(s))(s+a-t) | ds] da + 2 | Q_0 | \\
& + 2 \int_0^t | g(l(a,s), Q(s)) | ds \\
\leq & \int_0^t | F(l(\cdot, s), Q(s)) | ds + \int_0^t [\int_{t-s}^t | G(l(\cdot, s), Q(s))(s+a-t) | da] ds \\
& + \int_0^\infty | \phi(a) | da + \int_0^t [\int_t^\infty | G(l(\cdot, s), Q(s))(s+a-t) | da] ds + 2 | Q_0 | \\
& + 2 \int_0^t | g(l(a,s), Q(s)) | ds \\
\leq & \int_0^t | F(l(\cdot, s), Q(s)) - F(0,0) | ds + \int_0^t | F(0,0) | ds + \| \phi \|_{L^1} \\
& + \int_0^t [\int_0^\infty | G(l(\cdot, s), Q(s))(s+a-t) | da] ds + 2 | Q_0 |
\end{aligned}$$

$$
\begin{aligned}
&+ 2\int_0^t \mid g(l(a,s),Q(s)) \mid ds \text{ (Adding and subtracting} F(0,0)) \\
\leq\ & c_1(2r)\int_0^t [\| l(\cdot,s) \|_{L^1} + \mid Q(s) \mid] ds + \int_0^t \mid F(0,0) \mid ds + r \\
&+ \int_0^t \| G(l(\cdot,s),Q(s)) \|_{L^1} ds + 2 \mid Q_0 \mid + 2\int_0^t \mid g(l(a,s),Q(s)) \mid ds \\
\leq\ & c_1(2r)\int_0^t \| l(\cdot,s) \|_{L^1} ds + c_1(2r)\int_0^t \mid Q(s) \mid ds + \int_0^t \mid F(0,0) \mid ds + r \\
&+ c_2(2r)\int_0^t [\| l(\cdot,s) \|_{L^1} ds + \mid Q(s) \mid] ds + \int_0^t \| G(0,0) \|_{L^1} ds + 2 \mid Q_0 \mid \\
&+ 2c_3(2r)\int_0^t [\| l(\cdot,s) \|_{L^1} + \mid Q(s) \mid] ds \\
&+ 2\int_0^t \mid g(0,0) \mid ds \text{ (Adding and subtracting } G(0,0), g(0,0)) \\
=\ & (c_1(2r) + c_2(2r) + 2c_3(2r))\int_0^t \| l(\cdot,s) \|_{L^1} ds + \int_0^t \mid F(0,0) \mid ds + \int_0^t \| G(0,0) \|_{L^1} ds \\
&+ 2\int_0^t \mid g(0,0) \mid ds + r + 2 \mid Q_0 \mid + (c_1(2r) + c_2(2r) + 2c_3(2r))\int_0^t \mid Q(s) \mid ds \\
\leq\ & (c_1(2r) + c_2(2r) + 2c_3(2r))\int_0^t \| l(\cdot,s) \|_{L^1} ds + \int_0^t \mid F(0,0) \mid ds + \int_0^t \| G(0,0) \|_{L^1} ds \\
&+ 2\int_0^t \mid g(0,0) \mid ds + r + 2 \mid Q_0 \mid \\
&+ (c_1(2r) + c_2(2r) + 2c_3(2r))R
\end{aligned}
$$

(As t ranges from 0 *to* T, $\int_0^t \mid Q(s) \mid ds$ will be bounded by a constant R)

$\leq \left[\frac{t(c_1(2r)+c_2(2r)+2c_3(2r)+|F(0,0)|+\|G(0,0)\|_{L^1}+2|g(0,0)|)+(c_1(2r)+c_2(2r)+2c_3(2r))R+2|Q_0|}{2r} + 1/2\right] 2r$

$\leq 2r$

where we have chosen $T > 0$ such that

$\frac{T[c_1(2r)+c_2(2r)+2c_3(2r)+|F(0,0)|+\|G(0,0)\|_{L^1}+2|g(0,0)|]+(c_1(2r)+c_2(2r)+2c_3(2r))R+2|Q_0|}{2r} + 1/2 \leq 1$

Thus, we have proved that

$\| K(l(a,t),Q(t)) \|_{L^1\times\Re} \leq 2r$

$\Rightarrow \sup_{0\leq t\leq T} \| K(l(a,t),Q(t)) \|_{L^1\times\Re} = \| K(l(a,t),Q(t)) \|_{L_T} \leq 2r$

Next, we prove the continuity of the function $K(l(\cdot,t),Q(t))$

We now prove that for $(l,Q) \in M$, the function $t \to K(l(\cdot,t),Q(t))$ is continuous from [0,T] to $L^1 \times \Re$.

Let $(l,Q) \in M$ and let $0 \le t < \hat{t} \le T$. Then,

$$
\begin{aligned}
& \| K(l(\cdot,t),Q(t)) - K(l(\cdot,\hat{t}),Q(\hat{t})) \|_{L^1\times\Re} \\
= \quad & \int_0^t [\ | F(l(\cdot,t-a),Q(t)) + \int_{t-a}^t G(l(\cdot,s),Q(s))(s+a-t)ds - F(l(\cdot,\hat{t}-a),Q(\hat{t})) \\
& - \int_{\hat{t}-a}^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds\ |\ ]da + \int_t^\infty [\ |\ \phi(a-t) \\
& + \int_0^t G(l(\cdot,s),Q(s))(s+a-t)ds - \phi(a-\hat{t}) \\
& - \int_0^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds\ |\ ]da \\
& + 2[|\ Q_0 + \int_0^t g(l(a,s),Q(s))ds - Q_0 - \int_0^{\hat{t}} g(l(a,s),Q(s))ds\ |] \\
\\
\le \quad & \int_0^t [|\ F(l(\cdot,t-a),Q(t)) + \int_{t-a}^t G(l(\cdot,s),Q(s))(s+a-t)ds - F(l(\cdot,\hat{t}-a),Q(\hat{t})) \\
& - \int_{\hat{t}-a}^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds\ |\ ]da + \int_t^\infty [\ |\ \phi(a-t) \\
& + \int_0^t G(l(\cdot,s),Q(s))(s+a-t)ds - \phi(a-\hat{t}) \\
& - \int_0^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds\ |\ ]da + 2[|\ \int_0^{t-\hat{t}} g(l(a,s),Q(s))ds\ |] \\
\\
\le \quad & \int_0^t [|\ F(l(\cdot,t-a),Q(t-a)) \\
& + \int_{t-a}^t G(l(\cdot,s),Q(s))(s+a-t)ds - F(l(\cdot,\hat{t}-a),Q(\hat{t}-a)) \\
& - \int_{\hat{t}-a}^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds\ |\ ]da + \int_t^{\hat{t}} [\ |\ \phi(a-t) \\
& + \int_0^t G(l(\cdot,s),Q(s))(s+a-t)ds \\
& - F(l(\cdot,\hat{t}-a),Q(\hat{t}-a)) - \int_{\hat{t}-a}^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds\ |\ ]da + \int_{\hat{t}}^\infty [\ |\ \phi(a-t) \\
& + \int_0^t G(l(\cdot,s),Q(s))(s+a-t)ds - \phi(a-\hat{t}) - \int_0^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds\ |\ ]da \\
& + 2[|\ \int_0^{t-\hat{t}} g(l(a,s),Q(s))ds\ |] \\
\text{(as} \quad & 2[|\ \int_0^t g(l(a,s),Q(s))ds - \int_0^{\hat{t}} g(l(a,s),Q(s))ds\ |] \\
\le \quad & 2[|\ \int_0^{t-\hat{t}} g(l(a,s),Q(s))ds\ |])
\end{aligned}
$$

$$\stackrel{\text{def}}{=} \quad J_1 + J_2 + J_3 + J_4$$

Consider J_1 first.

As $\mid t - \hat{t} \mid \to 0$, $\int_0^t [\mid F(l(\cdot, t-a), Q(t-a)) - F(l(\cdot, \hat{t}-a), Q(\hat{t}-a)) \mid]da \to 0$ by the continuity of F from $L^1 \times \Re \to \Re$ and by the continuity of $s \to l(\cdot, s), Q(s)$ from $[0, T]$ *to* $L^1 \times \Re$

Now, let $0 < \hat{t} - t < t$ *and* $0 \leq t < \hat{t} < T$.

Then,

$$\int_0^t [\mid \int_{t-a}^t G(l(\cdot, s), Q(s))(s + a - t)ds + \int_{\hat{t}-a}^{\hat{t}} G(l(\cdot, s), Q(s))(s + a - \hat{t})ds \mid]da$$

$$\begin{aligned}
\leq \quad & \int_0^{\hat{t}-t} [\int_{t-a}^t \mid G(l(\cdot, s), Q(s))(s + a - t) \mid ds + \int_{\hat{t}-a}^{\hat{t}} \mid G(l(\cdot, s), Q(s))(s + a - \hat{t}) \mid ds \,]da \\
& + \int_{\hat{t}-t}^t [\int_{t-a}^{\hat{t}-a} \mid G(l(\cdot, s), Q(s))(s + a - t) \mid ds + \int_{\hat{t}-a}^t \mid G(l(\cdot, s), Q(s))(s + a - t) \\
& - G(l(\cdot, s), Q(s))(s + a - \hat{t}) \mid ds \; + \int_t^{\hat{t}} \mid G(l(\cdot, s), Q(s))(s + a - \hat{t}) \mid ds \,]da
\end{aligned}$$

Changing the order of integration,we get

$$\begin{aligned}
= \quad & \int_{2t-\hat{t}}^t [\int_{t-s}^{\hat{t}-t} \mid G(l(\cdot, s), Q(s))(s + a - t) \mid da]ds \\
& + \int_t^{\hat{t}} [\int_{\hat{t}-s}^{\hat{t}-t} \mid G(l(\cdot, s), Q(s))(s + a - \hat{t}) \mid da]ds \\
& + \int_{2t-\hat{t}}^t [\int_{\hat{t}-t}^{\hat{t}-s} \mid G(l(\cdot, s), Q(s))(s + a - t) \mid da]ds \\
& + \int_{\hat{t}-t}^{2t-\hat{t}} [\int_{t-s}^{\hat{t}-s} \mid G(l(\cdot, s), Q(s))(s + a - t) \mid da]ds \\
& + \int_0^{\hat{t}-t} [\int_{t-s}^t \mid G(l(\cdot, s), Q(s))(s + a - t) \mid da]ds \\
& + \int_{\hat{t}-t}^t [\int_{\hat{t}-s}^t \mid G(l(\cdot, s), Q(s))(s + a - t) - G(l(\cdot, s), Q(s))(s + a - \hat{t}) \mid da]ds \\
& + \int_t^{\hat{t}} [\int_{\hat{t}-t}^t \mid G(l(\cdot, s), Q(s))(s + a - \hat{t}) \mid da]ds \\
= \quad & \int_t^{\hat{t}} [\int_{\hat{t}-s}^t \mid G(l(\cdot, s), Q(s))(s + a - \hat{t}) \mid da]ds \\
& + \int_{\hat{t}-t}^t [\int_{\hat{t}-s}^t \mid G(l(\cdot, s), Q(s))(s + a - t)
\end{aligned}$$

$$-G(l(\cdot,s),Q(s))(s+a-\hat{t}) \mid da]ds + \int_0^{\hat{t}-t}[\int_{t-s}^{t} \mid G(l(\cdot,s),Q(s))(s+a-t) \mid da]ds$$
$$+ \int_{\hat{t}-t}^{t}[\int_{t-s}^{\hat{t}-s} \mid G(l(\cdot,s),Q(s))(s+a-t) \mid da]ds$$

$$\begin{aligned}
\leq\ & \int_{\hat{t}-t}^{t}[\int_0^{\hat{t}-t} \mid G(l(\cdot,s),Q(s))(b) \mid db]ds + \int_{\hat{t}-t}^{t}[\int_{\hat{t}-t}^{s} \mid G(l(\cdot,s),Q(s))(s+a-t) \\
& -G(l(\cdot,s),Q(s))(s+a-\hat{t}) \mid da]ds + \int_0^{\hat{t}-t} \parallel G(l(\cdot,s),Q(s)) \parallel_{L^1} ds \\
& + \int_t^{\hat{t}} \parallel G(l(\cdot,s),Q(s)) \parallel_{L^1} ds \\
\stackrel{\text{def}}{=}\ & I_1 + I_2 + I_3 + I_4
\end{aligned}$$

Now, $I_3, I_4 \rightarrow 0\ as\ \mid t-\hat{t} \mid \rightarrow 0$ by the continuity of the function G from $L^1 \times \Re \rightarrow L^1$.

$I_2 \rightarrow 0\ as\ \mid t-\hat{t} \mid \rightarrow 0$ by uniform continuity of translation on the compact set.

$I_1 \rightarrow 0\ as\ \mid t-\hat{t} \mid \rightarrow 0$ since, $\int_0^{t-\hat{t}} \mid G(l(\cdot,s),Q(s))(b) \mid db \rightarrow 0$ when $\mid t-\hat{t} \mid \rightarrow 0$.

Thus $J_1 \rightarrow 0\ as\ \mid t-\hat{t} \mid \rightarrow 0$ for $0 < \hat{t}-t < t$ and when $t = 0$.

Consider J_2.

$$\begin{aligned}
J_2 =\ & \int_t^{\hat{t}}[\ \mid \phi(a-t) + \int_0^t G(l(\cdot,s),Q(s))(s+a-t)ds - F(l(\cdot,\hat{t}-a),Q(\hat{t}-a)) \\
& - \int_{\hat{t}-a}^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds \mid]da \\
\leq\ & \int_0^{\hat{t}-t} \mid \phi(a) \mid da + \int_0^{\hat{t}-t}[\int_0^t \mid G(l(\cdot,s),Q(s))(s+c) \mid ds\ ]dc + \int_0^{\hat{t}-t} \mid F(l(\cdot,s),Q(s)) \mid ds \\
& + \int_{t-\hat{t}}^{0}[\int_{-c}^{\hat{t}} \mid G(l(\cdot,s),Q(s))(s+c) \mid ds\ ]dc
\end{aligned}$$

Since, $\int_0^t \mid G(l(\cdot,s),Q(s))(s+c) \mid ds, \int_0^{\hat{t}} \mid G(l(\cdot,s),Q(s))(s+c) \mid ds,$
$\int_0^{\hat{t}-t} \mid F(l(\cdot,s),Q(s)) \mid ds$ are integrable, $\Rightarrow J_2 \rightarrow 0\ as\ \mid t-\hat{t} \mid \rightarrow 0.$

Consider J_3.

$$\begin{aligned}
J_3 =\ & \int_{\hat{t}}^{\infty}[\ \mid \phi(a-t) + \int_0^t G(l(\cdot,s),Q(s))(s+a-t)ds - \phi(a-\hat{t}) \\
& - \int_0^{\hat{t}} G(l(\cdot,s),Q(s))(s+a-\hat{t})ds \mid]da
\end{aligned}$$

$$\begin{aligned}
&\leq \int_{\hat{t}}^{\infty} \mid \phi(a-t) - \phi(a-\hat{t}) \mid da + \int_{\hat{t}}^{\infty} [\int_0^t \mid G(l(\cdot,s),Q(s))(s+a-t) \\
&\quad - G(l(\cdot,s),Q(s))(s+a-\hat{t}) \mid ds]da + \int_{\hat{t}}^{\infty} [\int_t^{\hat{t}} \mid G(l(\cdot,s),Q(s))(s+a-\hat{t}) \mid ds]da \\
&\leq \int_0^{\infty} \mid \phi(a+\hat{t}-t) - \phi(a) \mid da + \int_0^t [\int_{\hat{t}}^{\infty} \mid G(l(\cdot,s),Q(s))(s+a-t) \\
&\quad - G(l(\cdot,s),Q(s))(s+a-\hat{t}) \mid da]ds + \int_t^{\hat{t}} [\int_{\hat{t}}^{\infty} \mid G(l(\cdot,s),Q(s))(s+a-\hat{t}) \mid da]ds
\end{aligned}$$

Therefore, $J_3 \to 0 \; as \; \mid t-\hat{t} \mid \to 0$ by the continuity of G from $L^1 \times \Re \to L^1$.

Consider J_4.

$J_4 = \; 2[\mid \int_0^{t-\hat{t}} g(l(a,s),Q(s))ds \mid]$

Now $J_4 \to 0, \; as \; \mid t-\hat{t} \mid \to 0$

Thus,

$\parallel K(l(\cdot,t),Q(t)) - K(l(\cdot,\hat{t}),Q(\hat{t})) \parallel_{L^1\times\Re} \to 0.$

Therefore, for $(l,Q) \in M$, the function $t \to K(l(\cdot,t),Q(t))$ is continuous from $[0,T]$ to $L^1 \times \Re$.

Therefore, K maps M into M.

(iii) To prove K is a strict contraction in M.

$$\begin{aligned}
&\parallel K(l_1,Q_1) - K(l_2,Q_2) \parallel_{L^1\times\Re} \\
&\leq \int_0^t \mid F(l_1(\cdot,t-a),Q_1(t-a)) - F(l_2(\cdot,t-a),Q_2(t-a)) \mid da \\
&\quad + \int_0^t [\int_{t-a}^t \mid G(l_1(\cdot,s),Q_1(s))(s+a-t) - G(l_2(\cdot,s),Q_2(s))(s+a-t) \mid ds] \, da \\
&\quad + \int_t^{\infty} [\int_0^t \mid G(l_1(\cdot,s),Q_1(s))(s+a-t) - G(l_2(\cdot,s),Q_2(s))(s+a-t) \mid ds \,]da \\
&\quad + 2[\int_0^t \mid g(l_1(a,s),Q_1(s)) - g(l_2(a,s),Q_2(s)) \mid ds] \\
&\leq \int_0^t \mid F(l_1(\cdot,s),Q_1(s)) - F(l_2(\cdot,s),Q_2(s)) \mid ds + \int_0^t [\parallel G(l_1(\cdot,s),Q_1(s)) \\
&\quad - G(l_2(\cdot,s),Q_2(s)) \parallel_{L^1}]ds + 2[\int_0^t \mid g(l_1(a,s),Q_1(s)) - g(l_2(a,s),Q_2(s)) \mid ds],
\end{aligned}$$

by changing the order of integration.

Using, Lipschitz continuity of F, G, g, we have the above equation can be re-

written as

$$
\begin{aligned}
& \| K(l_1, Q_1) - K(l_2, Q_2) \|_{L^1 \times \Re} \\
\leq\ & c_1(2r) \int_0^t \| l_1(\cdot, s), Q_1(s)) - (l_2(\cdot, s), Q_2(s)) \|_{L^1 \times \Re}\, ds \\
& + c_2(2r) \int_0^t \| l_1(\cdot, s), Q_1(s)) - (l_2(\cdot, s), Q_2(s)) \|_{L^1 \times \Re}\, ds \\
& + 2c_3(2r) \int_0^t \| l_1(\cdot, s), Q_1(s)) - (l_2(\cdot, s), Q_2(s)) \|_{L^1 \times \Re}\, ds \\
=\ & (c_1(2r) + c_2(2r) + 2c_3(2r)) \int_0^t \| l_1(\cdot, s) - (l_2(\cdot, s) \|_{L^1}\, ds \\
& + (c_1(2r) + c_2(2r) + 2c_3(2r) \int_0^t \mid Q_1(s) - Q_2(s) \mid ds \\
=\ & t(c_1(2r) + c_2(2r) + 2c_3(2r))[\| l_1(\cdot, s) - (l_2(\cdot, s) \|_{L^1} + \mid Q_1(s) - Q_2(s) \mid] \\
\leq\ & 1/2[\| l_1(\cdot, s) - (l_2(\cdot, s) \|_{L^1} + \mid Q_1(s) - Q_2(s) \mid]
\end{aligned}
$$

where $0 \leq t \leq T$ and $T > 0$ such that
$\frac{T[c_1(2r)+c_2(2r)+2c_3(2r)+|F(0,0)|+\|G(0,0)\|_{L^1}+2|g(0,0)|]+(c_1(2r)+c_2(2r)+2c_3(2r))K+2|Q_0|}{2r} \leq 1/2$

Therefore,

$\| K(l_1(\cdot, t), Q_1(t)) - K(l_2(\cdot, t), Q_2(t)) \|_{L_T}$

$= \sup_{0 \leq t \leq T} 1/2[\| l_1(\cdot, s) - (l_2(\cdot, s) \|_{L^1} + \mid Q_1(s) - Q_2(s) \mid]$

$\leq 1/2 \| (l_1, Q_1) - (l_2 Q_2) \|_{L_T}$

Hence, K is a strict contraction in M and by the contraction mapping theorem [47], there is a unique fixed point $(l, Q) \in M$ such that $K(l, Q) = (l, Q)$. This unique fixed point (l, Q) *of* K *in* M is the unique solution to the integral equation (6.11) - (6.13). Hence, proved that a unique solution to the integral equation (6.11) - (6.13) exists.

6.3 Continuous Dependence of Solutions on Initial Data and Semigroup Property

In this section,we give propositions to show the dependence of the solution on the initial data and the semigroup property of the solution.

The following proposition shows that the solutions of the general model depend continuously on the initial age distributions.

Proposition 6.3.1 *Let equations (6.11) - (6.13) hold, let* $\phi, \hat{\phi} \in L^1, Q_0, \hat{Q_0} \in \Re$,*let* $T > 0$ *and let* $(l, Q), (\hat{l}, \hat{Q}) \in L_T$ *such that* $(l, Q), (\hat{l}, \hat{Q})$ *is the solution of the general model on* $[0, T]$ *for* $(\phi, Q_0), (\hat{\phi}, \hat{Q_0})$ *respectively. Let* $r > 0$ *such that* $\| (l, Q) \|_{L_T}, \| (\hat{l}, \hat{Q}) \|_{L_T} \leq r$. *Then,*

$$\begin{aligned} & \| (l(\cdot, t), Q(t)) - (\hat{l}(\cdot, t), \hat{Q}(t)) \|_{L^1 \times \Re} \\ \leq \ & \exp[(c_1(r) + c_2(r))t][\| \phi - \hat{\phi} \|_{L^1} + \mid Q_0 - \hat{Q_0} \mid] \ for \ 0 \leq t \leq T. \end{aligned} \tag{6.18}$$

Proof Let $0 \leq t \leq T$ and define

$$\begin{aligned} V(t) &= \int_0^\infty \mid l(a, t) - \hat{l}(a, t) \mid da + \mid Q(t) - \hat{Q}(t) \mid \\ &= \int_{-t}^\infty \mid l(t + c, t) - \hat{l}(t + c, t) \mid dc + \mid Q(t) - \hat{Q}(t) \mid \end{aligned}$$

For that, it is enough if we prove that

$$\limsup_{h \to 0^+} h^{-1}[V(t + h) - V(t)] \leq (c_1(r) + c_2(r))V(t) \ for \ 0 \leq t \leq T \tag{6.19}$$

since equation (6.18) follows from (6.19) [94].

For $0 < h < T - t$, we have

$$\begin{aligned} & h^{-1}[V(t + h) - V(t)] \\ = \ & h^{-1} \int_{-t-h}^{-t} \mid l(t + h + c, t + h) - \hat{l}(t + h + c, t + h) \mid dc \end{aligned}$$

$$
\begin{aligned}
&+ h^{-1}\int_{-t}^{\infty}[\mid l(t+h+c,t+h)-\hat{l}(t+h+c,t+h)\mid \\
&-\mid l(t+c,t)-\hat{l}(t+c,t)\mid]dc + h^{-1}\mid Q(t+h)-\hat{Q}(t+h)\mid \\
&- h^{-1}\mid Q(t)-\hat{Q}(t)\mid \\
\leq\ & h^{-1}\int_0^h[\mid l(a,t+h)-F(l(\cdot,t),Q(t))\mid +\mid F(l(\cdot,t),Q(t))-F(\hat{l}(\cdot,t),\hat{Q}(t))\mid \\
&+\mid F(\hat{l}(\cdot,t),\hat{Q}(t))-\hat{l}(a,t+h)\mid]da + \int_0^{\infty}[\mid h^{-1}[l(a+h,t+h)-l(a,t)] \\
&- G(l(\cdot,t),Q(t))(a)\mid +\mid G(l(\cdot,t),Q(t))(a)-G(\hat{l}(\cdot,t),\hat{Q}(t))(a)\mid \\
&+\mid h^{-1}[\hat{l}(a+h,t+h)-\hat{l}(a,t)]-G(\hat{l}(\cdot,t),\hat{Q}(t))(a)\mid]da \\
&+ h^{-1}\mid Q(t+h)-\hat{Q}(t+h)\mid -h^{-1}\mid Q(t)-\hat{Q}(t)\mid
\end{aligned}
$$

Applying $\limsup_{h\to 0^+}$ on both sides of the above inequality and using equations (6.6) and (6.7) (i.e.) the balance law and the birth law of the general model, we get

$$
\begin{aligned}
&\limsup_{h\to 0^+} h^{-1}[V(t+h)-V(t)] \\
\leq\ & \limsup_{h\to 0^+} h^{-1}[\int_0^h \mid F(l(\cdot,t),Q(t))-F(\hat{l}(\cdot,t),\hat{Q}(t))\mid da \\
&+\int_0^{\infty}\mid G(l(\cdot,t),Q(t))(a)-G(\hat{l}(\cdot,t),\hat{Q}(t))(a)\mid da] \\
=\ & \mid F(l(\cdot,t),Q(t))-F(\hat{l}(\cdot,t),\hat{Q}(t))\mid +\parallel G(l(\cdot,t),Q(t))-G(\hat{l}(\cdot,t),\hat{Q}(t))\parallel_{L^1}
\end{aligned}
$$

Using Lipschitz continuity of F and G, the above becomes

$\leq c_1(r)\parallel (l(\cdot,t),Q(t))-(\hat{l}(\cdot,t),\hat{Q}(t))\parallel_{L^1\times\Re} + c_2(r)\parallel (l(\cdot,t),Q(t))-(\hat{l}(\cdot,t),\hat{Q}(t))\parallel_{L^1\times\Re}$

$= (c_1(r)+c_2(r))\parallel (l(\cdot,t),Q(t))-(\hat{l}(\cdot,t),\hat{Q}(t))\parallel_{L^1\times\Re}$

$= (c_1(r)+c_2(r))V(t)$

Hence, we have proved equation (6.19) which implies that the solutions of the general model depend continuously on the initial age distributions.

The following proposition proves that the solutions of the integral equation (6.11) - (6.13) possess the semigroup property.

Proposition 6.3.2 *Let F, G and g be Lipschitz continuous functions so that equations (6.14) - (6.16) hold. Let* $\phi \in L^1, Q_0 \in \Re$*, let* $T > 0$ *and let* $(l, Q) \in L_T$ *such that* (l, Q) *is a solution of the integral equation (6.11) - (6.13) on* $[0, T]$*. Let* $\hat{T} > 0$*,and let* $(l, Q) \in L_{\hat{T}}$ *such that for* $t \in [0, \hat{T}]$

$$\hat{l}(a,t) = \begin{cases} F(\hat{l}(\cdot, t-a), \hat{Q}(t-a)) + \int_0^a G(\hat{l}(\cdot, s+t-a), \hat{Q}(s+t-a))(s)\, ds \text{ a.e } a \in (0,t) \\ l(a-t, T) + \int_{a-t}^a G(\hat{l}(\cdot, s+t-a), \hat{Q}(s+t-a))(s)\, ds \text{ a.e } a \in (t, \infty) \end{cases}$$

$\hat{Q}(t) = Q_0 + \int_0^{t+T} g(\hat{l}(a,s), \hat{Q}(s))ds$

Define $l(\cdot, t) = \hat{l}(\cdot, t-T)$ *and* $Q(t) = \hat{Q}(t-T)$ *for* $t \in (T, T+\hat{T}]$.

Then, $(l, Q) \in L_{T+\hat{T}}$ *and* (l, Q) *is a solution of the integral equation (6.11) - (6.13) on* $[0, T+\hat{T}]$.

Proof We are given that $(l, Q) \in L_T$ and (l, Q) is a solution of the integral equation (6.11) - (6.13) on $[0, T]$. Now, we have to prove $(l, Q) \in L_{T+\hat{T}}$ and (l, Q) is a solution of the integral equation (6.11) - (6.13) on $[0, T+\hat{T}]$. For that, it is sufficient if we prove (l, Q) is a solution of the integral equation (6.11) - (6.13) on $(T, T+\hat{T}]$.

Let $t \in (T, T+\hat{T}]$. For almost all $a \in (0, t-T)$

$$\begin{aligned} l(a,t) &= \hat{l}(a, t-T) \\ &= F(\hat{l}(\cdot, t-T-a), \hat{Q}(t-T-a)) \\ &\quad + \int_0^a G(\hat{l}(\cdot, s+t-T-a), \hat{Q}(s+t-T-a))(s)ds \\ &= F(l(\cdot, t-a), Q(t-a)) \\ &\quad + \int_0^a G(l(\cdot, s+t-a), Q(s+t-a))(s)ds \end{aligned} \tag{6.20}$$

by replacing $(\hat{l}, \hat{Q})$ by (l, Q).

For almost all $a \in (t-T, t)$

$$l(a,t) = \hat{l}(a, t-T)$$

$$
\begin{aligned}
&= l(a-t+T,T) + \int_{a-t+T}^{a} G(\hat{l}(\cdot, s+t-T-a), \hat{Q}(s+t-T-a))(s)ds \\
&= F(l(\cdot, t-a), Q(t-a)) + \int_{0}^{a-t+T} G(l(\cdot, s+t-a), Q(s+t-a))(s)ds \\
&\quad + \int_{a-t+T}^{a} G(l(\cdot, s+t-a), Q(s+t-a))(s)ds \\
&= F(l(\cdot, t-a), Q(t-a)) \\
&\quad + \int_{0}^{a} G(l(\cdot, s+t-a), Q(s+t-a))(s)ds \qquad (6.21)
\end{aligned}
$$

by substituting for $l(a-t+T,T)$ using equation (6.11) of the integral equation.

For almost all $a \in (t, \infty)$

$$
\begin{aligned}
l(a,t) &= \hat{l}(a, t-T) \\
&= l(a-t+T,T) + \int_{a-t+T}^{a} G(\hat{l}(\cdot, s+t-T-a), \hat{Q}(s+t-T-a))(s)ds \\
&= \phi(a-t) + \int_{a-t}^{a-t+T} G(l(\cdot, s+t-a), Q(s+t-a))(s)ds \\
&\quad + \int_{a-t+T}^{a} G(\hat{l}(\cdot, s+t-T-a), \hat{Q}(s+t-T-a))(s)ds \\
&= \phi(a-t) + \int_{a-t}^{a} G(l(\cdot, s+t-a), Q(s+t-a))(s)ds \qquad (6.22)
\end{aligned}
$$

by substituting for $l(a-t+T,T)$ using integral equation (6.12).

Hence using equations (6.20) - (6.22), we conclude that $(l,Q) \in L_{T+\hat{T}}$ and (l,Q) is a solution of the integral equation (6.11) and (6.12) on $[0, T+\hat{T}]$.

Next, we prove that (l,Q) is a solution of the integral equation (6.13) on $[0, T+\hat{T}]$.

Replace t by $t-T$ in the equation,

$\hat{Q}(t) = Q_0 + \int_0^{t+T} g(\hat{l}(a,s), \hat{Q}(s))ds$

and then replace $\hat{l}$ by l and $\hat{Q}$ by Q.

Then,

$Q(t) = \hat{Q}(t-T) = Q_0 + \int_0^t g(l(a,s), Q(s))ds$

Thus, (l,Q) is a solution of the integral equation (6.13) on $[0, T+\hat{T}]$.

Hence, we have proved that $(l,Q) \in L_{T+\hat{T}}$ and (l,Q) is a solution of the integral equation (6.11) - (6.13) on $[0, T+\hat{T}]$.

Thus from propositions 6.2.1, 6.2.2, 6.3.1, 6.3.2, we conclude that our general model (6.1) - (6.5) has a unique solution and this solution depends continuously on the initial age distributions and has the semigroup property.
In the following two sections, we give examples which are particular cases of our abstract nonlinear evolution equation (6.1) - (6.5).

6.4 Example 1 : Age Dependent Epidemic Model

In this section, we give an example of an age dependent epidemic model that fits into our abstract situation.

6.4.1 Introduction

In many diseases, the chronological age of the individual is an important factor in assessing their vulnerability and infectiousness. A variety of age dependent models have been discussed in [44]. Dietz 1982 proposed such a model for river blindness (onchocersiasis) and used it to compare various possible control strategies. Age may also be interpreted as the time from entry into a particular population class such as the susceptibles, infectives or the removed group in a basic SIR model. The two interpretations of age are often the same. Age-structured epidemiology models with either continuous age or age groups are essential for the incorporation of age-related mixing behavior, fertility rates, and death rates, for the estimation of the basic reproduction ratio from age-specific data, and for the comparison of vaccination strategies with age-specific risk groups and age-dependent vaccination rates. Indeed, some of the early epidemiology models incorporated continuous age structure [34]. Modern mathematical analysis of age-structured models appears to have started with Hoppensteadt [44], who formulated epidemiology models with both continuous chronological age and infection class age (time since infection), showed that they were well posed, and found threshold conditions for endemic-

ity. In age-structured epidemiology models, proportionate and preferred mixing parameters can be estimated from age-specific force of infection data [95]. Mathematical aspects such as existence and uniqueness of solutions, steady states, stability, and thresholds have now been analysed for many epidemiology models with age structure.

There are numerous papers on age dependent epidemic models in the literature; They are the following: There have been studies on SIS and SIR models with continuous age structure including vertical transmission [96, 97, 98], age-dependent disease transmission [42, 99, 100, 101], infection class age, cross immunity, inter-cohort transmission [102], short infectious period [103], and optimal vaccination patterns [104].

Age-structured models have been used in the epidemiology modeling of many diseases [38]. Dietz [42], Hethcote, Anderson and May [105], and Rouderfer, Becker, and Hethcote [106] used continuous age-structured models for the evaluation of measles and rubella vaccination strategies. Tudor [192] found threshold conditions for a measles model with age groups. Hethcote [106] considered optimal ages of vaccination for measles on three continents. Halloran et al., Ferguson, Anderson, and Garnett, and Schuette and Hethcote [31, 107] used age-structured models to study the effects of chickenpox vaccination programs. Grenfell and Anderson and Hethcote [31] have used age-structured models in evaluating pertussis vaccination programs. Irregular and biennial oscillations of measles incidences have led to various mathematical analyses some of which involve age structure. Ferguson, Nokes, and Anderson proposed finely age-stratified models with stochastic fluctuations that can shift the dynamics between biennial and triennial cycle attractors. Earn et al. [31] proposed a simple, time-forced SEIR model with slow variation in the average rate of recruitment of new susceptibles. In recent years HIV, which leads to AIDS, has emerged as an important new infectious disease. Many age-structured models have been developed for HIV/AIDS. Bongaarts and May, Anderson, and

McLean [31] used models with age structure to examine the demographic effects of AIDS in African countries.

6.4.2 The model

In this subsection, we describe the age dependent epidemic model which fits into our abstract situation. We consider a population that is divided into two classes: Susceptibles S and Infectives I. Susceptibles are individuals of the population, who can catch the disease. Infectives are people who already have the disease and can infect others. $S(t)$ denotes the number of susceptibles and $I(a,t)$ denotes the number of infectives. The assumption is that the number of susceptibles depend only on time t whereas the number of infectives depend on a as well as t. Here, a is the time that has lapsed after susceptibles have entered the infective class.(i.e) it is the age from exposure to the disease. In this epidemic model, we start with an initial number of susceptibles and an initial number of infectives. The assumption is that, once infected, individuals from susceptible class move on to the infective class. A is a positive constant and is the inflow of individuals per time into the population due to births or immigration. μ_o is a positive constant and denotes the death rate due to natural causes and not due to infection.

Then, the rate of change of susceptibles is given by

$$\frac{dS}{dt} \;=\; A \;-\; \mu_o S \;-\; S\int_0^\infty k(a)I(a,t)da$$

where $k(a)$ denotes the measure of infectiousness of the infectives . The last term on the right hand side in the above equation gives the removal rate of the susceptibles due to exposure from the infection.

By law of conservation, the change in the number of infectives is equal to the number of infectives removed.(i.e) mortality due to the infection. Therefore, if

$\mu(a)$ denotes the death rate due to infection, then

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -\mu(a)I(a,t)$$

If $I(0,t)$ is the number of new individuals who enter the infective class, then

$$I(0,t) = S\int_0^\infty k(a)I(a,t)da$$

where the right hand side denotes the number of persons removed from the susceptible class due to infection.

$$S(0) = S_0 \text{ and } I(a,0) = I_0(a)$$

denote the initial number of susceptibles and the initial number of infectives respectively.

The functions $k(a),\ \mu(a)$ are nonnegative, bounded functions and depend on the age of infection a.

Thus, the model is given by

$$\begin{aligned}
&\tfrac{dS}{dt} = A - \mu_o S - S\textstyle\int_0^\infty k(a)I(a,t)da\\
&\tfrac{\partial I}{\partial t} + \tfrac{\partial I}{\partial a} = -\mu(a)I(a,t)\\
&I(0,t) = S\textstyle\int_0^\infty k(a)I(a,t)da\\
&S(0) = S_0\\
&I(a,0) = I_0(a)
\end{aligned}$$

6.4.3 Analysis of the age dependent epidemic model

In this section, we show that the age dependent epidemic model is a particular case of the general nonlinear model and conclude the existence, uniqueness, continuous dependence of the solution on the initial age distributions and the semigroup property of the solution of the age dependent epidemic model.

Table 6.1: **Parameters of the age dependent epidemic model**

Parameters	Description
A	Inflow of individuals per time into the population due to births or immigration.
μ_o	Death rate due to natural causes and not due to infection.
$k(a)$	Measure of infectiousness of the infectives
$\mu(a)$	Death rate due to infection

Comparing the age dependent epidemic model with the general model (6.1) - (6.5), we get

$$\begin{aligned} F(\Phi, x) &= x \int_0^\infty k(a)\Phi(a)da \\ G(\Phi, x) &= -\mu(a)\Phi \\ g(\Phi, x) &= A - \mu_o x - x \int_0^\infty k(a)\Phi(a)da \end{aligned}$$

where F, G, g are defined from

$$\begin{aligned} F &: L^1 \times \Re \to \Re \\ G &: L^1 \times \Re \to L^1 \\ g &: L^1 \times \Re \to \Re \end{aligned}$$

Our aim now is to prove the wellposedness and the semigroup property of this model using the results from sections 6.2 and 6.3.

Proposition 6.4.1 *Let F be defined as $F : L^1 \times \Re \to \Re$ and $F(\Phi, x) = x \int_0^\infty k(a)\Phi(a)da$. Let $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$ for $\Phi \in L^1$ and $x \in \Re$. Then, F is Lipschitz continuous (i.e) F satisfies equation (6.14).*

Proof $| F(\Phi_1, x_1) - F(\Phi_2, x_2) | = | x_1 \int_0^\infty k(a)\Phi_1(a)da - x_2 \int_0^\infty k(a)\Phi_2(a)da |$

Adding and subtracting $x_2 \int_0^\infty k(a)\Phi_1(a)da$ and using triangle inequality, the above equation can be written as

$| F(\Phi_1, x_1) - F(\Phi_2, x_2) |$

$\leq | x_1 - x_2 | \int_0^\infty | k(a) | | \Phi_1(a) | da + | x_2 | \int_0^\infty | k(a) | | \Phi_1(a) - \Phi_2(a) | da$

Assuming that $k(a)$ is bounded by a positive constant M_1, the above equation can be written as

$| F(\Phi_1, x_1) - F(\Phi_2, x_2) |$

$\leq M_1 | x_1 - x_2 | \| \Phi \|_{L^1} + M_1 | x_2 | \| \Phi_1 - \Phi_2 \|_{L^1}$

Since, $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$, we get

$| F(\Phi_1, x_1) - F(\Phi_2, x_2) |$

$\leq rM_1 | x_1 - x_2 | + rM_1 \| \Phi_1 - \Phi_2 \|_{L^1}$

$= c_1(r)[| x_1 - x_2 | + \| \Phi_1 - \Phi_2 \|_{L^1}]$

where $c_1(r) = rM_1$

Therefore, we have proved that F is Lipschitz continuous.

Proposition 6.4.2 *Let G be defined as* $G : L^1 \times \Re \to L^1$ *and* $G(\Phi, x) = -\mu(a)\Phi$. *Let* $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$ *for* $\Phi \in L^1$ *and* $x \in \Re$. *Then, G is Lipschitz continuous (i.e) G satisfies equation (6.15).*

Proof $\| G(\Phi_1, x_1) - G(\Phi_2, x_2) \|_{L^1} = \int_0^\infty | G(\Phi_1, x_1) - G(\Phi_2, x_2) | da$

$= \int_0^\infty | \mu(a) | | \Phi_1 - \Phi_2 | da$

Assuming that the mortality rate $\mu(a)$ is bounded by a positive constant M_2, the above becomes

$\| G(\Phi_1, x_1) - G(\Phi_2, x_2) \|_{L^1}$

$\leq M_2 \int_0^\infty | \Phi_1 - \Phi_2 | da$

$\leq M_2 | x_1 | \int_0^\infty | \Phi_1 - \Phi_2 | da + M_2 | x_1 | | x_1 - x_2 |$

Since, $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$, we have the above to be

$\| G(\Phi_1, x_1) - G(\Phi_2, x_2) \|_{L^1}$

$\leq M_2 r[\| \Phi_1 - \Phi_2 \|_{L^1} + | x_1 - x_2 |]$

where $c_2(r) = rM_2$

Hence, G is Lipschitz continuous.

Proposition 6.4.3 *Let g be defined as* $g : L^1 \times \Re \to \Re$ *and* $g(\Phi, x) = A - \mu_o x - x \int_0^\infty k(a)\Phi(a)da$. *Let* $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$ *for* $\Phi \in L^1$ *and* $x \in \Re$. *Then, g is Lipschitz continuous (i.e) g satisfies equation (6.16).*

Proof

$$\begin{aligned} \mid g(\Phi_1, x_1) - g(\Phi_2, x_2) \mid &= \mid A - \mu_o x_1 - x_1 \int_0^\infty k(a)\Phi_1(a)da - A + \mu_o x_2 + \\ &\quad x_2 \int_0^\infty k(a)\Phi_2(a)da \mid \end{aligned}$$

$=\mid -\mu_o(x_1 - x_2) - x_1 \int_0^\infty k(a)\Phi_1(a)da + x_2 \int_0^\infty k(a)\Phi_2(a)da \mid$

Adding and subtracting $x_2 \int_0^\infty k(a)\Phi_1(a)da$ and using triangle inequality, the above becomes

$\mid g(\Phi_1, x_1) - g(\Phi_2, x_2) \mid$

$\leq [\mid \mu_o \mid + \int_0^\infty \mid k(a) \mid\mid \Phi_1(a) \mid da] \mid x_1 - x_2 \mid +$

$\mid x_2 \mid \int_0^\infty \mid k(a) \mid\mid \Phi_1(a) - \Phi_2(a) \mid da$

Since $k(a)$ is bounded, the above becomes,

$\mid g(\Phi_1, x_1) - g(\Phi_2, x_2) \mid$

$\leq (\mid \mu_o \mid + M_1 \parallel \Phi_1 \parallel_{L^1}) \mid x_1 - x_2 \mid + \mid x_2 \mid M_1 \parallel \Phi_1 - \Phi_2 \parallel_{L^1} + \mid \mu_o \mid \parallel \Phi_1 - \Phi_2 \parallel_{L^1}$

Since, $\parallel (\Phi, x) \parallel_{L^1 \times \Re} \leq r$, we have the above to be

$\mid g(\Phi_1, x_1) - g(\Phi_2, x_2) \mid$

$\leq (\mid \mu_o \mid + M_1 r)(\parallel \Phi_1 - \Phi_2 \parallel_{L^1} + \mid x_1 - x_2 \mid)$

where $c_3(r) = \mid \mu_o \mid + M_1 r$. Hence, proved that g is Lipschitz continuous.

Since, F, G, g are Lipschitz continuous, it follows from propositions 6.2.1, 6.2.2, 6.3.1, 6.3.2 that the age dependent epidemic model has a unique solution and this solution depends continuously on the initial age distributions and has the semigroup property.

6.5 Example 2: Microbial Growth in a Chemostat

In this section, we give a model of microbial growth in a chemostat which fits into our abstract model.

6.5.1 Introduction

A chemostat is a continuous culture device used in microbiology for growing and harvesting microbes. It consists of two primary parts: a nutrient reservoir and a growth chamber. It can keep a bacterial culture growing at a reduced growth rate over an indefinite time period. Growth of the culture is controlled by the concentration of the limiting nutrient. The limiting nutrient is a essential growth factor necessary for bacterial growth, but present in the lowest concentration in the growth media.

Chemostats allow the growth rate and yield to be controlled independently. The most important feature of a chemostat is that all fermentation parameters; growth chamber volume, dissolved oxygen, nutrient concentrations, pH, cell density, etc, are vital in controlling yield. The chemostat can be viewed as a laboratory idealization of a natural lake system and is useful for studying the growth and interaction of microorganisms limited by the short supply of some nutrient or nutrients.

In the basic set up, the culture vessel is assumed to be well stirred. One or more populations of microorganisms grow and/or compete for a single, growth-limiting nutrient that is supplied at a constant rate. The contents of the culture vessel are removed at the same constant rate as the medium containing the nutrient is supplied, and thus the volume of the culture vessel remains constant. Figure 6.1 gives a schematic representation of the chemostat.

There is lot of literature which deal with the growth of microorganisms in the chemostat. Most originate from bioengineering and microbiology, where the chemostat finds a wide variety of applications, from theoretical studies of bacteria to the use of bacteria in biological waste decomposition and water purification [108, 109]. As well as being an experimental system that generates reproducible results, it has been modeled extensively with good success.

Also, from previous work, it is found that although approaches and applications are varied, most of the models rely on a simple relationship between two fun-

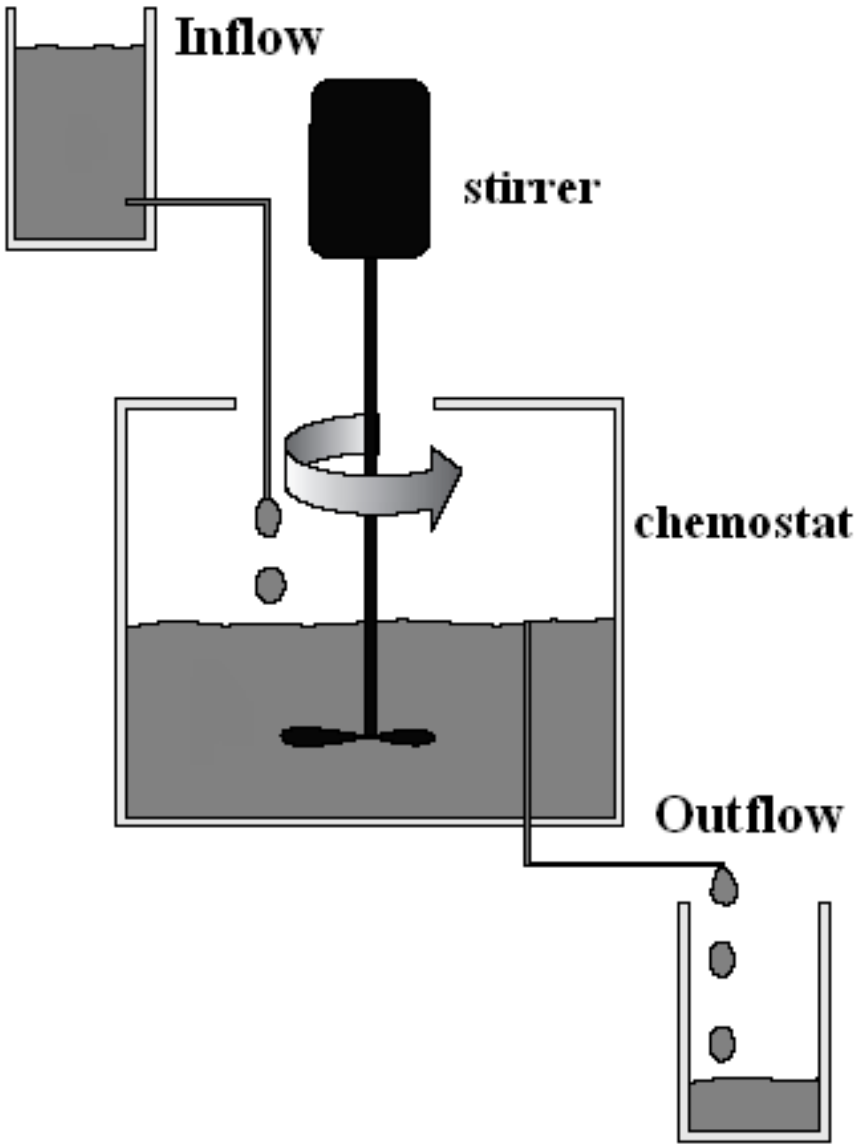

Figure 6.1: **Schematic representation of a chemostat**

damental processes, nutrient uptake and cellular growth. In particular, in most models these processes are assumed to be proportional. The constant of proportionality is referred to as the growth yield constant or yield constant. The notion of yield dates from the beginning of continuous bacterial culture, and is for example defined by Monod [110] as the ratio K of the amount of bacterial substance formed per amount of limiting nutrient utilized. In most of the early models of microbial growth in the chemostat, besides assuming constant yield, it was assumed that growth was a monotone increasing function of substrate concentration. However, for some organisms, high concentrations of substrate can be detrimental, as mentioned in [111]. In [112], there is a detailed description of the mechanisms involved. Inhibition was subsequently incorporated into models of bacterial growth [113, 114]. Attempting to fit experimental data, many authors have used different functional forms to model inhibition [115, 116, 117]. Under the assumption of constant yield, mathematical models predict that there can be no sustained oscillations [118, 119, 120, 121]. In the case of chemical reactors, the yield is obtained from mass balance equations. For biological reactors, it is more complicated [122] gives a review of various thermodynamical models. In subsequent work on the subject, [123, 124, 125] assume that growth and uptake are related through a linear function of the substrate concentration. In [126, 127, 128], linear and nonlinear functions modeling yield are considered and conditions are derived for the existence of a Hopf bifurcation. In this work, a mathematical model of growth of microorganisms in the chemostat is considered and analysed. The model is a system consisting of an integro differential equation and a partial differential equation. We prove the existence, uniqueness, the semigroup property and the continuous dependence of the solutions on the initial data for the model.

6.5.2 The model

In this section, we describe the model of growth of microorganisms in a chemostat. Consider a population of cells contained in some perfectly stirred tank of volume V. Fresh medium containing substrate essential for maintenance and growth is supplied at a constant rate Q. At the same rate medium containing both cells and unused substrate is removed from the tank. The population in the tank is called a continuous culture. The ratio $D = Q/V$ is called the dilution rate, and is a control variable of the process. We assume that the environmental influence on the behaviour of individual cells is fully described by the availability of one particular compound of the medium called the limiting substrate or limiting nutrient. Let $s(t)$ be the concentration of the limiting substrate also called limiting nutrient at time t. s_{in} denotes the constant input substrate concentration. Let $n(a,t)$ be the population of microorganisms of age a at time t where a is the chronological age of the microorganism. We assume that the cells divide into two new cells of age zero. $\beta(a)$ is the mitosis rate of the microorganism of age a. Then, the rate of change of the limiting substrate is given by

$$\frac{ds}{dt} = D(s_{in} - s(t)) - 2s\int_0^\infty \beta(a)n(a,t)da$$

Let $\mu(a)$ be the death rate of the microorganism of age a. Then, the rate of change of the population of the micro organisms is given by

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -(\mu(a) + \beta(a) + D)n(a,t)$$

If $n(0,t)$ is the number of microorganisms of age 0 called the renewal condition, then

$$n(0,t) = 2s\int_0^\infty \beta(a)n(a,t)da$$

Table 6.2: **Parameters of the chemostat model**

Parameters	Description
D	Dilution rate
s_{in}	Constant input substrate concentration
$\beta(a)$	Mitosis rate of the microorganism of age a
$\mu(a)$	Death rate of the microorganism of age a.

$$s(0) \;=\; s_0 \; and \; n(a,0) \;=\; n_0(a)$$

denote the initial concentration of the substrate and the initial population of the micro organisms respectively.

The functions $\beta(a),\ \mu(a)$ are nonnegative, bounded functions and depend on the age of the cell a.

Thus, the model is given by

$$\begin{aligned}
\frac{ds}{dt} &= D(s_{in} - s(t)) - 2s\int_0^\infty \beta(a)n(a,t)da \\
\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} &= -(\mu(a) + \beta(a) + D)n(a,t) \\
n(0,t) &= 2s\int_0^\infty \beta(a)n(a,t)da \\
s(0) &= s_0 \\
n(a,0) &= n_0(a)
\end{aligned}$$

6.5.3 Analysis of the Chemostat model

In this section, we show that the chemostat model is a particular case of the general nonlinear model and conclude the existence, uniqueness, continuous dependence of the solution on the initial age distributions and the semigroup property of the solution of the model.

Comparing the chemostat model with the general nonlinear model, we get

$$\begin{aligned} F(\Phi, x) &= 2x \int_0^\infty \beta(a)\Phi(a)da \\ G(\Phi, x) &= -(\mu(a) + \beta(a) + D)\Phi \\ g(\Phi, x) &= Ds_{in} - Dx - 2x \int_0^\infty \beta(a)\Phi(a)da \end{aligned}$$

for $\Phi \in L^1$ and $x \in \Re$ where F, G, g are defined by

$$\begin{aligned} F &: L^1 \times \Re \to \Re, \\ G &: L^1 \times \Re \to L^1, \\ g &: L^1 \times \Re \to \Re. \end{aligned}$$

Our aim now is to prove the wellposedness and the semigroup property of this model using the results from sections 6.2 and 6.3.

Proposition 6.5.1 *Let F be defined as* $F : L^1 \times \Re \to \Re$ *and* $F(\Phi, x) = 2x \int_0^\infty \beta(a)\Phi(a)da$. *Let* $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$ *for* $\Phi \in L^1$ *and* $x \in \Re$. *Then, F is Lipschitz continuous (i.e) F satisfies equation (6.14).*

Proof $| F(\Phi_1, x_1) - F(\Phi_2, x_2) | = | 2x_1 \int_0^\infty \beta(a)\Phi_1(a)da - 2x_2 \int_0^\infty \beta(a)\Phi_2(a)da |$

Adding and subtracting $2x_2 \int_0^\infty \beta(a)\Phi_1(a)da$ and using triangle inequality, the above becomes

$| F(\Phi_1, x_1) - F(\Phi_2, x_2) |$

$\leq 2 | x_1 - x_2 | \int_0^\infty | \beta(a) | | \Phi_1(a) | da + 2 | x_2 | \int_0^\infty | \beta(a) | | \Phi_1(a) - \Phi_2(a) | da$

Assuming that $\beta(a)$ is bounded by a positive constant M_1, the above becomes

$| F(\Phi_1, x_1) - F(\Phi_2, x_2) |$

$\leq 2M_1 | x_1 - x_2 | \| \Phi \|_{L^1} + 2M_1 | x_2 | \| \Phi_1 - \Phi_2 \|_{L^1}$

Since, $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$, we get

$| F(\Phi_1, x_1) - F(\Phi_2, x_2) |$

$\leq 2rM_1 | x_1 - x_2 | + 2rM_1 \| \Phi_1 - \Phi_2 \|_{L^1}$

$= c_1(r)[| x_1 - x_2 | + \| \Phi_1 - \Phi_2 \|_{L^1}]$

where $c_1(r) = 2rM_1$

Therefore, we have proved that F is Lipschitz continuous.

Proposition 6.5.2 *Let G be defined as $G : L^1 \times \Re \to L^1$ and $G(\Phi, x) = -(\mu(a) + \beta(a) + D)\Phi$. Let $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$ for $\Phi \in L^1$ and $x \in \Re$. Then, G is Lipschitz continuous (i.e) G satisfies equation (6.15).*

Proof $\| G(\Phi_1, x_1) - G(\Phi_2, x_2) \|_{L^1} = \int_0^\infty | G(\Phi_1, x_1) - G(\Phi_2, x_2) | da$

$= \int_0^\infty | \mu(a) + \beta(a) + D | | \Phi_1 - \Phi_2 | da$

Assuming that the death rate $\mu(a)$ is bounded by a positive constant M_2, the above becomes

$\| G(\Phi_1, x_1) - G(\Phi_2, x_2) \|_{L^1}$

$\leq (M_1 + M_2 + D) \int_0^\infty | \Phi_1 - \Phi_2 | da$

$\leq (M_1 + M_2 + D)[\int_0^\infty | \Phi_1 - \Phi_2 | da + | x_1 - x_2 |]$

$\leq (M_1 + M_2 + D) | x_1 | [\int_0^\infty | \Phi_1 - \Phi_2 | da + | x_1 - x_2 |]$

Since, $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$, we have the above to be

$\| G(\Phi_1, x_1) - G(\Phi_2, x_2) \|_{L^1}$

$\leq r(M_1 + M_2 + D)[\| \Phi_1 - \Phi_2 \|_{L^1} + | x_1 - x_2 |]$

where $c_2(r) = r(M_1 + M_2 + D)$

Hence, G is Lipschitz continuous.

Proposition 6.5.3 *Let g be defined as $g : L^1 \times \Re \to \Re$ and $g(\Phi, x) = Ds_{in} - Dx - 2x \int_0^\infty \beta(a)\Phi(a)da$. Let $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$ for $\Phi \in L^1$ and $x \in \Re$. Then, g is Lipschitz continuous (i.e) g satisfies equation (6.16).*

Proof

$$| g(\Phi_1, x_1) - g(\Phi_2, x_2) | = | Ds_{in} - Dx_1 - 2x_1 \int_0^\infty \beta(a)\Phi_1(a)da - Ds_{in} + Dx_2 + 2x_2 \int_0^\infty \beta(a)\Phi_2(a)da |$$

$=| -D(x_1 - x_2) - 2x_1 \int_0^\infty \beta(a)\Phi_1(a)da + 2x_2 \int_0^\infty \beta(a)\Phi_2(a)da |$

Adding and subtracting $2x_2 \int_0^\infty \beta(a)\Phi_1(a)da$ and using triangle inequality, the above becomes

$| g(\Phi_1, x_1) - g(\Phi_2, x_2) |$

$\leq [| D | + 2 \int_0^\infty | \beta(a) || \Phi_1(a) | da] | x_1 - x_2 | +$

$2 | x_2 | \int_0^\infty | \beta(a) || \Phi_1(a) - \Phi_2(a) | da$

Since $\beta(a)$ is bounded, we have,

$| g(\Phi_1, x_1) - g(\Phi_2, x_2) |$

$\leq (| D | + 2M_1 \| \Phi \|_{L^1}) | x_1 - x_2 | + 2 | x_2 | M_1 \| \Phi_1 - \Phi_2 \|_{L^1}$

$\leq (| D | + 2M_1 \| \Phi \|_{L^1}) | x_1 - x_2 | + 2 | x_2 | M_1 \| \Phi_1 - \Phi_2 \|_{L^1} + | D | \| \Phi_1 - \Phi_2 \|_{L^1}$

Since, $\| (\Phi, x) \|_{L^1 \times \Re} \leq r$, we have the above to be

$| g(\Phi_1, x_1) - g(\Phi_2, x_2) |$

$\leq (| D | + 2M_1 r)(\| \Phi_1 - \Phi_2 \|_{L^1} + | x_1 - x_2 |)$

where $c_3(r) = | D | + 2M_1 r$.

Hence, proved that g is Lipschitz continuous.

Since, F, G, g are Lipschitz continuous, it follows from propositions 6.2.1, 6.2.2, 6.3.1, 6.3.2 that the chemostat model has a unique solution and this solution depends continuously on the initial age distributions and has the semigroup property.

6.6 Conclusions

In this work, we studied a nonlinear evolution equation arising in an age dependent population. The existence and uniqueness of the solutions of this abstract model were proved and the semigroup property and the continuous dependence of the solutions on the initial data obtained. Also examples were provided of an epidemic model and a chemostat model which were shown as particular situations of the general model. In many epidemic models, the chronological age of the individual is an important factor. In the epidemic model, the wellposedness of the age dependent model was proved.

In the second example, a new model for growth of microorganisms in a chemostat was proposed. The model, a system consisting of an integro differential equation

and a partial differential equation was shown to be another particular situation of the general non linear model. It was shown that the chemostat model had a unique solution and this solution depended continuously on the initial age distributions and had the semigroup property.

Chapter 7

Conclusions

In this work, mathematical models arising in population dynamics and epidemiology were studied. Biological situations such as age dependent epidemic, microbial growth in a chemostat, prion proliferation in the presence of a chaperone, spread of the SARS virus and the transmission dynamics of *Neospora caninum* infection in cattle were identified and studied/modeled. The results of the study were found to have biological significance providing solutions such as control, eradication of the disease, designing of vaccination strategies etc. Chapters one and two give the introduction and mathematical preliminaries respectively.

In chapter three, the replication of prions by nucleated polymerization under the effects of a chaperone was modeled. According to this model, the biological processes of coagulation, splitting and the inhibitory effects of the chaperone can be described by a coupled system consisting of ordinary differential equations and a partial differential equation. The model was converted into a system of ordinary differential equations and the stability of the steady states were studied. It was shown that the steady state solutions of the model are locally asymptotically stable. In the absence of the chaperone, the conditions for the threshold of the disease were found out using the basic reproduction number. Numerical simulations on the model were performed and it was shown that a disease free state could be achieved in the presence of a chaperone. The duration of the disease free state was found to increase with the amount of chaperone and this amount of chaperone was computed from the model.

In chapter four, the propagation of the SARS epidemic using the double epidemic hypothesis was modeled. The model, a system of ordinary differential equations was studied and the conditions for the stability of the disease free state and the one disease state were drawn. The conditions for the control of the infection caused by virus A which is the SARS virus were determined from the model. Thus, the milder infection caused by virus B was shown to act like a vaccine against the

SARS virus. These studies will help in developing a vaccination strategy to fight the SARS epidemic.

In chapter five, the transmission of *N.caninum* infection among cattle was modeled through a system of ordinary differential equations and the conditions for the stability of the steady states were drawn. The threshold of the disease were found out through the basic reproduction number. Numerical simulations were performed on the model, and it was shown that by increasing the removal rate of the cattle, the disease could be controlled. It was found that this could be achieved by culling of infected cattle. Thus, it was established that culling the infective population helps in controlling and eradication of the disease.

In chapter six, a non-linear evolution equation in a Banach space was formulated and studied. The model was studied in an abstract space and the space $L^1 \times \Re$ was chosen as the tractable mathematical setting for the general model. The existence, uniqueness, continuous dependence of the solutions on the initial data and the semigroup property of the solutions of the general model were established. Also, two examples, an age dependent epidemic model and an age dependent chemostat model were presented as particular cases of the general model.

In many epidemic models, the chronological age of the individual is an important factor. In this example, the wellposedness of the age dependent SI model was proved.

As a second example, a new model for growth of microorganisms in a chemostat was proposed. The model, a system consisting of an integro differential equation and a partial differential equation was shown to be another particular situation of the general non linear model. It was shown that the chemostat model has a unique solution and this solution depends continuously on the initial age distributions and has the semigroup property.

Scope for further studies

The results of the above studies will help in analysing the spread and control of

infectious diseases. These mathematical models will help in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases. The geographical spread of epidemics and dispersion of populations is very important in most of the real life situations and incorporating these give further understanding of the of the dynamics of population and diseases. These suggest formulation of new mathematical models which includes the diffusion of populations.

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Appendix

List of Publications and Presentations

Publications

1 Padma Murali and Rajiv Kumar, Modeling and analysis of prion dynamics in the presence of a chaperone, Mathematical Biosciences, Vol:213, pp 50 - 55, 2008.

2 Padma Murali and Rajiv Kumar, Modeling and Analysis of *Neospora caninum* infection in Cattle, Advances in Theoretical and Applied Mathematics, 2008 (in press)

3 Padma Murali and Rajiv Kumar, Semigroup Solution of a General Nonlinear Model in a Banach Space (communicated)

4 Padma Murali and Rajiv Kumar, A mathematical model of the spread of the SARS epidemic using the double epidemic hypothesis (communicated)

5 Padma Murali and Rajiv Kumar, A Mathematical model of microbial growth in a chemostat (communicated)

Paper Presentations

1 Padma Murali and Rajiv Kumar, Semigroup Solution of a General Nonlinear Model in a Banach Space, at Second International Conference on Nonlinear Systems : Modeling, Analysis and Simulation, Dec. 19 - 22, 2006, Nanded, Maharashtra

2 Padma Murali and Rajiv Kumar, Modeling and analysis of prion dynamics in the presence of a chaperone, at National Symposium on Mathematical Methods and Applications, Dec. 22, 2007, IIT Madras, Tamilnadu,

Biography of Padma B

Mrs. Padma B. has completed her Bachelor of Science (B. Sc) from University of Madras in the year 1995 and Master of Science (M. Sc) from Annamalai University in 2001. She joined BITS, Pilani in the year 2003 as a research scholar in Mathematics Group and completed M.Phil as partial fulfillments of the doctoral program. She has presented papers in conferences and her research articles have been accepted for publication in international peer reviewed journals. She is currently working as a faculty in Mathematics Group, BITS, Pilani.

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Prof. Rajiv Kumar is an Associate Professor of Mathematics at BITS, Pilani. He completed his Bachelor of Science (B. Sc)from Kanpur University in the year 1980 and Master of Science (M. Sc) in 1983 and Ph.D. in 1989 both from IIT, Kanpur. Prof. Rajiv Kumar was Research Associate in IIT Kanpur during the period 1988-89 and also completed Post Doctoral research from TIFR Bangalore and IIT Kanpur in 1992. He has more than 20 years of teaching and research experience and has supervised several postgraduate and undergraduate students. He has published several research articles in renowned journals and presented papers, delivered lectures in several national and international conferences. Prof. Rajiv Kumar has handled several math courses at BITS Pilani and is actively involved in graduate course development. He is also expert member for many committees such as faculty recruitment, research board, senate etc. and life member of Indian society of industrial and applied Mathematics. His research interests are Differential Equations, Dynamical Systems, Nonlinear Analysis, Population Dynamics,Industrial Mathematics, Numerical Linear Algebra and Graph theory.