Study of Evolution Equations of Prion Dynamics in the Presence of Chaperone

THESIS

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CERTIFICATE

This is to certify that the thesis titled **"Study of Evolution Equations of Prion Dynamics in the Presence of Chaperone"** submitted by **Mr. Kapil Kumar Choudhary**, ID No. **2017PHXF0438P** for the award of Ph.D. of the institute embodies original work done by him under our supervision.

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Abstract

Prions are infectious proteins. These infectious prion proteins are responsible for the degeneration of the central nervous system of humans and animals. These infectious agents are responsible for fatal diseases known as scrapie for sheep, creutzfeld–jacob or kuru for humans and bovine spongiform encephalopathy (BSE) for cattle. The prion proliferation dynamics is recognized as nucleated polymerization. In this theory, there are two essential forms of prions, one of them is non-infectious monomer PrP^C and the other is an infectious polymer PrP^{Sc}. Polymers are very stable above a critical size and have a trend to attach the non-infectious monomers and transform them into the infectious form. Also, when polymers break into smaller proteins below critical size they respond like normal prion proteins. Inclusion of chaperone leads to an important role due to its impact on prion population. There are pharmacological, chemical and molecular chaperones that suppress the growth of prion proteins and therefore, can be considered as a potential therapeutic agent. Several researchers have been worked on prion proliferation models. Thus, it is interested to study the prion dynamics in the presence of chaperone.

We extend existing results on continuous models of prion dynamics by the presence of chaperone. The aim of the thesis is study of prion proliferation models in the presence of chaperone. In this work, we investigate the existence of mild, classical and weak solutions of prion-chaperone models. Moreover, we transform the model into a system of ODEs and study the global asymptotic stability of equilibrium points together with effect of chaperone on prion proliferation numerically.

In the first goal, a prion equation together with chaperone equation is studied. We transform the problem into a semilinear evolution equation under some assumptions and establish the existence of the unique mild solution in the Banach space $\mathbb{R} \times L_1((z_0, \infty); (q+z)dz)$ by using C_0 semigroup theory.

Our second aim is to study a model which includes monomer, polymer and chaperone equations. We discuss the existence and uniqueness of a positive global classical solution of the model for the bounded degradation rates by using evolution system theory in the state space $\mathbb{R} \times \mathbb{R} \times L_1(Z, zdz)$. Moreover, the existence of a global weak solution for unbounded degradation rates is based on weak compactness argument.

Further, we extend the results of second goal and analyze the existence and uniqueness of weak solutions of a prion proliferation model in the presence of a chaperone for a wide class of degradation rates. In addition, the stability analysis results for disease, as well as disease-free equilibrium points are aslo discussed. The effect of chaperone on prion population is also presented numerically.

Finally, the well-posedness of a prion proliferation model in the presence of a chaperone with polymer coagulation and general incidence terms is established in the product space $\mathbb{R} \times \mathbb{R} \times L_1(Z, zdz)$. Moreover, we study the global asymptotic stability for disease-free equilibrium and effect of chaperone on prion proliferation numerically.

List of Symbols

$\mathcal{L}(X)$	The space of bounded linear operators on X
$\mathbb{N}$	The set of natural numbers
$\mathbb{C}$	The set of complex numbers
$BC^1(Z,\mathbb{R}^+)$	The space of bounded continuously differentiable functions from Z into $\mathbb{R}^+$
$BUC(Z)$	The space of bounded, uniformly continuous functions on Z
$C_0(\mathbb{R}^+)$	The space of all continuous functions on $\mathbb{R}^+$ vanishing at infinity
$AC[a,b]$	The space of absolutely continuous functions on $[a,b]$
$C[a,b]$	The space of continuous functions on $[a,b]$
$C^1[a,b]$	The space of continuously differential functions on $[a,b]$
X_w	Banach space X endowed with its weak topology
$\mathbb{1}_S$	The characteristic function of the set S
ACP	Abstract Cauchy Problem
IVP	Initial Value Problem

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Dedicated To

My Parents, who encouraged me to commence this journey

My Supervisor, who made it possible

Chapter 1

Introduction

1.1 Objectives of Thesis

Several researchers have worked on models of prion dynamics. Chaperones play an important role in suppressing the production of prion polymers, and are called potential therapeutic agents against a variety of degenerative diseases. Inclusion of chaperone leads to an interesting physical problem due to its impact on prion population. The objective of the thesis is to study prion dynamic problems in the presence of chaperone. A prion proliferation model incorporating the chaperone consists of two ODE's and a partial integro-differential equation. The following objectives are fulfilled in this thesis by using semigroups operator theory and weak compactness argument

(i) To study a prion equation together with chaperone term in a product space $\mathbb{R} \times L_1((z_0, \infty)$ $;(q+z)dz)$ under different degradation rates and find the existence of classical and mild solutions for associated different degradation rates.

(ii) To investigate the existence of classical and weak solutions of a prion proliferation model in the presence of a chaperone for bounded and unbounded degradation rates, respectively.

(iii) To analyze the existence and uniqueness of weak solutions of a prion proliferation model in the presence of a chaperone for a wide class of degradation rates and study the stability analysis for disease, as well as disease-free states together with effect of chaperone on polymer population numerically.

(iv) To establish the well-posedness of a prion proliferation model in the presence of a chaperone including polymer coagulation in the product space $\mathbb{R} \times \mathbb{R} \times L_1(Z, zdz)$. Moreover, to study the effect of chaperone on prion proliferation numerically and the global asymptotic stability for disease-free equilibrium.

Before discussing the mathematical form of a prion proliferation model in the presence of chaperone, let us briefly explain some biological terms which are involved in the work.

Prion

Mathematics has influenced practically every aspect of biology today, from evolution to biochemistry. Biology's impact on mathematics has been transformational, and biology has acted as a catalyst for the production of novel mathematics. At the end of the twentieth century, a collection of unusual diseases has created confusion regarding everything that has known about disease-causing agents. Biologists and mathematicians collaborated to identify and characterize mechanisms to explain a host of fatal neurodegenerative diseases like Bovine Spongiform Encephalopathy (BSE or 'mad cow disease') in cattle, variant Creutzfeldt–Jakob disease (vCJD) or Kuru in humans, and Scrapie in sheep. Initially, these studies were primarily focused on identifying the infectious agent that caused the diseases. As a group, the above-mentioned diseases are called transmissible spongiform encephalopathy (TSEs).
Before the 1980s, slow or unconventional viruses were assumed to be the source of TSEs. Carleton Gajdusek (Nobel Prize winner) [31] studied TSEs disease Kuru and explained in 1977 that such viruses keep many unusual properties. The discovery of the prion, a proteinaceous infectious particle, posed a fundamental contradiction in the central dogma in molecular biology. However, not just for mammalian diseases, but also for heritable phenotypes in yeast, protein-only inheritance is becoming more widely accepted. Since prion diseases cover so many diverse systems and time scales, these are an especially interesting biological phenomenon for mathematical analysis. Prion disease can be studied at the population level such as in a herd of sheep or a herd of deer, as a traditional epidemic model where infections are spread among an initially uninfected (susceptible) population. All prion diseases are defined by misfolded protein aggregates that act as templates to convert normally folded protein and amplify via fragmentation. Several mathematical formulations have concentrated primarily on the dynamics of the aggregates through modeling either discrete or continuous sizes using ordinary differential equations (ODEs) or partial differential equations (PDEs), respectively. Experiments on Griffith's predicted protein-only form of disease transmission prompted more research.
In 1982, Prusiner established that the infectious agent was not a virus but a protein of abnormal shape and created the term prion to refer to a proteinaceous infectious particle, see [67]. Many of the discrepancies between what was known about viruses and what was known about the agent causing TSEs, as noticed by Gajdusek, were explained by his hypothesis. Soon after, a group of researchers discovered the host gene coding for the prion protein, named PrP for

prion protein, in mammals [64]. Nowak et al [63] were first to construct the nucleated polymerization model (NPM), which is now considered as the standard prion aggregate kinetics. The infectious units in this model aggregate above a critical size. Aggregates of the misfolded prion form of the protein are thought to be unstable below this critical size and are quickly resolved into monomers. Masel et al [59] conducted a comprehensive analysis of NPM in 1999.
Hence, it is concluded that a prion is an infectious protein. These infectious prion proteins are responsible for the degeneration of the central nervous system of humans and animals. Because prion research is new, various notations for two essential proteins are currently in use. We use the terms PrP^C and PrP^{Sc}. In both cases, PrP refers to prion protein. The superscript 'C' refers to cellular, meaning the regular uninfectious protein produced by the body and 'Sc' refers to scrapie, meaning infectious protein. According to the nucleated polymerization [26, 41, 45], PrP^{Sc} is a polymeric form of PrP while PrP^C is monomeric. Below a critical size, the polymerization process is very slow. The polymer is stabilised above this size and subsequent polymerization is comparably quick. These prion proteins are thought to be the cause of fatal diseases like (vCJD) or Kuru for humans and BSE or 'mad cow disease' for cattle and Scrapie for sheep, see [63]. These diseases occur when the prion protein PrP^C misfolds to PrP^{Sc}, which is able to induce further misfolding in healthy PrP^C proteins. It is now widely accepted that the responsible agent for these diseases is a protein, known as prion, which can self-replicate through an autocatalytic mechanism, see [40, 67].

Nucleated Polymerization

The nucleated polymerization theory was proposed in [45] as a PrP^C to PrP^{Sc} conversion process. A mathematical model consisting of an infinite number of coupled ordinary differential equations (ODEs) was presented in [59] to better understand this mechanism on a qualitative level. The construction of the models [28, 38, 48, 69] is based on the leading theory of nucleated polymerization [16, 44]. Prions PrP^{Sc} are considered to be polymers form of normal protein monomers PrP^C according to the nucleated polymerization hypothesis. These PrP^{Sc} are very stable above some critical size z_0, and polymerize sharply. The meaning of the word polymerize is that PrP^{Sc} increases its size by attaching PrP^C monomer unit in a string like fashion. When a PrP^C monomer is coupled with a PrP^{Sc} polymer, it gets transformed into the infectious PrP^{Sc} form. Figure (1.1) depicts the polymerization process:

Another feature of nucleated polymerization is that PrP^{Sc} polymers may also break into smaller polymers. Usually, one infectious PrP^{Sc} polymer breaks into two smaller infectious PrP^{Sc} polymers and after that both PrP^{Sc} attach to PrP^C. When polymers fall below the critical size z_0, they act as normal PrP^C monomers.

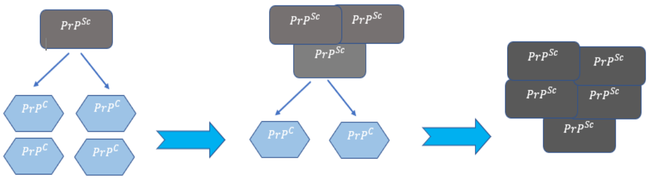

Fig. 1.1: Interaction of PrP^{Sc} with PrP^{C}(normal cellular proteins)

General Incidence and Polymer Coagulation

PrP^{Sc} attaches to PrP^{C} and converts it to PrP^{Sc} through nucleated polymerization. Proteins are frequently found as single units, hence they are often known as monomers. Each polymer can attach to a PrP^{C} monomer from either end and transforms it to the infectious form of PrP^{Sc} rapidly. Thus, the polymer can grow its length by one unit of protein and such process is said to be lengthening. In [28, 38, 69], the prion proliferation models are studied with mass action incidence for the lengthening process of infectious polymers attaching to and converting non-infectious monomers. Greer et al [37] generalized this form of incidence in a way that reduces lengthening when the total amount of infectious protein become large in proportion to the number of polymers. They introduced general incidence and polymer coagulation terms in the prion proliferation model and studied the effect of both the terms on nucleated polymerization. The meaning of polymer coagulation implies the combination of two polymers to form one larger polymer.

Chaperone

Protein misfolding and aggregation are responsible for a vast range of neurodegenerative disorders in humans and animals. The ubiquitous cellular molecular chaperones, which are stress-induced proteins along with newly discovered pharmacological and chemical chaperones have been found to be useful in preventing the misfolding of various diseases causing proteins, reducing the intensity of various neurodegenerative diseases and several other protein-misfolding diseases including prion disease. These pharmacological, chemical and molecular chaperones inhibit the growth of prion proteins PrP^{Sc}, and therefore, can be considered as a potential therapeutic agent, see [22, 32]. The presence of chaperone leads to an interesting physical problem due to its impact on prion population.

The above discussion shows that chaperone may help the protein to find correct conformation. Chaperones play an important role in suppressing the production of prion polymers and

Table 1.1: Chaperone Concept

	Name	Function
1	Chaperone	A class of proteins that prevent other proteins from unfolding undesirably by providing a proper environment for folding.
2	Medical chaperone	A class of small molecules that control the folding or dynamical activities of proteins or RNAs by binding to their specific sites.
3	Chemical chaperone	A class of osmolytes such as glycerol and trehalose: they stabilize any protein nonspecifically.
4	Pharmaceutical chaperone	A class of small enzyme inhibitors that bind to and stabilize proteins and prevent their degradation by the ubiquitin system.

called potential therapeutic agents against a variety of degenerative diseases, including neurodegenerative disorders such as TSEs. The functional characteristics of the different types of chaperones propose to their use as potential therapeutic agents for various degenerative diseases, including neurodegenerative disorders. Calnexin is a special class of chaperone, see [79], which recognize and target abnormally folded proteins for rapid degradation. Increased chaperone expression can suppress the neurotoxicity induced by protein misfolding, suggesting that chaperones could be used as possible therapeutic agents [13].

Chaperones, whether natural, chemical, or pharmaceutical, have been shown to be promising agents for the control of many protein conformational disorders. It is believed that chaperones are important in preventing protein misfolding and thereby reducing the effectiveness of neurodegenerative diseases. Chaperones are proteins that interact with nascent polypeptides during their production and translocation to different cellular compartments. They can be found throughout the cell. Molecular chaperones are proteins that facilitate folding and transport of polypeptides into organelles during their biosynthesis and that help in preventing protein aggregation during situations of cellular stress [74]. Chaperones can distinguish between native and non-native states of targeted proteins. However, it is yet to be unclear how they distinguish between correctly and incorrectly folded proteins, and how they retain and target the latter for disintegration.

In [49], a logical drug design technique and its application to prion diseases is reviewed. The probable mechanisms of various protein-misfolding diseases in humans, as well as the therapeutic approaches for countering them are reviewed in [19]. Also, the involvement of chemical, molecular and pharmacological chaperones in suppressing the effect of protein misfolding-induced consequences in humans is discussed in detail. Chemical chaperones have also been used as therapeutic agents in prion disease. In animal models [47, 60], a number of chemicals, including anthracyclines, porphyrins, and diazo dyes prevent prion replication. Pharmacological chaperones have been shown to be very effective in protecting certain receptor proteins from proteasomal degradation. It is feasible that chemical, pharmacological and molecular chaperones might change the mode of treatment in future and open a new door in clinical research into the neurodegenerative diseases.

1.2 Model of Prion Dynamics and Literature Survey

In this section, the role of mathematical modelling in understanding the dynamics of prion disease is discussed. Eigen [26] provided the first mathematical description of the autocatalytic proliferation of prion aggregates in 1996, which was influenced by Griffiths' third hypothesis [40] and observations of Prusiner [68] and Lansbury [18, 21, 52]. He formulated systems of differential equation to analyze two theories on protein-only amplification. In Eigen's first model, he explored the possibility that heterodimers act to template misfolding suggested by Prusiner [68]. He discussed a system with two protein species: A-normal conformation, and B-prion conformation, in which proteins of type A can form heterodimers with proteins of type B and are irreversibly transformed into type B. Eigen's second model examined two mechanisms where the infectious agents were not individual misfolded protein monomers: a cooperative auto-catalytic mechanism, which generalized his first model and aggregates of misfolded proteins according to the aggregation mechanism proposed from Lansbury [18, 21, 52]. These assumptions lead to a complicated set of differential equations but steady-state analysis declared important properties of the asymptotic dynamics as for the previous model.
Eigen's analysis investigated that in prion proliferation aggregation is necessarily involved [26]. In 1998, Nowak et al expanded Eigen's seminal work by including new experimental observations. Their mathematical model for prion infection dynamics was based on having prion aggregates act in two ways. Nowak et al [63] were first construct the nucleated polymerization model, which is now considered the standard prion aggregate kinetics. The infectious units in this model are aggregates above a critical size. Aggregates of the misfolded prion form of the protein are thought to be unstable below this critical size and are quickly resolved into monomers. Masel et al [59] conducted a comprehensive analysis of the nucleated polymerization model (NPM) in 1999. In particular, they recommended to link experimental observations on the time for the appearance of prion disease symptoms with the kinetic parameters of the NPM.

Masel et al [59] and Greer et al [38] with a generalization showed that the dynamics of aggregates under the NPM are consistent with the long-incubation time observed for prion phenotypes. In early twenty-first century, mathematicians continued formalizing the NPM. Prüss et al [69] demonstrated that the prion phenotypes were globally asymptotically stable and not merely locally stable, through deriving a Lyapunov function. Engler et al [28] analyzed the well-posedness of the generalization of the NPM where aggregate sizes were continuous, instead of discrete. In [59, 63], the NPM for PrP^{Sc} polymers and PrP^{C} monomers containing a discrete number of monomers are constructed and analyzed. Further, a model with continuous polymer size is formulated in [39] and analyzed in [28, 38, 69]. The prion proliferation model [28, 38, 69] is expressed by a coupled system consisting of one ODE for the number of non-infectious PrP^{C} monomers S which is given by

$$\frac{dS(t)}{dt} = \lambda - \gamma S(t) - S(t)\int_{z_0}^{\infty} \tau(y)u(t,y)dy + 2\int_0^{z_0} z \int_{z_0}^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dydz. \tag{1.1}$$

and a partial integro-differential equation for the population density function u of infectious PrP^{Sc} polymers of size z, is described as

$$\frac{\partial u(t,z)}{\partial t} = -S(t)\frac{\partial(\tau(z)u(t,z))}{\partial z} - \big(\mu(z)+\beta(z)\big)u(t,z) + 2\int_z^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dy \tag{1.2}$$

with the following initial and boundary data

$$S(0) = S^0,\ u(0,z) = u^0(z),\ u(t,z_0) = 0,\ \text{for}\ \ t \geq 0,\ z_0 < z < \infty. \tag{1.3}$$

The description of the parameters are given below in Table 1.2. Here, the last term on the right hand side of equation (1.1) represents the monomers gained when a PrP^{Sc} polymer splits with at least one polymer shorter than the minimum length z_0. We assume that such polymer piece degrades immediately into PrP^{C} monomers. The factor 2 in the expression accounts for the fact that a polymer of length z greater than z_0 splits into two PrP^{Sc} polymers. The term $-S(t)\frac{\partial(\tau(z)u(t,z))}{\partial z}$ in equation (1.2) denotes the loss of polymers of length z due to lengthening and $2\int_z^{\infty}\beta(y)\, k(z,y)\, u(t,y)\, dy$ accounts the number of PrP^{Sc} which are added to the population when longer polymers split into polymers of length z. The splitting density $k(z',z) \geq 0$ defined on $\mathcal{K} = \{(z',z) : z_0 < z < \infty,\ 0 < z' < z\}$ satisfies

$$k(z',z) = k(z-z',z) \quad \text{for all} \quad (z',z) \in \mathcal{K} \tag{1.4}$$

and is normalized by

$$2\int_0^z z'k(z',z)dz' = z, \quad \text{a.e. } z > z_0. \tag{1.5}$$

Table 1.2: Parameters of the Prion Proliferation Model

Parameters	Description
λ	Source rate of production for normal PrP^C
$\tau(z)$	Conversion rate of monomers PrP^C to polymers PrP^{Sc}
γ	Metabolic degradation rate of PrP^C
$\mu(z)$	Degradation rate of PrP^{Sc} due to metabolism
$\beta(z)$	Splitting rate of polymers to monomers
$k(x,z)$	Probability density function for splitting a polymer of size $z > z_0$ into two pieces of sizes $z-x$ and x
$S(t)$	Population of PrP^C monomers at time t
$u(z,t)$	Population of PrP^{Sc} polymers of length z at time t

Now, conservation of the number of monomers due to splitting and (1.4)-(1.5) implies that

$$\int_0^z k(z',z)dz' = 1, \quad \text{a.e. } z > z_0. \tag{1.6}$$

It should be mentioned that these constraints are satisfied by the self-similar density k of the form

$$k(z',z) = \frac{1}{z}k_0\left(\frac{z'}{z}\right), \quad z > z_0,\ 0 < z' < z \tag{1.7}$$

where k_0 denotes a non-negative integrable function defined on $(0,1)$ such that

$$k_0(z) = k_0(1-z), \ \ z \in (0,1) \ \ \text{and} \ \ \int_0^1 k_0(z)dz = 1. \tag{1.8}$$

Several researchers have worked on the monomer-polymer system (1.1)-(1.2), see [28, 38, 55, 69, 71, 77]. In [38], the problem (1.1)-(1.2) is transformed into a system of three ODEs under the following assumptions on associated parameters

$$\mu \equiv \text{constant}, \ \ \tau \equiv \text{constant} \ \ \text{and} \ \ \beta(z) = \beta z, \ k(y,z) = \frac{1}{z}, \quad z > z_0,\ 0 < y < z \tag{1.9}$$

and the stability results are proved for the disease steady-state and the disease-free steady-state. Further, this stability study has been subsequently improved in [69] by including the investigation of the global asymptotical stability issues for disease-free state and disease-state. The global asymptotic stability of the steady states and well-posedness of the mild solutions are demonstrated to the problem (1.2), see [28] under the assumptions considered in [38, 69].

In [71], the existence of classical and weak solutions to the monomer-polymer system (1.1)-(1.2) (with $\tau(z) = \tau$) are discussed for bounded kernels, namely

$$\mu, \beta \in L^+_\infty(Z); \;\; Z = (z_0, \infty), \tag{1.10}$$

and degradation rates $\mu, \beta \in L^+_{\infty,\mathrm{loc}}(Z)$ such that

$$\begin{cases} \text{there exists } \alpha \geq 1 \text{ and } \rho \in L^+_\infty(Z) \text{ such that} \\ \mu(z) + \beta(z) \leq \rho(z)\, z^\alpha, \;\; \text{a.e. } z \in Z \text{ and } \rho(z) \to 0 \text{ as } z \to \infty, \end{cases} \tag{1.11}$$

and

$$\begin{cases} \text{for each } \varepsilon > 0 \text{ there exists } \delta > 0 \text{ such that} \\ \sup_{|\xi| \leq \delta} \frac{\beta(z)}{z^\alpha} \int_{z_0}^{z} \mathbb{1}_\xi(y) k(y,z)\, dy \leq \varepsilon, \;\; \text{a.e. } z \in Z, \end{cases} \tag{1.12}$$

where $\mathbb{1}_\xi$ indicates the characteristic function on ξ and supremum is taken over all measurable subsets $\xi \subset Z$ with $|\xi| \leq \delta$, respectively. Moreover, they also discussed the global stability of disease-free equilibrium. The well-posedness to the problem (1.1)-(1.2) is established in [55] for a broad class of kernels, i.e., without placing growth conditions (1.11) on μ, β. Similar to [71], the existence of classical and weak solutions to the monomer-polymer system (1.1)-(1.2) are achieved in [77].

In [48], the authors are extended the prion proliferation model (1.1)-(1.2) by the presence of a chaperone. The mathematical model which describes the dynamics of prion proliferation in the presence of chaperone [48] is described by the following set of equations:
The monomer equation is described by

$$\frac{dS(t)}{dt} = \lambda - \gamma S(t) - \tau S(t) \int_{z_0}^{\infty} u(t,y) dy + 2 \int_0^{z_0} z \int_{z_0}^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dy dz. \tag{1.13}$$

The polymer and chaperone equations are governed by

$$\frac{\partial u(t,z)}{\partial t} = -\tau S(t) \frac{\partial u(t,z)}{\partial z} - \big(\mu(z) + \beta(z) + \delta_2 C(t)\big) u(t,z) + 2 \int_z^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dy \tag{1.14}$$

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t) \int_{z_0}^{\infty} u(t,y)\, dy, \tag{1.15}$$

respectively, where the initial and boundary conditions are as follows

$$S(0) = S^0, \; C(0) = C^0, \; u(0,z) = u^0(z), \; u(t,z_0) = 0, \; \text{for } \; t \geq 0, \; z_0 < z < \infty. \tag{1.16}$$

Here, all parameters γ, λ, τ, δ_0, δ_1, δ_2 are positive constants and $C(t)$ denotes the amount of chaperone in the system at time t. The parameter δ_2 represents the reducing rate of PrP^{Sc} population due to presence of chaperone. Chaperone degradation rate due to metabolic process is denoted by δ_0 and the parameter δ_1 denotes chaperone increasing rate in the system due to absorption in the body. From [48], it is observed that the system (1.13)-(1.15) can be transformed into a system of four ODEs and the stability analysis is discussed for the equilibrium points along with the effect of the chaperone numerically.

Greer et al [37] studied the prion proliferation model which includes prion polymerization, polymer coagulation and polymer splitting. In the general incidence and polymer coagulation case, the prion proliferation model [37] is described by

$$\frac{dS(t)}{dt} = \lambda - \gamma S(t) - \frac{S(t)}{1+\rho\int_{z_0}^{\infty} u(t,z)zdz}\int_{z_0}^{\infty}\tau(z)u(t,z)dz + 2\int_0^{z_0} z\int_{z_0}^{\infty}\beta(y)\, k(z,y)\, u(t,y)\, dydz \tag{1.17}$$

and

$$\begin{aligned}\frac{\partial u(t,z)}{\partial t} =& -\frac{S(t)}{1+\rho\int_{z_0}^{\infty} u(t,z)zdz}\partial_z(\tau(z)u(t,z)) - \big(\mu(z)+\beta(z)\big)u(t,z) + 2\int_z^{\infty}\beta(y)\, k(z,y)\, u(t,y)\, dy\\ &+ \mathbb{1}_{[z>2z_0]}\int_{z_0}^{z-z_0}\eta(z-y,y)u(t,z-y)u(t,y)\, dy - 2u(t,z)\int_{z_0}^{\infty}\eta(z,y)u(t,z)dz\end{aligned} \tag{1.18}$$

where the initial and boundary conditions are

$$S(0) = S^0,\ u(0,z) = u^0(z),\ u(t,z_0) = 0,\ \text{for}\ \ t \geq 0,\ z_0 < z < \infty.$$

Here, the function $\eta(y,z)$ denotes the rate at which two polymers of sizes y and z join together and ρ is a parameter associated with polymer lengthening. The stability of disease-free and endemic equilibriums are discussed in [37]. The existence of classical and weak solutions are proved in [56] for bounded and unbounded degradation rates, respectively, to the monomer-polymer system (1.17)-(1.18). Further, the uniqueness of weak solution is proved in [57].

1.3 Plan of the Thesis

As we know and evidenced by the preceding literature, mathematics plays an important role in epidemiology. The emphasis of the work is on prion proliferation model in the presence of chaperone. Based on literature survey and the gaps in research to this model, in the thesis, we show the existence of classical, mild and weak solutions to the models of prion dynamics in the presence of chaperone. Also, we study the behaviour of the solutions of such dynamical systems. For better understanding, let us summarize each chapter of the thesis.

The 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 semigroups operator theory and the results on semilinear evolution equation are illustrated. Also, the results for existence of solutions for linear and semilinear evolution equations are given which help us to show the existence of mild and classical solutions for prion-chaperone models. We also provide preliminary definitions and results for weak compactness argument. The section is concluded with some standard and preliminary definitions of stability analysis.

The aim of Chapter 3 is to investigate the mild and classical solutions of the partial integro-differential equation (1.2), together with chaperone equation (1.3) for different kernels. We transform the model into the semilinear evolution equation under assumptions (1.9) and establish the existence of the unique mild solution by semigroups operator theory. Moreover, the existence of the classical solution is proved for associated bounded degradation rates by using evolution operator theory.

In Chapter 4, evolution operator theory is used to show the existence and uniqueness of the classical solution to the problem (1.1)-(1.3) under the assumption (1.10) while the existence of a weak solution is discussed under the assumptions (1.11) and (1.12) by weak compactness argument. This chapter extends the work of [71] from the presence of chaperone.

Chapter 5 discusses the existence of a weak solution to the problem (1.1)-(1.3) for a broad class of kernels, i.e., without placing growth conditions (1.11) on μ, β which extends the results of [55] in the presence of chaperone. Also, we transform the problem into a system of four ODEs and it is demonstrated that there is a unique steady state, the disease-free equilibrium, that exists below and at the threshold and is globally asymptotically stable. Above the threshold, there is another steady state, the disease state, which is also global asymptotically stable.
Furthermore, in Chapter 6, the prion-chaperone model is studied together with general incidence and polymer coagulation terms. The existence of classical and weak solutions to the problem are proved for associated bounded and unbounded degradation rates, respectively. Moreover, we convert the problem into a system of ODEs and the global asymptotic stability is established for disease-free state.
At the end of the thesis, conclusions and some open problems are provided.

Chapter 2

Mathematical Preliminaries

2.1 Theory of Semigroups

2.1.1 Introduction

The beginning of the theory of one-parameter semigroups of linear operators on Banach spaces was in the first half of nineteenth century and reached its apex with Hille and Phillips "Semigroups and Functional Analysis" published in 1957, see [42]. In the 1970s and 80s, the theory was presented very well in the monographs by E.B. Davies [23], J.A. Goldstein [36], A. Pazy [66] and others.

Semigroups are useful for solving a wide range of problems known as evolution equations which can be found in various fields, including physics, chemistry, biology, engineering, and economics. They are usually described by an initial value problem (IVP) for a differential equation which can be either ordinary or partial. The theory of linear and nonlinear semigroups is well developed, see [12, 15, 35, 36, 62, 65, 66]. Semigroup approaches have also been successfully applied to problems, such as population dynamics or transport theory, see [4, 58, 78]. Semigroup theory is used to establish the existence of solutions of prion dynamics [28, 56, 71, 77] and coagulation-fragmentation [5, 6, 8, 9, 10, 51, 61] problems. Semigroup theory gives both necessary and sufficient requirements for the well-posedness of the abstract cauchy problem (ACP). Let $u(t)$ describes the state at time t and the time rate of change of $u(t)$ is given by some function of A. If, $u(0) = u_0$ is the initial data, then abstract Cauchy problem is given by

$$\begin{cases} \frac{du}{dt} = Au(t) \ ; \quad t \geq 0 \\ u(0) = u_0. \end{cases} \tag{2.1}$$

If the solution of (2.1) exists, then it is given by

$$u(t) = e^{At} u_0.$$

Definition 2.1.1. *A mathematical problem is said to be well posed if it satisfies the following conditions*

(a) Existence, that is, there is atleast one solution,

(b) Uniqueness, that is, there is atmost one solution,

(c) Stability, that is, the solution depends continuously on the data.

The well-posedness of the ACP (2.1) is an interesting topic. Semigroup theory can be used to identify the well posededness of the linear (or nonlinear) evolution problem. To apply the theory, we must identify first that we have a semigroup. Further, to continue with the solution, let $T(t)$ maps the solution $u(s)$ at time s to the solution $u(t+s)$ at time $t+s$. If A is assumed to be independent of time, then $T(t)$ is independent of s. The solution $u(t+s)$ at time $t+s$ can be computed as $T(t+s)u_0$. If the procedure is broken down into two steps, then
Step−1 :

$$T(s)u_0 = u(s)$$

Step−2 :

$$T(t)(u(s)) = T(t)T(s)u_0 = u(t+s) = T(t+s)u_0.$$

Semigroup Property

From the above steps, it is clear that the state of the system at time $t+s$ can be reached by either going straight 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, $T(\cdot)$ works as a transition operator. The semigroup property which is given by

$$T(t+s) = T(t)T(s) \quad t,s > 0 \tag{2.2}$$

is revealed by uniqueness of the solution. The semigroup property of the family of functions $\{T(t) : t \geq 0\}$ is a composition and not a multiplication. Note that $T(0)$ is the identity operator I, that is, there is no transition at time zero and the initial data exists. Now, to find out how A and T relate to each other, it is noticed that

$$T(t)(u_0) = T(t)(u(0)) = u(t) = e^{At}u_0,$$

$$\frac{d}{dt}T(t)(u_0) = A(T(t)(u_0))$$

so that $u(t) = T(t)(u(0))$ solves (2.1).

Let us review some basic definitions, examples and results from operator theory.

Definition 2.1.2. *(See, [66]) Let X be a Banach space. Then, a family $\{T(t) : t \geq 0\}$ of bounded linear operators from X into X is said to be semigroup if*

(a) $T(0) = I$, *where I is the identity operator,*

(b) $T(t+s) = T(t)T(s)$ *for every $t, s \geq 0$ (the semigroup property).*

Definition 2.1.3. *(See, [66]) A family $\{T(t) : t \geq 0\} \in \mathcal{L}(X)$ is said to be strongly continuous semigroup or C_0 semigroup on X if*

(a) $T(0) = I$, *where I is the identity operator,*

(b) $T(t+s) = T(t)T(s)$ *for every* $t, s \geq 0$,

(c) for each fixed $x \in X$, $T(t)x \to x$ *as* $t \to 0^+$.

Definition 2.1.4. *Let $\{T(t) : t \geq 0\}$ be a C_0 semigroup of bounded linear operators on X. Then, $T(t)$ is called*

(a) isometries if $\|T(t)f\| = \|f\|$ *for all* $t \geq 0$, $f \in X$,

(b) contractions if $\|T(t)\| \leq 1$ *for all* $t \geq 0$.

Definition 2.1.5. *(Infinitesimal generator, see [66]) The infinitesimal generator of a strongly continuous semigroup $\{T(t) : t \geq 0\}$ on X is the operator $A : D(A) \subseteq X \to X$ defined by*

$$Ax = \lim_{t \to 0^+} \frac{T(t)x - x}{t},$$

where $D(A) = \{x \in X : \lim_{t \to 0^+} \frac{T(t)x - x}{t} \text{ exists}\}$.

Definition 2.1.6. *(See, [70]) Let X and Y be two Banach spaces. A linear operator $A : D(A) \subseteq X \to Y$ is said to be*

(a) closed if for any sequence $(x_n) \in D(A)$ such that $x_n \to x$ and $Ax_n \to y$, then $x \in D(A)$ and $Ax = y$,

(b) closable if A has a closed extension, i.e., if $(x_n) \in D(A)$ such that $x_n \to 0$ and $Ax_n \to y$, then $y = 0$.

Example 2.1.1. *(Non-Closable Operator, see [70]) Let H be a Hilbert space. Let M be a linear subspace of H and e be a non-zero vector in H. Let F be a linear functional on M which is not continuous in the Hilbert space norm. Define the operator $T : D(T) = M \subseteq H \to H$ such that $T(x) = F(x)e$ for $x \in M$. Then T is not closable.*
Given F is not cotinuous, then there exists a sequence (x_n) in M such that $x_n \to 0$ in H and $F(x_n)$ does not converge to zero. Now, there exists a subsequence (x_{n_k}) of (x_n) such that $|F(x_{n_k})| \geq c$ for some $c > 0$. Define $x'_{n_k} = F(x_{n_k})^{-1}x_{n_k}$, then $x'_{n_k} \to 0$ as $k \to \infty$ and $T(x'_{n_k}) = F(x_{n_k})^{-1}T(x_{n_k}) = e \neq 0$. Hence, T is not closable.

Example 2.1.2. *(Closable but not Closed Operator) Let $H = L_2(0,1)$ and $A : D(A) \subset H \to H$ is defined by $Af = if'$, where*

$$D(A) = C_0^1(0,1) = \{ f \in C^1(0,1) : f(0) = f(1) = 0\}.$$

Then, A is closable operator but not closed. Since,

$$\begin{aligned}(Af,g) &= \int_0^1 if'(t)\,\overline{g(t)}\,dt \\ &= -i\int_0^1 f(t)\,\overline{g'}dt \\ &= \int_0^1 f(t)\,\overline{ig'}dt \\ &= (f,g*).\end{aligned}$$

This implies that, for all $f \in D(A), (Af,g) = (f,g*)$ where $A^*g = g^* = ig'$ and $\mathrm{D(A^*)} = \{\mathrm{g} \in \mathrm{H} : \mathrm{g}' \in \mathrm{L}_2(0,1)\}$. *Thus $D(A)$ is a proper subset of $D(A^*)$, i.e., A^* is an extension of A and hence, A is not self-adjoint operator. But A is a symmertic operator. Also, domain of A is densely defined and hence, A is closable. Here, A is not closed operator.*

Definition 2.1.7. *(See, [70]) Let X, Y be two Banach spaces and $A : D(A) \subseteq X \to Y$ is a linear operator. Define the operator $\bar{A} : D(\bar{A}) \subseteq X \to Y$ such that*

(a) $\bar{A}$ is an extension of A.

(b) $\bar{A}$ is a linear closed operator.

(c) if $S : D(S) \subseteq X \to Y$ is any linear operator with properties (a) and (b), then S is an extension of $\bar{A}$.

Then, the operator $\bar{A}$ is said to be closure of A.

Example 2.1.3. *(Translation Semigroups, see [27]) Let E be one of the following function spaces $C_0(\mathbb{R}^+)$ or $L_p(\mathbb{R}^+)$ for $p \in [1,\infty)$. Define $T(t)$ by*

$$(T(t)f)(x) = f(x+t)$$

as the (left) translation operator for $x,t \in \mathbb{R}^+$ and $f \in E$. Then $\{T(t) : t \geq 0\}$ is a C_0 semigroup.

Note: *The generator of the translation semigroup on $E = C_0(\mathbb{R}^+)$ is*

$$Af = \lim_{t\to 0^+} \frac{T(t)f - f}{t} = \frac{d}{dx}f = f'$$

where

$$D(A) = \{f \in E : f \text{ is differentiable and } f' \in E\}.$$

Note: *The generator of the translation semigroup on $E = L_p(\mathbb{R}^+), 1 \leq p < \infty$, is*

$$Af = \lim_{t\to 0^+} \frac{T(t)f - f}{t} = \frac{d}{dx}f = f'$$

where

$$D(A) = \{f \in E : f \text{ is absolutely continuous and } f' \in E\}.$$

Example 2.1.4. *(See, [77]) Let $X_0 = L_1(Z, zdz)$, $Z = (z_0, \infty)$. The operator $-A$, defined by*

$$Au = \partial_z(\tau u), \;\; u \in D(A) = \{u \in X_0 : \partial_z(\tau u) \in X_0, u(z_0) = 0\},$$

generates a C_0 semigroup $\{W(t) : t \geq 0\}$ on X_0 defined by

$$(W(t)f)(z) = \mathbb{1}_{[t,\infty)}(\Psi(z)) \frac{\tau\left(\Psi^{-1}(\Psi(z)-t)\right)}{\tau(z)} f\left(\Psi^{-1}(\Psi(z)-t)\right), \;\; z \in Z, \;\; t \geq 0,$$

with

$$\|W(t)\|_{\mathcal{L}(X_0)} \leq e^{\tau_0 t}, \;\; t \geq 0,$$

where $\Psi : Z \to (0,\infty)$ is a diffeomorphism defined by $\Psi(z) = \int_{z_0}^{z} \frac{dy}{\tau(y)}$ and $\tau_0 = \frac{\|\tau\|_\infty}{z_0}$ so that $\tau(z) \leq \tau_0 z$, $z \in Z$.

Definition 2.1.8. *(See, [36]) Let $A : D(A) \subset X \to X$ is linear, not necessary bounded operator on a real or complex Banach space X, then the resolvent set of A is denoted by $\rho(A)$ and defined as $\rho(A) = \{\lambda \in \mathbb{C} : (\lambda I - A)^{-1} \text{ exists and bounded}\}$.*

Theorem 2.1.1. *(Hille-Yosida Theorem) A linear (unbounded) operator $A : D(A) \subset X \to X$ generates a C_0 semigroup of contractions $\{T(t) : t \geq 0\}$ iff* *(a)* *A is closed and* $\overline{D(A)} = X$.

(b) *The resolvent set* $\rho(A)$ *of A contains* $\mathbb{R}^+$ *and for every* $\lambda > 0$

$$\|R(\lambda, A)\| \leq \frac{1}{\lambda}.$$

Proof. See [[66], Theorem 1.3.1]. □

Theorem 2.1.2. *Let* $\{T(t) : t \geq 0\}$ *is a* C_0 *semigroup of bounded linear operators on* X. *Then, there exists constants* $\omega \geq 0$ *and* $M \geq 1$ *such that*

$$\|T(t)\| \leq Me^{\omega t} \quad \text{for all } \ t \geq 0.$$

Proof. See [[66], Theorem 1.2.2]. □

Theorem 2.1.3. *(Well-posedness Theorem) Let* $A : D(A) \subset X \to X$ *is a linear operator. Then, the initial value problem* (2.1) *is well-posed if and only if A is the generator of a* C_0 *semigroup* $\{T(t) : t \geq 0\}$ *on* X. *In this case, for each* $u_0 \in D(A)$, *the unique solution of* (2.1) *is expressed by* $u(t) = T(t)u_0$.

Proof. See [[36], Theorem 2.1.2]. □

Definition 2.1.9. *(Dissipative Operators, see [66]) Let H be a Hilbert space, then an operator* $A : D(A) \subseteq H \to H$ *is said to be dissipative operator if*

$$Re(Au, u) \ \leq \ 0 \quad \text{for all } \ u \in D(A).$$

If $Re(Au, u) \ \geq \ 0$, *then A is said to be accretive.*

Example 2.1.5. *(See, [72]) Let* $H = L_2(0, 1)$ *and* $A : D(A) \subset H \to H$ *is defined by*

$$Af = f' \quad \text{for } \ f \in D(A)$$

where $D(A) = \{f \in H : f \in W^{1,2}(0, 1) \text{ and } f(0) = 0\}$. *Then,*

$$\begin{aligned} \text{Re}\langle Af, f\rangle &= \text{Re} \int_0^1 f(t)\overline{f'(t)}dt \\ &= \frac{1}{2}\int_0^1 \frac{d}{dt}\left(f(t)\overline{f(t)}\right) dt \\ &= \frac{1}{2}|f(1)|^2 \geq 0. \end{aligned}$$

Therefore, A is accretive operator and $-A$ *is a dissipative operator on* H.

Definition 2.1.10. *(m-Dissipative Operator, see [66]) A densely defined, dissipative operator $A : D(A) \subset H \to H$ is called m-dissipative if the operator $\lambda I - A$ is surjective, that is, $R(\lambda I - A) = H$ for some $\lambda > 0$.*

Example 2.1.6. *Let $H = L_2(\Omega), \Omega \subseteq \mathbb{R}^2$ and $Af = \triangle f$ for $f \in H^2(\Omega) \cap H_0^1(\Omega)$. By Green's first identity, we have*

$$\int_\Omega u \nabla^2 v + \int_\Omega \nabla u \nabla v = \int_{\partial\Omega} v \frac{\partial u}{\partial \eta} ds.$$

Therefore,

$$\int_\Omega u \nabla^2 u + \int_\Omega \nabla u \nabla u = 0$$

$$\int_\Omega u \triangle u + \int_\Omega |\nabla u|^2 = 0$$

$$\int_\Omega (-\triangle u)u = \int_\Omega |\nabla u|^2 \geq 0$$

$$\langle -\triangle u, u\rangle = \langle \nabla u, \nabla u\rangle \geq 0$$

Thus, $-\triangle$ is an accretive operator.

2.1.2 Lumer-Phillips Theorem

Let X^* be the dual space of Banach space X. Let us denote the value of $f^* \in X^*$ at $f \in X$ by $\langle f^*, f\rangle$ or $\langle f, f^*\rangle$. For every $f \in X$, the duality set, see [24, 66], is defined as

$$F(f) = \{f^* \in X^* : \langle f^*, f\rangle = \|f\|^2 = \|f^*\|^2\}.$$

It follows from Hahn-Banach theorem that $F(f) \neq \emptyset$ for every $f \in X$.

Definition 2.1.11. *(Dissipative Operator, see [46, 66]) Let $A : D(A) \subset X \to X$ is a linear operator. Then, A is dissipative if for every $f \in D(A)$ there is a $f^* \in F(f)$ such that Re $\langle Af, f^*\rangle \leq 0$.*

Theorem 2.1.4. *The following two statements are equivalent for an operator A on X*

(a) A is dissipative.

(b) $\|(\lambda I - A)x\| \geq \lambda \|x\|$ for all $x \in D(A)$ and $\lambda > 0$.

Proof. See [[66], Theorem 1.4.2]. □

Theorem 2.1.5. *Let A be a dissipative operator in X.*

(a) If for some $\lambda_0 > 0$, $R(\lambda_0 I - A) = X$ then $R(\lambda I - A) = X$ for all $\lambda > 0$.

(b) If A is closable then closure of A, i.e., $\bar{A}$ is also dissipative.

(c) *If $\overline{D(A)} = X$, then A is closable.*

Proof. See [[66], Theorem 1.4.5]. □

Theorem 2.1.6. *(Lumer-Phillips Theorem) Let $A : D(A) \subset X \to X$ be a densely defind linear operator. Then, the following statements are equivalent.*

(a) *If A is dissipative and there exists $\lambda_0 > 0$ such that the range of $\lambda_0 I - A$ is X, that is, $R(\lambda_0 I - A) = X$. Then, A is the generator of a C_0 semigroup of contractions on X.*

(b) *If A is the generator of a C_0 semigroup of contractions on X, then $R(\lambda I - A) = X$ for all $\lambda > 0$ and A is dissipative.*

or

A densely defined linear operator A is the generator of a C_0 semigroup of contractions iff it is m-dissipative.

Proof. See [[66], Theorem 1.4.3]. □

Example 2.1.7. *(See, [72]) Let $X = L_2(0,1)$ and consider the operator $A : D(A) \subset X \to X$,*

$$Af = f'$$

where $D(A) = \{f \in W^{1,2}(0,1) : f(0) = 0\}$. This is a closed operator with dense domain. Let $\phi \in D(A)$, then for $\lambda > 0$ and $f \in X$,

$$(\lambda I + A)\phi = \lambda\phi + \phi' = f$$

defines a linear ODE. After solving the differential equation, one gets,

$$\phi(t) = \int_0^t e^{-\lambda(t-s)} f(s)ds. \tag{2.3}$$

Therefore, $\|(\lambda I + A)\phi\| \geq \lambda \|\phi\|$ for all $\lambda > 0$ and $\phi \in D(A)$. It follows that $(\lambda I + A)D(A) = X$ for all $\lambda > 0$, and hence $(-A, D(A))$ is m-dissipative. Thus, $-A$ generates a C_0 semigroup of contractions on X.

Theorem 2.1.7. *Let A is dissipative with $R(I - A) = X$ and X is reflexive, then $\overline{D(A)} = X$.*

Proof. See [[66], Theorem 1.4.6]. □

Remark: We can not relax the condition of reflexivity in the Theorem 2.1.7. See the following example.

Example 2.1.8. *(See, [66]) Let $X = C[0,1]$ with the sup norm. Let*

$$Af = -f' \quad \text{for } f \in D(A)$$

where $D(A) = \{f : f \in C^1[0,1] \text{ and } f(0) = 0\}$.
For every $g \in X$, the equation $\lambda f - Af = g$ has a solution f given by

$$f(x) = \int_0^x e^{\lambda(\xi - x)} f(\xi) d\xi. \tag{2.4}$$

This indicates that $R(I - A) = X$ and from (1) we also have

$$\lambda |f(x)| \leq (1 - e^{-\lambda x}) \|g\| \leq \|\lambda f - Af\|. \tag{2.5}$$

This implies that $\lambda\|f\| \leq \|\lambda f - Af\|$ and therefore, A is dissipative. But $\overline{D(A)} = \{f : f \in X \text{ and } f(0) = 0\} \neq X = C[0,1]$.

Corollary 2.1.7.1. *If $A : D(A) \subset X \to X$ generates a C_0 semigroup $\{T(t) : t \geq 0\}$ on X. Then, A is a closed and densely defined linear operator.*

Proof. See, [[66], Corollary 1.2.5]. □

2.1.3 Positive Semigroups

In this section, E is assumed to be a Banach lattice.

Definition 2.1.12. *(Vector Lattice, see [14]) A vector lattice is a real vector space V that is ordered by some order relation ' $\leq$ ' if any two elements $f, g \in V$ have a least upper bound, denoted by $f \vee g = \sup(f, g) \in V$, and a greatest upper bound, denoted by $f \wedge g = \inf(f, g) \in V$, and the following properties are satisfied*

(a) if $f \leq g$, then $f + h \leq g + h$ for all $f, g, h \in V$,

(b) if $0 \leq f$, then $0 \leq tf$ for all $f \in V$ and $t \geq 0$.

Let V be a vector lattice, then the positive cone of V is defined by

$$V^+ = \{f \in V : 0 \leq f\}.$$

For $f \in V$, let us define

$$f^+ = f \vee 0, \quad f^- = (-f) \vee 0 \quad \text{and} \quad |f| = f \vee (-f),$$

the positive part, the negative part and the absolute value of f, respectively.

Definition 2.1.13. *(Lattice norm, see [14]) A norm on a vector lattice V is called a lattice norm if*

$$|f| \leq |g| \text{ implies } \|f\| \leq \|g\| \text{ for } f,g \in V.$$

Definition 2.1.14. *(Banch Lattice, see [14]) A real Banach space E endowed with an ordering '$\leq$' is said to be Banach lattice if $(E,\leq)$ is a vector lattice and the norm on E is a lattice norm.*

Example 2.1.9. *(See, [14]) All classical (real) Banach spaces $l_p, c_0, C(K)$ are Banach lattices for their usual norm and the point wise order.*

Note: There are a large number of ordered function spaces that are not Banach lattices.

Example 2.1.10. *(See, [14]) Consider the Banach space $C^1([0,1])$ with the norm*

$$\|f\| = \max_{t\in[0,1]} |f(t)| + \max_{t\in[0,1]} |f'(t)|$$

and the natural order $f \geq 0$ if $f(t) \geq 0$ for all $t \in [0,1]$. Since, $\sup\{s, 1-s\} \notin C^1([0,1])$, the space $C^1([0,1])$ is not a vector lattice.

Definition 2.1.15. *(Positive Operator, see [7, 14]) Let E and F are two Banach lattices. A linear operator $T : E \to F$ is called positive if $T(E^+) \subset F^+$ and it is denoted by $T \geq 0$.*

Definition 2.1.16. *(Positive C_0 Semigroup, see [14]) Let $\{T(t) : t \geq 0\}$ be a C_0 semigroup on E with generator A. Then, it is positive iff*

$$T(t)E^+ \subseteq E^+,$$

where $E^+ = \{\, f \in E \ :\ f \geq 0 \,\}$.

Definition 2.1.17. *(See, [14]) A C_0 semigroup $\{T(t) : t \geq 0\}$ on E with generator A is positive iff $R(\lambda,A) \geq 0$ for all sufficiently large real λ.*

Definition 2.1.18. *(Dispersive Operator, see [3]) An operator $A : D(A) \subset E \to E$ is called dispersive iff for every $f \in D(A)$, there is $\Phi \in N^+(f)$ such that $\langle Af, \Phi\rangle \leq 0$, where*

$$N^+(f) = \left\{\Phi \in (E^+)^* : \|\Phi\| \leq 1, \langle f, \Phi\rangle = \left\|f^+\right\|\right\}.$$

Theorem 2.1.8. *(See, [3]) Let $A : D(A) \subset E \to E$ be a linear operator. Then, the following statements are equivalent*

(a) A is the generator of a positive contraction C_0 semigroup.

(b) A is densely defined, $R(\lambda I - A) = E$ *for some* $\lambda > 0$*, and A is dispersive.*

Example 2.1.11. *(Example of Positive* C_0 *Semigroup, see [3]) Let* $X = L_p[0,1],\ 1 \le p < \infty$ *and the operator A is given by*

$$Af = f''$$

where

$$D(A) = \{f \in X : f \in C^1[0,1], f' \in AC[0,1], f'' \in L_p[0,1], f(0) = f(1) = 0\}.$$

Then, A is the generator of a positive contraction semigroup.

Let $f \in D(A)$*. Define* $M = \{\ x \in (0,1) : f(x) > 0\}$*. Then, M is open set and hence, there exists a countable collection of disjoint open intervals* (a_n, b_n) *such that* $M = \cup_{n=1}^{\infty}(a_n, b_n)$*.*
Case- (i) If $p = 1$*, consider*

$$\Phi(x) = \begin{cases} 1 & \text{for } x \in M \\ 0 & \text{for } x \notin M. \end{cases}$$

Then, $\Phi \in N^+(f)$ *and* $\langle Af, \Phi\rangle = \sum_{n=1}^{\infty} \int_{a_n}^{b_n} f''\, dx$*. This implies that*

$$\langle Af, \Phi\rangle = \sum_{n=1}^{\infty} \left(f'(b_n) - f'(a_n)\right) \le 0.$$

Hence, A is dispersive.
Case- (ii) If $p > 1$
Let $\Phi \in N^+(f)$*, then there exists* $c \ge 0$ *such that*

$$\Phi(x) = \begin{cases} c\ f(x)^{p-1} & \text{for } x \in M \\ 0 & \text{for } x \notin M. \end{cases}$$

Further,

$$\begin{aligned} \langle Af, \Phi\rangle &= \sum_{n=1}^{\infty} \int_{a_n}^{b_n} f''(x)\ \Phi(x)\ dx \\ &= -c \sum_{n=1}^{\infty} \int_{a_n}^{b_n} (p-1) \left(f'(x)\right)^2 dx \\ &\le 0. \end{aligned}$$

So, A is dispersive. Also, $I - A$ *is surjective and hence, A generates a positive contraction* C_0 *semigroup.*

Corollary 2.1.8.1. *(See, [3]) Let $A : D(A) \subset E \to E$ be a densely defined dispersive operator on E. If $(\lambda I - A)D(A)$ is dense in E for some $\lambda > 0$, then A is closable and $\overline{A}$ is the generator of a positive contraction C_0 semigroup.*

2.2 Perturbation Results

The evolution equation (or the corresponding linear operator) is frequently expressed as a (formal) sum of several terms having physical meanings and mathematical features. While the mathematical analysis may be simple for each individual term, it is unclear what happens once the sums are formed.
Problem : Let $\{T(t) : t \geq 0\}$ be a C_0 semigroup generated by $A : D(A) \subseteq X \to X$ and consider a second operator $B : D(B) \subseteq X \to X$. Now, questions arise, under which conditions the sum $A+B$ generates a C_0 semigroup? In this case, the generator A is said to be perturbed by the operator B.

Theorem 2.2.1. *(Bounded Perturbation Theorem) Let $A : D(A) \subset X \to X$ generates a C_0 semigroup $\{T(t) : t \geq 0\}$ on X such that $\|T(t)\| \leq Me^{\omega t}$ for all $t \geq 0$ and some $\omega \in \mathbb{R}, M \geq 1$. If $B \in \mathcal{L}(X)$, then $C = A+B$ also generates a C_0 semigroup $\{S(t) : t \geq 0\}$ such that $\|S(t)\| \leq Me^{(w+M\|B\|)t}$ for all $t \geq 0$.*

Proof. See [[66], Theorem 3.1.1]. □

Corollary 2.2.1.1. *(See, [[27], Corollary 3.1.5]) Let us assume that $(A, D(A))$ is the generator of a C_0 semigroup on the Banach space X_0. If B is a bounded operator on $X_1^A = (D(A), \|\cdot\|_1)$, then $A+B$ with domain $D(A+B) = D(A)$ generates a C_0 semigroup on X_0.*

Example 2.2.1. *(See, [27]) Let $X = C_0(\mathbb{R})$ and $A : D(A) \subset X \to X$ is defined by*

$$Af := f'$$

where $D(A) = C_0^1(\mathbb{R})$. Define the operator B by

$$Bf := f'(0) \times h \quad \text{for some } h \in C_0^1(\mathbb{R}) \text{ and } f \in C_0^1(\mathbb{R}).$$

Then, B is unbounded on X but bounded on $D(A) = C_0^1(\mathbb{R})$, and hence $A+B$ is a generator on X.

Theorem 2.2.2. *Let $A : D(A) \subseteq X \to X$ be a linear operator on X. A linear operator $B : D(B) \subseteq X \to X$ is such that $D(A) \subset D(B)$ and $A+tB$ is dissipative for $0 \leq t \leq 1$. If*

$$\|Bx\| \leq \alpha \|Ax\| + \beta \|x\|$$

for $x \in D(A)$ *where* $0 \leq \alpha < 1, \beta \geq 0$ *and for some* $t_0 \in [0,1], A + t_0 B$ *is m-dissipative. Then,* $A + tB$ *is m-dissipative for all* $t \in [0,1]$.

Proof. See [[66], Theorem 3.3.2]. □

Corollary 2.2.2.1. *Let* $A : D(A) \subseteq X \to X$ *be the infinitesimal generator of a* C_0 *semigroup of contractions. Let* B *be a dissipative operator suct that* $D(A) \subset D(B)$ *and* $\|Bx\| \leq \alpha \|Ax\| + \beta \|x\|$ *for* $x \in D(A)$ *where* $0 \leq \alpha < 1, \beta \geq 0$. *Then* $A + B$ *is the generator of a* C_0 *semigroup of contractions.*

Proof. See [[66], Corollary 3.3.3]. □

Corollary 2.2.2.2. *(See, [[14], Corollary 11.7]) Let* A *generates a positive* C_0 *semigroup on a Banach lattice* E *and* $B \in \mathcal{L}(E)$ *is a positive operator, then the semigroup generated by* $A + B$ *is positive.*

2.3 Linear and Semilinear ACP

Suppose X is a Banach space and $A : D(A) \subseteq X \to X$ is a linear operator. Then, the abstract Cauchy problem for A with initial condition $u_0 \in X$ is written as

$$\begin{cases} \frac{du}{dt} = Au \ ; \quad t \geq 0 \\ u(0) = u_0 \end{cases} \tag{2.6}$$

and a solution of (2.6) means that an X valued function $u(t)$ such that $u(t)$ is continuous for $t \geq 0$, continuously differentiable and $u(t) \in D(A)$ for $t > 0$ and (2.6) is satisfied.

Theorem 2.3.1. *Let* A *be a densely defined linear operator with a nonempty resolvent set* $\rho(A)$. *Then,* $u(t) = T(t)u_0$ *is a unique solution of the IVP (2.6) which is continuously differentiable on* $[0,\infty)$ *for every initial value* $u_0 \in D(A)$ *iff* A *is the infinitesimal generator of a* C_0 *semigroup.*

Proof. See [[66], Theorem 4.1.3]. □

The effectiveness of linear semigroup theory in solving linear evolution equations has prompted the development of extensions of linear ideas that allow for the investigation of semi-linear issues. Semilinear semigroup theory is not comprehensive comparison to linear semi-group theory, but it remains a valuable and strong approach of evaluating more complicated evolution equations.

2.3.1 Semilinear Abstract Cauchy Problem

Let X be a Banach space and $A : D(A) \subset X \to X$ be a linear operator. Further, let $F : [0,T] \times X \to X$ be a nonlinear operator, then the problem

$$\begin{cases} \frac{du}{dt} = Au + F(t, u(t)) \ ; \quad t > 0 \\ u(0) = u_0 \in D(A) \end{cases} \tag{2.7}$$

is called abstract semilinear Cauchy problem, where A generates a C_0 semigroup $\{T(t) : t \geq 0\}$ on X.

2.3.1.1 Classical and Mild Solutions

Definition 2.3.1. *(Classical Solution, see [66]) A function $u : [0,T) \to X$ is a classical solution of semilinear ACP (2.7) on $[0,T)$ if u is continuous on $[0,T)$, continuously differentiable on $(0,T)$, $u(t) \in D(A)$ for $0 < t < T$ and satisfies (2.7) on $[0,T)$.*

Proposition 2.3.1. *(See,[36]) Let u be a classical solution on $[0,T]$ to the semilinear ACP (2.7) and $\{T(t) : t \geq 0\}$ is C_0 semigroup associated with the linear operator $(A, D(A))$. Then, u satisfies the integral equation*

$$u(t) = T(t)u_0 + \int_0^t T(t-s)F(s, u(s))\, ds. \tag{2.8}$$

Definition 2.3.2. *(Mild Solution, see [66]) A continuous solution u of the integral equation*

$$u(t) = T(t)u_0 + \int_0^t T(t-s)F(s, u(s))\, ds$$

is called a mild solution of the initial value problem (2.7) on $[0,T]$.

Note: Every classical solution is mild solution but the converse is not true because u given by (2.8) is not necessarily differentiable.

Example 2.3.1. *If A be the infinitesimal generator of a C_0 semigroup of contractions on X and $f \in C(\mathbb{R}^+, X)$ such that*

$$v(t) = \int_0^t T(t-s) f(s)\, ds$$

is not differential. Then, a mild solution of

$$\begin{cases} \frac{du}{dt} = Au + f(t) \ ; \quad t \geq 0 \\ u(0) = u_0 \end{cases} \tag{2.9}$$

need not be classical solution.
Let A be the generator of translation semigroup on $C[0,\infty)$ defined by

$$T(t)f(s) = f(t+s).$$

Choose $f \in C[0,\infty)$ as

$$f(s) = \begin{cases} 3-s & 0 \le s \le 2 \\ s-1 & 2 < s < \infty \end{cases}$$

such that $T(t)f(s) = f(t+s) \notin D(A)$. Then, IVP (2.9) has a mild solution which is not classical solution.

Definition 2.3.3. *(Local Lipschitz Condition, see [66]) An operator $F : \mathbb{R}^+ \times X \to X$ is said to satisfy a local Lipschitz condition in u, uniformly in t on bounded intervals if for every $t' \ge 0$ and constant $\alpha \ge 0$, there is a constant $M(\alpha, t')$ such that*

$$\|F(t,x) - F(t,y)\| \le M(\alpha)\,\|x-y\|$$

whenever $x, y \in X,\ 0 \le t \le t',\ \|x\| \le \alpha,\ \|y\| \le \alpha$.

The following Theorems 2.3.2 and 2.3.3 provide the existence of solution results for semilinear evolution equation.

2.3.2 Local and Global Existence Theorem

Theorem 2.3.2. *(Local Existence Theorem) Suppose A generates a C_0 semigroup $\{T(t) : t \ge 0\}$ on X and $F : \mathbb{R}^+ \times X \to X$ is a nonlinear continuous operator satisfying the local Lipschitz condition. Then, for any $u_0 \in X$, there is a positive constant $t_{max} \le \infty$ such that the initial value problem (2.7) admits a unique mild solution u on $[0, t_{max})$. Moreover, if $t_{max} < \infty$ then*

$$\lim_{t \to t_{max}} \|u(t)\| = \infty.$$

Proof. See [[66], Theorem 6.1.4]. □

Theorem 2.3.3. *(Global Existence Theorem) Let $u_0 \in X$ and A generates a C_0 semigroup $\{T(t) : t \ge 0\}$ on X. Let the nonlinear operator $F : \mathbb{R}^+ \times X \to X$ satisfies the condition: for each $\alpha > 0$ there is a constant $M = M(\alpha)$ such that*

$$\|F(t,x) - F(t,y)\| \le M(\alpha)\,\|x-y\|$$

whenever $x, y \in X,\ 0 \le t \le \alpha$. Then, the problem (2.7) admits a unique mild solution on $\mathbb{R}^+$.

Proof. See [[36], Theorem 2.2.5]. □

Theorem 2.3.4. *Let A generates a C_0 semigroup $\{T(t) : t \geq 0\}$ on X. Let $u_0 \in D(A)$, and the nonlinear operator $F : [0,T] \times X \to X$ is continuously differentiable from $[0,T] \times X$ into X, then the mild solution of the problem (2.7) is a classical solution.*

Proof. See [[66], Theorem 6.1.5]. □

2.4 Evolution System Theory

Let X be a Banach space. For every t, $0 \leq t \leq T$, let $A(t) : D(A(t)) \subset X \to X$ be a linear operator in X. Consider the homogeneous IVP

$$\begin{cases} \frac{du(t)}{dt} = A(t)u(t) \ ; \quad 0 \leq s \leq t \leq T \\ u(s) = v. \end{cases} \tag{2.10}$$

Let us define the solution operator of the IVP (2.10) by

$$U(t,s)v = u(t) \quad \text{for } \ 0 \leq s \leq t \leq T$$

where u is the solution of (2.10) and $U(t,s)$ is a two parameter family of operators.

Definition 2.4.1. *(See, [66]) Let $U(t,s)$, $0 \leq s \leq t \leq T$, be a two parameter family of bounded linear operators on a Banach space X. Then, it is called an evolution system if the following two conditions are satisfied*

(a) $U(s,s) = I$, $U(t,r)U(r,s) = U(t,s)$ *for* $0 \leq s \leq r \leq t \leq T$.

(b) $(t,s) \to U(t,s)$ *is strongly continuous for* $0 \leq s \leq r \leq t \leq T$.

Stable Families

Definition 2.4.2. *(See, [66]) A family $\{A(t)\}_{t\in[0,T]}$ of infinitesimal generators of C_0 semigroup on X is called stable if there are constants $M \geq 1$ and ω (stability constants) such that*

$$(\omega,\infty) \subset \rho(A(t)) \quad \text{for } t \in [0,T]$$

and

$$\left\| \prod_{i=1}^{k} R(\lambda : A(t_i)) \right\| \leq M(\lambda-\omega)^{-k} \quad \text{for } \lambda > \omega$$

and every finite sequence $0 \leq t_1 \leq t_2, \cdots, t_k \leq T$, $k = 1,2,\dots$.

Note: If for $t \in [0,T], A(t) \in G(1,\omega)$, that is, $A(t)$ is the infinitesimal generator of a C_0 semigroup $S_t(s)$, $s \geq 0$, satisfying $\|S_t(s)\| \leq e^{\omega s}$ then the family $\{A(t)\}_{t\in[0,T]}$ is stable with constants $M = 1$ and ω. In particular, any family $\{A(t)\}_{t\in[0,T]}$ of infinitesimal generators of C_0 semigroups of contractions is stable.

Theorem 2.4.1. *Let $A(t)$ be the infinitesimal generator of a C_0 semigroup $S_t(s)$ on X for $t \in [0,T]$. The family of generators $\{A(t)\}_{t\in[0,T]}$ is stable if and only if there are constants $M \geq 1$ and ω such that $(\omega,\infty) \subset \rho(A(t))$ for $t \in [0,T]$ and either one of the following conditions is satisfied*

$$\left\| \prod_{i=1}^{k} S_{t_i}(s_i) \right\| \leq M \exp(\omega \sum_{i=1}^{k} s_i) \quad \text{for } s_i \geq 0$$

or

$$\left\| \prod_{i=1}^{k} R(\lambda_i : A(t_i)) \right\| \leq M \prod_{i=1}^{k} (\lambda_i - \omega)^{-1} \quad \text{for } \lambda_i > \omega$$

and any finite sequence $0 \leq t_1 \leq t_2, \cdots, t_k \leq T$, $k = 1,2,\ldots$.

Proof. See [[66], Theorem 5.2.2]. □

Theorem 2.4.2. *Let us assume that $\{A(t)\}_{t\in[0,T]}$ is a stable family of infinitesimal generators having stability constants M and ω. Let $B(t), 0 \leq t \leq T$ be a bounded linear operators on X. If $\|B(t)\| \leq K$ for all $t \in [0,T]$, then $\{A(t)+B(t)\}_{t\in[0,T]}$ is a stable family of infinitesimal generators with stability constants M and $\omega + KM$.*

Proof. See [[66], Theorem 5.2.3]. □

For $t \in [0,T]$, let $A(t)$ be the infinitesimal generator of a C_0 semigroup $S_t(s), s \geq 0$, on X. We consider the following assumptions.
(H_1) : $\{A(t)\}_{t\in[0,T]}$ is a stable family with stability constants M and ω.
(H_2) : Y is $A(t)-$admissible for $t \in [0,T]$ and the family $\{\tilde{A}(t)\}_{t\in[0,T]}$ of parts $\tilde{A}(t)$ of $A(t)$ in Y, is a stable family in Y with stability constants $\tilde{M}, \tilde{\omega}$.
(H_3) : For $t \in [0,T], Y \subset D(A(t)), A(t)$ is bounded operator from Y into X and $t \to A(t)$ is continuous in the $B(Y,X)$ norm $\|\cdot\|_{Y\to X}$.

Some Important Theorems

Theorem 2.4.3. *Let $A(t), 0 \leq t \leq T$, be the infinitesimal generator of a C_0 semigroup $S_t(s), s \geq 0$, on X. If the conditions $(H_1)-(H_3)$ hold for the family $\{A(t)\}_{t\in[0,T]}$, then there exists a unique evolution system $U(t,s), 0 \leq s \leq t \leq T$, in X satisfying*

$$(E_1) \qquad \|U(t,s)\| \leq M \exp\{\omega(t-s)\} \quad \text{for } 0 \leq s \leq t \leq T,$$

$$(E_2) \qquad \frac{\partial^+}{\partial t}U(t,s)v\Big|_{t=s} = A(s)v \quad \text{for } v \in \mathrm{Y}, 0 \le s \le t \le T,$$

$$(E_3) \qquad \frac{\partial}{\partial s}U(t,s)v = -U(t,s)A(s)v \quad \text{for } v \in \mathrm{Y}, 0 \le s \le t \le T,$$

where the derivative from the right in (E_2) and the derivative in (E_3) are in the strong sense in X.

Proof. See [[66], Theorem 5.3.1]. □

Theorem 2.4.4. *Let $A(t), 0 \le t \le T$ satisfy the conditions of Theorem (2.4.3) and let $U(t,s), 0 \le s \le t \le T$ be the evolution system given in Theorem (2.4.3). If*

$$(E_4) \qquad U(t,s)Y \subset Y \quad \text{for } 0 \le s \le t \le T,$$

and

$$(E_5) \qquad \text{for } v \in Y,\ U(t,s)v \text{ is continuous in } Y \quad \text{for } 0 \le s \le t \le T,$$

then for every $v \in Y$, $U(t,s)v$ is the unique $Y-$valued solution of the IVP (2.10).

Proof. See [[66], Theorem 5.4.3]. □

Now, to find an evolution system $U(t,s)$ that satisfies $(E_1)-(E_5)$, the condition (H_2) of Theorem (2.4.3) is replaced by the following condition:

(H_2^+) : There is a family $\{Q(t)\}_{t\in[0,T]}$ of isomorphisms of Y onto X such that for every $v \in Y$, $Q(t)v$ is continuously differentiable in X on $[0,T]$ and

$$Q(t)A(t)Q(t)^{-1} = A(t) + B(t)$$

where $B(t)$, $0 \le t \le T$, is strongly continuous family of bounded operators on X.

Lemma 2.4.5. *The conditions (H_1) and $(H_2)^+$ imply the condition (H_2).*

Proof. See [[66], Lemma 5.4.4]. □

Lemma 2.4.6. *Let $U(t,s)$, $0 \le s \le t \le T$ be an evolution system in X satisfying $\|U(t,s)\| \le M$ for $0 \le s \le t \le T$. If $H(t)$ is a strongly continuous family of bounded linear operators in X then there exists a unique family of bounded linear operators $V(t,s)$, $0 \le s \le t \le T$ in X such that*

$$V(t,s)x = U(t,s)x + \int_s^t V(t,r)H(r)U(r,s)x\,dr \quad \text{for } x \in X, \tag{2.11}$$

and $V(t,s)x$ is continuous in s,t for $0 \le s \le t \le T$.

Proof. See [[66], Lemma 5.4.5]. □

Theorem 2.4.7. *Let $A(t), 0 \leq t \leq T$, be the infinitesimal generator of a C_0 semigroup on X. If the family $\{A(t)\}_{t\in[0,T]}$ satisfies the conditions $(H_1),(H_2)^+$ and (H_3) then there exists a unique evolution system $U(t,s), 0 \leq s \leq t \leq T$, in X satisfying $(E_1)-(E_5)$.*

Proof. See [[66], Theorem 5.4.6]. □

Corollary 2.4.7.1. *Let $\{A(t)\}_{t\in[0,T]}$ be a family of infinitesimal generator of a C_0 semigroup on X. If the family $\{A(t)\}_{t\in[0,T]}$ satisfies the conditions $(H_1),(H_2)^+$ and (H_3) then for every $v \in Y$ the IVP (2.10) has a unique $Y-$valued solution u on $0 \leq s \leq t \leq T$.*

Proof. See [[66], Corollary 5.4.7]. □

2.5 Weak Compactness in L_1 Space

It is interesting to identify the condition under which a family of functions in $L_p(\Omega)$, $1 \leq p < \infty$ has compact closure. We know that the Ascoli-Arzela theorem gives the answer for the same question in $C(K)$, the space of continuous functions over compact metric space K with values in $\mathbb{R}$.

Definition 2.5.1. *(See, [17]) Let K be a compact metric space and F is a subset of $C(K)$. Then, F is said to be uniformly equicontinuous if for every $\varepsilon > 0$, there exists $\delta > 0$ such that*

$$|f(x) - f(y)| < \varepsilon \quad \text{for all} \;\; f \in F$$

whenever $d(x,y) < \delta$.

Theorem 2.5.1. *(Arzela-Ascoli Theorem, see [17]) Let K be a compact metric space and F is a subset of $C(K)$. Then, the closure of F in $C(K)$ is compact if F is bounded and uniformly equicontinuous.*

In the weak compactness sense, the properties of L_1 spaces differ from properties of L_p, $1 < p < \infty$, spaces. In particular, L_1 being non-reflexive, its unit ball is not weakly compact. Kakutani's theorem [[17], Theorem 3.17] and the reflexivity of $L_p(\Omega)$, $p \in (1,\infty)$, see [[17], Theorem 4.10] warrant that any bounded suquence in $L_p(\Omega)$ has a subsequence that converges weakly in $L_p(\Omega)$. The bounded sets of L_1 do not play an important role with respect to the weak topology of L_1 space because L_1 is not reflexive. In the following, Dunford-Pettis theorem provides an important characterization of weakly compact sets in L_1. The weak compactness argument in L_1 space is used to prove the existence of weak solution to the age/size structured population models, see [33, 34, 53, 54, 56, 71]

Definition 2.5.2. *(See, [11])*

(a) *Let $p \in [1,\infty)$. A sequence (f_n) in $L_p(\Omega)$ converges weakly to f (written as $f_n \rightharpoonup f$) in $L_p(\Omega)$ if*

$$\lim_{n\to\infty} \int_\Omega f_n(x)\varphi(x)\, d\mu(x) = \int_\Omega f(x)\varphi(x)\, d\mu(x)$$

for all $\varphi \in L_q$, where $q = \infty$ when $p = 1$ and $q = \frac{p}{p-1}$ when $p \in (1,\infty)$.

(b) *A sequence (f_n) in $L_\infty(\Omega)$ converges $*$- weakly to f (written as $f_n \overset{*}{\rightharpoonup} f$) in $L_\infty(\Omega)$ if*

$$\lim_{n\to\infty} \int_\Omega f_n(x)\varphi(x)\, d\mu(x) = \int_\Omega f(x)\varphi(x)\, d\mu(x)$$

for all $\varphi \in L_1(\Omega)$.

Example 2.5.1. *(See [[17], page 122]) Consider the sequence (g_n) of functions in $L_1(0,1)$ and defined by $g_n(x) = ne^{-nx}$. Then,*

(a) $g_n \to 0$ *a.e.*

(b) g_n *is bounded.*

(c) $g_n \nrightarrow 0$ *strongly*

(d) $g_n \nrightarrow 0$ *weakly* $\sigma(L_1, L_\infty)$.

Example 2.5.2. *(See [[17], page 122]) Consider the sequence (f_n) of functions in $L_p(0,1)$, $1 < p < \infty$, and defined by $f_n(x) = n^{1/p}e^{-nx}$. Then,*

(a) $f_n \to 0$ *a.e.*

(b) f_n *is bounded.*

(c) $f_n \nrightarrow 0$ *strongly*

(d) $f_n \rightharpoonup 0$ *weakly* $\sigma(L_p, L_q)$, *where* $\frac{1}{p} + \frac{1}{q} = 1$.

Definition 2.5.3. *(Equi-integrable families, see [17]) A subset $F \subset L_1(\Omega)$ is said to be equi-integrable if it satisfies the following conditions:*

(a) *F is bounded in $L_1(\Omega)$,*

(b) *$\forall \varepsilon > 0$, there exists $\delta > 0$ such that*

$$\int_A |f| d\mu < \varepsilon, \;\; \forall A \subset \Omega, \; A \text{ measurable } |A| < \delta, \;\; \forall f \in F$$

(c) $\forall \varepsilon > 0$, *there exists* $\omega \subset \Omega$ *measurable with* $|\omega| < \infty$ *such that*

$$\int_{\Omega-\omega} |f| d\mu < \varepsilon, \quad \forall f \in F.$$

Theorem 2.5.2. *(Dunford-Pettis Theorem) A subset F of $L_1(\Omega)$ has compact closure in the weak topology $\sigma(L_1, L_\infty)$ if and only if F is equi-integrable.*

Proof. See [11, 17, 25, 75]. □

Corollary 2.5.2.1. *For a given set F in $L_1(\Omega)$, the following properties are equivalent:*

(a) *F is contained in a weakly $\sigma(L_1, L_\infty)$ compact set of $L_1(\Omega)$*

(b) *F is equi-integrable.*

Lemma 2.5.3. *(See [[17], page 468]) Let $\vartheta_1, \vartheta_2 \in L_1(\Omega)$ such that $\vartheta_1 \leq \vartheta_2$ a.e. Then, the set $K = \{f \in L_1(\Omega) : \vartheta_1 \leq f \leq \vartheta_2 \text{ a.e. }\}$ is compact in weak topology $\sigma(L_1, L_\infty)$.*

Lemma 2.5.4. *(See [[17], page 468]) Let (f_n) be a bounded sequence in $L_1(\Omega)$ such that $\int_A f_n$ converges to a finite limit $\ell(A)$, for every measurable set $A \subset \Omega$. Then, there exists some $f \in L_1(\Omega)$ such that $f_n \rightharpoonup f$ weakly $\sigma(L_1, L_\infty)$.*

Lemma 2.5.5. *(See [[17], page 125]) Let (f_n) be a sequence in $L_1(\Omega)$ with $|\Omega| < \infty$ and $f \in L_1(\Omega)$. Then, the following properties are equivalent:*

(a) *$f_n \rightharpoonup f$ in $\sigma(L_1, L_\infty)$*

(b) *$\int_\Omega |f_n| < C$ and $\int_\omega f_n \to \int_\omega f$, $\forall \omega \subset \Omega$, ω measurable and $|\omega| < \infty$.*

Example 2.5.3. *(See [[30], page 181]) Let $X = L_1([0, 2\pi])$. Then, the sequence $f_n(x) = \sin nx$ converges weakly to 0 in $L_1([0, 2\pi])$.*

Lemma 2.5.6. *(See [[17], page 125]) Let (f_n) be a sequence of functions in $L_1(\Omega)$ with $|\Omega| = \infty$ and $f(x) \in L_1(\Omega)$ such that*

(a) *$f_n \geq 0 \quad \forall n$ and $f \geq 0$ a.e. on Ω,*

(b) *$\int_\Omega f_n \to \int_\Omega f$,*

(c) *$\int_\omega f_n \to \int_\omega f$, $\forall \omega \subset \Omega$, ω measurable and $|\omega| < \infty$.*

Then, $f_n \rightharpoonup f$ in $L_1(\Omega)$ with respect to the weak topology $\sigma(L_1, L_\infty)$.

Lemma 2.5.7. *(See [[17], page 468]) Let* $F \subset L_1(\Omega)$ *with* $|\Omega| < \infty$ *and* $G : [0,\infty) \to [0,\infty)$ *be a continuous function such that* $\lim_{t\to\infty} \frac{G(t)}{t} = \infty$*. Assume that there exists a constant* C *such that*

$$\int F(|f|) \leq C \quad \forall f \in F.$$

Then, F *is equi-integrable.*

Definition 2.5.4. *(Equicontinuity, see [76]) Let* X *be a Banach space. Then, a subset* F *in* $C([a,b];X)$ *is equicontinuous at* $t_0 \in [a,b]$ *if for each* $\varepsilon > 0$ *there exists* $\delta(\varepsilon, t_0) > 0$ *such that for each* $t \in [a,b]$ *with* $|t - t_0| < \delta$*, we have*

$$\|f(t) - f(t_0)\| \leq \varepsilon$$

uniformly with respect to $f \in F$*.*

Definition 2.5.5. *(Weak Equicontinuity, see [11]) Let* X *be a Banach space. Then, a subset* F *in* $C([a,b];X_w)$ *is weakly equicontinuous at* $t_0 \in [a,b]$ *if for each* $\varphi \in X^*$ *and* $\varepsilon > 0$ *there exists* $\delta = \delta(\varphi, \varepsilon, t_0) > 0$ *such that for each* $t \in [a,b]$ *with* $|t - t_0| < \delta$*, we have*

$$|\langle \varphi, f(t) \rangle - \langle \varphi, f(t_0) \rangle| \leq \varepsilon$$

uniformly with respect to $f \in F$*.*

Theorem 2.5.8. *(Arzela-Ascoli Theorem, see [[75], Theorem 1.3.1]) Let* X *be a Banach space. A subset* F *in* $C([a,b];X)$ *is relatively compact iff*

(a) F *is equicontinuous on* $[a,b]$*.*

(b) There exists a dense subset D *in* $[a,b]$ *such that for each* $t \in D$*,*

$$F(t) = \{f(t) : f \in F\}$$

is relatively compact in X*.*

Theorem 2.5.9. *(The weak variant of Arzela-Ascoli Theorem, see [[75], Theorem 1.3.2]) A subset* F *in* $C([a,b];X_w)$ *is relatively sequentially compact iff*

(a) F *is weakly equicontinuous on* $[a,b]$*,*

(b) there exists a dense subset D *of* $[a,b]$ *such that for each* $t \in D$*,*

$$F(t) = \{f(t) : f \in F\}$$

is weakly relatively compact in X*.*

2.6 Stability Theory

In this section, we recall a handful of results on dynamical systems which are to be used in Chapter 5 and Chapter 6 to study qualitative properties of prion-chaperone equations. A dynamical system gives a functional description of the solution of a physical problem or a mathematical model describing the physical problem. For example, the motion of the undamped pendulum is a dynamical system in the sense that the motion of the pendulum is described by its position and velocity as functions of time and the initial conditions. Mathematically speaking, a dynamical system is a function $\phi(t,x)$ defined for all $t \in \mathbb{R}$ and $E \subset \mathbb{R}^n$ which describes how points $x \in E$ move with respect to time.

Definition 2.6.1. *(See, [20]) Let E be an open subset in $\mathbb{R}^n$. A dynamical system on E is a C^1-map*

$$\phi : \mathbb{R} \times E \to E$$

and if $\phi_t(x) = \phi(t,x)$, then ϕ_t satisfies

1. $\phi_0(x) = x$ for all $x \in E$ and
2. $\phi_t \circ \phi_s(x) = \phi_{t+s}(x)$ for all $s,t \in \mathbb{R}$ and $x \in E$.

Definition 2.6.2. *(See, [20]) Let E be an open subset in $\mathbb{R}^n$ and $f \in C^1(E)$. For $x_0 \in E$, let $\phi(t,x_0)$ is the solution of initial value problem*

$$\dot{x} = f(x), \quad x(0) = x_0 \tag{2.12}$$

defined on its maximal interval of existence $I(x_0)$. Then, for $t \in I(x_0)$, the mapping $\phi_t : E \to E$ defined by

$$\phi_t(x) = \phi(t,x)$$

is called the flow of differential equation (2.12).

In many cases, mathematical models are used to describe physical phenomena and are represented by the autonomous differential equation of type (2.12) defined on an open set $E \subset \mathbb{R}^n$ and its flow ϕ_t. It's crucial to understand how slight perturbations in the initial data effect the desired behaviour of solution (2.12). If a sufficiently modest modification in the initial data leads to a significant departure in the associated solution, the solution derived from the given initial data is unsuitable because it does not even approximate the desired phenomena.

Let us consider an equilibrium point x_0 for the nonlinear autonomous system

$$\dot{x} = f(x), \qquad x \in \mathbb{R}^n. \tag{2.13}$$

Definition 2.6.3 (Stable). *An equilibrium point x_0 of (2.13) is said to be stable if for each $\varepsilon > 0$, there exists $\delta(\varepsilon) > 0$ such that the inequality $|\phi_t(x) - \phi_t(x_0)| < \varepsilon$ holds whenever $|x - x_0| < \delta$ for all $t \geq 0$.*

Definition 2.6.4 (Asymptotically Stable). *An equilibrium point x_0 of (2.13) is said to be asymptotically stable if it is stable and if there exists $\delta > 0$ such that $|x - x_0| < \delta$ implies that $|\phi_t(x) - \phi_t(x_0)| \to 0$ as $t \to \infty$.*

Definition 2.6.5 (Unstable). *An equilibrium point x_0 of (2.13) is said to be unstable if it is not stable.*

A continuous function $V : U \to \mathbb{R}$ where $U \subseteq \mathbb{R}^n$ is an open set with $x_0 \in U$, is called a Lyapunov function for the differential equation (2.13) at x_0 provided that

(i) $V(x_0) = 0$,

(ii) $V(x) > 0 \quad \text{for} \quad x \in U - \{x_0\}$,

(iii) the function $x \to \operatorname{grad} V(x)$ is continuous for $x \in U - \{x_0\}$, and on this set, $\dot{V}(x) := \operatorname{grad} V(x) \cdot f(x) \leq 0$.

If, in addition,

(iv) $\dot{V}(x) < 0 \quad \text{for} \quad x \in U - \{x_0\}$,

then V is called a strict Lyapunov function.

Theorem 2.6.1. *(Lyapunov's Stability Theorem, see [20]) If x_0 is an equilibrium point for the differential equation (2.13) and V is a Lyapunov function for the system at x_0, then x_0 is stable. If, in addition, V is a strict Lyapunov function, then x_0 is asymptotically stable.*

Chapter 3

Evolution Equation of a Prion Proliferation Model in the Presence of Chaperone [1]

3.1 Introduction

In this chapter, a mathematical model for the dynamics of prion proliferation in the presence of chaperone involving a coupled system consisting of an ordinary differential equation and a partial integro-differential equation is analyzed. For bounded reaction rates, we prove the existence and uniqueness of positive classical solutions with the help of evolution operator theory. In the case of unbounded reaction rates, the model is set up into a semilinear evolution equation form in the product Banach space $\mathbb{R} \times L_1((z_0,\infty);(q+z)dz)$ and the existence of a unique positive local mild solution is established by using C_0 semigroups theory of operators.
The prion proliferation model in the presence of chaperone, see Section 1.2, is described by the following set of equations

$$\frac{dS(t)}{dt} = \lambda - \gamma S(t) - \tau S(t)\int_{z_0}^{\infty} u(t,z)dz + 2\int_0^{z_0} z\int_{z_0}^{\infty} \beta(z')\, k(z,z')\, u(t,z')\, dz'dz, \tag{3.1}$$

$$\frac{\partial u(t,z)}{\partial t} = -\tau S(t)\frac{\partial u(t,z)}{\partial z} - \left[\mu(z)+\beta(z)+\delta_2 C(t)\right]u(t,z) + 2\int_z^{\infty} \beta(z')k(z,z')u(t,z')dz', \tag{3.2}$$

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t)\int_{z_0}^{\infty} u(t,z)\, dz, \tag{3.3}$$

subject to the conditions

$$S(0)=S_0,\ u(0,z)=u_0(z),\ u(t,z_0)=0,\ C(0)=C_0 \ \text{ for } \ t\geq 0,\ z_0<z<\infty \tag{3.4}$$

[1] A considerable part of this chapter is published in *Mathematical Methods in the Applied Sciences*, **44**, 1942-1955, 2021.

where all the constants λ, γ, τ, δ_0, δ_1 and δ_2 are positive and the description of these parameters is given in Chapter 1. We assume that the splitting density function $k(z,z')$ satisfies the conditions (1.4)-(1.8).

This chapter is assembled as follows: In Section 3.2, the system (3.2)-(3.4) is transformed into a semilinear evolution equation in the product Banach space $\mathbb{R}\times L_1\left((z_0,\infty);(q+z)dz\right)$ under the assumption (1.9). Then, the existence of the unique positive local mild solution is proved by using C_0 semigroup theory. The positive global classical solution of the coupled system (3.2)-(3.4) is discussed in Section 3.3 with the help of evolution system theory under the assumptions that the reaction rates $\mu(z)$ and $\beta(z)$ are bounded.

3.2 The Semilinear Autonomous Problem

To establish the existence and uniqueness of positive local mild solution, we first transform the system (3.2)-(3.4) into a semilinear evolution equation in the suitable Banach space. For this, assuming

$$\mu(z)=\mu,\ \beta(z)=\beta z \text{ and } k(z',z)=\begin{cases}\frac{1}{z} & \text{if } z>z_0 \text{ and } 0<z'<z\\ 0 & \text{otherwise.}\end{cases}$$

The system (3.2)-(3.4) becomes

$$\frac{dC(t)}{dt} = -\delta_0 C(t)+\delta_1 C(t)\int_{z_0}^{\infty}u(t,z)dz$$

$$\partial_t u(t,z)+\omega\partial_z u(t,z)+\Big(\mu+\beta z+\delta_2 C(t)\Big)u(t,z)=2\beta\int_z^{\infty}u(t,z')dz' \text{ and}$$

$$C(0)=C_0,\ u(0,z)=u_0(z),\ u(t,z_0)=0 \text{ for } t>0,\ z>z_0.$$

Substitute $\vartheta(t,z)=u(t,z+z_0)$ for $z\geq 0$, then the above system reduces to

$$\frac{dC(t)}{dt} = -\delta_0 C(t)+\delta_1 C(t)\int_0^{\infty}\vartheta(t,z)dz \tag{3.5}$$

$$\partial_t\vartheta(t,z)+\omega\partial_z\vartheta(t,z)+\Big(\mu_0+\beta z+\delta_2 C(t)\Big)\vartheta(t,z)=2\beta\int_z^{\infty}\vartheta(t,z')dz' \tag{3.6}$$

subject to the conditions

$$C(0)=C_0,\ \vartheta(0,z)=u_0(z+z_0)=\vartheta_0(z),\ \vartheta(t,0)=0 \text{ for } t>0,\ z>0 \tag{3.7}$$

where $\mu_0 = \mu + \beta z_0$ and ω plays the role of τS at ∞, i.e., $\omega = \tau S(\infty) = \frac{\lambda\tau}{\gamma}$ in the disease-free case or $\omega = \tau S(\infty) = \frac{(\mu+\beta z_0)^2}{\beta} = \frac{\mu_0^2}{\beta}$ in the disease case, refer to [28]. Choose the state space

$$E = \left\{ V = \begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \in \mathbb{R} \times L_1\left(\mathbb{R}^+; (q+z)dz\right) \;:\; ||V||_E < \infty \right\}$$

with the norm is defined as

$$\|V\|_E = \left\| \begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \right\|_E = q||\vartheta||_1 + ||z\vartheta||_1 + |\ell| \quad \text{for } q > 0$$

where $\|\cdot\|_1$ denotes the norm in $L_1(\mathbb{R}^+)$. It is easy to verify that E is a Banach Space. Define three operators $\mathcal{A} : D(\mathcal{A}) \subset E \to E$, $\mathcal{B} : D(\mathcal{B}) \subset E \to E$ and $\mathcal{F} : E \to E$ such as

$$\mathcal{A}\begin{pmatrix} \ell \\ \vartheta \end{pmatrix} = \begin{pmatrix} 0 \\ \omega\vartheta' + (\mu_0 + \beta z)\vartheta \end{pmatrix}, \; \mathcal{B}\begin{pmatrix} \ell \\ \vartheta \end{pmatrix} = \begin{pmatrix} -\delta_0 \ell \\ 2\beta \int_z^\infty \vartheta(z')dz' \end{pmatrix} \;\text{ for }\; \begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \in D(\mathcal{A}) = D(\mathcal{B})$$

and $\mathcal{F}\begin{pmatrix} \ell \\ \vartheta \end{pmatrix} = \begin{pmatrix} \delta_1 \, \ell \int_0^\infty \vartheta(z)dz \\ -\delta_2 \, \ell \, \vartheta \end{pmatrix}$ for $\begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \in E$, where

$$D(\mathcal{A}) = \left\{ \begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \in E : \vartheta \in W_1^1(\mathbb{R}^+) \cap L_1\left(\mathbb{R}^+; (q+z)dz\right), \, z^2\vartheta \in L_1(\mathbb{R}^+), \, z\vartheta' \in L_1(\mathbb{R}^+), \, \vartheta(0) = 0 \right\}.$$

Here, $\mathcal{A}$ and $\mathcal{B}$ are linear operators while $\mathcal{F}$ is a nonlinear operator. Finally, the system of equations (3.5)-(3.7) can be written as a semilinear evolution equation in the Banach space E as

$$\begin{cases} \frac{dV}{dt} = -(\mathcal{A} - \mathcal{B})V + \mathcal{F}(V) \, ; \quad t \geq 0 \\ V(0) = V_0 = \begin{pmatrix} C_0 \\ \vartheta_0(z) \end{pmatrix}. \end{cases} \tag{3.8}$$

Lemma 3.2.1. *Let* $E = \mathbb{R} \times L_1\left(\mathbb{R}^+; (q+z)dz\right)$ *be a Banach space with* $q > 0$, *then* $\Phi_V = \big(\operatorname{sgn}(\ell), \operatorname{sgn}(\vartheta)\big)$ *is a duality map defined as*

$$\Phi_V \begin{pmatrix} \ell \\ \vartheta(z) \end{pmatrix} = \int_0^\infty \vartheta(z) \operatorname{sgn}(\vartheta) \, (q+z) \, dz + \ell \operatorname{sgn}(\ell) \quad \text{for } V = \begin{pmatrix} \ell \\ \vartheta(z) \end{pmatrix} \in E.$$

Proof. Clearly, $\Phi_V \begin{pmatrix} \ell \\ \vartheta(z) \end{pmatrix} = \int_0^\infty \vartheta(z) \operatorname{sgn}(\vartheta) \, (q+z) \, dz + \ell \operatorname{sgn}(\ell) = \left\| \begin{pmatrix} \ell \\ \vartheta(z) \end{pmatrix} \right\|_E$ and $\|\Phi_V\| = 1$. Hence, by the definition of duality, Φ_V is a duality map for $V \in E$. □

Now, before proving the main result Theorem 3.2.2 of this section, the following Propositions 3.2.1 – 3.2.3 are required.

3.2.1 Positive Contraction Semigroup Generated by $\overline{A-B}$

Proposition 3.2.1. *The operator $\mathcal{A}: D(\mathcal{A}) \subset E \to E$ is a m-Accretive on E.*

Proof. Since,

$$\int_0^\infty [\ \omega\vartheta'(z) + (\mu_0 + \beta z)\vartheta(z)\ ]\ \mathrm{sgn}(\vartheta)\ q\ dz = q\mu_0 \,||\vartheta||_1 + q\beta\,||z\vartheta||_1 \tag{3.9}$$

and $$\int_0^\infty [\ \omega\vartheta'(z) + (\mu_0 + \beta z)\vartheta(z)\ ]\ \mathrm{sgn}(\vartheta)\ z\ dz = -\omega\,||\vartheta||_1 + \mu_0\,||z\vartheta||_1 + \beta\,\left|\left|z^2\vartheta\right|\right|_1, \tag{3.10}$$

adding equations (3.9) and (3.10), yields

$$(\mathcal{A}V, \Phi_V) = (q\mu_0 - \omega)\,||\vartheta||_1 + (q\beta + \mu_0)\,||z\vartheta||_1 + \beta\,\left|\left|z^2\vartheta\right|\right|_1.$$

This shows that $(\mathcal{A}V, \Phi_V) \geq (q\mu_0 - \omega)\,||\vartheta||_1 + (q\beta + \mu_0)\,||z\vartheta||_1 \geq 0$ provided $\mu_0 > \frac{\omega}{q}$ and for such q, $\mathcal{A}$ is Accretive and hence closable.

To compute the resolvent of $\mathcal{A}$, the equation $(\lambda I + \mathcal{A})V = \begin{pmatrix} m \\ f \end{pmatrix}$ is equivalent to solving

$$\begin{pmatrix} \lambda\ell \\ \lambda\vartheta + \omega\vartheta' + (\mu_0 + \beta z)\vartheta \end{pmatrix} = \begin{pmatrix} m \\ f \end{pmatrix}$$

that is,

$$\begin{cases} \lambda\vartheta + \omega\vartheta' + (\mu_0 + \beta z)\vartheta = f \\ \lambda\ell = m. \end{cases} \tag{3.11}$$

Hence,

$$V = (\lambda I + \mathcal{A})^{-1}\begin{pmatrix} m \\ f \end{pmatrix} = \begin{pmatrix} \frac{m}{\lambda} \\ \frac{1}{\omega}\int_0^z e^{\frac{-(\lambda+\mu_0)(z-y)}{\omega} - \frac{\beta(z^2-y^2)}{2\omega}} f(y)dy \end{pmatrix}.$$

Further, to show that $V = \begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \in D(\mathcal{A})$, we assume $\begin{pmatrix} m \\ f \end{pmatrix} \in \mathbb{R} \times L_1(\mathbb{R}^+)$. Then, one can easily obtain $||\vartheta||_1 + |\ell| \leq \frac{||f||_1}{\lambda+\mu_0} + |\ell|$ and $\begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \in \mathbb{R} \times L_1(\mathbb{R}^+)$. Also, if $\begin{pmatrix} \ell \\ zf \end{pmatrix} \in \mathbb{R} \times L_1(\mathbb{R}^+)$, then

$$\left|\left|z^2\vartheta\right|\right|_1 + |\ell| \leq \frac{2}{\lambda + \mu_0}\left[\frac{\omega\,||zf||_1}{\lambda + \mu_0} + \frac{\omega^2\,||f||_1}{(\lambda + \mu_0)^2}\right] + \frac{1}{\beta}\,||zf||_1 + |\ell|.$$

This indicates that $\begin{pmatrix} \ell \\ z^2\vartheta \end{pmatrix} \in \mathbb{R}\times L_1(\mathbb{R}^+)$ and similarly $\begin{pmatrix} \ell \\ z\vartheta \end{pmatrix} \in \mathbb{R}\times L_1(\mathbb{R}^+)$. Due to (3.11), $\begin{pmatrix} \ell \\ \vartheta' \end{pmatrix} \in \mathbb{R}\times L_1(\mathbb{R}^+)$ as well as $\begin{pmatrix} \ell \\ z\vartheta' \end{pmatrix} \in \mathbb{R}\times L_1(\mathbb{R}^+)$. Finally, by the definition of $D(\mathcal{A})$, $\begin{pmatrix} \ell \\ \vartheta \end{pmatrix} \in D(\mathcal{A})$ and consequently, $\mathcal{A}$ is m-Accretive operator on E. □

Proposition 3.2.2. *The operator $\overline{\mathcal{A}-\mathcal{B}}$ generates a C_0 semigroup of contraction on Banach space E.*

Proof. From Theorem (2.1.6), the proof is divided into two parts. In the first segment, Accretivity of $\overline{\mathcal{A}-\mathcal{B}}$ is proved while the second part deals with $R\big(\delta I+\overline{\mathcal{A}-\mathcal{B}}\big)=E$ for some $\delta>0$. It is easy to obtain the following estimates

$$\left|\left|\int_z^\infty \vartheta(y)dy\right|\right|_1 \le ||z\vartheta||_1, \quad \left|\left|z\int_z^\infty \vartheta(y)dy\right|\right|_1 \le \tfrac{1}{2}\left|\left|z^2\vartheta\right|\right|_1,$$

$$\int_0^\infty \left\{2\beta\int_z^\infty \vartheta(y)dy\right\}\operatorname{sgn}(\vartheta)\, q\, dz - \delta_0\ell\operatorname{sgn}(\ell) = 2q\beta\,||z\vartheta||_1 - \delta_0|\ell| \tag{3.12}$$

and

$$\int_0^\infty \left\{2\beta\int_z^\infty \vartheta(y)dy\right\}\operatorname{sgn}(\vartheta)\, z\, dz = \beta\left|\left|z^2\vartheta\right|\right|_1. \tag{3.13}$$

Adding equations (3.12) and (3.13), gives that

$$(\mathcal{B}V,\Phi_V) = 2q\beta\,||z\vartheta||_1 - \delta_0|\ell| + \beta\left|\left|z^2\vartheta\right|\right|_1.$$

Consequently,

$$\big((\mathcal{A}-\mathcal{B})V,\Phi_V\big) = (\mathcal{A}V,\Phi_V)-(\mathcal{B}V,\Phi_V) = (q\mu_0-\omega)\,||\vartheta||_1 + (\mu_0-q\beta)\,||z\vartheta||_1 + \delta_0|\ell|.$$

This indicates that $\mathcal{A}-\mathcal{B}$ is Accretive provided $\mu_0>q\beta$, $\mu_0>\frac{\omega}{q}$ and hence, $\mathcal{A}-\mathcal{B}$ is closable which immediately yields the Accretivity of $\overline{\mathcal{A}-\mathcal{B}}$, see Theorem (2.1.5).

To prove the second part, let $\begin{pmatrix} m \\ g \end{pmatrix} \in \mathbb{R}\times L_1\big(\mathbb{R}^+;(q+z)dz\big)$ and $\begin{pmatrix} m \\ g \end{pmatrix} \ge 0$. Set $V_1=(\lambda_0 I+\mathcal{A})^{-1}\begin{pmatrix} m \\ g \end{pmatrix}$ and define a sequence

$$V_{n+1} = V_1 + (\lambda_0 I+\mathcal{A})^{-1}(\mathcal{B}+\delta_0 I)V_n.$$

Then, $V_1\ge 0$ and $V_2-V_1=(\lambda_0 I+\mathcal{A})^{-1}(\mathcal{B}+\delta_0 I)V_1 \ge 0$, since $(\mathcal{B}+\delta_0 I)$ is positive. Therefore, by the induction, $V_{n+1} \geq V_n$ pointwise and which shows that the sequence $\{V_n\}_{n\geq 1}$ is non-negative and increasing pointwise. Now,

$$V_{n+1} = (\lambda_0 I + \mathcal{A})^{-1} \begin{pmatrix} m \\ g \end{pmatrix} + (\lambda_0 I + \mathcal{A})^{-1}(\mathcal{B} + \delta_0 I)V_n$$

and this yields

$$(\lambda_0 I + \mathcal{A})V_n = \begin{pmatrix} m \\ g \end{pmatrix} + (\mathcal{B} + \delta_0 I)V_{n-1},$$

i.e.,

$$\begin{pmatrix} \lambda_0 \ell_n \\ \omega \vartheta_n'(z) + (\lambda_0 + \mu_0 + \beta z)\vartheta_n(z) \end{pmatrix} = \begin{pmatrix} m \\ g \end{pmatrix} + \begin{pmatrix} -\delta_0 \ell_{n-1} + \delta_0 \ell_{n-1} \\ 2\beta \int_z^\infty \vartheta_{n-1}(y)dy + \delta_0 \vartheta_{n-1} \end{pmatrix}.$$

This is equivalent to,

$$\begin{cases} \omega \vartheta_n'(z) + (\lambda_0 + \mu_0 + \beta z)\vartheta_n = g + 2\beta \int_z^\infty \vartheta_{n-1}(y)dy + \delta_0 \vartheta_{n-1} \\ \lambda_0 \ell_n = m \end{cases}$$

i.e.,

$$\begin{cases} \omega \vartheta_n'(z) + (\lambda_0 - \delta_0 + \mu_0 + \beta z)\vartheta_n \leq g + 2\beta \int_z^\infty \vartheta_n(y)dy \\ \lambda_0 \ell_n = m \end{cases}$$

which allows to have
$(\lambda_0 - \delta_0 + \mu_0)\|\vartheta_n\|_1 \leq \|g\|_1 + \beta \ \|z\vartheta_n\|_1$ and $-\omega \ \|\vartheta_n\|_1 + (\lambda_0 - \delta_0 + \mu_0)\|z\vartheta_n\|_1 \leq \|zg\|_1$.

If, in addition $z^2 g \in L_1(\mathbb{R}^+)$, then one can easily obtain the bound of $z^2 g$ in E. Selecting q as above gives the bound for the sequence $\{V_n\}_{n\geq 1}$ as

$$\|V_n\|_E = \left\| \begin{pmatrix} \ell_n \\ \vartheta_n \end{pmatrix} \right\|_E \leq M \ \|g\| + \frac{m}{\lambda_0}.$$

One can achieve by the monotone convergence theorem that $V_n \to V_\infty$ as $n \to \infty$.

Since, $(\lambda_0 I + \mathcal{A})V_n = \begin{pmatrix} m \\ g \end{pmatrix} + (\mathcal{B} + \delta_0 I)V_{n-1}$, it means that

$$(\lambda_0 I + \mathcal{A} - \mathcal{B} - \delta_0 I)V_n = \begin{pmatrix} m \\ g \end{pmatrix} + (\mathcal{B} + \delta_0 I)(V_{n-1} - V_n).$$

Therefore, $((\lambda_0 - \delta_0)I + \mathcal{A} - \mathcal{B})\, V_n \to \begin{pmatrix} m \\ g \end{pmatrix}$ as $n \to \infty$ and hence $V_\infty \in D(\overline{\mathcal{A} - \mathcal{B}})$, with $V_\infty =$

$\left(\delta I+\overline{\mathcal{A}-\mathcal{B}}\right)^{-1}\begin{pmatrix} m \\ g \end{pmatrix}$, where $\delta=(\lambda_0-\delta_0)$. Also, $L_1=L_1^+-L_1^+$ and $\mathbb{R}=\mathbb{R}^+-\mathbb{R}^+$.
Thus, $R\left(\delta I+\overline{\mathcal{A}-\mathcal{B}}\right)=E$ and consequently $\overline{\mathcal{A}-\mathcal{B}}$ is m-Accretive. From the above two parts, it is concluded that $\overline{\mathcal{A}-\mathcal{B}}$ generates a C_0 semigroup of contraction on E. □

Proposition 3.2.3. *The semigroup $\{T(t):t\geq 0\}$ generated by $\overline{\mathcal{A}-\mathcal{B}}$ is a positive semigroup on E.*

Proof. Here, $\overline{\mathcal{A}-\mathcal{B}}$ is a densely defined operator. From Theorem 2.1.8, to prove the positivity of $\{T(t):t\geq 0\}$, it is sufficient to prove that $\overline{\mathcal{A}-\mathcal{B}}$ is dispersive. If $V=(p_0,p_1(z))\in E$, one may choose

$$\Phi_V=\left(\frac{[p_0]^+}{p_0},\frac{[p_1(z)]^+}{p_1(z)}\right)$$

where $[p_0]^+=\begin{cases} p_0 & \text{if } p_0>0 \\ 0 & \text{if } p_0\leq 0 \end{cases}$ and $[p_1(z)]^+=\begin{cases} p_1(z) & \text{if } p_1(z)>0 \\ 0 & \text{if } p_1(z)\leq 0. \end{cases}$

$$\begin{aligned}
((\mathcal{A}-\mathcal{B})V,\Phi_V) &= \left(\delta_0\, p_0\,,\frac{[p_0]^+}{p_0}\right)+\left(\omega p_1'(z)+(\mu_0+\beta z)p_1(z)-2\beta\int_z^\infty p_1(y)dy\,,\frac{[p_1(z)]^+}{p_1(z)}\right)\\
&= \delta_0[p_0]^+ + \int_0^\infty\left\{\omega p_1'(z)+(\mu_0+\beta z)p_1(z)-2\beta\int_z^\infty p_1(y)dy\right\}(q+z)\frac{[p_1(z)]^+}{p_1(z)}dz\\
&= \delta_0[p_0]^+ - 2q\beta\int_0^\infty z\,[p_1(z)]^+dz - q\omega[p_1(0)]^+ + q\int_0^\infty(\mu_0+\beta z)\,[p_1(z)]^+dz\\
&\quad -\beta\int_0^\infty z^2\,[p_1(z)]^+dz+\omega\int_0^\infty z\,[p_1'(z)]^+dz+\int_0^\infty(\mu_0+\beta z)\,z\,[p_1(z)]^+dz\\
&= \delta_0[p_0]^+ + (\mu_0-q\beta)\int_0^\infty z\,[p_1(z)]^+dz+q\mu_0\int_0^\infty[p_1(z)]^+dz.
\end{aligned}$$

This implies that $\left((\mathcal{A}-\mathcal{B})V,\Phi_V\right)\geq 0$ provided $\mu_0\geq q\beta$, and hence, the operator $\overline{\mathcal{A}-\mathcal{B}}$ is dispersive. Thus, $\overline{\mathcal{A}-\mathcal{B}}$ generates a positive C_0 semigroup of contraction on E. □

Finally, we are in position to prove the main result of this section below.

3.2.2 Existence of Mild Solution

Theorem 3.2.2. *The dynamical system (3.8) has a unique non-negative local mild solution.*

Proof. Due to the Propositions 3.2.3, the operator $\overline{\mathcal{A}-\mathcal{B}}$ generates a positive C_0 semigroup of contraction on E. To prove the existence of a unique local mild solution of the semilinear problem (3.8), it is sufficient to show that $\mathcal{F}:\mathbb{R}^+\times E\to E$ is continuous and $\mathcal{F}$ is locally

Lipschitz with respect to the second component, refer to Theorem 2.3.2. Given,

$$\mathcal{F}\left(t, \begin{pmatrix} \ell \\ \phi(z) \end{pmatrix}\right) = \begin{pmatrix} \delta_1 \ell \int_0^\infty \phi(z) dz \\ -\delta_2\, \ell\, \phi(z) \end{pmatrix}.$$

Let $\begin{pmatrix} \ell_m \\ \phi_m \end{pmatrix} \to \begin{pmatrix} \ell \\ \phi \end{pmatrix}$ that is, $\left|\left|\begin{pmatrix} \ell_m - \ell \\ \phi_m - \phi \end{pmatrix}\right|\right|_E \to 0$ as $m \to \infty$
or,

$$q\,||\phi_m - \phi||_1 + ||z(\phi_m - \phi)||_1 + |\ell_m - \ell| \to 0 \quad \text{as} \quad m \to \infty.$$

Then, one can evaluate

$$\begin{aligned}
\left|\left|\mathcal{F}\begin{pmatrix} \ell_m \\ \phi_m \end{pmatrix} - \mathcal{F}\begin{pmatrix} \ell \\ \phi \end{pmatrix}\right|\right|_E &= \left|\left|\begin{pmatrix} \delta_1 \ell_m \int_0^\infty \phi_m\, dz - \delta_1\, \ell\, \int_0^\infty \phi\, dz \\ -\delta_2\, \ell_m\, \phi_m + \delta_2\, \ell\, \phi \end{pmatrix}\right|\right|_E \\
&= \left|\left|\begin{pmatrix} \delta_1 \ell_m \int_0^\infty \phi_m\, dz - \delta_1\, \ell \int_0^\infty \phi_m\, dz + \delta_1\, \ell \int_0^\infty \phi_m\, dz - \delta_1\, \ell\, \int_0^\infty \phi\, dz \\ -\delta_2\, \ell_m\, \phi_m + \delta_2\, \ell_m\, \phi - \delta_2\, \ell_m\, \phi + \delta_2\, \ell\, \phi \end{pmatrix}\right|\right|_E \\
&= \left|\left|\begin{pmatrix} \delta_1 (\ell_m - \ell) \int_0^\infty \phi_m\, dz + \delta_1\, \ell \int_0^\infty (\phi_m - \phi)\, dz \\ -\delta_2\, \ell_m (\phi_m - \phi) + \delta_2 \phi (\ell - \ell_m) \end{pmatrix}\right|\right|_E \\
&\leq \Big\{ q\, \delta_2\, |\ell_m|\, ||\phi_m - \phi||_1 + q\, \delta_2\, |\ell_m - \ell|\, ||\phi||_1 \\
&\qquad + \delta_2\, |\ell_m|\, ||z(\phi_m - \phi)||_1 + \delta_2\, |\ell_m - \ell|\, ||z\phi||_1 \\
&\qquad\quad + \delta_1\, |\ell_m - \ell| \int_0^\infty |\phi_m|\, dz + \delta_1 \ell \int_0^\infty |\phi_m - \phi|\, dz \Big\}.
\end{aligned}$$

Therefore, $\left|\left|\mathcal{F}\begin{pmatrix} \ell_m \\ \phi_m \end{pmatrix} - \mathcal{F}\begin{pmatrix} \ell \\ \phi \end{pmatrix}\right|\right| \to 0$ as $m \to \infty$ and consequently $\mathcal{F}$ is continuous on $\mathbb{R}^+ \times E$.
Further, to show that $\mathcal{F}$ is locally Lipschitz in the second variable, we assume

$$\left|\left|\begin{pmatrix} \ell \\ \phi \end{pmatrix}\right|\right|_E \leq c \quad \text{and} \quad \left|\left|\begin{pmatrix} m \\ \psi \end{pmatrix}\right|\right|_E \leq c$$

i.e., $q\,||\phi||_1 + ||z\phi||_1 + |\ell| \leq c$ and $q\,||\psi||_1 + ||z\psi||_1 + |m| \leq c$. Then,

$$\begin{aligned}
\left|\left|\mathcal{F}\begin{pmatrix} \ell \\ \phi \end{pmatrix} - \mathcal{F}\begin{pmatrix} m \\ \psi \end{pmatrix}\right|\right|_E &= \left|\left|\begin{pmatrix} \delta_1 \ell \int_0^\infty \phi(z)\, dz - \delta_1\, m \int_0^\infty \psi(z)\, dz \\ -\delta_2\, \ell\, \phi + \delta_2\, m\, \psi \end{pmatrix}\right|\right| \\
&= \left|\left|\begin{pmatrix} \delta_1 (\ell - m) \int_0^\infty \psi\, dz + \delta_1\, \ell \int_0^\infty (\phi - \psi)\, dz \\ -\delta_2\, (\ell - m)\, \phi - \delta_2\, m\, (\phi - \psi) \end{pmatrix}\right|\right|.
\end{aligned}$$

This implies that

$$\begin{aligned}\left\|\mathcal{F}\begin{pmatrix}\ell\\ \phi\end{pmatrix}-\mathcal{F}\begin{pmatrix}m\\ \psi\end{pmatrix}\right\|_E &\leq \Big\{\ \delta_2\ |\ell-m|\ c+\delta_2\ |m|\ \big[q\,||(\phi-\psi)||_1+||z(\phi-\psi)||_1\big]\\ &\qquad +\delta_1\ |\ell|\ ||(\phi-\psi)||_1+\frac{\delta_1\ |\ell|}{q}\ ||z(\phi-\psi)||_1+\delta_1\ |\ell-m|\ ||\psi||_1\Big\}\\ &\leq \Big\{\ \delta_2\ |\ell-m|\ c+\delta_2\ c\ \big[q\,||(\phi-\psi)||_1+||z(\phi-\psi)||_1\big]\\ &\qquad +\frac{c\ \delta_1\ q}{q}\ ||(\phi-\psi)||_1+\frac{\delta_1\ c}{q}\ ||z(\phi-\psi)||_1+\delta_1\ |\ell-m|\ \frac{c}{q}\ \Big\}\\ &\leq \left(\delta_2 c+\frac{\delta_1 c}{q}\right)\left\|\begin{pmatrix}\ell\\ \phi\end{pmatrix}-\begin{pmatrix}m\\ \psi\end{pmatrix}\right\|_E .\end{aligned}$$

Thus, $\left\|\mathcal{F}\begin{pmatrix}\ell\\ \phi\end{pmatrix}-\mathcal{F}\begin{pmatrix}m\\ \psi\end{pmatrix}\right\|_E \leq L(c)\left\|\begin{pmatrix}\ell\\ \phi\end{pmatrix}-\begin{pmatrix}m\\ \psi\end{pmatrix}\right\|_E$ with $L(c)=\left(\delta_2 c+\frac{\delta_1 c}{q}\right)$. This implies that $\mathcal{F}$ is locally Lipschitz. Thus, Theorem (2.3.2) guarantees that, there exists $t_{max}>0$ such that the Problem (3.8) has a unique mild solution in $[0,t_{max})$ and the solution satisfies

$$V(t)=T_P(t)V_0+\int_0^t T_P(t-s)\mathcal{F}\big(V\big)ds \quad \text{for } \ t<t_{max} \tag{3.14}$$

where $\{T_P(t):t\geq 0\}$ is the semigroup generated by $P=\overline{\mathcal{A}-\mathcal{B}}$.
Since, $\mathcal{F}$ is not positive on E^+, one can not claim that the constructed local mild solution is non-negative. To accomplish it, the System (3.8) is written in an equivalent form as

$$\begin{cases}\frac{dV}{dt}=-(\mathcal{A}-\mathcal{B}+\rho I)V+(\mathcal{F}+\rho I)(V); \quad t\geq 0\\ V(0)=V_0\end{cases} \tag{3.15}$$

for some $\rho\in\mathbb{R}^+$ such that $\mathcal{F}+\rho I$ is positive. Set $P_\rho=(\mathcal{A}-\mathcal{B}+\rho I)$ and $Q=\mathcal{F}+\rho I$, then $\{T_{P_\rho}(t):t\geq 0\}=\{e^{-\rho t}T_P(t):t\geq 0\}$ and hence $\{T_{P_\rho}:t\geq 0\}$ is positive C_0 semigroup of contraction on E.
Let us define $C_{a,b}=\overline{I_a(t_0)}\times\overline{B_b(V_0)}$ where $\overline{I_a(t_0)}=\{t:|t-t_0|\leq a\}$ and $\overline{B_b(V_0)}=\{V\in E: ||V-V_0||_E\leq b\}$. Let $M=\sup_{C_{a,b}}||Q||$. Here, Q is locally Lipschitz with respect to the second variable, i.e.,

$$||Q(t,U)-Q(t,V)||\leq L_2(c)\,||U-V|| \quad \text{for all } \ U,V\in\overline{B_b(V_0)}$$

where $L_2(c)=\left(\delta_2 c+\frac{\delta_1 c}{q}+\rho\right)$, $||U||\leq c$ and $||V||\leq c$.

Introducing $F : C\big(I_a(0), B_b(V_0)\big) \to C\big(I_a(0), B_b(V_0)\big)$ by

$$F(\phi(t)) = e^{-\rho t}\ T_P(t)V_0 + \int_0^t e^{-\rho(t-s)} T_P(t-s)\ Q(\phi(s))\ ds,$$

which implies that,

$$||F(\phi(t)) - V_0||_\infty \le 2\,||V_0|| + M|t| \le 2\,||V_0|| + Mh \le b$$

and hence $F(\phi(t)) \in \overline{B_b(V_0)}$. Also,

$$||F(\phi_1(t)) - F(\phi_2(t))||_\infty \le L_2(c)\ |t|\ \ ||\phi_1 - \phi_2||_\infty \le L_2(c)\ h\ \ ||\phi_1 - \phi_2||_\infty,$$

where $L_2(c)\ h < 1$. This shows that F is a contraction on $C\Big(I_a(0), B_b(V_0)\Big)$ and by the Banach fixed point theorem, there exists $\psi \in C_{a,b}$ such that $F(\psi) = \psi$, i.e.,

$$\psi(t) = e^{-\rho t}\ T_P(t)V_0 + \int_0^t e^{-\rho(t-s)} T_P(t-s)\ Q(\psi(s))\ ds$$

where $|t| < h$ and $h \le \min\left\{a, \frac{1}{L_2(c)}, \frac{b-2||V_0||}{M}\right\}$.
Thus, if $V_0 \in E^+$ and $V : [0, t_{max}) \to E$ be the unique mild solution of (3.8), then this solution is non-negative on the maximal interval of its existence. □

Lemma 3.2.3. *The nonlinear operator $\mathcal{F} : E \to E$ is continuously differentiable.*

Proof. The nonlinear operator $\mathcal{F}$ is given by

$$\mathcal{F}\begin{pmatrix}\ell\\ \vartheta\end{pmatrix} = \begin{pmatrix}\delta_1\ \ell \int_0^\infty \vartheta(z)dz\\ -\delta_2\ \ell\ \vartheta\end{pmatrix}.$$

Then, for fixed $(\ell_0, \vartheta_0) \in E$, the differential $D_{(\ell_0,\vartheta_0)}\mathcal{F}$ of $\mathcal{F}$ is described by

$$\big(D_{(\ell_0,\vartheta_0)}\mathcal{F}\big)\begin{pmatrix}\ell\\ \vartheta\end{pmatrix} = \begin{pmatrix}\delta_1\ell \int_0^\infty \vartheta_0(z)dz + \delta_1\ell_0 \int_0^\infty \vartheta dz\\ -\delta_2\ell\vartheta_0 - \delta_2\ell_0\vartheta\end{pmatrix}.$$

Also, for $(\ell, \vartheta) \in E$, we have

$$\big\|D_{(\ell,\vartheta)}\mathcal{F} - D_{(\ell_0,\vartheta_0)}\mathcal{F}\big\| \le \left(\frac{\delta_1}{q} + \delta_2\right)\left\|\begin{pmatrix}\ell\\ \vartheta\end{pmatrix} - \begin{pmatrix}\ell_0\\ \vartheta_0\end{pmatrix}\right\|.$$

Thus, $\mathcal{F}$ is continuously differentiable from E into E for every $(\ell, \vartheta) \in E$. □

From Theorem 2.3.4 and Lemma 3.2.3, we can say the mild solution of the semilinear problem (3.8) with $(C_0, \vartheta_0) \in D(\mathcal{A} - \mathcal{B})$ is a classical solution.

3.3 Existence of Classical Solution

This part deals with the existence of a unique global classical solution of the system (3.2)-(3.4). Some notations and assumptions that are needed in the present section are as follows.
Consider $Z = (z_0, \infty)$ and reaction rates μ, β are bounded such that

$$\mu,\ \beta \in L_\infty^+(Z) \tag{3.16}$$

where $L_\infty^+(Z)$ is the positive cone in $L_\infty(Z)$.
Choose suitable spaces $X = L_1(Z, zdz)$ and $Y = \mathring{W}_1^1(Z, zdz) = \mathrm{cl}_{W_1^1(Z,zdz)} T(Z)$, where $T(Z)$ represents the space of all test functions on Z. Also, X^+ is the positive cone in X and $Y^+ = Y \cap X^+$. Now, define

$$\mathfrak{I}_{L,B} = \{C \in C^1(I_L)\ :\ B^{-1} \leq C(t) \leq ||C(t)||_{C^1(I_L)} \leq B\} \tag{3.17}$$

where $I_L = [0, L]$ and $B > 1$.
For given any interval J and any function $C : J \to \mathbb{R}^+$, introducing

$$\mathbb{F}^C(t)u = \omega \mathbb{A}u + \mathbb{B}^C(t)u - \mathbb{S}(u),\ \ u \in Y,\ t \in J \tag{3.18}$$

where, $\mathbb{S}(u) = -\big(\mu(z) + \beta(z)\big)u(z) + 2\int_z^\infty \beta(z')k(z,z')u(z')\,dz'$, $\mathbb{B}^C(t)u = \delta_2 C(t)u$ and $\mathbb{A} : Y \subset X \to X$ defined by $\mathbb{A}u = \frac{\partial u}{\partial z}$. Here, $\mathbb{A}$ generates a C_0-semigroup $\{e^{-\mathbb{A}t} : t \geq 0\}$ that satisfies $||e^{-\mathbb{A}t}||_{\mathcal{L}(X)} \leq e^{t/z_0}$.
Then, writing the equations (3.2)-(3.3) as

$$\dot{u} + \mathbb{F}^C(t)u = 0\ \text{ for }\ t > 0,\ u(0) = u_0 \tag{3.19}$$

$$\dot{C} = -\delta_0 C + \delta_1 C\,|u|_1\ \text{ for }\ t > 0,\ C(0) = C_0 \tag{3.20}$$

where $|\cdot|_1$ denotes the norm in $L_1(Z)$.
To prove the main result Theorem 3.3.1, the following Proposition 3.3.1 is required.

Proposition 3.3.1. *For given $B > 0, L_0 > 0$ and $0 < L \leq L_0$, $\left\{-\mathbb{F}^C(t) : t \in [0, L]\right\}$ generates a unique evolution system $\mathbb{U}_C(t,s)$, $0 \leq s \leq t \leq L$ in X for each $C \in \mathfrak{I}_{L,B}$. Moreover, there exists $\omega_0 = \omega_0(L_0, B) > 0$ such that*

$$||\mathbb{U}_C(t,s)||_{\mathcal{L}(X)} \leq e^{\omega_0(t-s)}, \quad 0 \leq s \leq t \leq L,\ C \in \mathfrak{I}_{L,B} \tag{3.21}$$

$$||\mathbb{U}_C(t,s)||_{\mathcal{L}(Y)} \leq \omega_0, \quad 0 \leq s \leq t \leq L,\ C \in \mathfrak{I}_{L,B} \tag{3.22}$$

and for $U, W \in \mathfrak{I}_{L,B}$

$$||\mathbb{U}_U(t,s) - \mathbb{U}_W(t,s)||_{\mathcal{L}(Y,X)} \leq \omega_0(t-s)\, ||U-W||_{C(I_L)}, \quad 0 \leq s \leq t \leq L. \tag{3.23}$$

Proof. Since, $\mathbb{S}$ and $\mathbb{B}^C(s)$ are bounded operators on X for any fixed $C \in \mathfrak{I}_{L,B}$ and any $s \in I_L$, hence by the bounded perturbation theorem 2.2.1, $-\mathbb{F}^C(s)$ is the infinitesimal generator of a C_0-semigroup $\{T_s(t) : t \geq 0\}$ on X and satisfies

$$\left|\left|e^{-t\mathbb{F}^C(s)}\right|\right|_{\mathcal{L}(X)} \leq e^{\tilde{w}t}, \quad t \geq 0 \tag{3.24}$$

where $\tilde{w} = \frac{\omega}{z_0} + \delta_2 B + ||\mathbb{S}||_{\mathcal{L}(X)}$.
From §2.4, $\left\{\mathbb{F}^C(s) : s \in [0,L]\right\}$ is a stable family for each $C \in \mathfrak{I}_{L,B}$. Now, for any $s \in I_L$, define $\mathbb{Q}^C(s) : Y \to X$ by $\mathbb{Q}^C(s) = \alpha I + \mathbb{F}^C(s)$, is an isomorphism that satisfies

$$\left|\left|\mathbb{Q}^C(s)\right|\right|_{\mathcal{L}(Y,X)} \leq \alpha + \omega + \delta_2 B + ||\mathbb{S}||_{\mathcal{L}(X)}, \quad s \in I_L,\ C \in \mathfrak{I}_{L,B} \tag{3.25}$$

where $\alpha = \tilde{w} + 1$ and I is the identity operator. Furthermore, for $u \in Y$

$$\mathbb{Q}^C(t)u \in C^1(I_L, X) \quad \text{with } \dot{\mathbb{Q}}^C(t)u = \frac{d}{dt}\mathbb{Q}^C(t)u = \delta_2 \dot{C}(t)u. \tag{3.26}$$

Therefore, the assumptions $(H_1), (H_2)^+$ and (H_3) of §2.4 are satisfied and hence, there exists a unique evolution system $\mathbb{U}_C(t,s), 0 \leq s \leq t \leq L$, in X corresponding to $\left\{\mathbb{F}^C(s) : s \in [0,L]\right\}$ for each $C \in \mathfrak{I}_{L,B}$ which satisfies the statements $(E_1)-(E_5)$ of §2.4, such that

$$||\mathbb{U}_C(t,s)||_{\mathcal{L}(X)} \leq e^{\tilde{w}(t-s)}, \quad 0 \leq s \leq t \leq L,\ C \in \mathfrak{I}_{L,B}. \tag{3.27}$$

In particular, (3.21) holds if $\tilde{w}$ is replaced by ω_0.
Again, following §2.4, for the evolution system $\mathbb{U}_C(t,s)$, $0 \leq s \leq t \leq L$, there exists a unique family of bounded linear operators $\mathbb{W}_C(t,s)$, $0 \leq s \leq t \leq L$ on X such that

$$\mathbb{U}_C(t,s) = \mathbb{Q}^C(t)^{-1}\mathbb{W}_C(t,s)\mathbb{Q}^C(t), \quad 0 \leq s \leq t \leq L \tag{3.28}$$

where $\mathbb{W}_C(t,s) \in \mathcal{L}(X)$ satisfies

$$\mathbb{W}_C(t,s)u = \mathbb{U}_C(t,s)u + \int_s^t \mathbb{W}_C(t,r)\mathbb{D}^C(r)\mathbb{U}_C(r,s)u\,dr$$

for $0 \le s \le t \le L$ and $u \in X$ with $\mathbb{D}^C(t) = \dot{\mathbb{Q}}^C(t)\mathbb{Q}^C(t)^{-1} \in \mathcal{L}(X),\ \ t \in I_L$.
Since, $\mathbb{Q}^C(t)^{-1}$ is the bounded operator, so there exists a constant $c_0(B)$ such that

$$\left|\left|\mathbb{Q}^C(t)^{-1}\right|\right|_{\mathcal{L}(X,Y)} \le c_0(B) \quad \text{for} \ \ t \in I_L,\ C \in \mathfrak{I}_{L,B}. \tag{3.29}$$

Also, $\mathbb{Q}^C(t)^{-1}$ is the resolvent of $-\mathbb{F}^C(t)$ on X. Therefore,

$$\left|\left|\mathbb{Q}^C(t)^{-1}\right|\right|_{\mathcal{L}(X)} \le 1 \quad \text{for } t \in I_L,\ C \in \mathfrak{I}_{L,B}.$$

Now, for $u \in X$ and $t \in I_L$

$$\begin{aligned}\left|\left|\mathbb{Q}^C(t)^{-1}u\right|\right|_Y &= \left|\left|\mathbb{Q}^C(t)^{-1}u\right|\right|_X + \left|\left|\frac{\partial}{\partial z}\mathbb{Q}^C(t)^{-1}u\right|\right|_X \\ &\le ||u||_X + \frac{1}{\omega}\left|\left|u - \left(\alpha + \mathbb{B}^C(t) - \mathbb{S}\right)\mathbb{Q}^C(t)^{-1}u\right|\right|_X \\ &\le \left[1 + \frac{1}{\omega}\left(1 + \alpha + B + ||\mathbb{S}||_{\mathcal{L}(X)}\right)\right] ||u||_X\end{aligned}$$

and

$$\begin{aligned}\left|\left|\mathbb{D}^{\mathbb{C}}(t)\right|\right|_{\mathcal{L}(X)} &\le \left|\left|\dot{\mathbb{Q}}^C(t)\right|\right|_{\mathcal{L}(Y,X)} \left|\left|\mathbb{Q}^C(t)^{-1}\right|\right|_{\mathcal{L}(X,Y)} \\ &\le \delta_2 \left|\left|\dot{C}\right|\right|_{C(I_L)} c_0(B) \le c_0'(B).\end{aligned}$$

From above, one can obtain

$$||\mathbb{W}_C(t,s)||_{\mathcal{L}(X)} \le c_0(L_0,B), \ \ 0 \le s \le t \le L,\ C \in \mathfrak{I}_{L,B}. \tag{3.30}$$

Using estimates (3.25), (3.29) and (3.30) in (3.28), the inequality (3.22) is achieved.
Let $U,W \in \mathfrak{I}_{L,B}$ and $u \in Y$. Consider the map

$$\psi : [r \mapsto \mathbb{U}_U(t,r)\mathbb{U}_W(r,s)u] \in C^1\big((s,t),X\big) \cap C\big([s,t],Y\big),$$

where $0 \le s \le t \le L$. Then from $(E_1)-(E_5)$ in §2.4, it is noticed that

$$\psi(s)-\psi(t)=\mathbb{U}_U(t,s)u-\mathbb{U}_W(t,s)u=-\int_s^t \frac{\partial}{\partial r}\mathbb{U}_U(t,r)\mathbb{U}_W(r,s)u\,dr$$
$$=\int_s^t \mathbb{U}_U(t,r)\big(\mathbb{F}^U(r)-\mathbb{F}^W(r)\big)\mathbb{U}_W(r,s)u\,dr.$$

Therefore, (3.21) and (3.22) provide

$$\|\mathbb{U}_U(t,s)u-\mathbb{U}_W(t,s)u\|_X \leq \int_s^t \|\mathbb{U}_U(t,r)\|_{\mathcal{L}(X)}\left\|\mathbb{F}^U(r)-\mathbb{F}^W(r)\right\|_{\mathcal{L}(Y,X)}\|\mathbb{U}_W(r,s)\|_{\mathcal{L}(Y)}\|u\|_Y\,dr$$
$$\leq c_1(L_0,B)(t-s)\,\|U-W\|_{C(I_L)}\,\|u\|_Y$$

for $0\leq s\leq t\leq L$ and hence statement (3.23) is proved. □

Finally, in the following theorem the existence of a unique global classical solution is discussed. Moreover, the compact support of the solution is also established in Proposition 3.3.2.

3.3.1 Classical Solution Theorem

Theorem 3.3.1. *Let us assume that (1.4)-(1.6) and (3.16) are satisfied, then for any given $C_0>0$ and $u_0\in Y^+$, the Problem (3.19)-(3.20) admits a unique global positive classical solution (C,u) such that $C\in C^1(\mathbb{R}^+)$, $C(t)>0$ for $t>0$, and $u\in C^1(\mathbb{R}^+,X)\cap C(\mathbb{R}^+,Y^+)$.*

Proof. We first show that for any $M>0$, there exists $L=L(M)\in(0,1]$ for which (3.19)-(3.20) admits a unique solution (C,u) on I_L with the assumptions as stated in theorem, provided that $(C_0,u_0)\in\mathbb{R}^+\times Y^+$ such that

$$M^{-1}\leq C_0 \quad\text{and}\quad C_0+||u_0||_Y\leq M.$$

Now, define a complete metric space

$$E_L=\left\{u\in C(I_L,X^+):||u(t)||_X\leq M+1,\;\; t\in I_L\right\}$$

and take an arbitrary $\bar{u}\in E_L$, then $|u(t)|_1\in C(I_L)$. If u is replaced by $\bar{u}$, then (3.20) possesses a unique solution $C_{\bar{u}}\in C^1(I_L)$ and is given by

$$C_{\bar{u}}(t)=C_0\,e^{-\delta_0 t+\delta_1\int_0^t|\bar{u}(\sigma)|_1 d\sigma},\;\; t\in I_L. \tag{3.31}$$

Since, $\dot{C}_{\bar{u}}=-\delta_0 C_{\bar{u}}+\delta_1 C_{\bar{u}}\,|\bar{u}(t)|_1$ for $t\in I_L$, we have

$$\dot{C}_{\bar{u}}\leq c_2(M)\;\text{ and }\;\dot{C}_{\bar{u}}\geq-\delta_0 C_{\bar{u}}\geq -c_2(M),$$

where $c_2(M) > 0$ is a constant depending on M but not on $L \in (0,1]$. This follows that

$$-c_2(M) \leq \dot{C}_{\bar{u}}(t) \leq c_2(M), \;\; t \in I_L. \tag{3.32}$$

Thus, (3.31)-(3.32) shows the existence of $B = B(M) > 1$ which depends on $M > 0$ but not on $L \in (0,1]$ such that $C_{\bar{u}} \in \mathfrak{I}_{L,B}$ whenever $\bar{u} \in E_L$ and $\mathfrak{I}_{L,B}$ is given by (3.17). Also, one can derive that

$$|C_{\bar{u}_1}(t) - C_{\bar{u}_2}(t)| \leq c_2(M)\,||\bar{u}_1 - \bar{u}_2||_{E_L} \;\text{ for }\; 0 \leq t \leq L \leq 1 \text{ and } \bar{u}_1, \bar{u}_2 \in E_L. \tag{3.33}$$

Define $F : E_L \to E_L$ by

$$F(\bar{u})(t) = \mathbb{U}_{C_{\bar{u}}}(t,0)u_0 \;\text{ for }\; t \in I_L,\; \bar{u} \in E_L.$$

Let $\mathbb{U}_{C_{\bar{u}}}(t,s),\; 0 \leq s \leq t \leq L$ is a unique evolution system in X corresponding to $\{\mathbb{F}^C(t) : t \in I_L\}$ and $\omega_0 = \omega_0(1, B(M))$. Then from §2.4, the equation

$$\dot{u}(t) + \mathbb{F}^C(t)u = 0 \;\text{ for }\; t > 0,\; u(0) = u_0$$

admits a unique classical solution $u \in C^1(I_L, X) \cap C(I_L, Y)$.
To show that F is a contraction which consequently implies our first claim. Choosing $L = L(M) \in (0,1]$ sufficiently small, the inequality (3.21) yields that for $\bar{u} \in E_L$ and $t \in I_L$,

$$||F(\bar{u})(t)||_X \leq e^{\omega_0 L}\,||u_0||_X \leq M + 1.$$

Equations (3.23) and (3.33) ensure that for $\bar{u}_1, \bar{u}_2$ and $t \in I_L$,

$$\begin{aligned} ||F(\bar{u}_1)(t) - F(\bar{u}_2)(t)||_X &= \left|\left|\mathbb{U}_{U_{\bar{u}_1}}(t,0)u_0 - \mathbb{U}_{W_{\bar{u}_2}}(t,0)u_0\right|\right|_X \\ &\leq c_1(L_0, B)\; t\, ||U_{\bar{u}_1} - W_{\bar{u}_2}||_{C(I_L)}\, ||u_0||_Y \\ &\leq \omega_0\; L\; c_2(M)\, ||\bar{u}_1 - \bar{u}_2||_{E_L} \\ &\leq \frac{1}{2}\, ||\bar{u}_1 - \bar{u}_2||_{E_L}. \end{aligned}$$

Since, $\mathbb{S}$ is not positive on X^+, it is not guaranteed that the constructed local classical solution is non-negative and hence, rewriting (3.19) in the equivalent form as

$$\frac{du}{dt} + \big(\omega\mathbb{A} + \mathbb{B}^C(t) + rI\big)u = \big(\mathbb{S} + rI\big)u = \mathbb{L}(u) \;\text{ for }\; t \in [0,L],\; u(0) = u_0. \tag{3.34}$$

Then,

$$\mathbb{L}(u) \in X^+ \ \text{ for } \ u \in X^+ \tag{3.35}$$

due to the choice of the constant r. From Corollary 2.2.2.2, $\omega\mathbb{A} + \mathbb{B}^C(t) + rI$ generates a positive semigroup on X for each fixed $t \in I_L$ and hence the evolution system $\bar{\mathbb{U}}_C(t,s),\ 0 \le s \le t \le L$ generated by $\{\omega\mathbb{A} + \mathbb{B}^C(t) + rI : t \in I_L\}$ is positive as well.

Now, for fixed $\bar{u} \in E_L$, the mapping $\widehat{u} \mapsto \Lambda_{\bar{u}}(\widehat{u})$ from a suitable closed ball $C\big([0,\tilde{L}],X\big)$, containing u_0, into itself is defined as

$$\Lambda_{\bar{u}}(\widehat{u})(t) = \bar{\mathbb{U}}_{\bar{u}}(t,0)u_0 + \int_0^t \bar{\mathbb{U}}_{\bar{u}}(t,s)\mathbb{L}\big(\widehat{u}(s)\big)ds, \ \ t \in I_L.$$

which is a contraction provided $\tilde{L} \in (0,L]$ for sufficiently small $L \in (0,1]$.
Since, the choice of $L = L(M)$ only depends on M, from [71, 56] the system (3.2)-(3.4) possesses a unique maximal solution $(C,u) \in C^1(J,\mathbb{R}^+ \times X) \cap C(J,\mathbb{R}^+ \times Y^+)$ on a maximal interval J which is open in $\mathbb{R}^+$. Now, we claim that, if $t^+ := \sup J < \infty$, then

$$\liminf_{t \to t^+} C(t) = 0 \quad \text{or} \quad \limsup_{t \to t^+} \big(C(t) + \|u(t)\|_Y\big) = \infty. \tag{3.36}$$

From the equation (3.20), it is clear that

$$\|C\|_{C^1(J)} \le a(t^+) \ \text{ and } \ C(t) > 0 \ \text{ for } \ t \in J. \tag{3.37}$$

Consequently, there exists $B\big(t^+\big) > 0$ such that for each $0 < L < t^+$, one has $C \in \mathfrak{I}_{L,B}$ and hence, it follows from Proposition 3.3.1 that

$$\|\mathbb{U}_C(t,s)\|_{\mathcal{L}(Y)} \le b(t^+), \quad 0 \le s \le t \le t^+$$

and

$$\|u(t)\|_Y = \|\mathbb{U}_C(t,0)u_0\|_Y \le b(t^+)\,\|u_0\|_Y\,. \tag{3.38}$$

Thus, (3.36) can not true in the sense of (3.37)-(3.38). This contradiction proves that the solution (C,u) exists for all times. □

Proposition 3.3.2. *Let (C,u) be the unique global classical solution of the system (3.2)-(3.4) for $C_0 > 0$ and $u_0 \in X^+$ with (1.4)-(1.6) and (3.16) hold. If supp $(u_0) \subset [z_0, R_0]$ for some $R_0 > z_0$, then supp $(u) \subset [z_0, R(t)]$, $t \ge 0$ where $R(t) = R_0 + \omega t, \ \ t \ge 0$.*

Proof. Define $\Phi \in C^1(\mathbb{R}^+, L_1(Z))$ by $\Phi(t,z) = \int_z^\infty u(t,z')dz', \ \ z \in Z,\ t \ge 0$. Now,

$$\begin{aligned}\frac{d}{dt}\Phi(t,z) &= \int_z^\infty \dot{u}(t,z')dz' \\ &= \omega u(t,z) - \delta_2 C(t)\int_z^\infty u(t,z')dz' + \int_z^\infty \mathbb{S}[u(t)](z')dz'\end{aligned}$$

and

$$\begin{aligned}\frac{d}{dt}\int_{R(t)}^\infty \Phi(t,z)dz &= \int_{R(t)}^\infty \frac{d}{dt}\Phi(t,z)dz - R'(t)\Phi\big(t,R(t)\big) \\ &\leq \int_{R(t)}^\infty \int_z^\infty \mathbb{S}[u(t)](z')dz'dz \\ &\leq 2\,||\beta||_\infty \int_{R(t)}^\infty \Phi(t,z)dz.\end{aligned}$$

Therefore,

$$\int_{R(t)}^\infty \Phi(t,z)dz \leq e^{2||\beta||_\infty}\int_{R_0}^\infty \int_z^\infty u_0(z')dz'dz = 0, \quad t \geq 0,$$

and hence $u(t,z) = 0$ for $z \in (R(t),\infty)\,,\ \ t \geq 0$. □

Chapter 4

Existence of Solutions of a Prion proliferation Model in the Presence of Chaperone [1]

4.1 Introduction

The present chapter is based on the study of a prion proliferation system coupled with chaperone which consists of two ODEs and a partial integro-differential equation. The existence and uniqueness of a positive global classical solution of the system is proved for the bounded degradation rates by the idea of evolution system theory in the state space $\mathbb{R}\times\mathbb{R}\times L_1(Z,zdz)$. Moreover, the global weak solutions for unbounded degradation rates are discussed by weak compactness argument. Again by following Section 1.2, the monomer, polymer and chaperone equations are described by

$$\frac{dS(t)}{dt} = \lambda - \gamma S(t) - \tau S(t)\int_{z_0}^{\infty} u(t,y)dy + 2\int_0^{z_0} z\int_{z_0}^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dydz \tag{4.1}$$

$$\frac{\partial u(t,z)}{\partial t} = -\tau S(t)\frac{\partial u(t,z)}{\partial z} - \big(\mu(z)+\beta(z)+\delta_2 C(t)\big)u(t,z) + 2\int_z^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dy \tag{4.2}$$

and

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t)\int_{z_0}^{\infty} u(t,y)\, dy \tag{4.3}$$

respectively, under the conditions

$$S(0)=S^0,\ C(0)=C^0,\ u(0,z)=u^0(z),\ u(t,z_0)=0,\ \text{for}\ \ t\geq 0,\ z_0<z<\infty. \tag{4.4}$$

Here, the parameters $\gamma,\ \lambda,\ \tau,\ \delta_0,\ \delta_1$ and δ_2 are positive constants and the description of these parameters are given in Chapter 1. The function $k(z,y)$ satisfies the assumptions (1.4)-(1.8).

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[1] A considerable part of this chapter is published in *Evolution Equations and Control Theory*, 2022, doi: 10.3934/eect.2021039.

This chapter is organized as follows: In Section 4.2, some auxiliary results are stated including the existence and uniqueness of global classical solution of the problem (4.1)-(4.3) with bounded kernels μ and β. For this, the idea is to solve the equations (4.1) and (4.3) for a fixed suitable function $\tilde{u}$ and then substitute the obtained solutions $S_{\tilde{u}}$ and $C_{\tilde{u}}$ into equation (4.2). Further, by using evolution system theory, the equation (4.2) is solved for classical solution $u_{\tilde{u}}$ and a fixed point argument for the map $\tilde{u} \to u_{\tilde{u}}$ provides the local existence and uniqueness of a solution (S, C, u) to the problem (4.1)-(4.3). In Section 4.3, the existence of a weak solution of the system (4.1)-(4.3) is proved by using weak compactness technique under the assumptions that μ and β are unbounded. The finite speed of propagation for the classical and weak solutions to the equation (4.2) is also demonstrated.

4.2 Well-Posedness of the Problem in the Classical Sense for Bounded Kernels

4.2.1 Preliminaries

Consider $Z = (z_0, \infty)$ and kernels β, μ are bounded. More precisely, let

$$\beta, \mu \in L_\infty^+(Z) \tag{4.5}$$

for $L_\infty^+(Z)$ being the positive cone in $L_\infty(Z)$. Now, define the state space

$$X_0 = L_1(Z, zdz)$$

for the population density u, equipped with the norm $\|\cdot\|_0 := \|\cdot\|_{L_1(Z,\, zdz)}$ and

$$X_1 = \mathring{W}_1^1(Z, zdz) = \mathrm{cl}_{W_1^1(Z,zdz)} D(Z),$$

where $D(Z)$ be the space of all test functions on Z, equipped with the norm

$$\|u\|_1 := \|u\|_0 + \|\partial_z(u)\|_0,\ u \in X_1.$$

Also, the positive cone of X_0 and X_1 are represented by X_0^+ and $X_1^+ = X_1 \cap X_0^+$, respectively. To proceed further in obtaining the desired outcomes, the following two lemmas, Lemma 4.2.1 [[56], Lemma 3.1(a)] and Lemma 4.2.2 [[71], Lemma 2.1] are needed.

Lemma 4.2.1. *The operator $E : X_0 \to X_0$, defined by*

$$E[u](z) = -\big(\mu(z) + \beta(z)\big)u(z) + 2\int_z^\infty \beta(y)\, k(z,y)\, u(y)\, dy$$

is a linear and bounded operator corresponding to (1.4)-(1.5) and (4.5) such that

$$\|E[u]\|_0 \leq b^* \left(\|\mu\|_\infty + \|\beta\|_\infty\right) \|u\|_0, \quad u \in X_0,\ b^* \geq 2.$$

Taking a weight function $\phi(z)$, one can have

$$\int_{z_0}^\infty \phi(z)E[u](z)\, dz = -\int_{z_0}^\infty \phi(z)\mu(z)u(z)\, dz + \int_{z_0}^\infty u(z)\beta(z)\left(-\phi(z) + 2\int_{z_0}^z \phi(y)k(y,z)\, dy\right) dz. \quad (4.6)$$

Lemma 4.2.2. *The operator $-A$, defined by*

$$Au = \partial_z u, \quad u \in X_1,$$

generates a C_0 semigroup $\{e^{-tA} : t \geq 0\}$ on X_0 and it is described by

$$[e^{-tA}u](z) = \begin{cases} u(z-t)\ ; & z > z_0 + t \\ 0 \quad ; & z_0 < z \leq z_0 + t, \end{cases} \quad t \geq 0,$$

with

$$\left\| e^{-tA}u \right\|_{X_0} \leq e^{\frac{t}{z_0}} \|u\|_{X_0}, \quad t \geq 0. \quad (4.7)$$

Also, this semigroup is stable in the sense of [§2.4].

Now, for given $K > 1$, $T > 0$, define $J_T = [0, T]$ and

$$\Im_{T,K} = \{v \in C^1(J_T)\ :\ K^{-1} \leq v(t) \leq \|v(t)\|_{C^1(J_T)} \leq K\}. \quad (4.8)$$

Then, for given $S, C \in \Im_{T,K}$, introduce the operator

$$\mathbb{H}_S^C(t)u = \tau S(t)Au + \delta_2 C(t)u - E(u), \quad u \in X_1,\ t \in J_T. \quad (4.9)$$

According to Lemma 4.2.1 and Lemma 4.2.2, the operator family $\{-\mathbb{H}_S^C(s) : s \in [0,T]\}$ generates an evolution operator on X_0, refer to [§2.4].
In order to obtain the main result, Theorem 4.2.3 in the next section, the following proposition is required.

Proposition 4.2.1. *Let $K > 1, T_0 > 0$ and $0 < T \leq T_0$. Then, $\left\{-\mathbb{H}_S^C(t) : t \in [0,T]\right\}$ generates a unique evolution system $\mathbb{U}_S^C(t,r)$, $0 \leq r \leq t \leq T$ in X_0 for each $S, C \in \Im_{T,K}$. Moreover, there* *exists* $w_0 = w_0(T_0, K) > 0$ *such that*

$$\left\| \mathbb{U}_S^C(t,r) \right\|_{\mathcal{L}(X_0)} \le e^{w_0(t-r)}, \tag{4.10}$$

$$\left\| \mathbb{U}_S^C(t,r) \right\|_{\mathcal{L}(X_1)} \le w_0, \tag{4.11}$$

and for $S, C, S_1, C_1 \in \Im_{T,K}$

$$\left\| \mathbb{U}_S^C(t,r) - \mathbb{U}_{S_1}^{C_1}(t,r) \right\|_{\mathcal{L}(X_1,X_0)} \le w_0(t-r) \left(\|S - S_1\|_{C(J_T)} + \|C - C_1\|_{C(J_T)} \right) \tag{4.12}$$

where $0 \le r \le t \le T$.

Proof. From Lemma 4.2.1, Lemma 4.2.2 and a well-known Bounded Perturbation Theorem 2.2.1, $-\mathbb{H}_S^C(r)$ generates a C_0-semigroup on X_0 for any $r \in J_T$ and any fixed $S, C \in \Im_{T,K}$, that satisfies

$$\left\| e^{-t\mathbb{H}_S^C(r)} \right\|_{\mathcal{L}(X_0)} \le e^{\tilde{w}t}, \quad t \ge 0 \tag{4.13}$$

where $\tilde{w} = \frac{\tau K}{z_0} + \|E\|_{\mathcal{L}(X_0)} + \delta_2 K$.

From Theorem 2.4.2, $\left\{ -\mathbb{H}_S^C(r) : r \in [0,T] \right\}$ is a stable family for each $S, C \in \Im_{T,K}$. Now, for any $t \in J_T$, define $Q_S^C(t) : X_1 \to X_0$ by $Q_S^C(t) = wI + \mathbb{H}_S^C(t)$ which is an isomorphism that satisfies

$$\left\| Q_S^C(t) \right\|_{\mathcal{L}(X_1,X_0)} \le w + \frac{\tau K}{z_0} + \delta_2 K + \|E\|_{\mathcal{L}(X_0)}, \ \ t \in J_T \text{ and } S, C \in \Im_{T,K} \tag{4.14}$$

where I represents the identity operator and $w = \tilde{w} + 1$. Furthermore, for $u \in X_1$,

$$Q_S^C(t)u \in C^1(J_T, X_0) \ \text{ and } \ \dot{Q}_S^C(t)u = \frac{d}{dt} Q_S^C(t)u = \tau \dot{S}(t)\partial_z u + \delta_2 \dot{C}(t)u. \tag{4.15}$$

In consequence, the assumptions $(H_1), (H_2)^+$ and (H_3) of [§2.4] are fulfilled. This implies that a unique evolution system $\mathbb{U}_S^C(t,r)$, $0 \le r \le t \le T$ in X_0 exists corresponding to $\left\{ -\mathbb{H}_S^C(r) : r \in [0,T] \right\}$ for each $S, C \in \Im_{T,K}$ which satisfies the statements $(E_1) - (E_5)$ of [§2.4], such that

$$\left\| \mathbb{U}_S^C(t,r) \right\|_{\mathcal{L}(X_0)} \le e^{\tilde{w}(t-r)}. \tag{4.16}$$

In particular, if $\tilde{w}$ is replaced by w_0, then the inequality (4.10) holds.

Moreover, for the evolution system $\mathbb{U}_S^C(t,r)$, there exists a unique family of bounded linear operators $\mathbb{W}_S^C(t,r)$ in X_0, refer to [§2.4], such that

$$\mathbb{U}_S^C(t,r) = Q_S^C(t)^{-1} \mathbb{W}_S^C(t,r) Q_S^C(r), \ \ 0 \le r \le t \le T, \tag{4.17}$$

where $\mathbb{W}_S^C(t,r) \in \mathcal{L}(X_0)$ satisfies

$$\mathbb{W}_S^C(t,r)u = \mathbb{U}_S^C(t,r)u + \int_r^t \mathbb{W}_S^C(t,s)D_S^C(s)\mathbb{U}_S^C(s,r)u\, ds$$

for $0 \le r \le t \le T$ and $u \in X_0$ with $D_S^C(t) = \dot{Q}_S^C(t)Q_S^C(t)^{-1} \in \mathcal{L}(X_0),\ \ t \in J_T$. Since, $Q_S^C(t)^{-1}$ is a bounded operator, there exists a constant $c_1(K)$ such that

$$\left\| Q_S^C(t)^{-1} \right\|_{\mathcal{L}(X_0,X_1)} \le c_1(K) \quad \text{for } \ t \in J_T \text{ and } S,C \in \mathfrak{I}_{T,K}. \tag{4.18}$$

Also, the resolvent of $-\mathbb{H}_S^C(t)$ is $Q_S^C(t)^{-1}$ on X_0. Therefore,

$$\left\| Q_S^C(t)^{-1} \right\|_{\mathcal{L}(X_0)} \le 1 \quad \text{for } t \in J_T \text{ and } S,C \in \mathfrak{I}_{T,K}.$$

Further, for $t \in J_T,\ S,C \in \mathfrak{I}_{T,K}$ and $u \in X_0$,

$$\begin{aligned}\left\| Q_S^C(t)^{-1}u \right\|_{X_1} &= \left\| Q_S^C(t)^{-1}u \right\|_{X_0} + \left\| \frac{\partial}{\partial z} Q_S^C(t)^{-1}u \right\|_{X_0} \\ &\le \left[1 + \frac{K}{\tau}\left(1 + w + \delta_2 K + \|E\|_{\mathcal{L}(X_0)} \right) \right] \|u\|_{X_0}\end{aligned}$$

and consequently,

$$\begin{aligned}\left\| D_S^C(t) \right\|_{\mathcal{L}(X_0)} &\le \left\| \dot{Q}_S^C(t) \right\|_{\mathcal{L}(X_1,X_0)} \left\| Q_S^C(t)^{-1} \right\|_{\mathcal{L}(X_0,X_1)} \\ &\le \left(\tau \left\| \dot{S}(t) \right\|_{C(J_T)} + \delta_2 \left\| \dot{C}(t) \right\|_{C(J_T)} \right) c_1(K) \le c_2(K).\end{aligned}$$

It is clear from the proof of Lemma 2.4.6 and inequality (4.10) that there exists a constant $c_2(T_0,K)$ such that

$$\left\| \mathbb{W}_S^C(t,r) \right\|_{\mathcal{L}(X_0)} \le c_2(T_0,K), \ \ 0 \le r \le t \le T, \text{ and } S,C \in \mathfrak{I}_{T,K}. \tag{4.19}$$

Using estimates (4.14), (4.18) and (4.19) in (4.17), the inequality (4.11) is accomplished. Finally, to obtain the bound (4.12), let $u \in X_1$ and $S,C,S_1,C_1 \in \mathfrak{I}_{T,K}$. For $0 \le r \le t \le T$, consider the map

$$\phi : [s \mapsto \mathbb{U}_S^C(t,s)\mathbb{U}_{S_1}^{C_1}(s,r)u] \in C^1\big((r,t),X_0\big) \cap C\big([r,t],X_1\big).$$

Then, from $(E_1)-(E_5)$ in [§2.4], it is observed that

$$\phi(r)-\phi(t)=\mathbb{U}_S^C(t,r)u-\mathbb{U}_{S_1}^{C_1}(t,r)u=-\int_r^t \frac{\partial}{\partial s}\mathbb{U}_S^C(t,s)\mathbb{U}_{S_1}^{C_1}(s,r)u\,ds$$
$$=\int_r^t \mathbb{U}_S^C(t,s)\big(\mathbb{H}_S^C(s)-\mathbb{H}_{S_1}^{C_1}(s)\big)\mathbb{U}_{S_1}^{C_1}(s,r)u\,ds.$$

Therefore, (4.10) and (4.11) provide

$$\left\|\mathbb{U}_S^C(t,r)u-\mathbb{U}_{S_1}^{C_1}(t,r)u\right\|_{X_0}\le\int_r^t\|\mathbb{U}_S^C(t,s)\|_{\mathcal{L}(X_0)}\left\|\mathbb{H}_S^C(s)-\mathbb{H}_{S_1}^{C_1}(s)\right\|_{\mathcal{L}(X_1,X_0)}\left\|\mathbb{U}_{S_1}^{C_1}(s,r)\right\|_{\mathcal{L}(X_1)}\|u\|_{X_1}\,ds$$
$$\le c_2(T_0,K)(t-r)\left(\|S-S_1\|_{C(J_T)}+\|C-C_1\|_{C(J_T)}\right)\|u\|_{X_1}$$

for $0\le r\le t\le T$ and hence, inequality (4.12) holds. □

4.2.2 Classical Solution

This section deals with the global well-posedness of the system (4.1)-(4.3) in a classical sense for bounded kernels μ and β. By substituting

$$2\int_0^{z_0} z\int_{z_0}^{\infty}\beta(y)\,k(z,y)\,u(t,y)\,dydz := f(u),$$

the problem (4.1)-(4.3) can be rewritten, for $t>0$, as

$$\dot S=\lambda-\gamma S-\tau S\,|u|_1+f(u),\ S(0)=S^0, \tag{4.20}$$

$$\dot u+\mathbb{H}_S^C(t)u=0,\ u(0)=u^0, \tag{4.21}$$

$$\dot C=-\delta_0 C+\delta_1 C\,|u|_1,\ C(0)=C^0, \tag{4.22}$$

where $|\cdot|_1$ represents the norm in $L_1(Z)$.
Finally, the existence and uniqueness of a global classical solution are discussed in the following theorem.

Theorem 4.2.3. *Suppose (1.4)-(1.6) and (4.5) hold, then for any given $S^0,C^0>0$ and $u^0\in X_1^+$, the problem (4.1)-(4.3) possesses a unique globally positive classical solution (S,C,u) such that $S,C\in C^1(\mathbb{R}^+)$; $S(t),C(t)>0$ for $t>0$ and $u\in C^1(\mathbb{R}^+,X_0)\cap C(\mathbb{R}^+,X_1^+)$.*

Proof. Let $S^0,C^0>0$ and $u^0\in X_0^+\cap X_1$ be given and let $P>0$ be such that

$$P^{-1}\le S^0,C^0\le P \quad\text{and}\quad \left\|u^0\right\|_{X_1}\le P. \tag{4.23}$$

Construct a complete metric space

$$E_T = \left\{ u \in C(J_T, X_0^+) : \|u(t)\|_{X_0} \leq P+1, \ t \in J_T \right\}.$$

Let us choose an arbitrary $\tilde{u} \in E_T$, then $f(\tilde{u}), |\tilde{u}(t)|_1 \in C(J_T)$. Hence, equation (4.20) with u replaced by $\tilde{u}$ possesses a unique solution $S_{\tilde{u}} \in C^1(J_T)$ and is given by

$$S_{\tilde{u}}(t) = S^0 \, e^{-\gamma t - \tau \int_0^t |\tilde{u}(\sigma)|_1 d\sigma} + \int_0^t e^{-\gamma(t-s) - \tau \int_s^t |\tilde{u}(\sigma)|_1 d\sigma} \left[\lambda + f\left(\tilde{u}(s)\right)\right] \, ds. \tag{4.24}$$

Clearly,

$$S_{\tilde{u}}(t) \geq S^0 e^{-\gamma t - \tau \frac{P+1}{z_0} t} \geq c_1(P) \ \text{ for } \ 0 \leq t \leq T \leq 1. \tag{4.25}$$

Since, $S^0 < P$ and $f\left(\tilde{u}(t)\right) \leq \|\beta\|_\infty (P+1)$ for $t \in J_T$, one has

$$S_{\tilde{u}}(t) \leq c_2(P). \tag{4.26}$$

The above inequalities (4.25)-(4.26) together with equation (4.20) provide that

$$-c(P) \leq \dot{S}_{\tilde{u}}(t) \leq c(P), \ \ t \in J_T. \tag{4.27}$$

Therefore, (4.25)-(4.27) show the existence of $K = K(P) > 1$ which depends on $P > 0$ but independent of $T \in (0,1]$ such that $S_{\tilde{u}} \in \Im_{T,K(P)}$ whenever $\tilde{u} \in E_T$. Similarly, the equation (4.22) with u replacing by $\tilde{u}$, possesses a unique solution $C_{\tilde{u}} \in C^1(J_T)$ which is expressed by

$$C_{\tilde{u}}(t) = C^0 \, e^{-\delta_0 t + \delta_1 \int_0^t |\tilde{u}(\sigma)|_1 d\sigma}, \tag{4.28}$$

and similarly one can also obtain

$$-c(P) \leq \dot{C}_{\tilde{u}}(t) \leq c(P), \ \ t \in J_T. \tag{4.29}$$

Thus, (4.28)-(4.29) ensure the existence of $K = K(P) > 1$ depending on $P > 0$ but not on $T \in (0,1]$ such that $C_{\tilde{u}} \in \Im_{T,K(P)}$ whenever $\tilde{u} \in E_T$. Now, for $\tilde{u}_1, \tilde{u}_2 \in E_T$ and $0 \leq t \leq T \leq 1$,

$$|S_{\tilde{u}_1}(t) - S_{\tilde{u}_2}(t)| \leq c(P) \, \|\tilde{u}_1 - \tilde{u}_2\|_{E_T}, \tag{4.30}$$

and

$$|C_{\tilde{u}_1}(t) - C_{\tilde{u}_2}(t)| \leq c(P) \, \|\tilde{u}_1 - \tilde{u}_2\|_{E_T}. \tag{4.31}$$

Let $\mathbb{U}_{S_{\tilde{u}}}^{C_{\tilde{u}}}(t,r)$, $0 \leq r \leq t \leq T$ be a unique evolution system in X_0 corresponding to $\{-\mathbb{H}_{S_{\tilde{u}}}^{C_{\tilde{u}}}(t) : t \in J_T\}$ and $w_0 = w_0(1, K(P))$. Now, define $G : E_T \to E_T$ such as

$$G(\tilde{u})(t) = \mathbb{U}_{S_{\tilde{u}}}^{C_{\tilde{u}}}(t,0)u^0 \quad \text{for} \quad t \in J_T,\ \tilde{u} \in E_T,$$

which is the unique solution in $C^1(J_T, X_0) \cap C(J_T, X_1)$, refer to [§2.4], corresponding to the evolution equation,

$$\dot{u}(t) + \mathbb{H}_{S_{\tilde{u}}}^{C_{\tilde{u}}}(t)u = 0\ ,\ u(0) = u^0,\ t > 0.$$

Choosing $T = T(P) \in (0,1]$ sufficiently small, the inequality (4.10) yields that for $\tilde{u} \in E_T$ and $t \in J_T$,

$$\|G(\tilde{u})(t)\|_{X_0} \le e^{w_0 T} \left\|u^0\right\|_{X_0} \le P + 1.$$

Inequalities (4.12), (4.30) and (4.31) ensure that for $\tilde{u}_1, \tilde{u}_2 \in E_T$ and $t \in J_T$,

$$\begin{aligned} \|G(\tilde{u}_1)(t) - G(\tilde{u}_2)(t)\|_{X_0} &\le w_0 T\ c(P)\, \|\tilde{u}_1 - \tilde{u}_2\|_{E_T} \\ &\le \frac{1}{2}\, \|\tilde{u}_1 - \tilde{u}_2\|_{E_T}\,. \end{aligned}$$

Since, E is not positive on X_0^+, one can not say that $G(\tilde{u})(t)$ is non-negative. Hence, in order to prove the non-negativity of $G(\tilde{u})(t)$, we observe that $G(\tilde{u})$ also solves

$$\dot{u} + \big(A_{S_{\tilde{u}}}(t) + B_{C_{\tilde{u}}}(t) + pI\big)u = \big(E + pI\big)u = Q(u),\ \ u(0) = u^0,\ \ t \in [0,T], \tag{4.32}$$

with $A_{S_{\tilde{u}}}(t) = \tau S_{\tilde{u}}(t)\partial_z$ and $B_{C_{\tilde{u}}}(t) = \delta_2 C_{\tilde{u}}(t)I$, where I is an identity operator and $p = \|\mu\|_\infty + \|\beta\|_\infty > 0$. Then,

$$Q(u) \in X_0^+ \quad \text{for} \quad u \in X_0^+. \tag{4.33}$$

Since, Lemma 4.2.2 ensures that $-A_{S_{\tilde{u}}}(t)$ generates a positive C_0 semigroup on X_0, it readily follows from Corollary 2.2.2.2 that $-\left(A_{S_{\tilde{u}}}(t) + B_{C_{\tilde{u}}}(t) + pI\right)$ generates a positive semigroup on X_0 for each fixed $t \in J_T$. Hence, from [§2.4] the evolution system $\bar{\mathbb{U}}(t,r),\ 0 \le r \le t \le T$ generated by $\{-\left(A_{S_{\tilde{u}}}(t) + B_{C_{\tilde{u}}}(t) + pI\right) : t \in J_T\}$ is positive as well.

Let us define a mapping Λ from a suitable closed ball in $C\big([0,\widehat{T}], X_0\big)$, containing u^0, into itself such that

$$\Lambda(\bar{u})(t) = \bar{\mathbb{U}}(t,0)u^0 + \int_0^t \bar{\mathbb{U}}(t,s)Q\big(\bar{u}(s)\big)ds.$$

It is easy to check that Λ is a contraction for sufficiently small $\widehat{T} \in (0,T]$. Consequently, $u_0 = u^0$, $u_n = \Lambda(u_{n-1})$, $n \in \mathbb{N}$ is a sequence in $C\big([0,\widehat{T}], X_0^+\big)$ that converges to $G(\tilde{u})|_{[0,\widehat{T}]}$. This implies that

$$T' = \sup\{T^* \in (0,T] : G(\tilde{u})(t) \in X_0^+,\ 0 \le t \le T^*\} \ge \widehat{T}.$$

Assuming $T' < T$, then a repetition of the above arguments with u^0 substituted by $G(\tilde{u})(T') \in X_1^+$ leads to $T' = T$, which gives that $G : E_T \to E_T$ is a contraction. Since, the choice of

$T = T(P)$ depends only on P, therefore according to [56, 71], the system (4.1)-(4.3) admits a unique maximal solution $(S,C,u) \in C^1(I_0, \mathbb{R}\times\mathbb{R}\times X_0) \cap C(I_0, \mathbb{R}^+ \times \mathbb{R}^+ \times X_1^+)$ on a maximal interval I_0 which is open in $\mathbb{R}^+$.
Now, we claim that, if $\tau^* := \sup\,(I_0) < \infty$, then

$$\underline{\lim}_{t\to\tau^*}\, S(t) = 0,\ \ \underline{\lim}_{t\to\tau^*}\, C(t) = 0 \quad \text{or} \quad \overline{\lim}_{t\to\tau^*}\, \big(S(t)+C(t)+\|u(t)\|_{X_1}\big) = \infty. \tag{4.34}$$

For the global existence, we show that (4.34) does not occur in finite time. Using equations (1.5) and (4.6), we have

$$\begin{aligned}\dot{S}(t)+\dot{C}(t)+\frac{d}{dt}\int_{z_0}^{\infty} zu(t,z)\,dz &= \lambda-\gamma S(t)+2\int_{z_0}^{\infty} u(t,z)\beta(z)\int_0^{z_0} yk(y,z)\,dy\,dz\\ &\quad -\delta_0 C(t)+\delta_1 C(t)\int_{z_0}^{\infty} u(t,z)\,dz\\ &\quad -\delta_2 C(t)\int_{z_0}^{\infty} zu(t,z)\,dz+\int_{z_0}^{\infty} zE[u(t)](z)\,dz\\ &=\lambda-\gamma S(t)-\delta_0 C(t)-\int_{z_0}^{\infty} z\mu(z)u(t,z)\,dz\\ &\quad +\delta_1 C(t)\int_{z_0}^{\infty} u(t,z)\,dz-\delta_2 C(t)\int_{z_0}^{\infty} zu(t,z)\,dz.\end{aligned}$$

This implies that,

$$S(t)+C(t)+\|u(t)\|_{X_0} \le S^0+C^0+\left\|u^0\right\|_{X_0}+\lambda t, \ \ \text{for } t\in J_T,\ \delta_2 > \frac{\delta_1}{z_0}. \tag{4.35}$$

Using (4.20) and (4.35), the following estimates hold

$$\|S\|_{C^1(I_0)} \le h(\tau^*) \ \text{ and } \ S(t)>0, \ \text{ for } \ t\in I_0. \tag{4.36}$$

Also, the equation (4.22) and inequality (4.35) lead to the following

$$\|C\|_{C^1(I_0)} \le h(\tau^*) \ \text{ and } \ C(t)>0, \ \text{ for } \ t\in I_0. \tag{4.37}$$

Consequently, there exists $K\big(h(\tau^*)\big) > 0$ such that for each $0 < T < \tau^*$, one has $S,C \in \mathfrak{I}_{T,K}$ and hence, it is obvious from Proposition 4.2.1 that

$$\left\|\mathbb{U}_S^C(t,r)\right\|_{\mathcal{L}(X_1)} \le h(\tau^*), \quad 0\le r\le t\le \tau^*$$

and then,

$$\|u(t)\|_{X_1} = \left\|\mathbb{U}_S^C(t,0)u^0\right\|_{X_1} \le h(\tau^*)\left\|u^0\right\|_{X_1}, \ \ t\in I_0. \tag{4.38}$$

Thus, (4.34) can not hold in the sense of (4.36)-(4.38). This contradiction shows that the classical solution (S,C,u) exists for all times. □

Finally, in the next proposition, we consider compactly supported initial data and prove that u enjoys the property of finite speed of propagation, refer to [50], where (S,C,u) represents the solution of the system (4.1)-(4.3).

Proposition 4.2.2. *Let us assume (1.4)-(1.6) and (4.5) hold. If $S^0>0, C^0>0$ and if $u^0\in X_1^+$ such that supp $(u^0)\subset[z_0,V_0]$ for some $V_0>z_0$, then classical solution (S,C,u) of the problem (4.1)-(4.3) proved in Theorem 4.2.3 satisfies supp $(u)\subset[z_0,V(t)]$, where $V(t)=V_0+\tau\int_0^t S(s)\,ds,\ \ t\geq 0$.*

Proof. Let us introduce $\Psi\in C^1\big(\mathbb{R}^+,L_1(Z)\big)$ such that $\Psi(t,z)=\int_z^\infty u(t,y)\,dy,\ \ z\in Z,\ t\geq 0$. Then, from (4.2) and (1.6) the following estimates can be easily obtained

$$\begin{aligned}\frac{d}{dt}\Psi(t,z)&=\int_z^\infty \dot{u}(t,y)\,dy\\&=\tau S(t)u(t,z)-\delta_2 C(t)\int_z^\infty u(t,y)\,dy+\int_z^\infty E[u(t)](y)\,dy\end{aligned}$$

and

$$\begin{aligned}\frac{d}{dt}\int_{V(t)}^\infty \Psi(t,z)\,dz&=\int_{V(t)}^\infty \frac{d}{dt}\Psi(t,z)dz-V'(t)\Psi\big(t,V(t)\big)\\&\leq\int_{V(t)}^\infty\int_z^\infty E[u(t)](y)\,dy\,dz\\&\leq 2\,\|\beta\|_\infty\int_{V(t)}^\infty \Psi(t,z)\,dz.\end{aligned}$$

Hence,

$$\int_{V(t)}^\infty \Psi(t,z)\,dz\leq e^{2t\|\beta\|_\infty}\int_{V_0}^\infty\int_z^\infty u^0(y)\,dydz=0,$$

which provides that $u(t,z)=0$ for $z\in\big(V(t),\infty\big),\ \ t\geq 0.$ □

4.3 Existence of Weak Solution for Unbounded Kernels

The main motivation of this section is to prove the existence of weak solution to the problem (4.1)-(4.3) under some relaxation in condition (4.5) such as kernels μ and β are unbounded. More precisely, in the following, we assume that

$$\begin{cases}\text{there exists } \alpha\geq 1 \text{ and } \rho\in L_\infty^+(Z) \text{ such that}\\ \mu(z)+\beta(z)\leq\rho(z)\,z^\alpha,\ \ \text{a.e. } z\in Z \text{ and } \rho(z)\to 0 \text{ as } z\to\infty.\end{cases}\tag{4.39}$$

In addition, we also require

$$\begin{cases} \text{for each } \varepsilon > 0 \text{ there exists } \delta > 0 \text{ such that} \\ \sup_{|\xi|\leq\delta} \frac{\beta(z)}{z^{\alpha}} \int_{z_0}^{z} \mathbb{1}_{\xi}(y)k(y,z)\,dy \leq \varepsilon, \text{ a.e. } z \in Z, \end{cases} \tag{4.40}$$

where the supremum is taken over all measurable subsets $\xi \subset Z$ with $|\xi| \leq \delta$ and $\mathbb{1}_{\xi}$ represents the characteristic function on ξ.

In the following, $L_{1,\mathrm{w}}(Z)$ represents the weak topological space of $L_1(Z)$.

Definition 4.3.1. *For given $S^0, C^0 > 0$ and $u \in L_1^+(Z, zdz)$, the triplet (S, C, u) is called a weak solution corresponding to (4.1)-(4.3) if the following hold*

(a) $f(u) \in C(\mathbb{R}^+)$,

(b) $S, C \in C^1(\mathbb{R}^+)$ are non-negative solutions of (4.1) and (4.3), respectively,

(c) $u \in C(\mathbb{R}^+, L_{1,\mathrm{w}}(Z)) \cap L_{\infty,\mathrm{loc}}\left(\mathbb{R}^+, L_1^+(Z, zdz)\right)$,

(d) For all $\phi \in W_\infty^1(Z)$ and $t > 0$, it follows that $E[u] \in L_1\big((0,t)\times Z\big)$ and

$$\int_{z_0}^{\infty} \phi(z)u(t,z)\,dz = \int_{z_0}^{\infty} \phi(z)u^0(z)\,dz + \tau \int_0^t S(\sigma) \int_{z_0}^{\infty} \phi'(z)u(\sigma,z)\,dz\,d\sigma \\ - \delta_2 \int_0^t C(\sigma) \int_{z_0}^{\infty} \phi(z)u(\sigma,z)\,dz\,d\sigma + \int_0^t \int_{z_0}^{\infty} \phi(z)E[u(\sigma)](z)\,dz\,d\sigma.$$

For the existence of weak solution, the following lemmas are needed.

Lemma 4.3.1. *Let $A_S^C(t) = \tau S(t)A + \delta_2 C(t)$, for $S, C \in C(J_T)$ with $S(t), C(t) > 0$ and $t \in J_T$. Then, there is an evolution system $\mathbb{U}_{A_S^C}(t,r), 0 \leq r \leq t \leq T$ in $L_1(Z)$ corresponding to $-A_S^C(t), t \in J_T$ and for any $\delta > 0$, it satisfies*

$$\sup_{|\xi|\leq\delta} \int_{\xi} \mathbb{U}_{A_S^C}(t,r)\phi\,dz \leq \sup_{|\xi|\leq\delta} \int_{\xi} \phi\,dz, \;\; 0 \leq r \leq t \leq T, \; \phi \in L_1^+(Z),$$

where the supremum is taken over all measurable sets $\xi \subset Z$ with $|\xi| \leq \delta$.

Proof. According to Lemma 4.2.2, it is clear that the operator $-\partial_z$ with domain $\mathring{W}_1^1(Z)$ generates a positive C_0-semigroups of contractions on $L_1(Z)$ and it allows that

$$\left\|e^{-tA_S^C(r)}\right\|_{\mathcal{L}(L_1(Z))} \leq 1, \;\; \left\|e^{-tA_S^C(r)}\right\|_{\mathcal{L}(\mathring{W}_1^1(Z))} \leq 1, \;\; t \geq 0, \; r \in J_T.$$

From Theorems [2.4.1, 2.4.2 ,2.4.3], there exists a unique evolution system $\mathbb{U}_{A_S^C}(t,r), 0 \leq r \leq t \leq T$ in $L_1(Z)$ corresponding to $-A_S^C(t), t \in J_T$. Let ξ is any measurable subset of Z such that

$|\xi| \leq \delta$ and choose $\phi \in L_1^+(Z)$. Then,

$$\int_\xi \left[e^{-tA_S^C(r)}\phi \right](z)dz = \int_{z_0}^\infty \mathbb{1}_{\xi - t\tau S(r)}(z)\ e^{-\delta_2 C(r)t}\phi(z)\ dz \leq \sup_{|\xi'|\leq\delta} \int_{\xi'} \phi(z)\ dz$$

for $t \geq 0$ and $r \in J_T$. From equations (3.5) and (3.15) in [§5, [66]], we have

$$\int_\xi \mathbb{U}_{A_S^C}(t,r)\phi\ dz \leq \sup_{|\xi'|\leq\delta} \int_{\xi'} \phi\ dz,\ \ 0 \leq r \leq t \leq T,$$

which provides the required assertion. □

Lemma 4.3.2. *Let us assume g_n and g are measurable functions on Z such that $g_n \to g$ a.e. and let $u_n \to u$ in $L_{1,\mathrm{w}}^+(Z)$.*
(a) If $\|g_n\|_\infty \leq c$, then $g_n u_n \to gu$ in $L_{1,\mathrm{w}}(Z)$.
(b) If ρ and α are as in (4.39) and if $|g_n(z)| \leq \rho(z)z^\alpha$ for a.e. $z \in Z$ and

$$\int_{z_0}^\infty z^\alpha u_n(z)\ dz \leq c,\ \ n \in \mathbb{N},$$

then $g_n u_n \to gu$ in $L_{1,\mathrm{w}}(Z)$.

For the proof of Lemma 4.3.2, see [71]. In the following theorem, we relax the boundedness conditions on μ, β and discuss the existence of a weak solution.

4.3.1 Weak Solution Theorem

Theorem 4.3.3. *Let us assume that (1.4)-(1.6) and (4.39)-(4.40) hold. Then, for any given $S^0, C^0 > 0$ and $u^0 \in L_1^+(Z, z^\alpha dz)$, the system (4.1)-(4.3) possesses at least one global weak solution (S, C, u) in the sense of Definition 4.3.1. Moreover, u belongs to $L_{\infty,\mathrm{loc}}(\mathbb{R}^+, L_1(Z, z^\alpha dz))$.*

Proof. Suppose $u_n^0 \in D^+(Z)$ be such that $u_n^0 \to u^0$ in $L_1(Z, z^\alpha dz)$. Define $\mu_n := \min\{\mu, n\}$ and $\beta_n := \min\{\beta, n\}$. This implies that μ_n, β_n satisfy (4.39) and (4.40). Hence, Theorem 4.2.3 provides the existence of

$$(S_n, C_n, u_n) \in C^1\left(\mathbb{R}^+, \mathbb{R} \times \mathbb{R} \times X_0\right) \cap C\left(\mathbb{R}^+, \mathbb{R}^+ \times \mathbb{R}^+ \times X_1^+\right)$$

such that, for $t > 0$,

$$\dot{S}_n = \lambda - \gamma S_n - \tau S_n\ |u_n|_1 + f_n(u_n),\ \ S_n(0) = S^0 \tag{4.41}$$

$$\partial_t u_n + \tau S_n(t)\partial_z u_n + \delta_2 C_n(t)u_n = E_n[u_n],\ \ u_n(0) = u_n^0 \tag{4.42}$$

$$\dot{C}_n = -\delta_0 C_n + \delta_1 C_n \, |u_n|_1, \;\; C_n(0) = C^0 \tag{4.43}$$

where

$$f_n(u_n) = 2\int_0^{z_0} z \int_{z_0}^{\infty} \beta_n(y)\, k(z,y)\, u_n(t,y)\, dy\, dz,$$

and

$$E_n[u_n](z) = -\big(\mu_n(z)+\beta_n(z)\big)u_n(z) + 2\int_z^{\infty} \beta_n(y)\, k(z,y)\, u_n(y)\, dy.$$

Let $T>0$ be arbitrary, then from (4.35) there exists $b_0(T)>0$ which is independent of $n\geq 1$ such that

$$S_n(t)+C_n(t)+\|u_n(t)\|_{X_0} \leq b_0(T), \quad t\in J_T,\; n\geq 1,\; \delta_2 > \delta_1/z_0. \tag{4.44}$$

Equation (1.5) entails that,

$$2\int_{z_0}^{z} (y)^{\alpha} k(y,z)\, dy \leq (z)^{\alpha}, \quad \text{a.e. } z>z_0. \tag{4.45}$$

Recall that $u_n(t)$ has compact support due to Proposition 4.2.2. Hence, (4.42) and (4.45) yield,

$$\begin{aligned}\frac{d}{dt}\int_{z_0}^{\infty} z^{\alpha} u_n(t,z)\, dz = \big[\alpha\ \tau S_n(t)\int_{z_0}^{\infty} z^{\alpha-1} u_n(t,z)\, dz - \delta_2 C_n(t)\int_{z_0}^{\infty} z^{\alpha} u_n(t,z)\, dz\\ -\int_{z_0}^{\infty} z^{\alpha}\big(\mu_n(z)+\beta_n(z)\big)u_n(t,z)\, dz\\ +2\int_{z_0}^{\infty} u_n(t,z)\beta_n(z)\int_{z_0}^{z}(y)^{\alpha}k(y,z)\, dy\, dz\big]\\ \leq \frac{\alpha\ \tau}{z_0} S_n(t)\int_{z_0}^{\infty} z^{\alpha} u_n(t,z)\, dz.\end{aligned}$$

Therefore, Gronwall's inequality and estimate (4.44) ensure that

$$\|u_n(t)\|_{L_1(Z, z^{\alpha}dz)} \leq b_0(T), \quad t\in J_T,\; n\geq 1. \tag{4.46}$$

Further, (4.43) and (4.44) imply that

$$\dot{C}_n \leq \frac{\delta_1 C_n(t)}{z_0}\int_{z_0}^{\infty} z u_n(t,z)\, dz \leq \frac{\delta_1 b_0(T)}{z_0}\|u_n(t)\|_{X_0} \leq b(T), \;\; t\in J_T,$$

which provides that

$$|C_n(t)-C_n(s)| \leq b(T)\, |t-s|, \;\; t,s\in J_T,\; n\geq 1, \tag{4.47}$$

where $b(T)>0$ is independent of $n\geq 1$. Thus, from (4.44), (4.47) and the Arzela-Ascoli Theorem 2.5.1, the sequence $(C_n)_{n\geq 1}$ is relatively compact in $C(J_T)$.

Now, using (1.6), (4.39) and (4.46) for $f_n(u_n)$, we have

$$f_n\big(u_n(t)\big) \leq 2z_0 \,\|\rho\|_\infty \,\|u_n(t)\|_{L_1(Z,z^\alpha dz)} \leq b(T), \;\; t \in J_T, \; n \geq 1.$$

Therefore, equation (4.41) and the estimate on $f_n\big(u_n(t)\big)$ warrant that

$$|S_n(t) - S_n(s)| \leq b(T) \; |t-s|, \;\; t,s \in J_T, \; n \geq 1 \tag{4.48}$$

where $b(T) > 0$ is independent of $n \geq 1$. Due to (4.44) and (4.48), the Arzela-Ascoli Theorem 2.5.1 guarantees that the sequence $(S_n)_{n\geq 1}$ is relatively compact in $C(J_T)$.

Next, to prove that (u_n) is relatively sequentially compact in $C\left(J_T, L_{1,\mathrm{w}}(Z)\right)$, it is sufficient to show from Theorem 2.5.9 that the set $(u_n)_{n\geq 1}$ is weakly equicontinuous on J_T and for each $t \in J_T$, the set $\{u_n(t) \;:\; n \geq 1\}$ is weakly relatively compact in $L_{1,\mathrm{w}}(Z)$.
To prove the second part, let $\mathbb{U}_{S_n}^{C_n}(t,r)$ be the evolution system in $L_1(Z)$ corresponding to the operator $A_{S_n}^{C_n}(t) = \tau S_n(t) A + \delta_2 C_n(t)$, then

$$u_n(t) = \mathbb{U}_{S_n}^{C_n}(t,0)u_n^0 + \int_0^t \mathbb{U}_{S_n}^{C_n}(t,r) E_n[u_n(r)] \; dr, \quad t \in J_T.$$

Therefore, for given $\delta > 0$, the positivity of $u_n(t)$ and Lemma 4.3.1 guarantee that

$$\sup_{|\xi|\leq\delta} \int_\xi u_n(t,z) \; dz \leq \sup_{|\xi|\leq\delta} \int_\xi u_n^o(z) \; dz + 2\int_0^t \sup_{|\xi|\leq\delta} \int_{z_0}^\infty u_n(\sigma,z)\beta_n(z) \int_{z_0}^z \mathbb{1}_\xi(y) k(y,z) \; dy \; dz \; d\sigma.$$

Since, $u_n^0 \to u^0$ in $L_1(Z,z^\alpha dz)$ and due to (4.40) and (4.46), one can conclude that

$$\lim_{|\xi|\to 0} \sup_{n\geq 1, t\in J_T} \int_\xi u_n(t,z) \; dz = 0. \tag{4.49}$$

Also, inequality (4.44) provides

$$\lim_{R\to 0} \sup_{n\geq 1, t\in J_T} \int_R^\infty u_n(t,z) \; dz = 0. \tag{4.50}$$

Thanks to Dunford-Pettis Theorem 2.5.2, the equations (4.49) and (4.50) together with (4.44) ensure that $\{u_n(t) \; ; \; t \in J_T, \; n \geq 1\}$ is relatively compact in $L_{1,\mathrm{w}}(Z)$.
To prove the first part, let $\phi \in D(Z)$ be arbitrary and testing (4.42) by ϕ provides,

$$\begin{aligned}\left|\int_{z_0}^{\infty}\phi(z)[u_n(t,z)-u_n(s,z)]\,dz\right| &\leq \tau\int_s^t S_n(\sigma)\int_{z_0}^{\infty}|\phi'(z)|u_n(\sigma,z)\,dz\,d\sigma \\ &+\delta_2\int_s^t C_n(\sigma)\int_{z_0}^{\infty}\phi(z)u_n(\sigma,z)\,dz\,d\sigma \\ &+\int_s^t\int_{z_0}^{\infty}|\phi(z)|\left(\mu_n(z)+\beta_n(z)\right)u_n(\sigma,z)\,dz\,d\sigma \\ &+2\int_s^t\int_{z_0}^{\infty}u_n(\sigma,z)\beta_n(z)\int_{z_0}^{z}|\phi'(z)|k(y,z)\,dy\,dz\,d\sigma\end{aligned}$$

for $0\leq s\leq t\leq T$. This implies together with (1.6), (4.39), (4.44) and (4.46) that,

$$\left|\int_{z_0}^{\infty}\phi(z)[u_n(t,z)-u_n(s,z)]\,dz\right|\leq b(T,\phi)\;|t-s|,\quad s,t\in J_T. \tag{4.51}$$

Now, for $\phi\in L_\infty(Z)$, there exists $\phi_j\in D(Z)$ such that $\phi_j\to\phi$ a.e. and $\left\|\phi_j\right\|_\infty\leq\|\phi\|_\infty$, see in [1]. Then, Egorov's theorem warrant that there is a measurable subset ξ of (z_0,R) where $R>z_0$ such that

$$\left\|\phi-\phi_j\right\|_{L_\infty((z_0,R)\setminus\xi)}\leq\frac{\varepsilon}{6\,b_0(T)},$$

where $b_0(T)$ stems from (4.44).
Since, $\{u_n(t)\;;\;t\in J_T,\;n\geq 1\}$ is relatively compact in $L_{1,\mathrm{w}}(Z)$, there is a measurable subset ξ of (z_0,R) where $R>z_0$ such that

$$\int_R^{\infty}u_n(t,z)\,dz+\int_{\xi}u_n(t,z)\,dz\leq\frac{\varepsilon}{12\;\|\phi\|_\infty},\quad t\in J_T,\;n\geq 1.$$

Therefore, (4.51) provides,

$$\begin{aligned}\left|\int_{z_0}^{\infty}\phi(z)[u_n(t,z)-u_n(s,z)]\,dz\right| &\leq\left\|\phi-\phi_j\right\|_{L_\infty((z_0,R)\setminus\xi)}\left(|u_n(t)|_1+|u_n(s)|_1\right) \\ &+\left(\left\|\phi_j\right\|_\infty+\|\phi\|_\infty\right)\int_R^{\infty}\left(u_n(t,z)+u_n(s,z)\right)\,dz \\ &+\left(\left\|\phi_j\right\|_\infty+\|\phi\|_\infty\right)\int_{\xi}\left(u_n(t,z)+u_n(s,z)\right)\,dz \\ &+b(T,\phi_j)\;|t-s| \\ &\leq\varepsilon+b(T,\phi_j)\;|t-s|\end{aligned}$$

for $t,s\in J_T$ and $n\geq 1$. Consequently,

$$\limsup_{s\to t}\sup_{n\geq 1}\left|\int_{z_0}^{\infty}\phi(z)[u_n(t,z)-u_n(s,z)]\,dz\right|=0, \tag{4.52}$$

which shows that for every $t \in J_T$, $\{u_n \; : \; n \geq 1\}$ is equicontinuous in $L_{1,\mathrm{w}}(Z)$.
Thus, for each $T > 0$, (S_n, C_n, u_n) is relatively compact in $C\big(J_T, \mathbb{R} \times \mathbb{R} \times L_{1,\mathrm{w}}(Z)\big)$ and hence, one can find a subsequence (again denoted by $(S_n, C_n, u_n)_{n \geq 1}$) and a function $(S, C, u) \in C\big(\mathbb{R}^+, \mathbb{R} \times \mathbb{R} \times L_{1,\mathrm{w}}(Z)\big)$ such that for each $T > 0$,

$$(S_n, C_n, u_n) \to (S, C, u) \quad \text{in} \;\; C\big(J_T, \mathbb{R} \times \mathbb{R} \times L_{1,\mathrm{w}}(Z)\big). \tag{4.53}$$

Now, we claim that (S, C, u) be a weak solution corresponding to (4.1)-(4.3) and it follows that $\big(S(t), C(t), u(t)\big) \in \mathbb{R}^+ \times \mathbb{R}^+ \times L_1^+(Z)$ for $t > 0$ due to $\big(S_n(t), C_n(t), u_n(t)\big) \in \mathbb{R}^+ \times \mathbb{R}^+ \times L_1^+(Z)$. Again, for fixed $T > 0$, (4.46) and (4.53) provide that

$$\|u(t)\|_{L_1(Z, z^\alpha dz)} \leq b_0(T), \quad t \in J_T, \tag{4.54}$$

and in particular, $u \in L_{\infty,\mathrm{loc}}\big(\mathbb{R}^+, L_1(Z, z^\alpha dz)\big)$. Let $\phi \in W_\infty^1(Z)$ be an arbitrary. Then, (4.53) entails that

$$\lim_{n \to \infty} \int_{z_0}^{\infty} \phi(z) u_n(t,z) \; dz = \int_{z_0}^{\infty} \phi(z) u(t,z) \; dz, \quad t \in J_T. \tag{4.55}$$

Furthermore, for $t \in J_T$,

$$\begin{aligned}
&\left| \int_0^t C_n(\sigma) \int_{z_0}^{\infty} \phi(z) u_n(\sigma,z) \; dz \; d\sigma - \int_0^t C(\sigma) \int_{z_0}^{\infty} \phi(z) u(\sigma,z) \; dz \; d\sigma \right| \\
&\qquad \leq \int_0^t C_n(\sigma) \left| \int_{z_0}^{\infty} \phi(z) [u_n(\sigma,z) - u(\sigma,z)] \; dz \right| \; d\sigma \\
&\qquad + \int_0^t |C_n(\sigma) - C(\sigma)| \int_{z_0}^{\infty} |\phi(z)| u(\sigma,z) \; dz \; d\sigma.
\end{aligned}$$

By applying Lebesgue's dominated convergence theorem and having (4.44) and (4.53), one can obtain that

$$\lim_{n \to \infty} \int_0^t C_n(\sigma) \int_{z_0}^{\infty} \phi(z) u_n(\sigma,z) \; dz \; d\sigma = \int_0^t C(\sigma) \int_{z_0}^{\infty} \phi(z) u(\sigma,z) \; dz \; d\sigma \tag{4.56}$$

for $t \in J_T$. Similarly, for $t \in J_T$, it is easy to show that

$$\lim_{n \to \infty} \int_0^t S_n(\sigma) \int_{z_0}^{\infty} \phi'(z) u_n(\sigma,z) \; dz \; d\sigma = \int_0^t S(\sigma) \int_{z_0}^{\infty} \phi'(z) u(\sigma,z) \; dz \; d\sigma. \tag{4.57}$$

As $\mu_n(z) + \beta_n(z) \leq \rho(z) \; z^\alpha$, a.e. $z \in Z$, then Lemma 4.3.2, (4.46), (4.53) and Lebesgue's dominated convergence theorem imply that

$$\lim_{n \to \infty} \int_0^t \int_{z_0}^{\infty} \phi(z) \big(\mu_n(z) + \beta_n(z)\big) u_n(\sigma,z) \; dz \; d\sigma = \int_0^t \int_{z_0}^{\infty} \phi(z) \big(\mu(z) + \beta(z)\big) u(\sigma,z) \; dz \; d\sigma$$

as well as

$$\lim_{n\to\infty}\int_0^t\int_{z_0}^{\infty}\phi(z)\int_z^{\infty}u_n(\sigma,y)\beta_n(y)k(z,y)\,dy\,dz\,d\sigma=\int_0^t\int_{z_0}^{\infty}\phi(z)\int_z^{\infty}u(\sigma,y)\beta(y)k(z,y)\,dy\,dz\,d\sigma$$

where Fubini's theorem is used for the second limit. Consequently, both the above equations lead to,

$$\lim_{n\to\infty}\int_0^t\int_{z_0}^{\infty}\phi(z)E_n[u_n(\sigma)]\,dz\,d\sigma=\int_0^t\int_{z_0}^{\infty}\phi(z)E[u(\sigma)]\,dz\,d\sigma. \tag{4.58}$$

As, (S,C,u) is a weak solution corresponding to (4.1)-(4.3), equations (4.55)-(4.58) provide the fourth part of Definition 4.3.1. Further, from Lemma 4.3.2, it is easy to verify that

$$\lim_{n\to\infty}f_n\big(u_n(t)\big)=f\big(u(t)\big),\quad t\in J_T.$$

Further, (4.44) and (4.53) lead to,

$$\lim_{n\to\infty}\int_0^t|u_n(\sigma)|_1\,d\sigma=\int_0^t|u(\sigma)|_1\,d\sigma,\quad t\in J_T.$$

Thus, equation (4.41) warrants that

$$S(t)=S^0\,e^{-\gamma t-\tau\int_0^t|u(\sigma)|_1d\sigma}+\int_0^t e^{-\gamma(t-s)-\tau\int_s^t|u(\sigma)|_1d\sigma}\left[\lambda+f\left(u(s)\right)\right]\,ds,$$

and equation (4.43) yields,

$$C(t)=C^0\,e^{-\delta_0 t+\delta_1\int_0^t|u(\sigma)|_1d\sigma},$$

for $t\in J_T$. Since, $u\in C\big(\mathbb{R}^+,L_{1,w}(Z)\big)$, Lemma 4.3.2 and (4.54) imply that $f(u)\in C(J_T)$. Also, $|u|_1\in C(J_T)$, therefore we conclude that $S,C\in C^1(J_T)$ solve (4.1) and (4.3), respectively.

□

The finite speed of propagation for the weak solution corresponding to (4.2) is established in the following proposition.

Proposition 4.3.1. *Let us assume (1.4)-(1.6) and (4.39)-(4.40) hold and let (S,C,u) is a global weak solution to the problem (4.1)-(4.3) for $S^0,C^0>0$ and $u^0\in L_1^+(Z,z^{\alpha}dz)$. If supp $(u^0)\subset[z_0,V_0]$ for some $V_0>z_0$, then supp $u(t)\subset[z_0,V(t)]$, where $V(t)=V_0+\tau\int_0^t S(s)\,ds,\ \ t\geq 0$.*

Proof. First of all, choose the sequence $(u_n^0)\subset D^+(Z)$ as in the proof of Theorem 4.3.3 such that supp $(u_n^0)\subset(z_0,V_0)$. Then, Proposition 4.2.2 guarantees that the approximate sequence $(S_n,C_n,u_n)_{n\geq1}$ described by equations (4.41)-(4.43) satisfies

$$\text{supp }(u_n(t))\subset[z_0,V_n(t)],$$

where $V_n(t) = V_0 + \tau \int_0^t S_n(s)\, ds, \;\; t \geq 0.$
Therefore,

$$\lim_{n\to\infty} V_n(t) = V(t)$$

and due to (4.53) and Lemma 4.3.2(b) the following holds

$$\int_{V(t)}^{\infty} u(t,z)\, dz = \lim_{n\to\infty} \int_{V_n(t)}^{\infty} u_n(t,z)\, dz = 0.$$

This provides that $u(t,z) = 0$ for $z \in (V(t), \infty)$, and so supp $u(t) \subset [z_0, V(t)]$, for $t \geq 0$. $\square$

Chapter 5

Weak Solution and Qualitative Behavior of Prion-Chaperone Equations [1]

5.1 Introduction

In this chapter, we look at a prion proliferation system in the presence of a chaperone which consists of two ODEs and an integro-partial differential equation. The existence of weak solution results obtained in [55] is extended by incorporating chaperone by using a weak compactness argument. Further, we study the uniqueness of solutions under the sufficient conditions proposed in [55]. In addition, it is demonstrated that there is a unique steady state, the disease-free equilibrium, that exists below and at the threshold and is globally asymptotically stable. Above the threshold, there is another steady state, the disease state, which is globally asymptotically stable. At the end, we study the effect of chaperone on polymer population numerically. The mathematical model of monomer, polymer and chaperone terms is expressed by a system consisting of two ODEs and an integro-partial differential equation as

$$\frac{dS(t)}{dt} = \lambda - \gamma S(t) - \tau S(t)\int_{z_0}^{\infty} u(t,y)dy + 2\int_0^{z_0} z\int_{z_0}^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dydz \tag{5.1}$$

$$\frac{\partial u(t,z)}{\partial t} = -\tau S(t)\frac{\partial u(t,z)}{\partial z} - \big(\mu(z)+\beta(z)+\delta_2 C(t)\big)u(t,z) + 2\int_z^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dy \tag{5.2}$$

and

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t)\int_{z_0}^{\infty} u(t,y)\, dy \tag{5.3}$$

respectively, under the conditions

$$S(0) = S^0,\ C(0) = C^0,\ u(0,z) = u^0(z),\ u(t,z_0) = 0, \text{ for } t \geq 0,\ z_0 < z < \infty. \tag{5.4}$$

[1] A considerable part of this chapter is published in *Acta Applicandae Mathematicae*, 2022, doi: https://link.springer.com/content/pdf/10.1007/s10440-022-00512-y.

Here, the parameters γ, λ, τ, δ_0, δ_1 and $\delta_2 > \delta_1/z_0$ are positive constants and the description of these parameters are given in Chapter 1. The function $k(z,y)$ satisfies the assumptions (1.4)-(1.8). The function $U(t) = \int_{z_0}^{\infty} u(t,z)dz$ denotes the number of PrP^{Sc} polymers at time t and $P(t) = \int_{z_0}^{\infty} u(t,z)zdz$ is the total number of PrP^{Sc} monomers in polymers at time t. Therefore, under the assumptions (1.9), the problem (5.1)-(5.3) is transformed into a system of four ODEs

$$\begin{aligned} \dot{U} &= \beta P - \mu U - 2\beta z_0 U - \delta_2 CU \\ \dot{S} &= \lambda - \gamma S - \tau US + \beta z_0^2 U \\ \dot{P} &= \tau US - \mu P - \delta_2 CP - \beta z_0^2 U \\ \dot{C} &= -\delta_0 C + \delta_1 CU \end{aligned} \tag{5.5}$$

with initial values

$$U(0) = U^0 \geq 0,\ S(0) = S^0 \geq 0,\ P(0) = P^0 \geq 0 \text{ and } C(0) = C^0 \geq 0.$$

The main goal of present chapter is to extend the existence of weak solution results obtained in [55] in the presence of chaperone and to show the uniqueness of weak solution to the problem (5.1)-(5.3) under the sufficient conditions provided in [55]. Moreover, we study the stability results for disease-free as well as disease equilibrium points to the system (5.5). Finally, the effect of chaperone on polymer is also discuss numerically.

Theorem 5.1.1. *Suppose that $\lambda, \mu, \beta, \tau, \gamma, \delta_0, \delta_1, \delta_2, z_0 > 0$. The system (5.5) induces a global semiflow on $Q = \{(U,S,P,C) \in \mathbb{R}^4 : U, S, P - z_0 U, C \geq 0\}$. There exists precisely one disease-free equilibrium $(0, \lambda/\gamma, 0, 0)$ which is globally asymptotically stable iff $\beta\lambda\tau \leq \gamma(\mu + \beta z_0)^2$ and $\delta_1 < \tau$. Also, if $\beta\lambda\tau > \gamma(\mu + \beta z_0)^2$, then there exists precisely one disease equilibrium*

$$\left(\frac{(\mu+\beta z_0)^2}{\beta\tau}, \frac{\beta\lambda\tau - \gamma(\mu+\beta z_0)^2}{\mu\tau(\mu+2\beta z_0)}, \frac{\beta\lambda\tau - \gamma(\mu+\beta z_0)^2}{\beta\mu\tau}, 0 \right)$$

which is globally asymptotically stable in $Q \backslash [\{0\} \times \mathbb{R}^+ \times \{0\} \times \{0\}]$.

The basic reproduction number, i.e., the number of new infections produced by a single infective prion is $R_0 = \beta\lambda\tau/\gamma(\mu+\beta z_0)^2$. The disease dies out and disease-free state is globally asymtotically stable if $R_0 \leq 1$. For $R_0 > 1$, there exists a unique nontrivial steady state, the disease state, which is also globally asymtotically stable.

This chapter is assembled as follows: Section 5.2 deals with the existence of weak solution for a broad class of kernels, i.e., without placing growth conditions (1.11) on μ, β which extends the results of Chapter 4. Section 5.3 collects some fundamental properties of weak solutions provided in [55] and Section 5.4 presents the precise version of the uniqueness result of weak solution as well as the proof. In the last Section 5.5, we provide the proof of Theorem 5.1.1. Before we start next section, let us mention the definition of weak solution to the problem (5.1)-(5.3). Finally, the effect of chaperone on polymer population is discussed numerically.

From the system (5.1)-(5.3), we have

$$\begin{aligned} C(t)+S(t)+\int_{z_0}^{\infty} z\,u(t,z)\,dz-C^0-S^0-\int_{z_0}^{\infty} z\,u^0(z)\,dz \\ =\lambda t-\gamma\int_0^t S(s)\,ds-\delta_0\int_0^t C(s)\,ds+\delta_1\int_0^t C(s)\int_{z_0}^{\infty} u(s,z)\,dz\,ds \\ -\int_0^t\int_{z_0}^{\infty} z\mu(z)u(s,z)\,dz\,ds-\delta_2\int_0^t C(s)\int_{z_0}^{\infty} zu(s,z)\,dz\,ds. \end{aligned} \tag{5.6}$$

The definition of weak solutions to the problem (5.1)-(5.3) is given as:

Definition 5.1.1. *For given $S^0>0, C^0>0$ and $u^0\in L_1^+(Z,zdz)$, the triplet (S,C,u) is called a weak solution corresponding to the problem (5.1)-(5.3) if the following hold*
(a) $S,C\in C^1(\mathbb{R}^+)$ are non-negative solutions of (5.1) and (5.3), respectively,
(b) $u\in L_{\infty,\mathrm{loc}}\left(\mathbb{R}^+,L_1^+(Z,zdz)\right)$ is such that for all $\phi\in W^{1,\infty}(Z)$ and $t>0$, it follows that

$$[(s,z)\longmapsto(\mu(z)+\beta(z))\,u(s,z)]\in L_1\left((0,t)\times Z\right), \tag{5.7}$$

and

$$\begin{aligned} \int_{z_0}^{\infty}\phi(z)u(t,z)\,dz=\int_{z_0}^{\infty}\phi(z)u^0(z)\,dz+\tau\int_0^t S(s)\int_{z_0}^{\infty}\phi'(z)u(s,z)\,dz\,ds \\ -\delta_2\int_0^t C(s)\int_{z_0}^{\infty}\phi(z)u(s,z)\,dz\,ds-\int_0^t\int_{z_0}^{\infty}\phi(z)\mu(z)u(s,z)\,dz\,ds \\ -2\int_0^t\int_{z_0}^{\infty}\beta(z)u(s,z)\int_{z_0}^{z}\left(\frac{\phi(z)}{z}-\frac{\phi(y)}{y}\right)yk(y,z)\,dy\,dz\,ds \\ -2\int_0^t\int_{z_0}^{\infty}\beta(z)u(s,z)\frac{\phi(z)}{z}\int_0^{z_0} yk(y,z)\,dy\,dz\,ds, \end{aligned}$$

(c) (S,C,u) satisfies (5.6).

5.2 Existence of Weak Solutions

Similar to [55], we require besides (1.4)-(1.6) that k satisfies the following properties: for any given $R>z_0$, there holds

$$\lim_{\delta\to 0}\sup_{E\subset(z_0,R),|E|\le\delta}\ \operatorname*{ess\,sup}_{z\in(z_0,R)}\beta(z)\int_{z_0}^{z}\mathbb{1}_E(y)k(y,z)\,dy=0, \tag{5.8}$$

where $|E|$ represents the Lebesgue measure of E and there exists any $z_1 \in Z$ and $\delta* > 0$ such that

$$\int_{z_1}^{z} \left(1 - \frac{y}{z}\right) k(y,z)\, dy \geq \delta*, \quad z \geq 2z_1. \tag{5.9}$$

In case of k subject to (1.7) and (1.8), it is noticed that

$$\int_{z_0}^{z} \mathbb{1}_E(y) k(y,z)\, dy = \int_{z_0/z}^{1} \mathbb{1}_{\frac{1}{z}E}(y) k_0(y)\, dy,$$

so that (5.8) is automatically true for $\beta \in L_{\infty,\text{loc}}(Z)$ due to $z_0 > 0$ and integrability of k_0. In such situation, the following estimate also holds for $z > 2z_1$

$$\int_{z_1}^{z} \left(1 - \frac{y}{z}\right) k(y,z)\, dy \geq \frac{1}{2} \left(\int_0^{1/2} z k_0(z)\, dz + \int_{1/2}^{1} (1-z) k_0(z)\, dz \right)$$

and (5.9) holds thanks to (1.8). To state the existence result Theorem 5.2.1, we shall adopt the notation $L_{1,\text{w}}(Z, zdz)$ for the space $L_1(Z, zdz)$ equipped with its weak topology.

Theorem 5.2.1. *Let k satisfies above mentioned properties (1.4)-(1.6), (5.8) and (5.9). Also, assume that $\mu, \beta \in L^+_{\infty,\text{loc}}(Z)$ then there exists a weak solution (S, C, u) with $u \in C(\mathbb{R}^+, L_{1,\text{w}}(Z, zdz))$ for given initial data $S^0 > 0, C^0 > 0$ and $u^0 \in L_1^+(Z, zdz)$.*

Before proceeding to prove the theorem, let us briefly mention the idea of the proof along with important Lemmas and Propositions which are needed.
The weak compactness argument is imposed to prove the existence of a global weak solution. We first obtain a sequence (S_n, C_n, u_n) of global classical solutions from Theorem 4.2.3 for suitably approximated bounded kernels. Then, for any $T > 0$, Arzelà-Ascoli theorem 2.5.1 and Dunford-Pettis theorem 2.5.2 are used to study the compactness of the sequence in the space $C\left([0,T], \mathbb{R}^+ \times \mathbb{R}^+ \times L_{1,\text{w}}(Z, zdz)\right)$. Then, any cluster point of the sequence represents a global weak solution to the problem (5.1)-(5.3) for unbounded kernels.

For $u^0 \in L_1^+(Z, zdz)$, a refined form of De la Vallée-Poussin theorem, see [43], provides the existence of a non-decreasing and non-negative convex function $\Phi \in C^\infty(\mathbb{R}^+)$ with $\Phi(0) = 0$ such that Φ' is concave,

$$\int_{z_0}^{\infty} \Phi(z) u^0(z)\, dz < \infty,$$

and

$$\lim_{s\to\infty} \Phi'(s) = \lim_{s\to\infty} \frac{\Phi(s)}{s} = \infty. \tag{5.10}$$

This allows to take a sequence $(u_n^0)_{n\in\mathbb{N}}$ of compactly supported non-negative smooth functions such that

$$\sup_{n\in\mathbb{N}} \int_{z_0}^{\infty} \Phi(z) u_n^0(z)\, dz < \infty \quad \text{and} \quad u_n^0 \to u^0 \quad \text{in} \quad L_1^+(Z). \tag{5.11}$$

Let $\mu_n = \mathbb{1}_{[z_0,n]}\mu$ and $\beta_n = \mathbb{1}_{[z_0,n]}\beta$ for $n > z_0$. Then, it ensures from Theorem 4.2.3 that there exist non-negative classical solutions

$$(S_n, C_n, u_n) \in C^1\left(\mathbb{R}^+, \mathbb{R}\times\mathbb{R}\times L_1(Z, zdz)\right),$$

corresponding to the problem (5.1)-(5.3) when (μ, β, u^0) is replaced by (μ_n, β_n, u_n^0). Also, supp $u_n(t)$ is a compact subset of $[z_0, \infty)$ for each $t \geq 0$ and $S_n > 0, C_n > 0, u_n(t) \geq 0$. This allows to test (5.2) with any $\phi \in W^{1,\infty}_{\text{loc}}(Z)$ and to obtain the weak formulation stated in Definition 5.1.1. Let $T > 0$ be fixed. It is noticed from (5.6) that

$$\begin{aligned} S_n(t) + C_n(t) + \int_{z_0}^{\infty} z u_n(t,z)\, dz + \int_0^t \int_{z_0}^{\infty} z\mu_n(z) u_n(s,z)\, dzds \\ + (\delta_2 - \delta_1/z_0)\int_0^t C_n(s)\int_{z_0}^{\infty} z u_n(s,z)\, dzds \leq b(T), \end{aligned} \tag{5.12}$$

for $\delta_2 > \frac{\delta_1}{z_0}$, $t \in [0,T]$ and $n > z_0$.

Lemma 5.2.2. *For $t \in [0,T]$, there exists a constant $b(T)$ independent of $n > z_0$ such as*

$$\int_{z_0}^{\infty} \Phi(z) u_n(t,z)\, dz \leq b(T), \tag{5.13}$$

$$\int_0^t \int_{z_0}^{\infty} \Phi(z)\mu_n(z) u_n(\sigma,z)\, dzd\sigma \leq b(T), \tag{5.14}$$

$$\int_0^t I_{1,n}(\sigma) d\sigma \leq b(T), \tag{5.15}$$

$$\int_0^t I_{2,n}(\sigma) d\sigma \leq b(T), \tag{5.16}$$

$$\int_0^t C_n(\sigma)\int_{z_0}^{\infty} \Phi(z) u_n(\sigma,z)\, dzd\sigma \leq b(T) \tag{5.17}$$

where

$$I_{1,n}(\sigma) = \int_{z_0}^{\infty} u_n(\sigma,z)\beta_n(z)\int_{z_0}^{z}\left(\frac{\Phi(z)}{z} - \frac{\Phi(y)}{y}\right) yk(y,z)\, dydz,$$

and

$$I_{2,n}(\sigma) = \int_{z_0}^{\infty} u_n(\sigma,z)\beta_n(z)\frac{\Phi(z)}{z}\int_0^{z_0} yk(y,z)\, dydz.$$

Proof. Considering $\phi = \Phi$ in the definition 5.1.1 for u_n yields

$$\begin{aligned}
&\int_{z_0}^{\infty} \Phi(z)u_n(t,z)\, dz + \delta_2 \int_0^t C_n(\sigma) \int_{z_0}^{\infty} \Phi(z)u_n(\sigma,z)\, dzd\sigma \\
&\quad + \int_0^t \int_{z_0}^{\infty} \Phi(z)\mu_n(z)u_n(\sigma,z)\, dzd\sigma + 2\int_0^t (I_{1,n}(\sigma) + I_{2,n}(\sigma))\, d\sigma \\
&\quad = \int_{z_0}^{\infty} \Phi(z)u_n^0(z)\, dz + \tau \int_0^t S_n(\sigma) \int_{z_0}^{\infty} \Phi'(z)u_n(\sigma,z)\, dzd\sigma. \qquad (5.18)
\end{aligned}$$

The function $z \to \frac{\Phi(z)}{z}$ is non-decreasing because Φ is convex. This provides that $I_{1,n}$ is non-negative. Also, $I_{2,n}$ and the third term on the left hand side of (5.18) are non-negative due to the non-negativity of μ_n, β_n and Φ. On the other hand, since Φ' is concave with $\Phi'(0) \geq 0$, we have $-\Phi'(z) \leq \Phi'(0) - \Phi'(z) \leq -z\Phi''(z)$. This implies after integration with respect to z and using $\Phi(0) = 0$ that $z\Phi'(z) \leq 2\Phi(z)$ for $z \in Z$. One can deduce from (5.12) that

$$\begin{aligned}
\int_0^t S_n(s) \int_{z_0}^{\infty} \Phi'(z)u_n(s,z)\, dzds &\leq (1/z_0)b(T) \int_0^t \int_{z_0}^{\infty} z\Phi'(z)u_n(s,z)\, dzds \\
&\leq b(T) \int_0^t \int_{z_0}^{\infty} \Phi(z)u_n(s,z)\, dzds, \qquad (5.19)
\end{aligned}$$

for $t \in [0,T]$ and $n > z_0$. From (5.18), (5.19) and Gronwall's inequality, the required assertions hold. □

The estimates mentioned in Lemma 5.2.2 will be used to establish the weak compactness properties of the sequence (S_n, C_n, u_n).

Proposition 5.2.1. *There exists a weakly compact subset K_T of $L_1(Z, zdz)$ such that $u_n(t) \in K_T$ for $n > z_0$ and $t \in [0,T]$. Moreover,*

$$\int_0^T \int_{z_0}^{\infty} \beta_n(z)u_n(\sigma,z)\, dzd\sigma \leq b(T), \qquad (5.20)$$

where $b(T) > 0$ being a constant independent of $n > z_0$.

Proof. This Proposition can be proved by [[55], Lemma 4.1] together with Lemma 4.3.1. □

Lemma 5.2.3. *The family $\{u_n : n > z_0\}$ is weakly equicontinuous in $L_1(Z, zdz)$ for every $t \in [0,T]$.*

Proof. According to Theorem 4.3.3, for $\phi \in L_\infty(Z)$, we have

$$\lim_{s \to t} \sup_{n \geq z_0} \left| \int_{z_0}^{\infty} \phi(z)[u_n(t,z) - u_n(s,z)]\, dz \right| = 0,$$

for $t \in J_T$. This implies together with (5.10) that, for $t \in J_T$,

$$\lim_{s\to t} \sup_{n\geq z_0} \left| \int_{z_0}^{\infty} \phi(z)[u_n(t,z) - u_n(s,z)]\, zdz \right| = 0.$$

$\square$

Lemma 5.2.4. *The family $\{C_n : n > z_0\}$ is relatively compact in $C([0,T])$.*

Proof. It follows from (5.3) and (5.12) that

$$\begin{aligned} |C_n(t) - C_n(s)| &\leq \delta_0 \left| \int_s^t C_n(\sigma)\, d\sigma \right| + \delta_1 \left| \int_s^t C_n(\sigma) \int_{z_0}^{\infty} u_n(\sigma,z)\, dzd\sigma \right| \\ &\leq \delta_0 b(T)\, |t-s| + \frac{\delta_1}{z_0} b(T)\, |t-s|. \end{aligned}$$

Therefore,

$$\lim_{s\to t} \sup_{n>z_0} |C_n(t) - C_n(s)| = 0,$$

and the required result follows from the Arzelà-Ascoli theorem 2.5.1. $\square$

Lemma 5.2.5. *The family $\{S_n : n > z_0\}$ is relatively compact in $C([0,T])$.*

Proof. For the function $\phi(z) = z$, the truncated equation (5.2) together with (1.5) and positivity of $u_n(t)$ provides

$$\begin{aligned} 2\int_{z_0}^{\infty} u_n(t,z)\beta_n(z) \int_0^{z_0} yk(y,z)\, dydz = \tau S_n(t) \int_{z_0}^{\infty} u_n(t,z)dz - \frac{d}{dt}\int_{z_0}^{\infty} zu_n(t,z)\, dz \\ - \delta_2 C_n(t) \int_{z_0}^{\infty} zu_n(t,z) - \int_{z_0}^{\infty} z\mu_n(z)u_n(t,z)\, dz, \end{aligned}$$

and this implies that

$$\left| 2\int_s^t \int_{z_0}^{\infty} u_n(\sigma,z)\beta_n(z) \int_0^{z_0} yk(y,z)\, dydzd\sigma \right| \leq b(T)|t-s| + \left| \int_{z_0}^{\infty} z[u_n(t,z) - u_n(s,z)]dz \right|.$$

Thus, it follows from (5.1), (5.12) and Lemma 5.2.3 that

$$\lim_{s\to t} \sup_{n>z_0} |S_n(t) - S_n(s)| = 0,$$

and the assertion is complete from the Arzelà-Ascoli theorem 2.5.1. $\square$

Proposition 5.2.1, Lemmas 5.2.3-5.2.5 and Arzelà-Ascoli theorem [2.5.9, 2.5.1] imply that there exists a subsequence (again denoted by $(S_n), (C_n), (u_n)$ and functions $S, C \in C(\mathbb{R}^+), u \in$

$C(\mathbb{R}^+, L_{1,\mathrm{w}}(Z,zdz))$ such that for each $T>0$,

$$S_n \to S \quad \text{in} \quad C([0,T]), \tag{5.21}$$

$$C_n \to C \quad \text{in} \quad C([0,T]), \tag{5.22}$$

$$u_n \to u \quad \text{in} \quad C([0,T], L_{1,\mathrm{w}}(Z,zdz)). \tag{5.23}$$

It is clear that $S(t) \geq 0, C(t) \geq 0$ and $u(t) \geq 0$. According to [55], it is easy to show that (S,C,u) is a weak solution corresponding to the system (5.1)-(5.3).

It should be noted that the differentiability of μ and β is not necessary for the existence of weak solution but for the uniqueness result, the (weak) differentiability of μ and β is essential, see Theorem 5.4.1 in Section 5.4.

5.3 Ansatz of Weak Solutions

Here, we discuss the required properties of weak solutions for the uniqueness. In the work here, the function k is measurable and non-negative which satisfies (1.4)-(1.6). We also additionally assume, similar to [55], that

$$\lim_{y \searrow z} \int_z^y k(x,y)dx = 0, \quad z > z_0, \tag{5.24}$$

and

$$\mu, \beta \in W^{1,\infty}_{\mathrm{loc}}(Z) \quad \text{with} \quad \mu, \beta \geq 0. \tag{5.25}$$

Defining

$$G(z) = \int_{z_0}^{z} g(y)\, dy, \quad z > z_0,$$

there holds for some constant $c_0 > 0$,

$$(\mu+\beta)(z) \leq c_0 \left((\mu+\beta)(y) + G(y) + y\right), \quad y > z > z_0, \tag{5.26}$$

and

$$|\mu'(z)| + |\beta'(z)| \leq c_0\, g(z), \quad z > z_0, \tag{5.27}$$

as well as

$$\left|\partial_z \left(\beta(z) \int_0^{z_0} xk(x,z)\, dx\right)\right| + |B_2(y,z)| \leq c_0\, g(z), \quad z > y \geq z_0, \tag{5.28}$$

where

$$B_2(y,z) = \partial_z \left(\beta(z) \int_y^z k(x,z)\, dx\right) \quad \text{for } z > y \geq z_0, \tag{5.29}$$

and $g \in W^{1,\infty}_{\text{loc}}(Z)$ is a strictly positive function such that $\tau g'(z) \leq c_0 g(z),\ z > z_0$. In addition, we shall need to make the crucial assumption that

$$\int_{z_0}^{z} g(y)\left|2B_2(y,z) - (\mu' + \beta')(z)\right| dy \leq g(z)\left(c_0 + (\mu + \beta)(z)\right) \tag{5.30}$$

for $z > z_0$. Also, we assume that there exists $\delta > 0$ with

$$\int_0^z \frac{y}{z}\left(1 - \frac{y}{z}\right) k(y,z)\ dy \geq \delta,\ \ z > z_0. \tag{5.31}$$

Clearly (5.24) and (5.31) hold for k subject to (1.7), (1.8). It is also noticed that (5.26) permits

$$\lim_{z\to\infty} (\mu + \beta)(z) \int_z^{\infty} |f(y)|\ dy = 0, \quad \text{for } f \in L_1(Z, v(z)dz), \tag{5.32}$$

together with $v(y) = (\mu + \beta)(z) + G(z) + z$ for $z \in Z$.

Lemma 5.3.1. *Suppose that (S, C, u) is a weak solution corresponding to a fixed initial value $(S^0, C^0, u^0) \in \mathbb{R}^+ \times \mathbb{R}^+ \times L_1^+(Z, zdz)$. Then*

$$[(s,z) \longmapsto z\,(1 + \mu(z))\,u(s,z)] \in L_1\left((0,t) \times Z\right), \quad t > 0, \tag{5.33}$$

and if (5.24)-(5.31) are true, then

$$\lim_{R\to\infty} R \int_0^t \int_R^{\infty} \beta(z) u(s,z)\ dz\ ds = 0,\ \ t > 0. \tag{5.34}$$

Proof. The property (5.33) can be easily obtained from (5.6) and the non-negativity of μ, S, C and u. To verify (5.34), we consider $\phi(z) = R \wedge z = \min\{R, z\}$ in definition 5.1.1 with $R > z_0$ and using equations (5.1) and (5.3). Then, one has

$$\begin{aligned}
C(t) - C^0 + S(t) - S^0 + \int_{z_0}^{\infty} (R \wedge z)\left(u(t,z) - u^0(z)\right)\ dz \\
= \lambda t - \gamma \int_0^t S(s)\ ds - \delta_0 \int_0^t C(s)\ ds + \delta_1 \int_0^t C(s) \int_{z_0}^{\infty} u(s,z)\ dz\ ds \\
- \int_0^t \int_{z_0}^{\infty} (R \wedge z)\mu(z) u(s,z)\ dz\ ds - \delta_2 \int_0^t C(s) \int_{z_0}^{\infty} (R \wedge z) u(s,z)\ dz\ ds \\
+ 2 \int_0^t \int_R^{\infty} \beta(z) u(s,z) \int_{z_0}^{z} \left(\frac{R \wedge y}{y} - \frac{R}{z}\right) yk(y,z)\ dy\ dz\ ds - \tau \int_0^t S(s) \int_R^{\infty} u(s,z)\ dz\ ds \\
+ 2 \int_0^t \int_R^{\infty} \beta(z) u(s,z) \left(1 - \frac{R}{z}\right) \int_0^{z_0} yk(y,z)\ dy\ dz\ ds
\end{aligned}$$

for $t > 0$. Now, (5.33) indicates that (5.6) is true iff the last two integral terms on the right-hand-side in above equation tend to 0 as $R \to \infty$. Hence, writing

$$\left(1-\frac{R}{z}\right)\int_0^{z_0} yk(y,z)\,dy = \left(1-\frac{R}{z}\right)\int_0^{R} yk(y,z)\,dy - \int_{z_0}^{R}\left(\frac{R\wedge y}{y}-\frac{R}{z}\right)yk(y,z)\,dy$$

it is concluded that

$$\lim_{R\to\infty}\int_0^t\int_R^\infty \beta(z)u(s,z)\left\{(z-R)\int_0^R \frac{y}{z}k(y,z)\,dy + R\int_R^z\left(1-\frac{y}{z}\right)k(y,z)\,dy\right\}dz\,ds = 0.$$

Inequality (5.31) guarantees that the part in curly bracket is bounded below by

$$R\int_0^z \frac{y}{z}\left(1-\frac{y}{z}\right)k(y,z)\,dy \geq R\delta$$

for $z > 2R$ and the required assertion (5.34) follows. □

Lemma 5.3.2. *Let us assume (5.24)-(5.30) hold and $(S,C,u),(\hat{S},\hat{C},\hat{u})$ are two weak solutions corresponding to the same initial data $(S^0,C^0,u^0)\in(0,\infty)\times(0,\infty)\times L_1^+(Z,zdz)$ such that $u,\hat{u}\in L_{1,\mathrm{loc}}(\mathbb{R}^+,L_1(Z,G(z)dz))$. Defining*

$$E(t,z) = \int_z^\infty (u-\hat{u})(t,y)\,dy,\quad (t,z)\in\mathbb{R}^+\times Z,$$

leads to

$$\begin{aligned}\partial_t E(t,z)+\tau S(t)\partial_z E(t,z) =& \tau\hat{u}(t,z)(S-\hat{S})(t)+(\mu+\beta)(z)E(t,z)+\int_z^\infty(\mu'+\beta')(y)E(t,y)\,dy\\ &-\delta_2 C(t)E(t,z)-\delta_2\left(C(t)-\hat{C}(t)\right)\int_z^\infty \hat{u}(t,y)\,dy\\ &-2\int_z^\infty B_2(z,y)E(t,y)\,dy. \end{aligned}\tag{5.35}$$

5.4 Uniqueness

In this section, we discuss the uniqueness result. In addition to (5.24)-(5.30), consider

$$\int_y^z \left|(\mu'+\beta')(x)\right|dx \leq c_1(1+(\mu+\beta)(z)),\quad z>y>z_0,\tag{5.36}$$

as well as

$$\int_{z'}^z \left|B_2(z',y)(y)\right|dy \leq c_1(1+(\mu+\beta)(z)),\quad z>z'>z_0,\tag{5.37}$$

for some $c_1 > 0$. We then have the following uniqueness result.

Theorem 5.4.1. *Let (5.24)-(5.30), (5.36) and (5.37) hold. Then, in the sense of definition 5.1.1 there exists at most one weak solution* (S,C,u) *with*

$$u \in L_{\infty,\mathrm{loc}}\left(\mathbb{R}^+, L_1(Z, G(z)dz)\right) \cap L_{1,\mathrm{loc}}\left(\mathbb{R}^+, L_1(Z, (\mu+\beta)(z)G(z)dz)\right)$$

for given any initial data $S^0 > 0, C^0 > 0$ *and* $u^0 \in L_1^+(Z, zdz) \cap L_1(Z, (\mu+\beta)(z)G(z)dz)$.

The proof is presented in the following section.

5.4.1 Estimates on Difference of Solutions

This subsection deals with reasonable estimates on the primitive of the difference of two solutions which help to prove Theorem 5.4.1.

Lemma 5.4.2. *There exists* $b(T) > 0$ *such that the following estimates hold for* $0 < t < T$,

(i)

$$|(C-\hat{C})(t)| \le b(T) \int_0^t |E(s,z_0)|\, ds,$$

(ii)

$$|(S-\hat{S})(t)| \le b(T) \int_0^t \int_{z_0}^\infty g(z)\, |E(s,z)|\, dz\, ds,$$

(iii)

$$|E(t,z_0)| \le b(T) \int_0^t \int_{z_0}^\infty g(z)\, |E(s,z)|\, dz\, ds.$$

Proof. To prove part (i), it follows from (5.3) that

$$\begin{aligned}|C(t)-\hat{C}(t)| \le & \int_0^t \left(\delta_0 + \delta_1 \int_{z_0}^\infty \hat{u}(s,z)\, dz\right) |C(s)-\hat{C}(s)|\, ds \\ & + \delta_1 \|C\|_{L_\infty(0,T)} \int_0^t \left| \int_{z_0}^\infty (u-\hat{u})(s,z)\, dz \right| ds \\ \le & \, b(T) \int_0^t |C(s)-\hat{C}(s)|\, ds + c\int_0^t |E(s,z_0)|\, ds.\end{aligned}$$

Applying Gronwall's inequality, we have

$$|C(t)-\hat{C}(t)| \le b(T) \int_0^t |E(s,z_0)|\, ds.$$

The proof of the part (ii) follows from [[55], Lemma 3.3]. Finally, to establish the part (iii), we proceed as follows. Considering $\phi \equiv 1$ in definition (5.1.1) and applying integration by parts, one can obtain by using (1.5) and $\partial_z E = \hat{u} - u$,

$$
\begin{aligned}
|E(t,z_0)| &= \left| \int_{z_0}^{\infty} (u-\hat{u})(t,z)\, dz \right| \\
&= \Big| \int_0^t \int_{z_0}^{\infty} \Big(2\beta(z) \int_{z_0}^{z} k(y,z)dy - (\beta+\mu)(z)\Big)(u-\hat{u})(s,z)\, dz\, ds \\
&\quad - \delta_2 \int_0^t C(s) \int_{z_0}^{\infty} (u-\hat{u})(s,z)\, dz\, ds - \delta_2 \int_0^t (C(s)-\hat{C}(s)) \int_{z_0}^{\infty} \hat{u}(s,z)\, dz\, ds \Big| \\
&\le \Big| \int_0^t \int_{z_0}^{\infty} \Big(2\beta(z) \int_{z_0}^{z} k(y,z)dy - (\beta+\mu)(z)\Big)(u-\hat{u})(s,z)\, dz\, ds \Big| \\
&\quad + \delta_2 \|C\|_{L_\infty(0,T)} \int_0^t |E(s,z_0)|\, ds + b(T) \int_0^t |C(s)-\hat{C}(s)|\, ds \\
&\le c \int_0^t |E(s,z_0)|\, ds + c \int_0^t \int_{z_0}^{\infty} g(z)\, |E(s,z)|\, dz\, ds + b(T) \int_0^t |C(s)-\hat{C}(s)|\, ds \\
&\le b(T) \int_0^t |E(s,z_0)|\, ds + b(T) \int_0^t \int_{z_0}^{\infty} g(z)\, |E(s,z)|\, dz\, ds.
\end{aligned}
$$

Thus, Gronwall's inequality provides the required assertion. □

Further, let $R > z_0$ be arbitrary and multiplying the equation (5.35) by $g(z)\mathrm{sign}E(t,z)$, we have

$$
\begin{aligned}
g(z)\ \mathrm{sign}(E)(t,z)\partial_t E(t,z) &= -\tau g(z)\mathrm{sign}(E)(t,z)S(t)\partial_z E(t,z) - \hat{S}(t))g(z)\ \mathrm{sign}(E)(t,z) \\
&\quad + g(z)\ \mathrm{sign}(E)(t,z)(\mu+\beta)(z)E(t,z) - \delta_2 C(t)g(z)\ \mathrm{sign}(E)(t,z)E(t,z) \\
&\quad + g(z)\ \mathrm{sign}(E)(t,z) \int_z^{\infty} (\mu'+\beta')(y)E(t,y)dy + \tau\hat{u}(t,z)(S(t) \\
&\quad - 2g(z)\ \mathrm{sign}(E)(t,z) \int_z^{\infty} B_2(z,y)E(t,y)dy \\
&\quad - \delta_2(C(t)-\hat{C}(t))g(z)\ \mathrm{sign}(E)(t,z) \int_z^{\infty} \hat{u}(t,y)dy
\end{aligned}
$$

and this leads to

$$
\begin{aligned}
\int_{z_0}^{R} g(z)|E(t,z)|dz &\le b(T) \int_0^t |E(t,z_0)ds + b(T) \int_0^t \int_{z_0}^{R} g(z)|E(s,z)|dzds \\
&\quad + c \int_0^t |S(t)-\hat{S}(t)| \int_{z_0}^{R} (1+G(y))\hat{u}(s,z)dzds \\
&\quad + \delta_2 \int_0^t C(s) \int_{z_0}^{R} g(z)|E(t,z)|dzds + V(t,R) \\
&\quad + \delta_2 \int_0^t |C(s)-\hat{C}(s)| \int_{z_0}^{R} g(z)\ \mathrm{sign}(E)(s,z) \int_z^{\infty} \hat{u}(s,y)dydzds
\end{aligned}
$$

where

$$V(t,R) = G(R)\int_0^t \int_R^\infty \left|(\mu' + \beta')(z)\right| |E(s,z)| \, dzds$$
$$+ 2\int_0^t \int_R^\infty |E(s,z)| \int_{z_0}^R g(y)|B_2(y,z)| \, dydzds.$$

This implies that

$$\int_{z_0}^R g(z)|E(t,z)|dz \le b(T)\int_0^t |E(t,z_0)ds + b(T)\int_0^t \int_{z_0}^R g(z)|E(s,z)|dzds$$
$$+ c\int_0^t |S(t) - \hat{S}(t)| \int_{z_0}^R (1+G(z))\hat{u}(s,z)dzds + V(t,R)$$
$$+ \delta_2 \int_0^t |C(s) - \hat{C}(s)| \int_{z_0}^R \hat{u}(s,z)(1+G(z))dzds \tag{5.38}$$

for $R > z_0$ and $0 < t < T$. Further, it can be claimed according to [55] that $E \equiv 0$ and so $u \equiv \hat{u}$. This completes the proof of Theorem 5.4.1.

5.5 Stability Results and Effect of Chaperone

In this section, we discuss the proof of Theorem 5.1.1 as well as effect of chaperone on prion population numerically. We replace $P(t)$ by $W(t) = P(t) - z_0 U(t)$ in the system (5.5). The resulting system of equations is

$$\begin{aligned} z_0\dot{U} &= \beta z_0 W - (\mu + \beta z_0)(z_0 U) - \delta_2 C(z_0 U) \\ \dot{S} &= \lambda - \gamma S - \frac{\tau S}{z_0}(z_0 U) + \beta z_0 (z_0 U) \\ \dot{W} &= \frac{\tau S}{z_0}(z_0 U) - (\mu + \beta z_0)W - \delta_2 C W \\ \dot{C} &= -\delta_0 C + \delta_1 C U \end{aligned} \tag{5.39}$$

with initial conditions

$$U(0) = U^0 \ge 0, S(0) = S^0 \ge 0, W(0) = W^0 = P^0 - z_0 U^0 \ge 0 \text{ and } C(0) = C^0.$$

Further, performing a scaling of the variables for the system (5.39) by setting

$$z_0 U(t) = eE(\alpha t),\ S(t) = fF(\alpha t),\ W(t) = gG(\alpha t),\ C(t) = hH(\alpha t)$$

where $\alpha = \mu + \beta z_0, e = \frac{(\mu+\beta z_0)z_0}{\tau}, f = g = \frac{(\mu+\beta z_0)^2}{\beta\tau}, \sigma = 1, k = \frac{\beta\lambda\tau}{(\mu+\beta z_0)^3} > 0, \xi = \frac{\gamma}{\mu+\beta z_0} > 0, \rho = \left(\frac{\beta z_0}{\mu+\beta z_0}\right)^2 \in (0,1), h = \frac{\mu+\beta z_0}{\delta_2} > 0, \nu = \frac{\delta_0}{\mu+\beta z_0} > 0, \psi = \frac{\delta_1}{\tau} > 0$, we have

$$\begin{aligned} \dot{E} &= G - \sigma E - EH \\ \dot{F} &= k - \xi F - FE + \rho E \\ \dot{G} &= FE - G - HG \\ \dot{H} &= -\nu H + \psi EH \end{aligned} \tag{5.40}$$

with initial values $E(0) = E_0 \geq 0, F(0) = F_0 \geq 0, G(0) = G_0 \geq 0$ and $H(0) = H_0 \geq 0$. We compute the steady state solutions for the above system. For this, set $\dot{E} = \dot{F} = \dot{G} = \dot{H} = 0$. Then, $H = 0$ or $E = \frac{\nu}{\psi}$. For $H = 0$, the system becomes

$$\begin{aligned} G - \sigma E &= 0 \\ k - \xi F - FE + \rho E &= 0 \\ FE - G &= 0. \end{aligned} \tag{5.41}$$

Solving the above, the disease free equilibrium point is obtained as

$$\varepsilon_1 = (0, \frac{k}{\xi}, 0, 0) = (\bar{E}, \bar{F}, \bar{G}, \bar{H})$$

and the disease state equilibrium point is given by

$$\varepsilon_2 = (\widehat{E}, \widehat{F}, \widehat{G}, \widehat{H}) = \left(\frac{k-\sigma\xi}{\sigma-\rho}, \sigma, \sigma\frac{k-\sigma\xi}{\sigma-\rho}, 0\right).$$

Proposition 5.5.1. *Let k, σ, ξ, ν, $\psi > 0$ and $\rho \in (0,1)$. Then, for each $(E(0), F(0), G(0), H(0)) \in (\mathbb{R}^+)^4$, the system (5.40) possesses a unique bounded solution in $(\mathbb{R}^+)^4$ defined for all positive times.*

Proof. Let $f : (\mathbb{R}^+)^4 \to (\mathbb{R}^+)^4$ is defined by

$$\begin{aligned} f(E,F,G,H) &= (f_1, f_2, f_3, f_4) \\ &= (G - \sigma E - EH, k - \xi F - FE + \rho E, FE - G - HG, -\nu H + \psi EH). \end{aligned}$$

We noticed that f is Lipschitz continuous on bounded sets of $(\mathbb{R}^+)^4$. Now, for $(E,F,G,H) \in (\mathbb{R}^+)^4$ and $t \geq 0$, it holds that $f_1 \geq 0$ when $E = 0$, $f_2 \geq 0$ when $F = 0$,, $f_3 \geq 0$ when $G = 0$, and $f_4 \geq 0$ when $H = 0$. From [Corollary A.5, [73]], there exists a unique positive solution of (5.40) in $(\mathbb{R}^+)^4$ for $t \geq 0$.

From the function $\phi = \left(\frac{\sigma+\rho}{2\sigma}\right)E + F + G + \left(\frac{\sigma+\rho}{2\sigma\psi}\right)H$, we get

$$\dot{\phi} = k - \left(\frac{\sigma+\rho}{2\sigma}\right)G - \left(\frac{\sigma-\rho}{2}\right)E - \xi F - GH - \nu\left(\frac{\sigma+\rho}{2\sigma\psi}\right)H \leq k - b^*\phi,$$

where $b^* = \min\left\{\frac{\sigma-\rho}{2}, \xi, \frac{\nu(\sigma+\rho)}{2\sigma\psi}\right\}$. This implies that

$$0 \leq \phi(t) \leq \frac{k}{b^*} + \phi(0)e^{-tb^*}$$

whenever $(E_0, F_0, G_0, H_0) \in (\mathbb{R}^+)^4$ and $t \geq 0$. This indicates that the solution is bounded and hence existence of a unique bounded positive global solution is proved. □

Theorem 5.5.1. *The disease free-state equilibrium* $(0, \frac{k}{\xi}, 0, 0)$ *is locally asymptotically stable in the positive octant iff* $k < \sigma\xi$.

Proof. The Jacobian matrix of the system about the equilibrium point $(0, \frac{k}{\xi}, 0, 0)$ is

$$\begin{pmatrix} -\sigma & 0 & 1 & 0 \\ -\frac{k}{\xi}+\rho & -\xi & 0 & 0 \\ \frac{k}{\xi} & 0 & -1 & 0 \\ 0 & 0 & 0 & -\nu \end{pmatrix}.$$

The eigenvalues of above matrix are $\sqrt{\frac{k}{\xi}} - \sigma$, $-\sqrt{\frac{k}{\xi}} - \sigma, -\xi$ and $-\nu$. The equilibrium point is locally asymptotically stable iff all eigenvalues of the Jacobian matrix have negative real part. Here, all eigenvalues will have negative real part iff $k < \sigma\xi$. □

Theorem 5.5.2. *The disease state equilibrium* $\varepsilon_2 = (\widehat{E}, \widehat{F}, \widehat{G}, \widehat{H})$ *is locally asymptotically stable in the positive octant iff* $\widehat{E} < \frac{\nu}{\psi}$.

Proof. The Jacobian matrix of the system about the equilibrium point ε_2 is

$$\begin{pmatrix} -\sigma & 0 & 1 & \widehat{E} \\ -\sigma+\rho & -\xi-\widehat{E} & 0 & 0 \\ \sigma & -\widehat{E} & -1 & \sigma\widehat{E} \\ 0 & 0 & 0 & -\nu+\psi\widehat{E} \end{pmatrix}.$$

The characteristic equation of the Jacobian matrix is given by

$$(\nu - \psi\widehat{E} + \lambda)(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0,$$

where

$$a_1 = \widehat{E} + \xi + 1 + \sigma,\ a_2 = (\widehat{E} + \xi)(1 + \sigma),\ a_3 = (\sigma - \rho)\widehat{E}. \tag{5.42}$$

One eigenvalue of Jacobian matrix is $-\nu + \psi\widehat{E}$ and this eigenvalue has negative real part if $\widehat{E} < \frac{\nu}{\psi}$. Here, $a_1 > 0,\ a_2 > 0,\ a_3 > 0$ and $a_1 a_2 - a_3 > 0$, then by Routh-Hurwitz criterion, the other eigenvalues have negative real parts. Thus, the proof of lemma is complete. □

5.5.1 Global Stability of Equilibrium Points

Theorem 5.5.3. *Suppose $k > 0, \sigma > 0, \xi > 0$ and $\rho > 0$. The disease free steady state $(0, \frac{k}{\xi}, 0, 0)$ of the system (5.40) is globally asymptotically stable in the positive octant if $\rho < \sigma,\ k \le \sigma\xi$ and $\psi < 1$.*

Proof. For this purpose, we construct a Lyapunov functional

$$\Psi(E,F,G,H) = \frac{1}{2}(F - \bar{F})^2 + (2\sigma - \rho - \bar{F})(E + G + H).$$

Since $\rho < \sigma$ and $\frac{k}{\xi} \le \sigma$, then $2\sigma - \rho - \bar{F} > 0$. Now,

$$\begin{aligned}
\dot{\Psi} &= (2\sigma - \rho - \bar{F})(\dot{E} + \dot{G} + \dot{H}) + (F - \bar{F})\dot{F} \\
&= -\xi(F - \bar{F})^2 + EH(1 - \psi)(-2\sigma + \rho + \bar{F}) + GH(-2\sigma + \rho + \bar{F}) + \nu H(-2\sigma + \rho + \bar{F}) \\
&\quad + (F - \bar{F})(\rho E - EF) + (2\sigma - \rho - \bar{F})(EF - \sigma E) \\
&= -\xi(F - \bar{F})^2 + EH(1 - \psi)(-2\sigma + \rho + \bar{F}) + GH(-2\sigma + \rho + \bar{F}) + \nu H(-2\sigma + \rho + \bar{F}) \\
&\quad - E(F - \sigma)^2 + (\rho\sigma - \sigma^2)E \\
&< 0.
\end{aligned}$$

Thus, Ψ is a Lyapunov function for (5.40) in the positive octant. Also, $\dot{\Psi} = 0$ only if $\bar{F} = \frac{k}{\xi},\ \bar{E} = \bar{G} = \bar{H} = 0$. Now, the only invariant subset of the set $F = \bar{F}$ is the disease free steady state, hence it is globally asymptotically stable in the positive octant from LaSalle's invariance principle, see [2]. □

Theorem 5.5.4. *Suppose $k > 0, \sigma > 0, \xi > 0$ and $\rho \in [0, \sigma)$. For $k > \sigma\xi$, the disease state $\left(\frac{k - \sigma\xi}{\sigma - \rho}, \sigma, \sigma\frac{k - \sigma\xi}{\sigma - \rho}, 0\right)$ of the system (5.40) is globally asymptotically stable in $(\mathbb{R}^+)^4 - [\{0\} \times \mathbb{R}^+ \times \{0\} \times \{0\}]$ if $-\nu + (1 + \sigma)(1 + \psi)\widehat{E} \le 0$.*

Proof. Set $u = E - \widehat{E},\ v = F - \widehat{F},\ w = G - \widehat{G}$ and $x = H - \widehat{H}$. We compute the derivatives of the following functions:

$$\begin{aligned}\frac{d}{dt}\left(u - \widehat{E}\log(E/\widehat{E})\right) &= \frac{\dot{E}}{\widehat{E}}(E - \widehat{E}) \\ &= (G - \sigma E - EH)(E - \widehat{E})/E \\ &= G - \sigma E - EH - \frac{G\widehat{E}}{E} + \sigma\widehat{E} + H\widehat{E}, \end{aligned} \tag{5.43}$$

$$\frac{d}{dt}\left(v - \widehat{F}\log(F/\widehat{F})\right) = \frac{\dot{F}}{\widehat{F}}(F - \widehat{F}) = \frac{-\xi v^2}{F} + \frac{\rho uv}{F} - EF + \sigma E - \frac{\sigma^2\widehat{E}}{F} + \sigma\widehat{E}, \tag{5.44}$$

$$\frac{d}{dt}\left(w - \widehat{G}\log(G/\widehat{G})\right) = \frac{\dot{G}}{\widehat{G}}(G - \widehat{G}) = EF - G - GH - \frac{EF\widehat{G}}{G} + \widehat{G} + \widehat{G}H, \tag{5.45}$$

and

$$\frac{d}{dt}\left(x - \widehat{H}\log(H/\widehat{H})\right) = \frac{\dot{H}}{\widehat{H}}(H - \widehat{H}) = -\nu H + \psi EH - \psi E\widehat{H} + \nu\widehat{H}. \tag{5.46}$$

Now, we construct a Lyapunov function

$$\begin{aligned}\Upsilon_0(E,F,G,H) = (1+\psi)\left(u - \widehat{E}\log(E/\widehat{E})\right) + (1+\psi)\left(v - \widehat{F}\log(F/\widehat{F})\right) \\ + (1+\psi)\left(w - \widehat{G}\log(G/\widehat{G})\right) + \left(x - \widehat{H}\log(H/\widehat{H})\right),\end{aligned}$$

so that

$$\begin{aligned}\dot{\Upsilon}_0 = (1+\psi)\left(\frac{-\xi v^2}{F} - GH\right) + (1+\psi)\frac{\rho uv}{F} - EH - \nu H \\ - (1+\psi)\widehat{E}\left[\frac{G}{E} + \frac{\sigma^2}{F} + \frac{\sigma EF}{G} - (\sigma+1)H - 3\sigma\right].\end{aligned}$$

It can be noticed that Υ_0 tends to infinity at the boundary of the positive octant of $\mathbb{R}^4$. Since, the second term of $\dot{\Upsilon}_0$ does not have negative sign and to remove this term, we consider modified Lyapunov function as

$$\Upsilon(E,F,G,H) = \Upsilon_0(E,F,G,H) + \frac{\rho}{\sigma - \rho}(v - \sigma\log F)(1+\psi).$$

Here, $\Upsilon(E,F,G,H)$ tends to infinity at the boundary of the positive octant of $\mathbb{R}^4$ and is bounded below. This implies that

$$\begin{aligned}
\dot{\Upsilon} &= \dot{\Upsilon}_0 + \left(\frac{\rho}{\sigma-\rho}\right)\frac{\dot{v}}{F}(F-\widehat{F})(1+\psi) \\
&= \dot{\Upsilon}_0 - \frac{\rho(\xi+E)v^2(1+\psi)}{(\sigma-\rho)F} - \frac{\rho uv(1+\psi)}{F} \\
&= -(1+\psi)\left(\frac{\xi v^2}{F}+GH\right) - (1+\psi)\widehat{E}\left(\frac{G}{E}+\frac{\sigma^2}{F}+\frac{\sigma EF}{G}-3\sigma\right) \\
&\quad + H(1+\psi)(\sigma+1)\widehat{E} - EH - vH - \frac{\rho(\xi+E)v^2(1+\psi)}{(\sigma-\rho)F} \\
&< 0,
\end{aligned}$$

where $-v+(1+\sigma)(1+\psi)\widehat{E} \le 0$ and $\rho < \sigma$. In the second term $\widehat{E} > 0$ in the disease case and set $p = \frac{G}{E} > 0, q = \frac{\sigma^2}{F} > 0$. Consider the function

$$\phi(p,q) = p + q + \frac{\sigma^3}{pq} - 3\sigma$$

on $(0,\infty)\times(0,\infty)$ which is strictly positive for $p+q \ge 3\sigma$ and for $pq \le \frac{\sigma^2}{3}$. Therefore, ϕ has an absolute minimum in $(0,\infty)\times(0,\infty)$ and one can find after computing the derivative that $(p,q) = (\sigma,\sigma)$ is the unique absolute minimum. Thus, for all $k > \sigma\xi$ and $\rho \in [0,\sigma)$, the function Υ is a Lyapunov function for system (5.40) and $\dot{\Upsilon} = 0$ only if $E = \sigma, G = \sigma E, H = 0$. The only invariant set contained in the set $\dot{\Upsilon} = 0$ is the disease equilibrium $(\widehat{E},\sigma,\sigma\widehat{E},0)$. Hence, La Salle's theorem [2] implies convergence of the solutions to this equilibrium, for all initial conditions not in the set $[\{0\}\times\mathbb{R}^+\times\{0\}\times\{0\}]$. This shows that the disease-state is globally asymptotically stable in $(\mathbb{R}^+)^4 - [\{0\}\times\mathbb{R}^+\times\{0\}\times\{0\}]$. The solution obviously converges to the disease-free state if the initial condition is in $[\{0\}\times\mathbb{R}^+\times\{0\}\times\{0\}]$. □

Thus, Theorems 5.5.3 and 5.5.4 complete the proof of Theorem 5.1.1.

5.5.2 Numerical Illustration

For the simulations, we used the experimental data for prion proliferation. The model includes nine parameters: $\lambda, \gamma, \mu, \beta, \tau, z_0, \delta_0, \delta_1$ and δ_2.

The critical size z_0 of polymer is estimated as $6-30$, see [59]. The value of parameters are taken from [38, 59] and are follows as: $z_0 = 6, \lambda = 4400$ day^{-1}, $\tau = 0.3$ (SAF/sq)$^{-1}$ day^{-1}, $\beta = 0.0001$ (SAF/sq)$^{-1}$ day^{-1}, $\mu = 0.04$ day^{-1}, $\gamma = 5.0$ day^{-1}, $\delta_0 = 0.1$ day^{-1}, $\delta_1 = 0.0002$ day^{-1} and $\delta_2 = 0.002$ day^{-1}, where SAF/sq represents scripe associated fibrils per squre unit of measurement. Figure 5.2 shows that the solutions $(E(t),F(t),G(t),H(t))$ corresponding to the different initial values converge to the globally attracting disease steady state. Effect of the chaperone is obtained when we study the polymers population along with chaperone concentration. Figure (5.1a) indicates the polymer population for different chaperone dosages and as expected we observed that polymers population decrease along with increasing chaperone doses. From the Figure (5.1b), it is noticed that the polymer population decreases as chaperone increasing rate δ_1 increases in the system.

(a) Polymer population U for varying amounts of chaperone C (200, 400, 600, 800 and 1000 units of chaperone)

(b) Polymer population U for different δ_1(chaperone increasing rate in the system)

Fig. 5.1: Effect of chaperone on polymer population

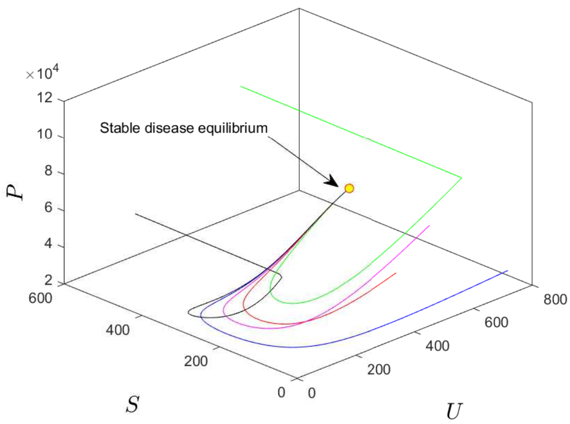


Fig. 5.2: Global stability of disease state equilibrium

Chapter 6

Analysis of a Prion-Chaperone Model with Polymer Coagulation

6.1 The Model

This chapter deals a mathematical model which consists of a non-linear partial integro-differential equation coupled with two ODEs. This model describes the relation between infectious, non-infectious prion proteins and chaperone. The well-posedness of the system is proved for bounded kernels by using evolution operator theory in the state space $\mathbb{R} \times \mathbb{R} \times L_1(Z, zdz)$. The existence of a global weak solution for unbounded kernels is also discussed with the help of a weak compactness argument. In addition, we investigated the stability analysis results theoretically and effect of chaperone on prion proliferation numerically. Here, a prion proliferation model with general incidence, polymer coagulation and chaperone is analyzed which is an extension of the model taken into account in [37, 56]. The meaning of polymer coagulation and general incidence terms are given in Chapter 1. The model can mathematically be expressed by a coupled system consisting of two ODEs, for the number of non-infectious monomers S and chaperone population C, which are given by

$$\begin{aligned} \frac{dS(t)}{dt} = \lambda - \gamma S(t) - & \frac{S(t)}{1+\rho \int_{z_0}^{\infty} u(t,z) z dz} \int_{z_0}^{\infty} \tau(z) u(t,z) dz \\ & + 2\int_0^{z_0} z \int_{z_0}^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dy dz \end{aligned} \tag{6.1}$$

$$\frac{dC(t)}{dt} = -\delta_0 C(t) + \delta_1 C(t) \int_{z_0}^{\infty} u(t,y)\, dy \tag{6.2}$$

and a partial integro-differential equation for the population density function u of infectious polymers of size z, is described as

$$
\begin{aligned}
\frac{\partial u(t,z)}{\partial t} =& - \frac{S(t)}{1+\rho \int_{z_0}^{\infty} u(t,z)zdz} \partial_z(\tau(z)u(t,z)) - \big(\mu(z)+\beta(z)+\delta_2 C(t)\big)u(t,z) \\
&+2\int_z^{\infty} \beta(y)\, k(z,y)\, u(t,y)\, dy + \mathbb{1}_{[z>2z_0]} \int_{z_0}^{z-z_0} \eta(z-y,y)u(t,z-y)u(t,y)\, dy \\
&-2u(t,z)\int_{z_0}^{\infty} \eta(z,y)u(t,y)dy
\end{aligned} \tag{6.3}
$$

for $z \in Z = (z_0, \infty)$. The following initial conditions are taken

$$
S(0) = S^0,\ C(0) = C^0,\ u(0,z) = u^0(z), \quad z_0 < z < \infty \tag{6.4}
$$

together with the boundary data

$$
u(t,z_0) = 0,\ t > 0. \tag{6.5}
$$

The function k satisfies the following

$$
k(y,z) \geq 0,\ \ k(y,z) = k(z-y,z),\ \ \int_0^z k(y,z)dy = 1 \tag{6.6}
$$

for all $z > z_0,\ y \geq 0$ and $k(y,z) = 0$ if $z \leq z_0$ or $y > z$.
These conditions immediately entail

$$
2\int_0^z yk(y,z)\, dy = z, \quad z > z_0. \tag{6.7}
$$

Also, k is assumed of the form

$$
k(y,z) = \frac{1}{z}k_0\big(\frac{y}{z}\big),\ \ z > z_0,\ 0 < y < z \tag{6.8}
$$

with an integrable function $k_0 \geq 0$ defined on $(0,1)$ such that

$$
k_0(z) = k_0(1-z),\ \ z \in (0,1) \quad \text{and} \quad \int_0^1 k_0(z)dz = 1. \tag{6.9}
$$

For a particular case of $k_0 = 1$, equation (6.8) leads to the equidistribution rule

$$
k(y,z) = \frac{1}{z}, \qquad z > z_0,\ 0 < y < z. \tag{6.10}
$$

Further, the rate η is assumed to be symmetric and non-negative, that is,

$$
\eta(y,z) = \eta(z,y), \quad \eta(y,z) \geq 0\ \text{ for } y,z \in Z. \tag{6.11}
$$

The function $U(t)=\int_{z_0}^{\infty}u(t,z)dz$ and $P(t)=\int_{z_0}^{\infty}u(t,z)zdz$ denote the number of PrP^{Sc} polymers at time t and the total number of PrP^{Sc} monomers in polymers at time t, respectively. According to [37], the coagulation integral terms from (6.3) provide

$$\int_{z_0}^{\infty}u(t,z)\int_{z_0}^{\infty}u(t,y)\,dy\,dz=U^2(t),\quad \int_{z_0}^{\infty}\int_{z_0}^{z}u(t,y)\,u(t,z-y)\,dy\,dz=U^2(t).$$

Therefore, under the assumptions

$$\mu(z)=\mu,\tau(z)=\tau,\eta(y,z)=\eta,\beta(z)=\beta z \text{ and } k(y,z)=\begin{cases}\frac{1}{z} \text{ if } z>z_0 \text{ and } 0<y<z\\ 0 \quad \text{otherwise,}\end{cases} \tag{6.12}$$

the problem (6.1)-(6.5) transformed into a system of four ODEs

$$\begin{aligned} U'&=\beta P-\mu U-2\beta z_0U-\delta_2CU-\eta U^2\\ S'&=\lambda-\gamma S-\frac{\tau US}{1+\rho P}+\beta z_0^2U\\ P'&=\frac{\tau US}{1+\rho P}-\mu P-\delta_2CP-\beta z_0^2U\\ C'&=-\delta_0C+\delta_1CU\end{aligned} \tag{6.13}$$

with initial conditions

$$U(0)=U^0\geq 0,\ S(0)=S^0\geq 0,\ P(0)=P^0\geq 0, C(0)=C^0\geq 0.$$

In the absence of chaperone, that is, $C=0$, the system (6.1)-(6.5) is discussed in [37, 56]. In [37], the global qualitative outcomes for the disease-free and disease equilibria are analytically studied under the assumptions (6.12). In [56], the existence and uniqueness of the classical solution of the system are investigated for the bounded kernels, that are,

$$\eta\in BC^1(Z\times Z,\mathbb{R}^+),\quad \beta,\mu\in L_\infty^+(Z) \tag{6.14}$$

and

$$\tau\in BC^1(Z,\mathbb{R}^+),\qquad \tau(z)\geq\tau_*,\ \ z\in Z, \tag{6.15}$$

while the existence of a global weak solution is proved for unbounded kernels, that is,

$$\beta,\mu\in L_{\infty,\text{loc}}^+(Z) \tag{6.16}$$

and

$$\tau \in C([z_0,\infty)) \text{ such that } \tau_* \leq \tau(z) \leq \tau_0 z, \; z \geq z_0, \tag{6.17}$$

for some constants $\tau_0, \tau_* > 0$. Inclusion of chaperone leads to an interesting physical problem due to its impact on the prion population. Therefore, the main motivation of this chapter is to study a prion equation together with polymer coagulation and general incidence terms in the presence of chaperone. We are interested to deal with a partial integro-differential equation coupled with two ODEs and to show the well-posedness of the system in the product space $\mathbb{R} \times \mathbb{R} \times L_1(Z, zdz)$. In Section 6.2, We prove the well-posedness in the classical sense to the problem (6.1)-(6.5) under the assumption (6.14)-(6.15). Further, in Section 6.3, the existence of a weak solution to the problem is discussed under the conditions (6.16)-(6.17). The model is transformed into a system of ordinary differential equations. The equilibrium points are computed and their local and global stability analysis (via Lyapunov function) is studied in Section 6.4. Finally, effect of chaperone on prion proliferation is presented numerically.

6.2 Well-posedness in the Classical Sense for Bounded Degradation Rates

This section deals with the well-posedness to the problem (6.1)-(6.5) for bounded kernels with the help of evolution operator theory. In the whole work, it is assumed that

$$\lambda, \gamma, \delta_0, \delta_1 > 0 \text{ and } \rho \geq 0, \; \delta_2 > \delta_1 / z_0. \tag{6.18}$$

It is easy to find the following identities, see in [56],

$$\int_{z_0}^{\infty} \phi(z) E[u](z)\, dz = -\int_{z_0}^{\infty} \phi(z)\mu(z)u(z)\, dz + \int_{z_0}^{\infty} u(z)\beta(z) \left(-\phi(z) + 2\int_{z_0}^{z} \phi(y)k(y,z)\, dy \right) dz \tag{6.19}$$

and

$$\int_{z_0}^{\infty} \phi(z) Q[u,u](z)\, dz = \int_{z_0}^{\infty} \int_{z_0}^{\infty} (\phi(z+y) - \phi(z) - \phi(y)) \; \eta(z,y) \; u(z) \; u(y) \; dydz \tag{6.20}$$

where

$$E[u](z) = -\big(\mu(z) + \beta(z)\big)u(z) + 2\int_{z}^{\infty} \beta(y) \; k(z,y) \; u(y) \; dy$$

and

$$Q[u,w](z) = \mathbb{1}_{[z > 2z_0]} \int_{z_0}^{z-z_0} \eta(z-y,y)u(z-y)w(y)\, dy - 2u(z) \int_{z_0}^{\infty} \eta(y,z)w(y)\, dy.$$

For $\phi(z) = z$, Eqs. (6.7), (6.19) and (6.20) imply that a solution (S,C,u) corresponding to (6.1)-(6.5) satisfies

$$\begin{aligned} S(t)+C(t)+\int_{z_0}^{\infty} zu(t,z)\,dz = C^0+S^0+\int_{z_0}^{\infty} zu^0(z)\,dz+\lambda t \\ -\gamma\int_0^t S(s)\,ds-\delta_0\int_0^t C(s)\,ds-\int_0^t\int_{z_0}^{\infty} z\mu(z)u(s,z)\,dzds \\ +\delta_1\int_0^t C(s)\int_{z_0}^{\infty} u(s,z)\,dzds-\delta_2\int_0^t C(s)\int_{z_0}^{\infty} zu(s,z)\,dzds. \end{aligned} \tag{6.21}$$

Now, define the state space

$$X_0 = L_1(Z,zdz)$$

for the population density u, where the norm is defined by $\|\cdot\|_0 := \|\cdot\|_{L_1(Z,\,zdz)}$ and its positive cone is represented by $L_1^+(Z,zdz)$ and putting

$$X_1 = \{u \in X_0 : \partial_z(\tau u) \in X_0, u(z_0) = 0\}$$

equipped with the norm $\|u\|_1 := \|u\|_0 + \|\partial_z(\tau u)\|_0$, $u \in X_1$.

Theorem 6.2.1. *Let us assume (6.6), (6.7), (6.11), (6.14), (6.15) and (6.18) hold. Then, for any given* $S^0, C^0 > 0$ *and* $u^0 \in X_0^+$ *with* $\partial_z u^0 \in X_0$ *and* $u^0(z_0) = 0$, *the problem (6.1)-(6.5) admits a unique global classical solution* (S,C,u) *such that* $S,C \in C^1(\mathbb{R}^+)$ *and* $u \in C^1(\mathbb{R}^+, X_0)$ *with* $\partial_z u \in C(\mathbb{R}^+, X_0)$. *Also, the solution is positive, i.e.,* $S(t), C(t) > 0$ *and* $u(t) \in L_1^+(Z,zdz)$ *for* $t \geq 0$, *and satisfies (6.21).*

6.2.1 Proof of Classical Solution

The following lemmas are useful and can be readily obtained. Additionally all the assumptions mentioned in Theorem 6.2.1 hold.

Lemma 6.2.2. *(See, [56]) (i) The operator* $E : X_0 \to X_0$, *defined by*

$$E[u](z) = -\big(\mu(z)+\beta(z)\big)u(z)+2\int_z^{\infty} \beta(y)\,k(z,y)\,u(y)\,dy$$

is linear and bounded corresponding to (6.6)-(6.7) such that

$$\|E[u]\|_0 \leq b_*\left(\|\beta\|_\infty+\|\mu\|_\infty\right)\|u\|_0, \quad u \in X_0.$$

(ii) The operator $Q : X_j \times X_0 \to X_j$ is bilinear and bounded, refer to [56], with

$$\|Q[u,v]\|_j \le b_* \|\eta\|_{j,\infty} \|u\|_j \|v\|_0, \quad u \in X_j, v \in X_0,$$

for $j \in \{0,1\}$ where $\|\eta\|_{0,\infty} = \|\eta\|_\infty$ and $\|\eta\|_{1,\infty} = \|\eta\|_\infty + \|\eta_z\|_\infty$.

When $v \in X_0$ is fixed, it is worthwhile pointing out the property of $Q[\cdot, v]$ mapping X_j into itself for $j \in \{0,1\}$. For the existence of classical solution, this property is crucial.

Lemma 6.2.3. *(See, [77]) The operator $-A$, defined by*

$$Au = \partial_z(\tau u), \;\; u \in X_1,$$

generates a positive C_0 semigroup $\{W(t) : t \ge 0\}$ on X_0, defined by

$$(W(t)f)(z) = \mathbb{1}_{[t,\infty)}(\Psi(z)) \frac{\tau\big(\Psi^{-1}(\Psi(z)-t)\big)}{\tau(z)} f\big(\Psi^{-1}(\Psi(z)-t)\big), \;\; z \in Z, \;\; t \ge 0,$$

with

$$\|W(t)\|_{\mathcal{L}(X_0)} \le e^{\tau_0 t}, \;\; t \ge 0,$$

where $\Psi : Z \to (0,\infty)$ is a diffeomorphism defined by $\Psi(z) = \int_{z_0}^{z} \frac{dy}{\tau(y)}$ and $\tau_0 = \frac{\|\tau\|_\infty}{z_0}$ so that $\tau(z) \le \tau_0 z$, $z \in Z$. Also, this semigroup is stable in the sense of [§2.4].

Now, for given $K > 1$, $T \in (0,1]$, define $J_T = [0,T]$ and

$$\Im_{T,K} = \{v \in C^1(J_T) \; : \; K^{-1} \le v(t) \le \|v(t)\|_{C^1(J_T)} \le K\}. \tag{6.22}$$

Then, for given $V, C \in \Im_{T,K}$, introduce the operator

$$\mathbb{A}_V^C(t)u = V(t)Au + \delta_2 C(t)u - E(u), \;\; u \in X_1, \, t \in J_T. \tag{6.23}$$

According to Lemmas 6.2.2 and 6.2.3, the operator family $\{-\mathbb{A}_V^C(s) : s \in [0,T]\}$ generates an evolution operator on X_0, refer to [§2.4].

Proposition 6.2.1. *Let $K > 1, T_0 > 0$ and $0 < T \le T_0$. Then, $\{-\mathbb{A}_V^C(t) : t \in [0,T]\}$ generates a unique evolution system $\mathbb{U}_V^C(t,s)$, $0 \le s \le t \le T$ in X_0 for each $V, C \in \Im_{T,K}$. Moreover, there exists $w_0 = w_0(T_0, K) > 0$ such that*

$$\left\|\mathbb{U}_V^C(t,s)\right\|_{\mathcal{L}(X_0)} \le e^{w_0(t-s)}, \;\; V, C \in \Im_{T,K}, \tag{6.24}$$

$$\left\|\mathbb{U}_V^C(t,s)\right\|_{\mathcal{L}(X_1)} \le w_0, \qquad V, C \in \Im_{T,K}, \tag{6.25}$$

and for $V, C, V_1, C_1 \in \mathfrak{I}_{T,K}$

$$\left\| \mathbb{U}_V^C(t,s) - \mathbb{U}_{V_1}^{C_1}(t,s) \right\|_{\mathcal{L}(X_1,X_0)} \leq w_0(t-s) \left(\|V - V_1\|_{C(J_T)} + \|C - C_1\|_{C(J_T)} \right) \tag{6.26}$$

where $0 \leq s \leq t \leq T$.

One can achieve the estimates of proposition 6.2.1 according to Proposition 4.2.1. If (S, C, u) is a solution of the system (6.1)-(6.5), then u component can be expressed as

$$u(t) = \mathbb{U}_{V_u}^C(t,0)u^0 + \int_0^t \mathbb{U}_{V_u}^C(t,s) Q[u(s), u(s)]\, ds.$$

The above can be considered as a fixed point equation for u, where

$$V_u(t) = \frac{S(t)}{1 + \rho \int_{z_0}^{\infty} z u(t,z)\, dz}.$$

Now, we proceed further and discuss the local and global existence of the classical solution by using Leis and Walker's approach, see [56].

6.2.1.1 Proof of Local Existence

Let $S^0, C^0 > 0$ and $u^0 \in X_0^+ \cap X_1$ be given and let $P > 0$ be such that

$$P^{-1} \leq S^0, C^0 \leq P \quad \text{and} \quad \left\| u^0 \right\|_1 \leq P. \tag{6.27}$$

Construct a complete metric space for $\delta \in \{0, \rho\}$,

$$E_T^\delta = \Big\{ u \in C(J_T, X_0^+) : [t \mapsto \delta \|u(t)\|_0] \in C^1(J_T), \|u(t)\|_0 \leq 2P, \\ \left| \frac{d}{dt} \delta \|u(t)\|_0 \right| \leq r(P),\ t \in J_T,\ u(0) = u^0 \Big\}$$

where the metric is defined by

$$d_{E_T^\delta}(u,v) = \|u - v\|_{C(J_T, X_0)} + \delta \left\| \|u\|_0 - \|v\|_0 \right\|_{C^1(J_T)}, \quad u, v \in E_T^\delta,$$

and $r(P) = 2\rho P \left[\frac{(P + 2P\|\beta\|_\infty + \lambda)\|\tau\|_\infty}{z_0} + \|\mu\|_\infty + \|\beta\|_\infty + \delta_2 P e^{2P/z_0} \right]$.
Let $\tilde{u} \in E_T^\delta$ be fixed and put

$$2 \int_0^{z_0} z \int_{z_0}^{\infty} \beta(y)\, k(z,y)\, \tilde{u}(t,y)\, dy dz := f(\tilde{u}) \tag{6.28}$$

and

$$g(\tilde{u}(t)) = \frac{1}{1+\rho \left\|\tilde{u}(t)\right\|_0} \int_{z_0}^{\infty} \tau(z)\tilde{u}(t,z)\ dz. \tag{6.29}$$

Here, both $f(\tilde{u})$ and $g(\tilde{u})$ are non-negative functions. Then, $S_{\tilde{u}} \in C^1(J_T)$ given by

$$S_{\tilde{u}}(t) = S^0\ e^{-\gamma t - \int_0^t g(\tilde{u}(\sigma))d\sigma} + \int_0^t e^{-\gamma(t-s) - \int_s^t g(\tilde{u}(\sigma))d\sigma} \left[\lambda + f\left(\tilde{u}(s)\right)\right]\ ds, \quad t \in J_T, \tag{6.30}$$

represents the unique solution corresponding to (6.1) with $S_{\tilde{u}}(0) = S^0$, when u is replaced by $\tilde{u}$. Also, replacing u by $\tilde{u}$ in (6.2),

$$C_{\tilde{u}}(t) = C^0\ e^{-\delta_0 t + \delta_1 \int_0^t |\tilde{u}(\sigma)|_1 d\sigma}, \quad t \in J_T, \tag{6.31}$$

is the unique solution for the Eq. (6.2) with $C_{\tilde{u}}(0) = C^0$, where $|\cdot|_1$ denotes the norm in $L_1(Z)$. Eq. (6.7) and the assumptions on β, τ, imply that

$$f\left(\tilde{u}(t)\right) \le \|\beta\|_\infty \|\tilde{u}(t)\|_0 \quad \text{and} \quad g\left(\tilde{u}(t)\right) \le \frac{\|\tau\|_\infty}{z_0} \|\tilde{u}(t)\|_0 \tag{6.32}$$

for $0 \le t \le T$. Now, introduce

$$V_{\tilde{u}}(t) = \frac{S_{\tilde{u}}(t)}{1+\rho \int_{z_0}^{\infty} z\tilde{u}(t,z)\ dz}, \tag{6.33}$$

and

$$\dot{V}_{\tilde{u}}(t) = \frac{\dot{S}_{\tilde{u}}(t)}{1+\rho\left\|\tilde{u}(t)\right\|_0} - \frac{\rho S_{\tilde{u}}(t)}{(1+\rho\left\|\tilde{u}(t)\right\|_0)^2} \frac{d}{dt} \left\|\tilde{u}(t)\right\|_0, \quad \tilde{u} \in E_T^\delta, \quad t \in J_T.$$

From (6.1) and (6.30), it readily follows that a constant $K(P) > 1$ exists independent of $T \in (0,1]$ (and $\tilde{u}$) such that $V_{\tilde{u}} \in \Im_{T,K(P)}$ for $\tilde{u} \in E_T^\delta$. Also, it follows from (6.2) and (6.31) that there exists a constant $K(P) > 1$ independent of $T \in (0,1]$ (and $\tilde{u}$) such that $C_{\tilde{u}} \in \Im_{T,K(P)}$ for $\tilde{u} \in E_T^\delta$. On the other hand, one can easily obtain the following estimates

$$|V_{\tilde{u}_1}(t) - V_{\tilde{u}_2}(t)| \le T\ b(P)\ d_{E_T^\delta}(\tilde{u}_1, \tilde{u}_2) \tag{6.34}$$

and

$$|C_{\tilde{u}_1}(t) - C_{\tilde{u}_2}(t)| \le T\ b(P)\ d_{E_T^\delta}(\tilde{u}_1, \tilde{u}_2) \tag{6.35}$$

for $0 \le t \le T \le 1$ and $\tilde{u}_1, \tilde{u}_2 \in E_T^\delta$. Now, for fixed $\tilde{u} \in E_T^\delta$ and $\widehat{u} \in E_T^0$, we consider the equation

$$\dot{u} + \mathbb{A}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t)u = Q[u, \widehat{u}(t)], \quad u(0) = u^0, \quad t \in J_T, \tag{6.36}$$

where

$$-\mathbb{A}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t)u = -V_{\tilde{u}}(t)Au - \delta_2 C_{\tilde{u}}(t)u + E(u), \quad u \in X_1,\ t \in J_T,$$

is meaningful since $V_{\tilde{u}}, C_{\tilde{u}} \in \Im_{T,K(P)}$ and generates an evolution system on X_0 with properties as mentioned in Proposition 6.2.1. Here, $\tilde{u} \in E_T^{\delta}$ and $\widehat{u} \in E_T^0$ are still fixed, then according to Lemma 6.2.2(ii), the right-hand side of (6.36) is a bounded linear operator from X_1 into itself with respect to u which continuously depends on t. It is ensured from [§2.4] that equation (6.36) possesses a unique classical solution

$$u := u(\tilde{u}, \widehat{u}) \in C(J_T, X_1) \cap C^1(J_T, X_0). \tag{6.37}$$

For non-negativity of this solution, we introduce the constant

$$p = \|\mu\|_\infty + \|\beta\|_\infty + \frac{4P}{z_0}\|\eta\|_{1,\infty}.$$

Then, the problem

$$\dot{w} + (A_{V_{\tilde{u}}}(t) + \delta_2 C_{\tilde{u}}(t) + pI)w = P(t)[w], \quad w(0) = u^0, \quad t \in J_T, \tag{6.38}$$

is also solved by u, where the operator

$$-A_{V_{\tilde{u}}}(t)w := -V_{\tilde{u}}(t)\partial_z(\tau w), \quad w \in X_1,\ t \in J_T$$

generates an evolution system on X_0 according to Proposition 6.2.1 and the bounded operator $P(t) \in \mathcal{L}(X_0)$, given by

$$P(t)[w] = Q[w, \widehat{u}(t)] + E[w] + pw, \quad w \in X_0,$$

which is continuously depending on t and warrants that

$$P(t)[w] \in X_0^+, \quad w \in X_0^+ \tag{6.39}$$

for the suitable choice of the constant $p > 0$. From Lemma 6.2.3, the semigroup $\{W(t) : t \geq 0\}$ on X_0 generated by $-Au = -\partial_z(\tau u)$, $u \in X_1$, is a positive C_0 semigroup. Therefore, for each fixed $t \in J_T$, the operator $-(A_{V_{\tilde{u}}}(t) + \delta_2 C_{\tilde{u}}(t) + pI)$ generates a positive semigroup on X_0, see Corollary 2.2.2.2. The construction of evolution systems, see Theorem 2.4.3, yields that the evolution system generated by $-(A_{V_{\tilde{u}}} + \delta_2 C_{\tilde{u}} + pI)$ is positive as well. Then, the equation (6.39) and $u^0 \in X_0^+$ imply that $u(t) \in X_0^+$ for $t \in J_T$.

Next, for sufficiently small $T \in (0,1]$, we exhibit that the mapping $\widehat{u} \mapsto \Lambda_{\tilde{u}}[\widehat{u}] := u(\tilde{u}, \widehat{u})$ is contraction on E_T^0 keeping $\tilde{u} \in E_T^\delta$ still fixed. For this, note that

$$\Lambda_{\tilde{u}}[\widehat{u}] := u(\tilde{u}, \widehat{u}) \in C(J_T, X_1^+) \cap C^1(J_T, X_0)$$

satisfies

$$\dot{u} + \mathbb{A}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t)u = Q[u, \widehat{u}(t)], \quad u(0) = u^0, \ t \in J_T, \tag{6.40}$$

and can be written as

$$\Lambda_{\tilde{u}}[\widehat{u}](t) = \mathbb{U}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t,0)u^0 + \int_0^t \mathbb{U}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t,s)\, Q[\Lambda_{\tilde{u}}[\widehat{u}](s), \widehat{u}(s)]\, ds, \quad t \in J_T, \tag{6.41}$$

where the evolution system $\mathbb{U}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t,s)$ fulfills the properties mentioned in Proposition 6.2.1 with $w_0 = w_0(1, K(P))$. Consequently, Lemma 6.2.2 and Proposition 6.2.1 allow that

$$\|\Lambda_{\tilde{u}}[\widehat{u}](t)\|_q \leq e^{w_0[T(1-q)+q]} \left\|u^0\right\|_q + 2Pb_* \|\eta\|_{q,\infty} e^{w_0} \int_0^t \|\Lambda_{\tilde{u}}[\widehat{u}](s)\|_q \, ds, \tag{6.42}$$

for $q = 0, 1$ and $0 \leq t \leq T \leq 1$. Taking $q = 0$ in (6.42), Eq. (6.27) and Gronwall's lemma warrant that

$$\|\Lambda_{\tilde{u}}[\widehat{u}](t)\|_0 \leq 2P, \ \ 0 \leq t \leq T, \tag{6.43}$$

given that $T = T(P) \in (0,1]$ is picked sufficiently small which implies that $\Lambda_{\tilde{u}}[\widehat{u}](t) = u(\tilde{u}, \widehat{u}) \in E_T^0$ for $\widehat{u} \in E_T^0$. Moreover, putting $q = 1$ in (6.42), Gronwall's lemma leads to

$$\|\Lambda_{\tilde{u}}[\widehat{u}](t)\|_0 \leq m(P), \ \ 0 \leq t \leq T, \tag{6.44}$$

for some constant $m(P) > 0$. Now, to show that $\Lambda_{\tilde{u}} : E_T^0 \to E_T^0$ is contractive, let $\widehat{u}_1, \widehat{u}_2 \in E_T^0$. Then, for $0 \leq t \leq T$, Eq. (6.41) with (6.43), Lemma 6.2.2, Proposition 6.2.1 and Gronwall's lemma provide that

$$\|\Lambda_{\tilde{u}}[\widehat{u}_1](t) - \Lambda_{\tilde{u}}[\widehat{u}_2](t)\|_0 \leq T\, b(P)\, \|\widehat{u}_1 - \widehat{u}_2\|_{C(J_T, X_0)},$$

which shows that the mapping $\Lambda_{\tilde{u}}$ is contraction on E_T^0 for each $\tilde{u} \in E_T^\rho$ and $T = T(P) \in (0,1]$ is picked sufficiently small . Hence $\Lambda_{\tilde{u}}$ admits a unique fixed point $\Gamma(\tilde{u}) \in E_T^0$. According to (6.37), $\Gamma(\tilde{u}) \in C(J_T, X_1) \cap C^1(J_T, X_0)$.

Further, we consider the mapping $\Gamma = [\tilde{u} \mapsto \Gamma(\tilde{u})]$ and prove that it is contraction on E_T^ρ provided $T = T(P) \in (0,1]$ is small enough. Then, together with the corresponding solutions to (6.1) and (6.2), the corresponding unique fixed point will describe the local solution to (6.1)-(6.5). Eq.

(6.41) reads for fixed point $u = \Gamma(\tilde{u})$ of $\Lambda_{\tilde{u}}$ as

$$u(t) = \mathbb{U}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t,0)u^0 + \int_0^t \mathbb{U}_{V_{\tilde{u}}}^{C_{\tilde{u}}}(t,s)\; Q[u(s),u(s)]\; ds, \quad t \in J_T. \tag{6.45}$$

Now, take $\tilde{u}_1, \tilde{u}_2 \in E_T^\rho$ and put $u_1 = \Gamma(\tilde{u}_1)$ and $u_2 = \Gamma(\tilde{u}_2)$. Then, for $t \in J_T$, Eq.(6.45) entails with Lemma 6.2.2, Proposition 6.2.1 and Eq.(6.44) that

$$\begin{aligned}\|u_1(t) - u_2(t)\|_0 \leq & w_0 T \left[\|V_{\tilde{u}_1} - V_{\tilde{u}_2}\|_{C(J_T)} + \|C_{\tilde{u}_1} - C_{\tilde{u}_2}\|_{C(J_T)} \right] \left\| u^0 \right\|_{X_1} \\ & + 2Pb_* \|\eta\|_{1,\infty} m(P) w_0 T \left[\|V_{\tilde{u}_1} - V_{\tilde{u}_2}\|_{C(J_T)} + \|C_{\tilde{u}_1} - C_{\tilde{u}_2}\|_{C(J_T)} \right] \\ & + 4Pe^{w_0} b_* \|\eta\|_{1,\infty} \int_0^t \|u_1(s) - u_2(s)\|_0 \; ds\end{aligned}$$

and then by Gronwall's lemma, we have

$$\|u_1(t) - u_2(t)\|_0 \leq T\; b(P) \left[\|V_{\tilde{u}_1} - V_{\tilde{u}_2}\|_{C(J_T)} + \|C_{\tilde{u}_1} - C_{\tilde{u}_2}\|_{C(J_T)} \right], \;\; t \in J_T.$$

Therefore, Eqs. (6.34) and (6.35) yield,

$$\|u_1(t) - u_2(t)\|_0 \leq T\; b(P)\, \|\tilde{u}_1 - \tilde{u}_2\|_{C(J_T, X_0)}, \;\; t \in J_T \tag{6.46}$$

for some constant $b(P) > 0$. Further, for $u = \Gamma(\tilde{u})$ with $\tilde{u} \in E_T^\rho$, Eq. (6.45) can also be written as

$$\dot{u} + V_{\tilde{u}}(t)\partial_z(\tau u) + \delta_2 C_{\tilde{u}}(t)u = E[u(t)] + Q\big[u(t), u(t)\big], \;\; 0 \leq t \leq T. \tag{6.47}$$

Since $u(t) \in X_1$, the assumption (6.15) on τ implies that

$$\int_{z_0}^\infty z\partial_z(\tau u(t,z))\; dz = -\int_{z_0}^\infty \tau(z) u(t,z)\; dz. \tag{6.48}$$

Using equations (6.7), (6.19) and (6.20), one can obtain

$$\int_{z_0}^\infty zE[u(t)](z)\; dz + \int_{z_0}^\infty zQ\big[u(t), u(t)\big](z)\; dz = -\int_{z_0}^\infty z\mu(z) u(t,z)\; dz - f(u(t)). \tag{6.49}$$

Consequently, for $0 \leq t \leq T$ and $u = \Gamma(\tilde{u})$ with $\tilde{u} \in E_T^\rho$, it is observed from (6.47)-(6.49) that

$$\begin{aligned}\frac{d}{dt}\int_{z_0}^\infty zu(t,z)\; dz = & V_{\tilde{u}}(t) \int_{z_0}^\infty \tau(z) u(t,z)\; dz - \delta_2 C_{\tilde{u}}(t) \int_{z_0}^\infty zu(t,z)\; dz \\ & - \int_{z_0}^\infty z\mu(z) u(t,z)\; dz - f(u(t)).\end{aligned} \tag{6.50}$$

Also, equation (6.50) yields,

$$\left|\frac{d}{dt}\rho\,\|u(t)\|_0\right| \le \rho\left[V_{\tilde{u}}(t)\frac{\|\tau\|_\infty}{z_0} + \|\mu\|_\infty + \|\beta\|_\infty + \delta_2 C_{\tilde{u}}(t)\right]\|u(t)\|_0 \le r(P), \;\; t \in J_T.$$

Now, Eqs. (6.27), (6.30) and (6.32) guarantee that

$$V_{\tilde{u}}(t) \le S_{\tilde{u}}(t) \le \lambda + P + 2P\,\|\beta\|_\infty, \;\; t \in J_T,$$

and Eqs. (6.27), (6.31) imply that,

$$C_{\tilde{u}}(t) \le Pe^{2P/z_0}, \;\; t \in J_T,$$

and hence $u = \Gamma(\tilde{u}) \in E_T^\rho$ for $\tilde{u} \in E_T^\rho$. Now, again considering $\tilde{u}_1, \tilde{u}_2 \in E_T^\rho$ and putting $u_1 = \Gamma(\tilde{u}_1)$ and $u_2 = \Gamma(\tilde{u}_2)$, Eq. (6.50) deduce that

$$\begin{aligned}\left|\frac{d}{dt}\int_{z_0}^\infty z[u_1(t,z)-u_2(t,z)]\,dz\right| \le{}& |V_{\tilde{u}_1}(t)-V_{\tilde{u}_2}(t)|\int_{z_0}^\infty \tau(z)u_1(t,z)\,dz\\ &+\delta_2 C_{\tilde{u}}(t)\left|\int_{z_0}^\infty z\,[u_1(t,z)-u_2(t,z)]\,dz\right|\\ &+\delta_2\,|C_{\tilde{u}_1}(t)-C_{\tilde{u}_2}(t)|\int_{z_0}^\infty z\,u_1(t,z)\,dz\\ &+V_{\tilde{u}_2}(t)\left|\int_{z_0}^\infty \tau(z)[u_1(t,z)-u_2(t,z)]\,dz\right|\\ &+\left|\int_{z_0}^\infty z\,\tau(z)[u_1(t,z)-u_2(t,z)]\,dz\right|\\ &+|f[u_1(t)-u_2(t)]|.\end{aligned}$$

Therefore, for $0 \le t \le T$,

$$\begin{aligned}\left|\frac{d}{dt}\int_{z_0}^\infty z[u_1(t,z)-u_2(t,z)]\,dz\right| \le{}& b(P)\,|V_{\tilde{u}_1}(t)-V_{\tilde{u}_2}(t)| + b(P)\;\|u_1(t)-u_2(t)\|_0\\ &+\|\beta\|_\infty\;\|u_1(t)-u_2(t)\|_0 + b(P)\,|C_{\tilde{u}_1}(t)-C_{\tilde{u}_2}(t)|\\ \\ \le{}& T\;b(P)\;d_{E_T^\rho}(\tilde{u}_1,\tilde{u}_2),\end{aligned}$$

and thus,

$$d_{E_T^\rho}(\Gamma(\tilde{u}_1),\Gamma(\tilde{u}_2)) \le T\;b(P)\;d_{E_T^\rho}(\tilde{u}_1,\tilde{u}_2), \quad \tilde{u}_1,\tilde{u}_2 \in E_T^\rho,$$

which indicates that the mapping $\tilde{u} \mapsto \Gamma(\tilde{u})$ is a contraction on E_T^ρ provided that $T = T(P) \in$

$(0,1]$ is picked small enough. Thus, there exists a unique fixed point u and along this u, the triplet (S_u, C_u, u) represents the unique solution corresponding to (6.1)-(6.5) on the interval $[0,T]$. Since the choice of $T = T(P)$ depends only on P from (6.27), the following proposition is immediate.

Proposition 6.2.2. *For given assumptions stated in Theorem 6.2.1, the problem (6.1)-(6.5) admits a unique maximal solution (S,C,u) belonging to $C(J,\mathbb{R}^+\times\mathbb{R}^+\times X_1^+)\cap C^1(J,\mathbb{R}\times\mathbb{R}\times X_0)$ on a maximal interval J which is open in $\mathbb{R}^+$. If $t^* = \sup J < \infty$, then*

$$\underline{\lim}_{t\to t^*} S(t) = 0, \;\; \underline{\lim}_{t\to t^*} C(t) = 0 \quad \text{or} \quad \overline{\lim}_{t\to t^*} \left(S(t)+C(t)+\|u(t)\|_{X_1}\right) = \infty. \tag{6.51}$$

Let us emphasize here that the solution (S,C,u) fulfills

$$u' + \mathbb{A}_{V_u}^{C_u}(t)u = Q[u,u], \quad u(0) = u^0, \;\; t\in J,$$

and u can be written as

$$u(t) = \mathbb{U}_{V_u}^{C_u}(t,0)u^0 + \int_0^t \mathbb{U}_{V_u}^{C_u}(t,s)\, Q[u(s),u(s)]\, ds, \quad t\in J.$$

6.2.1.2 Proof of Global Existence

We are now showing that (6.51) can not occur and the solution given by Proposition 6.2.2 exists on $J = \mathbb{R}^+$. One can obtain that,

$$\begin{aligned}
\dot S(t) + \dot C(t) + \frac{d}{dt}\int_{z_0}^{\infty} zu(t,z)\,dz &= \lambda - \gamma S(t) + 2\int_{z_0}^{\infty} u(t,z)\beta(z)\int_0^{z_0} yk(y,z)\,dy\,dz \\
&\quad - \delta_0 C(t) + \delta_1 C(t)\int_{z_0}^{\infty} u(t,z)\,dz \\
&\quad - \delta_2 C(t)\int_{z_0}^{\infty} zu(t,z)\,dz + \int_{z_0}^{\infty} zE[u(t)](z)\,dz \\
&= \lambda - \gamma S(t) - \delta_0 C(t) - \int_{z_0}^{\infty} z\mu(z)u(t,z)\,dz \\
&\quad + \delta_1 C(t)\int_{z_0}^{\infty} u(t,z)\,dz - \delta_2 C(t)\int_{z_0}^{\infty} zu(t,z)\,dz.
\end{aligned}$$

This implies that,

$$S(t) + C(t) + \|u(t)\|_{X_0} \le S^0 + C^0 + \left\|u^0\right\|_{X_0} + \lambda t, \;\; \text{for } t\in J \text{ and } \delta_2 > \frac{\delta_1}{z_0}. \tag{6.52}$$

Now, it is easy to find the following estimates

$$S(t) > 0, \ \ \|S\|_{C^1(J)} \leq h(t^*), \quad \text{for } t \in J, \tag{6.53}$$

and

$$C(t) > 0, \ \ \|C\|_{C^1(J)} \leq h(t^*), \quad \text{for } t \in J. \tag{6.54}$$

Consequently, there exists $P = P\left(h(T^*)\right) > 0$ such that for each $0 < T < t^*$, one has $S, C \in \mathfrak{I}_{T,K}$ and hence, it is obvious from Proposition 6.2.1 that

$$\left\|\mathbb{U}_{S_u}^{C_u}(t,s)\right\|_{\mathcal{L}(X_1)} \leq h(t^*), \quad 0 \leq s \leq t \leq t^*.$$

Lemma 6.2.2(ii) with Eq.(6.52) imply that

$$\|Q[u(t),u(t)]\|_1 \leq h(t^*)\, \|u(t)\|_1, \ \ t \in J.$$

Therefore,

$$\begin{aligned} \|u(t)\|_1 &\leq \left\|\mathbb{U}_{S_u}^{C_u}(t,0)\right\|_{\mathcal{L}(X_1)} \left\|u^0\right\|_1 + \int_0^t \left\|\mathbb{U}_{S_u}^{C_u}(t,s)\right\|_{\mathcal{L}(X_1)} \|Q[u(t),u(t)]\|_1 \ ds \\ &\leq h(t^*) \left\|u^0\right\|_1 + h(t^*) \int_0^t \|u(t)\|_1 \ ds, \ \ t \in J, \end{aligned}$$

so that Gronwall's lemma warrants

$$\|u(t)\|_1 \leq h(t^*), \quad t \in J. \tag{6.55}$$

Thus (6.51) can not be true in view of (6.53)-(6.55). This contradiction shows that the solution (S, C, u) exists for all times.

If we consider compactly supported initial data and coagulation kernel $\eta(z,y)$, then u enjoys the property of finite speed of propagation [50] according to [56], where (S, C, u) represents the solution of the system (6.1)-(6.5).

6.3 Existence of a Weak Solution for Unbounded Degradation Rates

We prove the existence of weak solutions to the problem (6.1)-(6.5) under the conditions (6.16) and (6.17).

Definition 6.3.1. *For given $S^0, C^0 > 0$ and $u^0 \in L_1^+(Z, zdz)$, the triplet (S, C, u) is called a global weak solution corresponding to (6.1)-(6.5) if the following hold*
(a) $S, C \in C^1(\mathbb{R}^+)$ are non-negative solutions to (6.1) and (6.2), respectively,
(b) $u \in L_{\infty,\mathrm{loc}}\left(\mathbb{R}^+, L_1^+(Z, zdz)\right)$ is a weak solution corresponding to (6.3), more precisely, it satisfies

$$[(\sigma, z) \mapsto (\mu(z) + \beta(z))\, u(\sigma, z)] \in L_1\left((0,t) \times Z\right) \tag{6.56}$$

$$[(\sigma, z, y) \mapsto \eta(z,y) u(\sigma, z) u(\sigma, y)] \in L_1\left((0,t) \times Z \times Z\right) \tag{6.57}$$

for all $t > 0$ and

$$\begin{aligned}
\int_{z_0}^{\infty} \phi(z) u(t,z)\, dz = & \int_{z_0}^{\infty} \phi(z) u^0(z)\, dz + \int_0^t \frac{S(\sigma)}{1 + \rho \left\| u(\sigma) \right\|_0} \int_{z_0}^{\infty} \phi'(z) \tau(z) u(\sigma, z)\, dz d\sigma \\
& - \delta_2 \int_0^t C(\sigma) \int_{z_0}^{\infty} \phi(z) u(\sigma, z)\, dz d\sigma - \int_0^t \int_{z_0}^{\infty} \phi(z) \mu(z) u(\sigma, z)\, dz d\sigma \\
& + \int_0^t \int_{z_0}^{\infty} \beta(z) u(\sigma, z) \big(-\phi(z) + 2 \int_{z_0}^{z} \phi(y) k(y,z)\, dy \big)\, dz d\sigma \\
& + \int_0^t \int_{z_0}^{\infty} \int_{z_0}^{\infty} \big(\phi(z+y) - \phi(z) - \phi(y) \big) \eta(z,y) u(\sigma, z) u(\sigma, y)\, dy dz d\sigma
\end{aligned}$$

for any $\phi \in W^{1,\infty}(Z)$,
(c) Eq. (6.21) holds.

To discuss the existence of a weak solution, we also assume that for the measurable function k which satisfy to (6.6)-(6.7) and given any $R > z_0$, it holds that

$$\lim_{\delta \to 0} \sup_{\xi \subset (z_0, R),\ |\xi| \leq \delta} \operatorname{ess\,sup}_{z \in (z_0, R)} \beta(z) \int_{z_0}^{z} \mathbb{1}_{\xi}(y) k(y,z)\, dy = 0 \tag{6.58}$$

where $|\xi|$ represents the Lebesgue measure of a measurable set $\xi \subset Z$. Moreover, let $z_1 \in Z$ and $\delta_* > 0$ such that

$$\int_{z_1}^{z} \left(1 - \frac{y}{z}\right) k(y,z)\, dy \geq \delta_*, \quad z \geq 2z_1. \tag{6.59}$$

The symmetric kernel η should be continuous function from $Z \times Z$ into $\mathbb{R}^+$ and satisfies

$$\eta(z,y) \leq K(y^{\alpha} z^{\nu} + z^{\alpha} y^{\nu}), \quad (z,y) \in Z \times Z, \tag{6.60}$$

for some constant $K \geq 1$ and (α, ν) with

$$0 \leq \alpha \leq \nu \leq 1, \quad \theta = \alpha + \nu \in [0,2], \tag{6.61}$$

providing the integrability of Q. If $\theta = \alpha + \nu \in (1,2]$, there are $0 < a < 1$, $B > 0$ and $\zeta > \theta - 1$ such that

$$\beta(z) \geq Bz^{\zeta}, \;\; 2\int_{z_0}^{z} yk(y,z)\, dy \leq az, \;\; z \in Z. \tag{6.62}$$

Theorem 6.3.1. *Let us assume that (6.6), (6.7), (6.11), (6.16), (6.17), (6.18) and (6.58)-(6.61) hold. If $\theta = \alpha + \nu \in (1,2]$, then also (6.62) holds. Let $S^0, C^0 > 0$ and $u^0 \in L_1^+(Z, zdz)$. Then, the system (6.1)-(6.5) possesses at least one global weak solution (S, C, u) within the context of Definition 6.3.1 and u belongs to $C\left(\mathbb{R}^+, L_{1,\mathrm{w}}(Z, zdz)\right)$.*

The existence of a global weak solution is based on a weak compactness argument. We first obtain a sequence $(S_n, C_n, u_n)_{n\in\mathbb{N}}$ of global classical solutions from Theorem 6.2.1 for suitably approximated bounded kernels. Then, Arzelà-Ascoli theorem [2.5.1, 2.5.9] and Dunford-Pettis theorem 2.5.2 are used to study the compactness of the sequence in the space $C([0,T], \mathbb{R}^+ \times\mathbb{R}^+ \times L_{1,\mathrm{w}}(Z, zdz))$ for any $T > 0$. Any cluster point of the sequence represents a global weak solution to (6.1)-(6.5) for unbounded kernels.

6.3.1 Proof of Weak Solution

For $u^0 \in L_1^+(Z, zdz)$, we can apply a refined version of the De la Vallée-Poussin theorem [43] which provides the existence of non-decreasing and non-negative convex function $\Phi \in C^\infty(\mathbb{R}^+)$ with $\Phi(0) = 0$ such that Φ' is concave and

$$\lim_{s\to\infty} \Phi'(s) = \lim_{s\to\infty} \frac{\Phi(s)}{s} = \infty \tag{6.63}$$

with

$$\int_{z_0}^{\infty} \Phi(z) u^0(z)\, dz < \infty.$$

Then, one can choose a sequence $(u_n^0)_{n\in\mathbb{N}}$ of smooth and compactly supported non-negative functions such that

$$\sup_{n\in\mathbb{N}} \int_{z_0}^{\infty} \Phi(z) u_n^0(z)\, dz < \infty \quad \text{and} \quad u_n^0 \to u^0 \quad \text{in} \quad L_1^+(Z). \tag{6.64}$$

Further, with the help of a mollifiers argument, we choose a sequence $(\tau_n)_{n\in\mathbb{N}}$ in $BUC^\infty([z_0,\infty))$ such that

$$0 < \frac{\tau_*}{2} \leq \tau_n(z) \leq \tau_0 z, \;\; z \geq z_0, \tag{6.65}$$

and

$$\tau_n \to \tau \quad \text{uniformly on compact subsets of } Z. \tag{6.66}$$

Also, we construct a sequence $(\eta_n)_{n\in\mathbb{N}}$ in $BUC^\infty(Z\times Z)$ which satisfies

$$\eta_n(y,z) \le K(y^\alpha z^\nu + z^\alpha y^\nu), \quad (y,z)\in Z\times Z, \tag{6.67}$$

for constants α,ν and K stemming from (6.60) and

$$\eta_n(z,y) = 0 \quad \text{for } (z,y)\in Z\times Z \ \text{ with } y+z > R_n,\ \ 2z_0 < R_n \to \infty, \tag{6.68}$$

and so on compact subsets of $Z\times Z$,

$$\eta_n \to \eta \quad \text{uniformly}. \tag{6.69}$$

For $n\in\mathbb{N}$, we put

$$P_n^0 = \sup\{z\in Z : z\in \operatorname{supp} u_n^0\}$$

and

$$H_n(T) = \phi_n^{-1}\Big(\int_0^T \big(S^0 + \int_{z_0}^\infty z u_n^0(z)\,dz + \lambda t\big)dt\Big),$$

$$\phi_n(s) = \int_{\max\{S_n^0,R_n\}}^s \frac{dz}{\tau_n(z)}$$

and then introduce

$$P_n(T) = \max\{P_{n-1}(T), H_n(T), n\},\ \ n\ge 1,\ \ P_0(T) = H_0(T).$$

Let $\mu_n = \mathbb{1}_{[z_0,P_n(T)]}\mu$ and $\beta_n = \mathbb{1}_{[z_0,P_n(T)]}\beta$ for $n\in\mathbb{N}$. Therefore, Theorem 6.2.1 warrants the existence of a global non-negative classical solution

$$(S_n,C_n,u_n)\in C^1\left(\mathbb{R}^+,\mathbb{R}\times\mathbb{R}\times X_0\right)\cap C\left(\mathbb{R}^+,\mathbb{R}\times\mathbb{R}\times X_1\right)$$

to (6.1)-(6.5) when $(\mu,\beta,\tau,\eta,u^0)$ is replaced by $(\mu_n,\beta_n,\tau_n,\eta_n,u_n^0)$. Further, the construction of P_n according to [56] and $\beta>0$ imply that

$$\operatorname{supp} u_n(t) \subset [z_0,P_n(T)] = \operatorname{supp} \beta_n,\ \ t\in[0,T].$$

Also, Eqs. (6.21) and (6.64) lead to

$$S_n(t) + C_n(t) + \int_{z_0}^\infty z u_n(t,z)\,dz + \int_0^t \int_{z_0}^\infty z\mu_n(z)u_n(s,z)\,dzds \le b(T), \tag{6.70}$$

for $\delta_2 > \frac{\delta_1}{z_0}$, $t \in [0,T]$ and $n \in \mathbb{N}$, where $b(T)$ is independent of n. We use later the following notations

$$E_n[u](z) = -\big(\mu_n(z) + \beta_n(z)\big)u(z) + 2\int_z^\infty \beta_n(y)\ k(z,y)\ u(y)\ dy$$

and

$$Q_n[u,w](z) = \mathbb{1}_{[z>2z_0]}\int_{z_0}^{z-z_0} \eta_n(z-y,y)u(z-y)w(y)\ dy - 2u(z)\int_{z_0}^\infty \eta_n(z,y)w(z)\ dz.$$

Note that the bilinear polymer coagulation term can be dealt from [29, 56] and the estimates on the moments can be derived as

$$M_{s,n}(t) = \int_{z_0}^\infty z^s u_n(t,z)\ dz, \quad t \in [0,T],$$

for $s > 0$ and $n \in \mathbb{N}$. Due to the compact support of $u_n(t,\cdot)$, all moments are well-defined. For the existence of a weak solution, the following auxiliary results are required.

Lemma 6.3.2. *Let us assume that $\theta = \alpha + \nu \in (1,2]$ in (6.60) and the condition (6.62) holds. Then, there exists a constant $b(T)$ independent of n with*

$$\int_0^T M_{\theta,n}(t)\ dt \le b(T), \quad n \in \mathbb{N}, \quad t \in [0,T]. \tag{6.71}$$

Proof. One can prove the lemma according to [[56], Corollary 4.2]. □

Lemma 6.3.3. *For $t \in [0,T]$, there exists a constant $b(T)$ independent of n with*

$$\int_{z_0}^\infty \Phi(z)u_n(t,z)\ dz \le b(T), \tag{6.72}$$

$$\int_0^t \int_{z_0}^\infty \Phi(z)\mu_n(z)u_n(\sigma,z)\ dz d\sigma \le b(T), \tag{6.73}$$

$$\int_0^t I_{1,n}(\sigma)d\sigma + \int_0^t I_{2,n}(\sigma)d\sigma \le b(T), \tag{6.74}$$

where

$$I_{1,n}(\sigma) = \int_{z_0}^\infty u_n(\sigma,z)\beta_n(z)\int_{z_0}^z \left(\frac{\Phi(z)}{z} - \frac{\Phi(y)}{y}\right) yk(y,z)\ dydz,$$

$$I_{2,n}(\sigma) = \int_{z_0}^\infty u_n(\sigma,z)\beta_n(z)\frac{\Phi(z)}{z}\int_0^{z_0} yk(y,z)\ dydz.$$

Proof. As we know that $u_n(t,\cdot)$ is compactly supported and thus we may test the corresponding Eq. (6.3) with Φ. By using (6.7) and (6.19)-(6.20) we obtain, for $t \in [0,T]$, $n \in \mathbb{N}$

$$\begin{aligned}
\int_{z_0}^{\infty} \Phi(z)u_n(t,z)\,dz = &\int_{z_0}^{\infty} \Phi(z)u_n^0(z)\,dz \\
&+ \int_0^t \frac{S_n(s)}{1+\rho\,\|u_n(\sigma)\|_0} \int_{z_0}^{\infty} \Phi'(z)\tau_n(z)u_n(s,z)\,dzd\sigma \\
&+ \int_0^t \int_{z_0}^{\infty} \int_{z_0}^{\infty} \bar{\Phi}(y,z)\eta_n(y,z)u_n(z)u_n(y)\,dydzd\sigma \\
&- \delta_2 \int_0^t C_n(\sigma) \int_{z_0}^{\infty} \Phi(z)u_n(\sigma,z)\,dzd\sigma \\
&- \int_0^t \int_{z_0}^{\infty} \Phi(z)\mu_n(z)u_n(\sigma,z)\,dzd\sigma \\
&- 2\int_0^t (I_{1,n}(\sigma)+I_{2,n}(\sigma))\,d\sigma,
\end{aligned}$$

where $\bar{\Phi}(y,z) = \Phi(y+z) - \Phi(z) - \Phi(y)$ for $y,z \in Z$. According to [[56], Lemma 4.3], the following estimate holds

$$\int_{z_0}^{\infty} \Phi(z)u_n(t,z)\,dz + \int_0^t \int_{z_0}^{\infty} \Phi(z)\mu_n(z)u_n(\sigma,z)\,dzd\sigma + \int_0^t I_{1,n}(\sigma)\,d\sigma + \int_0^t I_{2,n}(\sigma)\,d\sigma \le b(T)$$

and so assertion follows. □

Lemma 6.3.4. *Let us assume $A_V^C(t) = V(t)A + \delta_2 C(t)$, for $V,C \in C(J_T)$ with $V(t),C(t) > 0$ and τ satisfies (6.17). Let, $\mathbb{U}_{A_V^C}(t,s)$, $0 \le s \le t \le T$ represents the unique evolution system corresponding to $-A_V^C(t)$, $t \in J_T$ in $L_1(Z)$ and for any $M > z_0, \delta > 0$, put*

$$\lambda_M(\delta) = \tau_* M \sup_{\xi\subset(z_0,M),\ |\xi|\le\delta} \int_{\xi} \frac{dz}{\tau(z)}.$$

Then,

$$\sup_{\xi\subset(z_0,M),\ |\xi|\le\delta} \int_{\xi} \mathbb{U}_{A_V^C}(t,s)\phi\,dz \le \sup_{F\subset(z_0,M),\ |F|\le\lambda_M(\delta)} \int_F \phi\,dz,\ \ 0\le s\le t\le T,\ \phi\in L_1^+(Z),$$

where the supremum is taken over all measurable sets $\xi \subset Z$ with $|\xi| \le \delta$.

Proof. For any given measurable subset ξ of (z_0,M) and any $f \in L_1(Z)$, it follows from Lemma 6.2.3 that

$$\begin{aligned}
\int_{\xi} W(t)f dz &= \int_{\Psi^{-1}(t)}^{\infty} \mathbb{1}_{\xi}(z)\,(\Psi(z))\,\frac{\tau\big(\Psi^{-1}(\Psi(z)-t)\big)}{\tau(z)} f\big(\Psi^{-1}(\Psi(z)-t)\big)dz \\
&= \int_{z_0}^{\infty} \mathbb{1}_{\Psi^{-1}((\Psi(\xi)-t)\cap(0,\infty))}(z)f(z)dz
\end{aligned}$$

where Ψ is taken as in Lemma 6.2.3. Also, $\Psi^{-1}((\Psi(\xi)-t)\cap(0,\infty))\subset(z_0,M)$ and thus due to (6.17),

$$|\Psi^{-1}((\Psi(\xi)-t)\cap(0,\infty))|\leq\lambda_M(\delta).$$

The unique evolution system to $\left(-A_V^C(t)\right)_{t\in J_T}$ is given by

$$\mathbb{U}_{A_V^C}(t,s)=e^{\delta_2\int_s^t C(\sigma)d\sigma}\,W\left(\int_s^t V(\sigma)d\sigma\right),\quad 0\leq s\leq t\leq T,$$

and the required assertion follows. □

Proposition 6.3.1. *There exists a weakly compact subset K_T of $L_1(Z,zdz)$ such that $u_n(t)\in K_T$ for $n\in\mathbb{N}$ and $t\in[0,T]$. Moreover,*

$$\int_0^T\int_{z_0}^\infty \beta_n(z)u_n(\sigma,z)\;dzd\sigma\leq b(T),\quad n\in\mathbb{N},\tag{6.75}$$

where $b(T)>0$ being a constant independent of $n\in\mathbb{N}$.

Proof. This lemma can be proved according to [[56], Proposition 4.4] and using Lemma 6.3.4. □

Lemma 6.3.5. *The family $\{u_n : n\in\mathbb{N}\}$ is weakly equicontinuous in $L_1(Z,zdz)$ for every $t\in[0,T]$.*

Proof. According to Theorem 4.3.3, for $\phi\in L_\infty(Z)$, we have

$$\lim_{s\to t}\sup_{n\in\mathbb{N}}\left|\int_{z_0}^\infty\phi(z)[u_n(t,z)-u_n(s,z)]\;dz\right|=0,$$

for $t\in J_T$. This implies together with (6.63) that, for $t\in J_T$,

$$\lim_{s\to t}\sup_{n\in\mathbb{N}}\left|\int_{z_0}^\infty\phi(z)[u_n(t,z)-u_n(s,z)]\;zdz\right|=0.$$

□

Lemma 6.3.6. *The family $\{C_n : n\in\mathbb{N}\}$ is relatively compact in $C([0,T])$.*

Proof. From Eqs. (6.2) and (6.70), it follows that

$$\begin{aligned}|C_n(t)-C_n(s)|&\leq\delta_0\left|\int_s^t C_n(\sigma)\;d\sigma\right|+\delta_1\left|\int_s^t C_n(\sigma)\int_{z_0}^\infty u_n(\sigma,z)\;dzd\sigma\right|\\&\leq\delta_0 b(T)\,|t-s|+\frac{\delta_1}{z_0}b(T)\,|t-s|\,.\end{aligned}$$

Therefore,

$$\lim_{s\to t}\sup_{n\in\mathbb{N}}|C_n(t)-C_n(s)|=0,$$

and the assertion is complete from the Arzelà-Ascoli theorem 2.5.1. □

Lemma 6.3.7. *The family* $\{S_n : n\in\mathbb{N}\}$ *is relatively compact in* $C([0,T])$.

Proof. For the test function $\phi(z)=z$, the truncated Eq.(6.3) with (6.6), (6.20) and positivity of $u_n(t), C_n(t)$ provide

$$2\int_{z_0}^{\infty}u_n(t,z)\beta_n(z)\int_0^{z_0}yk(y,z)\,dydz=\frac{S_n(t)}{1+\rho\,\|u_n(t)\|_0}\int_{z_0}^{\infty}\tau_n(z)u_n(t,z)dz-\frac{d}{dt}\int_{z_0}^{\infty}zu_n(t,z)\,dz$$
$$-\delta_2C_n(t)\int_{z_0}^{\infty}zu_n(t,z)-\int_{z_0}^{\infty}z\mu_n(z)u_n(t,z)\,dz,$$

and then Eqs. (6.65) and (6.70) warrant

$$\left|2\int_{z_0}^{\infty}u_n(t,z)\beta_n(z)\int_0^{z_0}yk(y,z)\,dydz\right|\le b(T)|t-s|+\left|\int_{z_0}^{\infty}z[u_n(t,z)-u_n(s,z)]dz\right|.$$

Thus, Eq. (6.1) allows with (6.65), (6.70) and Lemma 6.3.5 that

$$\lim_{s\to t}\sup_{n\in\mathbb{N}}|S_n(t)-S_n(s)|=0,$$

and the required result follows from the Arzelà-Ascoli theorem 2.5.1. □

By Proposition 6.3.1, Lemmas 6.3.5-6.3.7 and Arzelà-Ascoli theorem [2.5.1, 2.5.9], it follows that there exists a subsequence (again denoted by $(S_n),(C_n),(u_n)$ and functions $S,C\in C(\mathbb{R}^+), u\in C\big(\mathbb{R}^+, L_{1,\mathrm{w}}(Z,zdz)\big)$ such that for each $T>0$,

$$S_n\to S,\ \ C_n\to C \quad \text{in} \quad C([0,T]), \tag{6.76}$$

$$u_n\to u, \quad \text{in} \quad C([0,T],L_{1,\mathrm{w}}(Z,zdz)). \tag{6.77}$$

It is clear that $S(t)\ge 0$, $C(t)\ge 0$ and $u(t)\ge 0$. Now (S,C,u) remains to be seen as a weak solution to (6.1)-(6.5). In each of the corresponding terms, we proceed to the limit, since (S_n,C_n,u_n) satisfies the weak formulation provided in Definition 6.3.1. Except for the chaperone term, this is very ordinary and similar to [56]. By applying Lebesgue's dominated convergence theorem and having Eqs. (6.70), (6.76) and (6.77), one can obtain that

$$\lim_{n\to\infty}\int_0^t C_n(\sigma)\int_{z_0}^{\infty}\phi(z)u_n(\sigma,z)\,dz\,d\sigma=\int_0^t C(\sigma)\int_{z_0}^{\infty}\phi(z)u(\sigma,z)\,dz\,d\sigma \tag{6.78}$$

for $t \in J_T$. Also, Eqs. (6.63), (6.73) and (6.77) entail that

$$\lim_{n\to\infty} \int_{z_0}^{\infty} \phi(z)\mu_n(z)u_n(t,z)\, dz = \int_{z_0}^{\infty} \phi(z)\mu(z)u(t,z)\, dz, \quad t \in J_T. \tag{6.79}$$

According to [56], it is easy to show that u satisfies the weak formulation. Also, it follows from (6.70), (6.74), (6.76), (6.77) that S and C satisfy Eqs. (6.1) and (6.2), respectively. Finally Eqs. (6.76)-(6.79) ensure that (6.21) also holds for (S,C,u).

6.4 Stability Analysis and Effect of Chaperone

In this section, we discuss stability issues and effect of chaperone on prion proliferation numerically. We replace $P(t)$ by $W(t) = P(t) - z_0U(t)$ (the number of PrP^{Sc} units not accounted for within the minimal polymer lengths) in the system (6.13). Then, the resulting system of equations is

$$\begin{aligned} (z_0U)' &= \beta z_0 W - (\mu+\beta z_0)(z_0U) - \delta_2 C(z_0U) - \frac{\eta}{z_0}(z_0U)^2 \\ S' &= \lambda - \gamma S - \frac{\tau S(z_0U)}{z_0(1+\rho(W+z_0U))} + \beta z_0(z_0U) \\ W' &= \frac{\tau S(z_0U)}{z_0(1+\rho(W+z_0U))} - (\mu+\beta z_0)W - \delta_2 CW + \frac{\eta}{z_0}(z_0U)^2 \\ C' &= -\delta_0 C + \delta_1 CU \end{aligned} \tag{6.80}$$

with initial conditions

$$U(0) = U^0 \geq 0, S(0) = S^0 \geq 0, W(0) = W^0 = P^0 - z_0U^0 \geq 0 \text{ and } C(0) = C^0.$$

Next, performing a scaling of the variables for the system of equations (6.80) by setting

$$z_0U(t) = eE(\alpha t),\ S(t) = fF(\alpha t),\ W(t) = gG(\alpha t),\ C(t) = hH(\alpha t)$$

where $\alpha = \mu + \beta z_0, e = \frac{(\mu+\beta z_0)z_0}{\tau}, f = g = \frac{(\mu+\beta z_0)^2}{\beta\tau}, k = \frac{\beta\lambda\tau}{(\mu+\beta z_0)^3}, \xi = \frac{\gamma}{\mu+\beta z_0}, \delta = \frac{\beta z_0}{\mu+\beta z_0}, h = \frac{\mu+\beta z_0}{\delta_2}, \omega = \frac{\rho(\mu+\beta z_0)^2}{\beta\tau}, \nu = \frac{\delta_0}{\mu+\beta z_0}, \psi = \frac{\delta_1}{\tau}$ and $\phi = \frac{\eta}{\tau}$. Then,

$$
\begin{aligned}
E' &= G - E - EH - \phi E^2 \\
F' &= k - \xi F - \frac{FE}{1+\omega(G+\delta E)} + \delta^2 E \\
G' &= \frac{FE}{1+\omega(G+\delta E)} - G - HG + \phi\delta E^2 \\
H' &= -\nu H + \psi EH
\end{aligned} \tag{6.81}
$$

subject to the conditions

$$E(0) = E^0 \geq 0, F(0) = F^0 \geq 0, G(0) = G^0 \geq 0, H(0) = H^0 \geq 0.$$

Proposition 6.4.1. *Let $\phi, \omega \geq 0$, $k, \xi > 0$ and $\delta \in (0,1)$. Then, for each $\left(E^0, F^0, G^0, H^0\right) \in (\mathbb{R}^+)^4$, the system (6.81) possesses a unique bounded solution in $(\mathbb{R}^+)^4$ defined for all positive time t.*

Proof. Let $f : (\mathbb{R}^+)^4 \to (\mathbb{R}^+)^4$ is defined by

$$
\begin{aligned}
&f(E,F,G,H) = (f_1, f_2, f_3, f_4) \\
&= \left(G - E - EH - \phi E^2, k - \xi F - \frac{FE}{1+\omega(G+\delta E)} + \delta^2 E, \frac{FE}{1+\omega(G+\delta E)} - G - HG + \phi\delta E^2, -\nu H + \psi EH\right).
\end{aligned}
$$

It is clear that f is Lipschitz continuous on bounded sets of $(\mathbb{R}^+)^4$. Now, for $(E,F,G,H) \in (\mathbb{R}^+)^4$ and $t \geq 0$, it holds that $f_1 = G \geq 0$ when $E = 0$, $f_2 = k + \delta^2 E \geq 0$ when $F = 0$, $f_3 = \frac{EF}{1+\omega\delta E} + \phi\delta E^2 \geq 0$ when $G = 0$, and $f_4 \geq 0$ when $H = 0$. From [Corollary A.5, [73]], there exists a unique positive solution of (6.81) in $(\mathbb{R}^+)^4$ for $t \geq 0$.
From the function $\phi = \left(\frac{1+\delta^2}{2}\right)E + F + G + \left(\frac{1+\delta^2}{2\psi}\right)H$, we get

$$\phi' = k - \left(\frac{1-\delta^2}{2}\right)G - \left(\frac{1-\delta^2}{2}\right)E - \xi F - GH - \left(\frac{1+\delta^2-2\delta}{2}\right)\phi E^2 - \nu\left(\frac{1+\delta^2}{2\psi}\right)H \leq k - b^*\phi,$$

where $b^* = \min\left\{\frac{1-\delta^2}{2}, \xi, \nu\right\}$. This implies that

$$0 \leq \phi(t) \leq \frac{k}{b^*} + \phi(0)e^{-tb^*}$$

whenever $(E^0, F^0, G^0, H^0) \in (\mathbb{R}^+)^4$ and $t \geq 0$. This indicates that the solution exists and bounded for all positive times. □

The basic reproduction number, i.e., the number of new infections produced by a single infective prion is $R_0 = k/\xi$.

Lemma 6.4.1. *The disease free state* $(0, k/\xi, 0, 0)$ *of the system (6.81) is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof. The Jacobian matrix of (6.81) at disease free equilibrium is given by

$$\begin{pmatrix} -1 & 0 & 1 & 0 \\ -\frac{k}{\xi}+\delta^2 & -\xi & 0 & 0 \\ \frac{k}{\xi} & 0 & -1 & 0 \\ 0 & 0 & 0 & -\nu \end{pmatrix}.$$

Eigenvalues of this matrix are $\frac{1}{\sqrt{\xi}}(-\sqrt{k}-\sqrt{\xi}), \frac{1}{\sqrt{\xi}}(\sqrt{k}-\sqrt{\xi}), -\xi$ and $-\nu$. The eigenvalues have negative real parts if $R_0 < 1$. Thus, by the Routh-Hurwitz criterion, the proof is complete. □

Lemma 6.4.2. *The disease free state* $(0, k/\xi, 0, 0)$ *of the system*

$$\begin{aligned} E' &= G - E - EH - \phi E^2 \\ F' &= k - \xi F - FE + \delta^2 E \\ G' &= FE - G - HG + \phi\delta E^2 \\ H' &= -\nu H + \psi EH \end{aligned}$$

is globally asymptotically stable if $R_0 = k/\xi \leq 1$ *and* $\psi < 1$.

Proof. We construct a Lyapunov functional

$$\Upsilon(E,F,G,H) = \frac{1}{2}(F-\bar{F})^2 + (2-\delta^2-\bar{F})(E+G+H).$$

Since $\delta < 1$ and $R_0 = \bar{F} = \frac{k}{\xi} \leq 1$, we have $2-\rho^2-\bar{F} > 0$. Now,

$$\begin{aligned} \Upsilon' &= (2-\delta^2-\bar{F})\dot{E} + (F-\bar{F})\dot{F} + (2-\delta^2-\bar{F})(\dot{G}+\dot{H}) \\ &= (2-\delta^2-\bar{F})\left[(-1+\psi)EH + (\delta-1)\phi E^2 + (F-1)E - (G+\nu)H\right] \\ &\quad + (F-\bar{F})(\xi\bar{F} - \xi F - FE + \delta^2 E) \\ &= -\xi(F-\bar{F})^2 - \nu H(2-\delta^2-\bar{F}) - EH(2-\delta^2-\bar{F})(1-\psi) + GH(-2+\delta^2+\bar{F}) \\ &\quad - \phi(1-\delta)(2-\delta^2-\bar{F})E^2 - E\left[(1-\delta^2)(1-\bar{F}) + (F-1)^2\right]. \end{aligned}$$

Thus, Υ' is non-positive if $R_0 = \frac{k}{\xi} \leq 1, \psi < 1$ and $\Upsilon' = 0$ only if $F = \bar{F}, E = G = H = 0$. From LaSalle's invariance principle, the disease-free equilibrium is globally asymptotically stable. □

Theorem 6.4.3. *The disease free state $(0, k/\xi, 0, 0)$ of the system (6.81) is globally asymptotically stable if $R_0 = k/\xi \leq 1 - \delta^2$ and $\psi < 1$.*

Proof. Construct the function

$$\Upsilon(E,F,G,H) = E + G + H + (F - \bar{F}) - \bar{F}\ln(F/\bar{F}),$$

and then the derivative of Υ is given by

$$\begin{aligned}
\Upsilon' &= -\xi\frac{(F-\bar{F})^2}{F} - \delta^2 E\frac{\bar{F}}{F} + E\left(\delta^2 - 1 + \frac{\bar{F}}{1+\omega(G+\delta E)}\right) \\
&\quad - HG - (1-\delta)\phi E^2 - (1-\psi)EH - \nu H \\
&\leq -\xi\frac{(F-\bar{F})^2}{F} - \delta^2 E\frac{\bar{F}}{F} + E\left(\delta^2 - 1 + \bar{F}\right) \\
&\quad - HG - (1-\delta)\phi E^2 - (1-\psi)EH - \nu H.
\end{aligned}$$

Thus, Υ' is non-positive if $R_0 = k/\xi \leq 1-\delta^2, \psi < 1$ and $\Upsilon' = 0$ only if $F = \bar{F}, E = G = H = 0$. Thanks to LaSalle's invariance principle, the disease-free equilibrium is globally asymptotically stable. □

Theorem 6.4.4. *If $R_0 > 1$, then the disease state equilibrium*

$$\left(\widehat{E},\widehat{F},\widehat{G},\widehat{H}\right) = \left(\frac{k-\xi}{(1+\delta)(1-\delta+\xi\omega)}, \frac{1-\delta+\omega k}{1-\delta+\omega\xi}, \frac{k-\xi}{(1+\delta)(1-\delta+\xi\omega)}, 0\right)$$

of the system (6.81) with $\phi = 0$ is locally asymptotically stable.

Proof. We consider the equivalent system corresponding to the system (6.81) such as

$$\begin{aligned}
E' &= G - E - EH - \phi E^2 \\
G' &= \frac{FE}{1+\omega(G+\delta E)} - G - HG + \phi\delta E^2 \\
(F+G)' &= k - \xi(F+G) + (\xi-1)G + \delta^2 E - HG + \phi\delta E^2 \\
H' &= -\nu H + \psi EH.
\end{aligned} \tag{6.82}$$

For the case $\phi = 0$, the Jacobian matrix of the system (6.82) at disease equilibrium is given by

$$\begin{pmatrix}
-1 & 1 & 0 & -\widehat{E} \\
1 - \frac{\omega\delta\widehat{E}}{r} & -1 - \frac{\widehat{E}(1+\omega)}{r} & \frac{\widehat{E}}{r} & -\widehat{G} \\
\delta^2 & \xi - 1 & -\xi & -\widehat{G} \\
0 & 0 & 0 & -\nu
\end{pmatrix}$$

where $r = 1 + \omega\widehat{E}(1+\delta)$. The characteristic equation of the Jacobian matrix is given by

$$(\nu+\lambda)(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0,$$

where

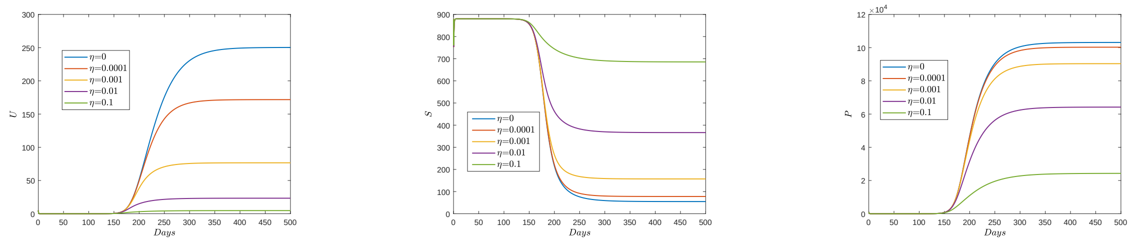
$$a_1 = 2 + \frac{\widehat{E}}{r} + \frac{\omega\widehat{E}}{r} + \xi,\ a_2 = 2\frac{\widehat{E}}{r} + \frac{\omega\widehat{E}}{r}(1+\delta+\xi),\ a_3 = \frac{\widehat{E}}{r}(1-\delta^2) + \frac{\omega\xi\widehat{E}}{r}(1+\delta).$$

One eigenvalue of the Jacobian matrix is $-\nu$. Here, $a_1 > 0,\ a_2 > 0,\ a_3 > 0$ and $a_1a_2 - a_3 > 0$, then by the Routh-Hurwitz criterion, the other eigenvalues have negative real parts. Thus, the proof is complete. □

6.4.1 Numerical Illustration

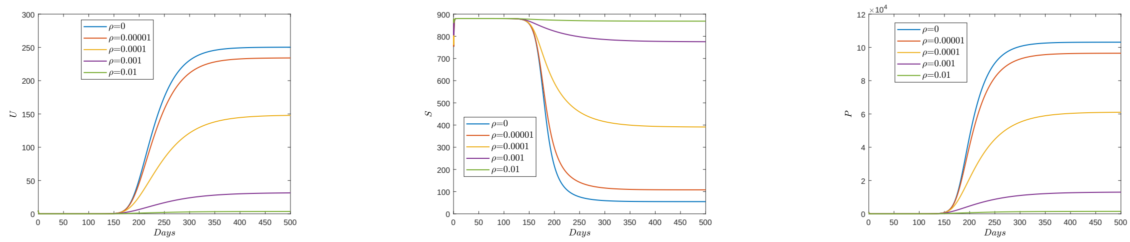
For the simulations, we take the experimental data as considered in [37, 48, 59] for prion proliferation. The model includes eleven parameters: $\lambda, \gamma, \mu, \beta, \tau, z_0, \eta, \rho, \delta_0, \delta_1$ and δ_2.

The critical size z_0 of polymer is estimated as $6-30$, see [59]. The model parameters values are taken from [37, 38, 59] and are follows as: $z_0 = 6, \lambda = 4400$ day^{-1}, $\tau = 0.3$ (SAF/sq)$^{-1}$ day^{-1}, $\beta = 0.0001$ (SAF/sq)$^{-1}$ day^{-1}, $\mu = 0.04$ day^{-1}, $\gamma = 5.0$ day^{-1}, $\eta = 0-0.1$ (SAF/sq)$^{-1}$ day^{-1}, $\rho = 0-0.01$, $\delta_0 = 0.1$ day^{-1}, $\delta_1 = 0.0002$ day^{-1} and $\delta_2 = 0.002$ day^{-1}, where SAF/sq represents scripe associated fibrils per squre unit of measurement. Figures 6.1 and 6.2 show the effect of the chaperone on population of U, S and P for varying $\eta(\rho = 0)$ and $\rho(\eta = 0)$, respectively. As expected, a comparison of these numerical simulations from Figures 4 and 2 of [37] indicates that the population of U and P take time to grow and the population of S takes time to grow while the population of S takes time to decrease due to the presence of chaperone. Thus, it is clear that chaperone is used to suppress the growth of prions. Further, the numerical results of polymer population for different chaperone dosages are plotted in Figure (6.3a). It is visible that the polymers population decrease along with increasing chaperone doses. Finally, from the Figures (6.3b) and (6.3c), we observe that the population of U and P decrease as chaperone increasing rate δ_1 increases in the system.



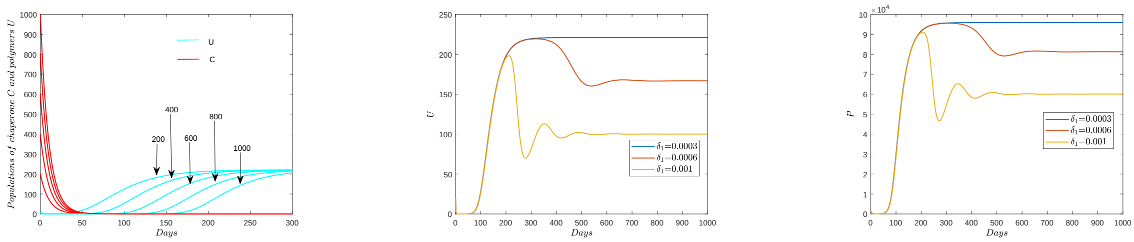
(a) **(b)** **(c)**

Fig. 6.1: In the presence of chaperone, population of U, S and P for varying η



(a) **(b)** **(c)**

Fig. 6.2: In the presence of chaperone, population of U, S and P for varying ρ



(a) **(b)** **(c)**

Fig. 6.3: (a) Polymer population U for varing amount of chaperone C (200, 400, 600, 800 and 1000 units of chaperone). (b) Polymer population U for different δ_1. (c) Population P for different δ_1.

Conclusions and Future Directions

Conclusions

In this thesis, we studied the solutions of prion proliferation models in the presence of chaperone. The existence of classical and weak solutions was established using semigroups operator theory and weak compactness argument, respectively. Moreover, we transformed the model into a system of ordinary differential equations and investigated the global asymptotic stability for equilibrium points. The effect of chaperone on prion proliferation is also discussed numerically.

We first discussed the solutions of a mathematical model which consists polymer and chaperone terms. The existence of a unique positive local mild solution under the certain assumptions on associated parameters was proved by using C_0 semigroups theory. Further, for bounded reaction rates, a unique positive classical solution was obtained with the help of evolution operator theory.

In our second aim, the well-posedness in the classical sense of a mathematical model which consists the relation between infectious and non-infectious prion proteins together with chaperone was discussed in a suitable space $\mathbb{R} \times \mathbb{R} \times L_1(Z, zdz)$ for bounded kernels. The proof relies on the fact of using evolution operator theory. Moreover, for unbounded kernels, the existence of a weak solution was proved by using weak compactness argument.

In the third goal, the existence of weak solution results, obtained in [55], was extended by incorporating chaperone, thanks to weak compactness argument. Further, we demonstrated the uniqueness of the solution under the sufficient conditions proposed in [55]. In addition, we studied that there is a unique steady state, the disease-free equilibrium, that exists below and at the threshold and is globally asymptotically stable. Above the threshold, there is another steady state, the disease state, which is globally asymptotically stable as well. The effect of chaperone on prion concentration was also shown numerically.

Finally, a mathematical model which consists of a non-linear partial integro-differential equation coupled with two ODEs was analyzed. The model includes prion polymerization, polymer splitting, polymer coagulation and chaperone. The well-posedness of the system was proved for bounded kernels by using evolution operator theory in the state space $\mathbb{R} \times \mathbb{R} \times L_1(Z, zdz)$.

The existence of a global weak solution for unbounded kernels was also discussed by weak compactness argument. Also, the model was transformed into a system of ordinary differential equations. The global stability (via Lyapunov function) was studied for disease-free equilibrium. Moreover, the effect of chaperone on prion proliferation was presented numerically.

Future Directions

Here, I want to note a biological term ‘Interferon’, see [32]. Interferon also works similar to chaperone. Thus, chaperone and interferon are useful to control polymer population. Now, in the following, I would like to mention some open problems related to our work for the future developments.

- It would be interesting to study a prion proliferation model under the presence of chaperone and interferon.
- Analysis of a prion proliferation model with polymer coagulation and general incidence terms under combined treatments chaperone and interferon.
- Existence of solutions and asymptotic behavior of new age/size structured population models by C_0 Semigroups/Integrated Semigroups theory are open tasks which are worth to work on.

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List of Publications

Published/ Accepted Articles

1. Rajiv Kumar, Kapil Kumar Choudhary and Rajesh Kumar, Study of the solution of a semilinear evolution equation of a prion proliferation model in the presence of chaperone in a product space, **Mathematical Methods in the Applied Sciences**, **44**: 1942-1955, 2021.
   (Impact Factor **2.321**, Indexed in **SCIE**)
   (https://doi.org/10.1002/mma.6894)

2. Kapil Kumar Choudhary, Rajiv Kumar and Rajesh Kumar, Global classical and weak solutions of the prion proliferation model in the presence of chaperone in a banach space, **Evolution Equations and Control Theory**, **11(4)**: 1175-1190, 2022.
   (Impact Factor **1.081**, Indexed in **SCIE**)
   (doi:10.3934/eect.2021039)

3. Kapil Kumar Choudhary, Rajiv Kumar and Rajesh Kumar, Weak solution and qualitative behavior of a prion proliferation model in the presence of chaperone, **Acta Applicandae Mathematicae**, doi: https://doi.org/10.1007/s10440-022-00512-y, 2022.
   (Impact Factor **1.081**, Indexed in **SCI**)
   (doi:https://doi.org/10.1007/s10440-022-00512-y)

Communicated Articles

1. Kapil Kumar Choudhary, Rajiv Kumar and Rajesh Kumar, Analysis of a prion proliferation model with polymer coagulation in the presence of chaperone, **Mathematical Methods in the Applied Sciences**, (Under Revision).

Workshops/Conferences

Presented Work

The following works have been presented in the National/International conferences

1. Analysis of a Prion Proliferation Model together with Polymer Coagulation in the Presence of Chaperone, National Conference of Academy for Progress of Mathematics on Recent Advances in Mathematical Analysis and Applications, DST-Centre for Interdisciplinary Mathematical Sciences, Institute of Science, Banaras Hindu University, Varanasi, 07-08 May 2022.

2. Classical Solution of a Prion Proliferation Model in the Presence of Chaperone in a Banach Space, Advances in Mechanics, Modelling, Computing, and Statistics (ICAMMCS), Department of Mathematics, BITS Pilani, Pilani Campus, 19-21 March 2022.

3. Study of Solutions to a Prion Equation in the Presence of Chaperone and Stability Analysis of an Equilibrium Point, 4th International Conference on Frontiers in Industrial and Applied Mathematics (FIAM-2021), SLIET, Punjab, 21-22 Dec 2021.

4. Global Classical and Weak Solutions of a Prion Proliferation Model in the Presence of Chaperone in a Banach Space, 35th Annual Conference of the Ramanujan Mathematical Society, Department of Mathematics, Central University of Rajasthan, Ajmer, 28-30 Dec 2020.

5. Analysis of a Semi-linear Evolution Equation in Product Space, International Conference on Mathematical Analysis and Its Applications (ICMAA-2019), South Asian University, Delhi, 14-16 Dec 2019.

Attended Workshops

1. International Workshop on Advanced Topics in Mathematics (IWATM-2020), Center for Applied Mathematics, IIIT Naya Raipur, 01-05 Oct 2020.

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