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Contents

INTRODUCTION

This theses is devoted to some population dynamics mathematical models describing prion diseases.

Prion diseases or transmissible spongiform encephalopathies (TSEs) are fatal and infectious neurodegenerative diseases affecting many mammals. They include animal bovine spongiform encephalopathy (BSE), responsible for the crisis of "mad cow" in the 1990s, or the Scrapie. In humans, there is the Kuru that decimated part of the Fore tribe in Papua New Guinea during the 20th century. More recently disease Kreuzfeld Jakob was transmitted between humans by injection of growth hormones and blood transfusions but also from BSE by eating contaminated beef products. Prion diseases attack the central nervous system and can be observed holes in the brains of diseased individuals, like a sponge, hence the name of spongiform encephalopathies.

The agent responsible for these diseases, known as prion name, provides strength properties to inactivation by heat, radiation and chemical treatments which make it unlikely that the presence of DNA as would be the case for a virus. In 1967, Griffith [21] proposes the hypothesis of a purely protein mechanism (for Proteinaceous infectious prion only) which is still very compelling and commonly accepted. Under this assumption, the causative agent of the disease is a protein, or PrP prion protein, which accumulates in abnormally folded form. This pathogenic form, called PrP^{sc} scrapie, has the ability to replicate by a self-propagating process, converting the normal form of the protein (PrP^C Cell) to PrP^{sc}. This hypothesis was supported by experimental work Prusiner [46] in

1982, which earned him a Nobel Prize in Physiology and Medicine in 1997.
In the absence of contamination, PrP^C is involved in the normal operation of the cell. Its functions are not yet known precisely but are probably essential. In adults, PrP^C is mainly produced in the brain and spinal cord, which explains that these bodies are affected by prion diseases.
Our work is inspired from those of Webb and his collaborators [13], [19], [49] and [20], in their works they describe the evolution of the prion monomers by a first order differential equation and the evolution of polymers by some partial differential equation of first order. The precise mechanism PrP^C conversion PrP^{sc} is still poorly determined. Since the model of Griffith, several models have been proposed (see [34] for a complete review). In this thesis we consider the nucleated polymerization Lansbury introduced by [26]. In this model, the PrP^{sc} is present in the cell in the form of polymers which can lie by attaching monomers PrPc. During the process of polymerization, the monomers of PrP^C are transformed into PrP^{sc} by a poorly understood process. The aggregation of the monomers to polymers is carried small very slowly until they reach a critical size that stabilizes and accelerates aggregation. Parallel to the elongation, the polymers can be fragmented; fragmentation was demonstrated by experimental studies.
The first model proposed by Griffith [21] in 1967. Regarding the nucleated polymerization mechanism, the most studied mathematical model is that of Masel [39]. It consists of an infinite number of coupled ordinary differential equations (ODE). The continuous version of this model is introduced by Greer et al. [20] which replaces the infinite system of (ODE) by coupling an (ODE) with a partial differential equation (PDE). The (PDE) is a nonlocal integro-differential equation usually called the transport-growing fragmentation or fragmentation. This equation contains two distinct terms representing the polymerization process and the other fragmentation polymers. These two processes are competing polymerization increasing the size of the polymers and fragmentation diminishing.
In our work given in chapter four, we consider the case of impulsive differential equation describing the evolution of prion monomers, the presence of impulse can be explained by the possibility that there is threshold of prion protein quantity needed by organisms and

the quantity of monomers must be upon this threshold, polymers are depending on length and time, so they are described by partial differential equation, the model obtained is the following

$$\begin{cases} v'(t) = \lambda - \gamma v(t) - \tau v(t) \displaystyle\int_{x_0}^{\infty} u(t,x)dx \\ \qquad +2 \displaystyle\int_0^{x_0} x \int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(t,y)dydx, \ t \neq t_i, \quad i = 1,2,\dots, \\ v(t_i^+) - v(t_i^-) = \lambda_i, \quad \lambda_i > 0, \quad i = 1,2,\dots, \\ \partial_t u(t,x) + \tau v(t)\partial_x u(t,x) + (\mu(x) + \beta(x))u(t,x) \\ \qquad = 2 \displaystyle\int_x^{\infty} \beta(y)\kappa(x,y)u(t,y)dy, \end{cases}$$

- $v(t)$ is the number of PrP^c monomers at time t,
- $u(t,x)$ is the density of PrP^{sc} polymers of length x at time t,
- x_0 is the lower bound for polymer length (that is polymers have length x with $x_0 < x < \infty$),
- λ is the source rate for PrP^c monomers produced continuously,
- λ_i is the number of PrP^c monomers produced discretely at time t_i,
- γ is the metabolic degradation rate for PrP^c,
- τ is the rate associated with lengthening of PrP^{sc} polymers by attaching to and converting PrP^c monomers,
- $\beta(x)$ is length-dependent rate of polymer breakage,
- $\kappa(x,y)$ is the probability, when a polymer of length y breaks, that one of the two resulting polymers has length x,
- $\mu(x)$ is the length-dependent metabolic degradation rate of PrP^{sc} polymers having length x.

The kernel $\kappa(y,x)$ should satisfy the following properties:

$$\kappa(y,x) \geq 0, \quad \kappa(y,x) = \kappa(x-y,x), \quad \int_0^x \kappa(y,x)dy = 1,$$

for all $x \geq x_0, y \geq 0$,

$$\begin{aligned} \kappa(y,x) &= 1/x, \qquad \text{if} \quad x > x_0 \quad \text{and} \quad 0 < y < x. \\ \kappa(y,x) &= 0, \qquad \text{elsewhere.} \end{aligned}$$

In the case without impulse effects we find the model studied Pujo-Menjouet et al. [49]

$$v'(t) = \lambda - \gamma v(t) - \tau v(t) \int_{x_0}^{\infty} u(t,x)dx + 2\int_0^{x_0} x \int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(t,y)dydx,$$

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

$$u(t,x_0) = 0, \quad v(0) = v^0 \geq 0, \quad u(0,x) = u^0(x),$$

They study the phenomena by transforming their model to a system constituted by three ordinary differential equations, they study the system obtained using theory of differential equations, more specifically they analyze existence and uniqueness of solution, after that they study the stability of steady states. In [54] the authors study a system equivalent to our model without impulse, they study the existence of solutions substituting the result from differential equation into the partial differential equation, they use properties of evolution semigroups to prove existence of solutions.
Other prion models exist we can cite the following

In [19]

$$v'(t) = \lambda - \gamma v(t) - \tau v(t) \int_{x_{min}}^{x^{max}} u(t,x)dx + \int_0^{x_{max}} x \left[2\beta \int_{x_{min}}^{x^{max}} b(y)\kappa(x,y)u(t,y)dy \right] dx,$$

$$\frac{\partial}{\partial t}u(t,x) + \tau v(t)\frac{\partial}{\partial x}u(t,x) + (\mu(x) + \beta b(x))u(t,x) = 2\int_x^{x_{max}} b(y)\kappa(x,y)u(t,y)dy,$$

$$u(t,x_{min}) = 0, \quad v(0) = v^0 \geq 0, \quad u(0,x) = u^0(x),$$

for $t \geq 0$ and $x_{min} \leq x \leq x_{max}$.

The main work of this thesis is given in chapter four, we use similar approach that used by walker to solve the impulsive system, we use the theory of semigroups to prove existence with respect to parameters.

This thesis is constituted by four chapters, in the first one we give some preliminary results, in the second one we give results on the model studied in [49], in the third chapter we study the model considered in [54] and in the last chapter we give our results concerning the impulsive model. We end this thesis by some conclusions and bibliography related to our work.

Chapter 1

PRELIMINARIES

1.1 Ordinary differential equations

1.1.1 Existence and uniqueness

Let $J \subseteq \mathbb{R}, U \subseteq \mathbb{R}^n$, and $\Lambda \in \mathbb{R}^k$ be open subsets, and suppose that $f : J \times U \times \Lambda \to \mathbb{R}^n$ is a smooth function. Here the term "smooth" means that the function f is continuously differentiable. An ordinary differential equation (ODE) is an equation of the form

$$\dot{x} = f(t, x, \lambda) \tag{1.1}$$

where the dot denotes differentiation with respect to the independent variable t (usually a measure of time), the dependent variable x is a vector of state variables, and λ is a vector of parameters. As convenient terminology, especially when we are concerned with the components of a vector differential equation, we will say that equation (1.1) is a system of differential equations. Also, if we are interested in changes with respect to parameters, then the differential equation is called a family of differential equations.

Example 1.1.1 *The forced van der Pol oscillator*

$$\begin{aligned}\dot{x}_1 &= x_2,\\ \dot{x}_2 &= b(1-x_1^2)x_2 - \omega^2 x_1 + acos\Omega t\end{aligned}$$

is a differential equation with $J = \mathrm{I\!R}$*,* $x = (x_1, x_2) \in U = \mathrm{I\!R}^2$*,*

$$\Lambda = \{(a, b, \omega, \Omega) : (a, b) \in \mathrm{I\!R}^2, \omega > 0, \Omega > 0\},$$

and $f : \mathrm{I\!R} \times \mathrm{I\!R}^2 \times \Lambda \to \mathrm{I\!R}^2$ *defined in components by*

$$(t, x_1, x_2, a, b, \omega, \Omega) \mapsto (x_2, b(1-x_1^2)x_2 - \omega^2 x_1 + acos\Omega t).$$

If $\lambda \in \Lambda$ is fixed, then a solution of the differential equation (1.1) is a function $\phi : J_0 \to U$ given by $t \mapsto \phi(t)$, where J_0 is an open subset of J, such that

$$\frac{d\phi}{dt}(t) = f(t, \phi(t), \lambda) \tag{1.2}$$

for all $t \in J_0$.

In this context, the words "trajectory", "phase curve", and "integral curve" are also used to refer to solutions of the differential equation (1.1). However, it is useful to have a term that refers to the image of the solution in $\mathrm{I\!R}^n$. Thus, we define the orbit of the solution ϕ to be the set $\{\phi(t) \in U : t \in J_0\}$.

When a differential equation is used to model the evolution of a state variable for a physical process, a fundamental problem is to determine the future values of the state variable from its initial value. The mathematical model is then given by a pair of equations

$$\dot{x} = f(t, x, \lambda), \qquad x(t_0) = x_0$$

where the second equation is called an initial condition. If the differential equation is defined as equation (1.1) and $(t_0, x_0) \in J \times U$, then the pair of equations is called an initial value problem. Of course, a solution of this initial value problem is just a solution ϕ of the differential equation such that $\phi(t_0) = x_0$.

If we view the differential equation (1.1) as a family of differential equations depending on the parameter vector and perhaps also on the initial condition, then we can consider corresponding families of solutions (when they exist) by listing the variables under consideration as additional arguments. For example, we will write $t \mapsto \phi(t, t_0, x_0, \lambda)$ to specify the dependence of a solution on the initial condition $x(t_0) = x_0$ and on the parameter vector λ.

The fundamental issues of the general theory of differential equations are the existence, uniqueness, extensibility, and continuity with respect to parameters of solutions of initial value problems. Fortunately, all of these issues are resolved by the following foundational results of the subject: Every initial value problem has a unique solution that is smooth with respect to initial conditions and parameters. Moreover, the solution of an initial value problem can be extended in time until it either reaches the domain of definition of the differential equation or blows up to infinity. The next three theorems are the formal statements of the foundational results of the subject of differential equations. They are, of course, used extensively in all that follows.

Theorem 1.1.1 ***(Existence and Uniqueness)*** *If $J \subseteq R$, $U \subseteq \mathbb{R}^n$, and $\Lambda \subseteq \mathbb{R}^k$ are open sets, $f : J \times U \times \Lambda \to \mathbb{R}^n$ is a smooth function, and $(t_0, x_0, \lambda_0) \in J \times U \times \Lambda$, then there exist open subsets $J_0 \subseteq J$, $U_0 \subseteq U$, $\Lambda_0 \subseteq \Lambda$ with $(t_0, x_0, \lambda_0) \in J_0 \times U_0 \times \Lambda_0$ and a function $\phi : J_0 \times J_0 \times U_0 \times \Lambda_0 \to \mathbb{R}^n$ given by $(t, s, x, \lambda) \mapsto \phi(t, s, x, \lambda)$ such that for each point $(t_1, x_1, \lambda_1) \in J_0 \times U_0 \times \Lambda_0$, the function $t \mapsto \phi(t, t_1, x_1, \lambda_1)$ is the unique solution defined on J_0 of the initial value problem given by the differential equation (1.1) and the initial condition $x(t_1) = x_1$.*

Recall that if $k = 1, 2, \ldots, \infty$, a function defined on an open set is called C^k if the function together with all of its partial derivatives up to and including those of order k are continuous on the open set. Similarly, a function is called real analytic if it has a convergent power series representation with a positive radius of convergence at each point of the open set.

Theorem 1.1.2 ***(Continuous Dependence)****. If, for the system (1.1), the hypotheses of Theorem 1.1.1 are satisfied, then the solution* $\phi : J_0 \times J_0 \times U_0 \times \Lambda_0 \to \mathbb{R}^n$ *of the differential equation (1.1) is a smooth function. Moreover, if* f *is* C^k *for some* $k = 1, 2, \ldots, \infty$ *(respectively,* f *is real analytic), then* ϕ *is also* C^k *(respectively, real analytic).*

As a convenient notation, we will write $|x|$ for the usual Euclidean norm of $x \in \mathbb{R}^n$. However, because all norms on Rn are equivalent, the results of this section are valid for an arbitrary norm on $\mathbb{R}^n$.

Theorem 1.1.3 ***(Extensibility)****. If, for the system (1.1), the hypotheses of Theorem 1.1.1 hold, and if the maximal open interval of existence of the solution* $t \mapsto \phi(t)$ *(with the last three of its arguments suppressed) is given by* (α, β) *with* $\infty \leq \alpha < \beta < \infty$*, then* $|\phi(t)|$ *approaches* ∞ *or* $\phi(t)$ *approaches a point on the boundary of* U *as* $t \to \beta$*.*

If there exist some finite T and $\lim_{t \to T} |\phi(t)| = \infty$, we say the solution blows up in finite time.

The existence and uniqueness theorem is so fundamental in science that it is sometimes called the "principle of determinism". The idea is that if we know the initial conditions, then we can predict the future states of the system. The principle of determinism is of course validated by the proof of the existence and uniqueness theorem. However, the interpretation of this principle for physical systems is not as clear as it might seem. The problem is that solutions of differential equations can be very complicated. For example, the future state of the system might depend sensitively on the initial state of the system. Thus, if we do not know the initial state exactly, the final state may be very difficult or impossible to predict.

The variables that we will specify as explicit arguments for the solution ϕ of a differential equation depend on the context, as we have mentioned above. However, very often we will write $t \mapsto \phi(t, x)$ to denote the solution such that $\phi(0, x) = x$. Similarly, when we wish to specify the parameter vector, we will use $t \mapsto \phi(t, x, \lambda)$ to denote the solution such that $\phi(0, x, \lambda) = x$.

Example 1.1.2 *The solution of the differential equation* $\dot{x} = x^2$, $x \in \mathbb{R}$, *is given by the elementary function*

$$\phi(t,x) = \frac{x}{1 - xt}$$

For this example, $J = \mathbb{R}$ *and* $U = \mathbb{R}$. *Note that* $\phi(0,x) = x$. *If* $x > 0$, *then the corresponding solution only exists on the interval* $J_0 = (-\infty, x^{-1})$.
Also, we have that $|\phi(t,x)| \to \infty$ *as* $t \to x^{-1}$. *This illustrates one of the possibilities mentioned in the extensibility theorem, namely, blow up in finite time.*

Lemma 1.1.1 ***(Generalized Gronwall's inequality)*** *Suppose* $\psi(t)$ *satisfies*

$$\psi(t) \le \alpha(t) + \int_0^t \beta(s)\psi(s)ds, \qquad t \in [0,T],$$

with $\alpha(t) \in \mathbb{R}$ *and* $\beta(t) \ge 0$. *Then*

$$\psi(t) \le \alpha(t) + \int_0^t \alpha(s)\beta(s)\exp\left(\int_s^t \beta(r)dr\right)ds, \qquad t \in [0,T],$$

Moreover, if in addition $\alpha(s) \le \alpha(t)$ *for* $s \le t$, *then*

$$\psi(t) \le \alpha(t)\exp\left(\int_s^t \beta(s)ds\right), \qquad t \in [0,T],$$

1.2 Some fixed point theorems

Let X be a real vector space. A norm on X is a map $\|.\| : X \to [0,\infty)$ satisfying the following requirements:

(i) $\|0\| = 0$, $\|x\| > 0$ for $x \in X \backslash \{0\}$.

(ii) $\|\alpha x\| = |\alpha|\|x\|$ for $\alpha \in \mathbb{R}$ and $x \in X$.

(iii) $\|x + y\| \le \|x\| + \|y\|$ for $x, y \in X$ (triangle inequality).

From the triangle inequality we also get the inverse triangle inequality

$$|\|f\| - \|g\|| \leq \|f - g\|.$$

The pair $(X, \|.\|)$ is called a normed vector space. Given a normed vector space X, we say that a sequence of vectors f_n converges to a vector f if $\lim_{n\to\infty} \|f_n - f\| = 0$. We will write $f_n \to f$ or $\lim_{n\to\infty} f_n = f$, as usual, in this case. Moreover, a mapping F: $X \to Y$ between two normed spaces is called continuous if $f_n \to f$ implies $F(f_n) \to F(f)$. In fact, it is not hard to see that the norm, vector addition, and multiplication by scalars are continuous.

In addition to the concept of convergence we also have the concept of a Cauchy sequence and hence the concept of completeness: A normed space is called complete if every Cauchy sequence has a limit. A complete normed space is called a Banach space.

Example 1.2.1 *Clearly $\mathbb{R}^n$ is a Banach space with the usual Euclidean norm*

$$|x| = \sqrt{\sum_{j=1}^{n} |x_j|^2}.$$

Let I be a compact interval and consider the continuous functions $C(I)$ on this interval. It forms a vector space if all operations are defined pointwise. Moreover, $C(I)$ becomes a normed space if we define

$$\|x\| = \sup_{t\in I} |x(t)|. \tag{1.3}$$

In fact, $C(I)$ is a Banach space.

Definition 1.2.1 *A fixed point of a mapping $K : C \subseteq X \to C$ is an element $x \in C$ such that $K(x) = x$. Moreover, K is called a contraction if there is a contraction constant $\theta \in [0, 1)$ such that*

$$\|K(x) - K(y)\| \leq \theta\|x - y\|, \qquad x, y \in C. \tag{1.4}$$

We also recall the notation $K^n(x) = K(K^{n-1}(x))$, $K^0(x) = x$.

Theorem 1.2.1 ***(Contraction principle)****. Let* C *be a (nonempty) closed subset of a Banach space* X *and let* $K : C \to C$ *be a contraction, then* K *has a unique fixed point* $\overline{x} \in C$ *such that*

$$\|K^n(x) - \overline{x}\| \leq \frac{\theta^n}{1-\theta}\|K(x) - x\|, \qquad x \in C. \tag{1.5}$$

1.2.1 The basic existence and uniqueness result

From the previous section, we show existence and uniqueness of solutions for the following initial value problem (IVP)

$$\dot{x} = f(t, x), \qquad x(t_0) = x_0. \tag{1.6}$$

We suppose $f \in C(U, \mathbb{R}^n)$, where U is an open subset of $\mathbb{R}^{n+1}$ and $(t_0, x_0) \in U$.
First of all note that integrating both sides with respect to t shows that (1.6) is equivalent to the following integral equation

$$x(t) = x_0 + \int_{t_0}^{t} f(s, x(s))ds. \tag{1.7}$$

At first sight this does not seem to help much. However, note that $x_0(t) = x_0$ is an approximating solution at least for small t. Plugging $x_0(t)$ into our integral equation we get another approximating solution

$$x_1(t) = x_0 + \int_{t_0}^{t} f(s, x_0(s))ds. \tag{1.8}$$

Iterating this procedure we get a sequence of approximating solutions

$$x_m(t) = K^m(x_0)(t), \qquad K(x)(t) = x_0 + \int_{t_0}^{t} f(s, x(s))ds. \tag{1.9}$$

Now this observation begs us to apply the contraction principle from the previous section to the fixed point equation $x = K(x)$, which is precisely our integral equation (1.7).

We will set $t_0 = 0$ for notational simplicity and consider only the case $t \geq 0$ to avoid excessive numbers of absolute values in the following estimates.
First of all we will need a Banach space. The obvious choice is $X = C([0,T], \mathbb{R}^n)$ for some suitable $T > 0$. Furthermore, we need a closed subset $C \subseteq X$ such that $K : C \to C$. We will try a closed ball of radius δ around the constant function x_0.
Since U is open and $(0, x_0) \in U$ we can choose $V = [0,T] \times \overline{B_\delta(x_0)} \subset U$, where $B_\delta(x_0) = \{x \in \mathbb{R}^n | |x - x_0| < \delta\}$, and abbreviate

$$M = \max_{(t,x)\in V} |f(t,x)|, \tag{1.10}$$

where the maximum exists by continuity of f and compactness of V . Then

$$|K(x)(t) - x_0| \leq \int_0^t |f(s, x(s))| ds \leq tM \tag{1.11}$$

whenever the graph of $x(t)$ lies within V , that is, $\{(t, x(t)) | t \in [0,T]\} \subset V$.
Hence, for $t \leq T_0$, where

$$T_0 = \min\{T, \frac{\delta}{M}\}, \tag{1.12}$$

we have $T_0 M \leq \delta$ and the graph of $K(x)$ restricted to $[0, T_0]$ is again in V .
In the special case $M = 0$ one has to understand this as $\frac{\delta}{M} = \infty$ such that $T_0 = T$. Moreover, note that since $[0, T_0] \subseteq [0,T]$ the same constant M will also bound $|f|$ on $V_0 = [0, T_0] \times \overline{B_\delta(x_0)} \subseteq V$.
So if we choose $X = C([0,T_0], \mathbb{R}^n)$ as our Banach space, with norm $\|x\| = \max_{0 \leq t \leq T_0} |x(t)|$, and $C = \{x \in X | \|x - x_0\| \leq \delta\}$ as our closed subset, then $K : C \to C$ and it remains to show that K is a contraction.
To show this, we need to estimate

$$|K(x)(t) - K(y)(t)| \leq \int_0^t |f(s, x(s)) - f(s, y(s))| ds. \tag{1.13}$$

Clearly, since f is continuous, we know that $|f(s,x(s))-f(s,y(s))|$ is small if $|x(s)-y(s)|$ is. However, this is not good enough to estimate the integral above. For this we need the following stronger condition: Suppose f is locally Lipschitz continuous in the second argument, uniformly with respect to the first argument, that is, for every compact set $V_0 \subset U$ the following number

$$L = \sup_{(t,x)\neq(t,y)\in V_0} \frac{|f(t,x)-f(t,y)|}{|x-y|} \tag{1.14}$$

(which depends on V_0) is finite. Then,

$$\begin{aligned} \int_0^t |f(s,x(s))-f(s,y(s))|ds &\leq L\int_0^t |x(s)-y(s)|ds \\ &\leq Lt\sup_{0\leq s\leq t}|x(s)-y(s)| \end{aligned} \tag{1.15}$$

provided the graphs of both $x(t)$ and $y(t)$ lie in V_0. In other words,

$$\|K(x)-K(y)\| \leq LT_0\|x-y\|, \qquad x,y\in C. \tag{1.16}$$

Moreover, choosing $T_0 < L^{-1}$ we see that K is a contraction and existence of a unique solution follows from the contraction principle.

Theorem 1.2.2 *(Picard-Lindelöf). Suppose $f \in C(U, \mathbb{R}^n)$, where U is an open subset of $\mathbb{R}^{n+1}$, and $(t_0, x_0) \in U$. If f is locally Lipschitz continuous in the second argument, uniformly with respect to the first, then there exists a unique local solution $\overline{x}(t) \in C^1(I)$ of the IVP (1.6), where I is some interval around t_0.*
More specific, if $V = [t_0, t_0+T] \times \overline{B_\delta(x_0)} \times U$ and M denotes the maximum of $|f|$ on V. Then the solution exists at least for $t \in [t_0, t_0+T_0]$ and remains in $\overline{B_\delta(x_0)}$, where $T_0 = \min\{T, \frac{\delta}{M}\}$. The analogous result holds for the interval $[t_0-T, t_0]$.

1.3 Stability and linearization

The concept of Lyapunov stability is meant to capture the intuitive notion of stability. An orbit is stable if solutions that start nearby stay nearby. To give the formal definition, let us consider the autonomous differential equation

$$\dot{x} = f(x) \tag{1.17}$$

defined on an open set $U \subset \mathbb{R}^n$ and its flow ϕ_t.

Definition 1.3.1 *A rest point x_0 of the differential equation (1.17) is stable (in the sense of Lyapunov) if for each $\varepsilon > 0$, there is a number $\delta > 0$ such that $|\phi_t(x) - x_0| < \varepsilon$ for all $t \geq 0$ whenever $|x - x_0| < \delta$.*

There is no reason to restrict the definition of stability to rest points. It can also refer to arbitrary solutions of the autonomous differential equation.

Definition 1.3.2 *Suppose that x_0 is in the domain of definition of the differential equation (1.17). The solution $t \mapsto \phi_t(x_0)$ of this differential equation is stable (in the sense of Lyapunov) if for each $\varepsilon > 0$, there is a $\delta > 0$ such that*

$$|\phi_t(x) - \phi_t(x_0)| < \varepsilon \qquad \text{for all } t \geq 0 \qquad \text{whenever} \qquad |x - x_0| < \delta.$$

A solution that is not stable is called unstable.

Definition 1.3.3 *A solution $t \to \phi_t(x_0)$ of the differential equation (1.17) is asymptotically stable if it is stable and there is a constant $a > 0$ such that*

$$\lim_{t \to \infty} |\phi_t(x) - \phi_t(x_0)| = 0 \qquad \text{whenever} \qquad |x - x_0| < a.$$

Let us note that the problem of the location of rest points for the differential equation $\dot{x} = f(x)$ is exactly the problem of finding the roots of the equation $f(x) = 0$.

1.3.1 Linearization method

To describe the linearization method for rest points, let us consider (homogeneous) linear systems of differential equations; that is, systems of the form

$$\dot{x} = Ax$$

where $x \in \mathbb{R}^n$ and A is a linear transformation of $\mathbb{R}^n$. If the matrix A does not depend on t, so that the linear system is autonomous. then there is an effective method that can be used to determine the stability of its rest point at $x = 0$. In fact, if all of the eigenvalues of A have negative real parts, then $x = 0$ is an asymptotically stable rest point for the linear system.

If x_0 is a rest point for the nonlinear system

$$\dot{x} = f(x),$$

then there is a natural way to produce a linear system that approximates the nonlinear system near x_0. Simply replace the function f in the differential equation with the linear function $x \mapsto Df(x_0)(x - x_0)$ given by the first nonzero term of the Taylor series of f at x_0. The linear differential equation

$$\dot{x} = Df(x_0)(x - x_0) \tag{1.18}$$

is called the linearized system associated with $\dot{x} = f(x)$ at x_0. The "principle of linearized stability" states that if the linearization of a differential equation at a steady state has a corresponding stable steady state, then the original steady state is stable. This principle is not a theorem, but it is the motivation for much of the theory of stability.

Let us note that by the change of variables $u = x - x_0$, the system (1.18) is transformed to the equivalent linear differential equation $\dot{u} = f(u + x_0)$ where the rest point corresponding to x_0 is at the origin. If we define $g(u) := f(u + x_0)$, then we have

$$\dot{u} = g(u) \quad \text{and } g(0) = 0.$$

Thus, it should be clear that there is no loss of generality if we assume that our rest point is at the origin. This fact is often a useful simplification. Indeed, if f is smooth at $x = 0$ and $f(0) = 0$, then

$$f(x) = f(0) + Df(0)x + R(x) = Df(0)x + R(x)$$

where $Df(0) : \mathbb{R}^n \to \mathbb{R}^n$ is the linear transformation given by the derivative of f at $x = 0$ and, for the remainder R, there is a constant $k > 0$ and an open neighborhood U of the origin such that

$$|R(x)| \leq k|x|^2$$

whenever $x \in U$. Because of this estimate for the size of the remainder and the fact that the stability of a rest point is a local property (that is, a property determined by the values of the restriction of the function f to an arbitrary open subset of the rest point), it is reasonable to expect that the stability of the rest point at the origin of the linear system $\dot{x} = Df(0)x$ will be the same as the stability of the original rest point. This expectation is not always realized. However, we do have the following fundamental stability theorem.

Theorem 1.3.1 *If x_0 is a rest point for the differential equation $\dot{x} = f(x)$ and if all eigenvalues of the linear transformation $Df(x_0)$ have negative real parts, then x_0 is asymptotically stable.*

It turns out that if x_0 is a rest point and $Df(x_0)$ has at least one eigenvalue with positive real part, then x_0 is not stable. If some eigenvalues of $Df(x_0)$ lie on the imaginary axis, then the stability of the rest point may be very difficult to determine. Also, we can expect qualitative changes to occur in the phase portrait of a system near such a rest point as the parameters of the system are varied.

1.4 Stability and the direct method of Lyapunov

Let us consider a rest point x_0 for the autonomous differential equation

$$\dot{x} = f(x), \qquad x \in \mathbb{R}^n. \tag{1.19}$$

Definition 1.4.1 *A continuous function $V : U \to R$, where $U \subseteq \mathbb{R}^n$ is an open set with $x_0 \in U$, is called a Lyapunov function for the differential equation (1.19) at x_0 provided that*

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

(ii) $V(x) > 0$ *for* $x \in U \backslash \{x_0\}$,

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

If, in addition

(iv) $\dot{V}(x) < 0$ *for* $x \in U \backslash \{x_0\}$,

then V is called a strict Lyapunov function.

Theorem 1.4.1 ***(Lyapunov's Stability Theorem)*** *If x_0 is a rest point for the differential equation (1.19) 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.*

1.5 C_0-semigroups and Cauchy problems

Let A be a closed operator on a Banach space X. We consider the abstract Cauchy problem

$$\begin{cases} u'(t) = Au(t) \qquad (t \geq 0), \\ u(0) = x, \end{cases} \tag{1.20}$$

where the independent variable t represents time, $u()$ is a function with values in a Banach space X, $A : D(A) \subset X \to X$ a linear operator, and $x \in X$ the initial value.

Definition 1.5.1 *A function $u : \mathbb{R}_+ \to X$ is called a classical solution of (1.20) if u is continuously differentiable with respect to X, $u(t) \in D(A)$ for all $t \geq 0$, and (1.20) holds.*

Definition 1.5.2 *A C_0-semigroup is a strongly continuous function $T : \mathbb{R}_+ \to \mathcal{L}(X)$ such that*

$$\begin{aligned} &T(t+s) = T(t)T(s) \qquad (t, s \geq 0), \\ &T(0) = I \quad \textit{and} \\ &\forall x_0 \in X, \|T(t)x_0 - x_0\| \to 0 \ \textit{as}\ t \searrow 0. \end{aligned}$$

Lemma 1.5.1 *For the generator $(A, D(A))$ of a strongly continuous semigroup $(T(t))_{t\geq 0}$, the following properties hold.*

(i) $A : D(A) \subseteq X \to X$ *is a linear operator.*

(ii) If $x \in D(A)$, then $T(t)x \in D(A)$ and

$$\frac{d}{dt}T(t)x = T(t)Ax = AT(t)x \qquad \textit{for all}\ t \geq 0. \tag{1.21}$$

(iii) For every $t \geq 0$ and $x \in X$, one has

$$\int_0^t T(s)xds \in D(A).$$

(iv) For every $t \geq 0$, one has

$$\begin{aligned} T(t)x - x &= A\int_0^t T(s)xds \qquad \textit{for}\ x \in X \\ &= \int_0^t T(s)Axds \qquad \textit{for}\ x \in D(A). \end{aligned} \tag{1.22}$$

If the operator A is the generator of a strongly continuous semigroup, it follows from Lemma 1.5.1 (ii) that the semigroup yields solutions of the associated abstract Cauchy problem.

Proposition 1.5.1 *Let $(A, D(A))$ be the generator of the strongly continuous semigroup $(T(t))_{t\geq 0}$. Then, for every $x \in D(A)$, the function*

$$u : t \mapsto u(t) := T(t)x$$

is the unique classical solution of (1.20).

The important point is that classical solutions exist if (and, by the definition of $D(A)$, only if) the initial value x belongs to $D(A)$. However, modifying slightly the concept of "solution" and requiring differentiability only for $t > 0$, we obtain such solutions for each $x \in X$ as soon as the semigroup $(T(t))_{t\geq 0}$ is immediately differentiable. This already suggests that different concepts of "solutions" might be useful. The most important one renounces differentiability and substitutes the differential equation by an integral equation.

Definition 1.5.3 *A continuous function $u : R_+ \to X$ is called a mild solution of (1.20) if $\int_0^t u(s)ds \in D(A)$ for all $t \geq 0$ and*

$$u(t) = A \int_0^t u(s)ds + x.$$

It follows from our previous results (use Lemma 1.5.1 (iv)) that for A being the generator of a strongly continuous semigroup, mild solutions exist for every initial value $x \in X$ and are again given by the semigroup.

Proposition 1.5.2 *Let $(A, D(A))$ be the generator of the strongly continuous semigroup $(T(t))_{t\geq 0}$. Then, for every $x \in X$, the orbit map*

$$u : t \mapsto u(t) := T(t)x$$

is the unique mild solution of the associated abstract Cauchy problem (1.20).

1.6 Evolution systems

Let X be a Banac space. For every t, $0 \leq t \leq T$, let $A : D(A(t)) \subset X \to X$ be a linear operator in X and let $f(t)$ be an X valued function. In this section we will study the initial value problem

$$\begin{cases} \dfrac{du(t)}{dt} = A(t)u(t) + f(t), & \text{pour} s < t \leq T, \\ u(s) = x \end{cases} \tag{1.23}$$

the initial value problem (1.23) is called an evolution problem. An X valued function $u : [s, T] \to X$ is a classical solution of (1.23), if u is continuous on $[s, T]$, $u(t) \in D(A(t))$ for $s < t \leq T$, u is continuously differentiable on $s < t \leq T$ and satisfies (1.23).
to give the formula of the solution of (1.23) we concentrate at the beginning on the homogeneous initial value problem

$$\begin{cases} \dfrac{du(t)}{dt} = A(t)u(t), & 0 < s < t \leq T, \\ u(s) = x \end{cases} \tag{1.24}$$

In order to obtain some feeling for the behavior of the solution of (1.24), we consider first the simple case where for $0 < t \leq T$, $A(t)$ is a bounded linear operator on X and $t \to A(t)$ is continuous in the uniform operator topology. For this case we have

Theorem 1.6.1 *Let X be a Banach space and for every t such that $0 < t \leq T$ let $A(t)$ be a bounded linear operator on X, if the function $t \to A(t)$ is continuous in the uniform operator topology, then for every $x \in X$ the initial value problem (1.24) has a unique classical solution u.*

Proof: The proof of this theorem is standard using Picard's iterations method. Let $\alpha = \max_{0 \leq t \leq T} \|A(t)\|$ and define a mapping S from $C([s, T] : X)$ into itself by

$$(Su)(t) = x + \int_s^t A(\tau) d\tau. \tag{1.25}$$

Denoting $\|u\|_\infty = \max_{s<t\leq T} \|u\|$, it is easy to check that

$$\|Su(t) - Sv(t)\| \leq \alpha(t-s)\|u-v\|_\infty, \qquad s \leq t < T. \tag{1.26}$$

Using (1.25) and (1.26) it follows by induction that

$$\|S^n u(t) - S^n v(t)\| \leq \frac{\alpha^n (t-s)^n}{n!}\|u-v\|_\infty, \qquad s \leq t < T$$

and therefore

$$\|S^n u - S^n v\|_\infty \leq \frac{\alpha^n (t-s)^n}{n!}\|u-v\|_\infty.$$

For n large enough, $\alpha^n(t-s)^n/n! < 1$ and by a well known generalization of the Banach contraction principle, S has a unique fixed point u in $C([s,T];X)$ for which

$$u(t) = x + \int_s^t A(\tau)d\tau \tag{1.27}$$

Since u is continuous, the right hand side of (1.27) is differentiable. Thus u is differentiable and its derivative, obtained by differentiating (1.27), satisfies $u'(t) = A(t)u(t)$. So, u is a solution of the initial value problem (1.24). Since every solution of (1.24) is also a solution of (1.27); the solution of (1.24) is unique. □ We define the "solution operator" of the initial value problem (1.24) by

$$U(t,s)x = u(t) \qquad \text{for } 0 \leq s \leq t \leq T \tag{1.28}$$

Where u is the solution of (1.24). $U(t,s)$ is a two parameter family of operators. From the uniqueness of the solution of the initial value problem (1.24) it follows readily that if $A(t) = A$ is independent of t then $U(t,s) = U(t-s)$ and the two parameter family of operator reduces to the one parameter family $U(t), t \geq 0$, which is of course the semigroup generated by A. The main properties of $U(t,s)$, in our special case where $A(t)$ is a bounded linear operator on X for $0 \leq t \leq T$ and $t \to A(t)$ is continuous in the uniform operator topology, are given in the next theorem.

Theorem 1.6.2 *For every* $0 \leq s \leq t \leq T$, $U(t,s)$ *is a bounded linear operator and*

(i) $\|U(t,s)\| \leq exp(\int_s^t \|A(\tau)\| d\tau)$.

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

(iii) $(t,s) \to U(t,s)$ *is continuous in the uniform operator topology for* $0 \leq s \leq t \leq T$.

(iv) $\partial U(t,s)/\partial t = A(t)U(t,s)$ *for* $0 \leq s \leq t \leq T$

(v) $\partial U(t,s)/\partial s = -U(t,s)A(s)$ *for* $0 \leq s \leq t \leq T$.

Proof: Since the problem (1.24) is linear it is obvious that $U(t,s)$ is a linear operator defined on all of X. From (1.27) it follows that

$$\|u(t)\| \leq \|x\| + \int_s^t \|A(\tau)\| \|u(\tau)\| d\tau$$

which by Gronwall's inequality implies

$$\|U(t,s)x\| = \|u(t)\| \leq \|x\| exp\left(\int_s^t \|A(\tau)\| d\tau\right) \tag{1.29}$$

and so $U(t,s)$ is bounded and satisfies (i).
From (1.28) it follows readily that $U(t,t) = I$ and from the uniqueness of the solution of (1.24) the relation $U(t,s) = U(t,r)U(r,s)$ for $0 \leq s \leq t \leq T$ follows. Combining (i) and (ii), (iii) follows. Finally, from (1.27) and (iii) it follows that $U(t,s)$ is the unique solution of the integral equation

$$U(t,s) = I + \int_s^t A(\tau)U(\tau,s) d\tau \tag{1.30}$$

in $B(X)$ (the space of all bounded linear operators on X). Differentiating (1.30) with respect to t yields (iv). Differentiating (1.30) with respect to s we find

$$\frac{\partial}{\partial s}U(t,s) = -A(s) + \int_s^t A(\tau)\frac{\partial}{\partial s}U(\tau,s)d\tau.$$

From the uniqueness of the solution of (1.30) it follows that

$$\frac{\partial}{\partial s}U(t,s) = -U(t,s)A(s).$$

□

The two parameter family of operators $U(t,s)$ replaces in the non-autonomous case, i.e., in the case where $A(t)$ depends on t, the one parameter semigroup $U(t)$ of the autonomous case. This motivates the following definition.

Definition 1.6.1 *A two parameter family of bounded linear operators $U(t,s)$, $0 \leq s \leq t \leq T$ on X is called an evolution system if the following two conditions are satisfied:*

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

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

Note that by analogy to the autonomous case, since we are not really interested in the uniform continuity of solutions, we have replaced the continuity of $U(t,s)$ in the uniform operator topology by strong continuity.
if there is an evolution system $U(t,s)$ associated with the initial value problem (1.23) where $f \in L^1(0,T:X)$ such that for every $v \in D(A(s))$, $U(t,s)v \in D(A(t))$ and $U(t,s)v$ is differentiable both in t and s satisfying

$$\frac{\partial}{\partial t}U(t,s)v = A(t)U(t,s)v \tag{1.31}$$

and

$$\frac{\partial}{\partial s}U(t,s)v = -U(t,s)A(s)v, \tag{1.32}$$

then every classical solution u of (1.23) with $x \in D(A(s))$ is given by

$$u(t) = U(t,s)x + \int_s^t U(t,r)f(r)fr. \tag{1.33}$$

Indeed, in this case the function $r \to U(t,r)u(r)$ is differentiable on $[s,T]$ and

$$\begin{aligned} \frac{\partial}{\partial r}U(t,r)u(r) &= -U(t,r)A(r)u(r) + U(t,r)A(r)u(r) + U(t,r)f(r) \\ &= U(t,r)f(r). \end{aligned} \tag{1.34}$$

Integrating (1.34) from s to t yields (1.33). Thus, in this case, the inhomogeneous initial value problem (1.23) has at most one classical solution u which, if it exists, is given by (1.33). However, for any evolution system $U(t,s)$ and $f \in L^1(0,T:X)$ the right-hand side of (1.33) is a well defined continuous function satisfying $u(s) = x$.

Chapter 2

MATHEMATICAL MODEL FOR THE DYNAMICS OF PRIONS

2.1 Introduction

In this chapter we analyze a system of ordinary differential equation, which is applicable to a model of prion proliferation dynamics. The model is a special case of a more general model. The variables and parameters of the model:

- $v(t)$ is the number of PrP^C monomers at time t,

- $u(t, x)$ is the density of PrP^{SC} polymers of length x at time t,

- x_0 is the lower bound for polymer length, that is, polymers have length x with $x_0 < x < \infty$,

- λ is the source rate for naturally produced PrP^C monomers,
- γ is the metabolic degradation rate for PrP^C,

- τ is a rate associated with lengthening of PrP^{SC} polymers by attaching to and converting PrP^{C} monomers,

- $\beta(x)$ is length-dependent rate of polymer breakage,

- $\kappa(x,y)$ is the probability, when a polymer of length y breaks, that one of the two resulting polymers has length x,

- $\mu(x)$ is the length-dependent metabolic degradation rate of PrP^{SC} polymers,

we obtain the following model equations:

$$v'(t) = \lambda - \gamma v(t) - \tau v(t)\int_{x_0}^{\infty} u(t,x)dx + 2\int_0^{x_0} x\int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(t,y)dydx,$$

$$\frac{\partial}{\partial t}u(t,x) + \tau v(t)\frac{\partial}{\partial x}u(t,x) + (\mu(x)+\beta(x))u(t,x) = 2\int_x^{\infty} \beta(y)\kappa(x,y)u(t,y)dy, \tag{2.1}$$

$$u(t,x_0) = 0, \quad v(0) = v^0 \geq 0, \quad u(0,x) = u^0(x),$$

where $t \geq 0$ and $1 \leq x_0 \leq x < \infty$.

The factor 2 in (2.1) arises from the symmetry of a fibril splitting into 2 pieces, one of length x and its complement of length $y-x$. Observe that the kernel $\kappa(y,x)$ should satisfy the following properties:

$$\kappa(y,x) \geq 0, \quad \kappa(y,x) = \kappa(x-y,x), \quad \int_0^x \kappa(y,x)dy = 1,$$

for all $x \geq x_0, y \geq 0$,

$$\begin{aligned} \kappa(y,x) &= 1/x, \qquad \text{if} \quad x > x_0 \quad \text{and} \quad 0 < y < x. \\ \kappa(y,x) &= 0, \qquad \text{elsewhere.} \end{aligned}$$

$\beta(x) = \beta x$ is linear, and $\mu(x) \equiv \mu$ is constant.

Under the assumptions above, the model can be reduced to a system of three ordinary differential equations. In fact, introducing the new functions

$$U(t) = \int_{x_0}^{\infty} u(t,y)dy \quad \text{and} \qquad P(t) = \int_{x_0}^{\infty} yu(t,x)dy,$$

representing the total number of polymers, and the total number of monomers in polymers at time t, and integrating the equation for $u(t,x)$ over $[x_0, +\infty[$, assuming $u(t,x_0) = 0$, and $\lim_{x\to\infty} u(t,x) = 0$, we obtain

$$\begin{aligned} \frac{d}{dt}U(t) &= -\tau V(t) u(t,x)|_{x_0}^{\infty} - \mu U(t) - \beta P(t) + 2\beta \int_{x_0}^{\infty} \int_{x}^{\infty} u(t,y)dydx \\ &= -\mu U(t) - \beta P(t) + 2\beta \int_{x_0}^{\infty} u(t,y)(y - x_0)dy \\ &= -\mu U(t) - \beta P(t) + 2\beta P(t) - 2\beta x_0 U(t). \end{aligned}$$

Multiplying the equation for $u(t,x)$ by x, assuming $\lim_{x\to\infty} xu(t,x) = 0$, and integrating yields

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

We thus obtain the following system of three ordinary differential equations:

$$\begin{cases} \dot{U} = -\mu U + \beta P - 2\beta x_0 U \\ \\ \dot{V} = \lambda - \gamma V - \tau V U + \beta x_0^2 U \\ \\ \dot{P} = \tau V U - \mu P - \beta x_0^2 U \end{cases} \tag{2.2}$$

with initial conditions

$$U(0) = u_0 \geq 0, \quad V(0) = V_0 \geq 0, \quad P(0) = P_0 \geq x_0 U_0.$$

Once the solutions of (2.2) are known, one has only to solve the linear partial integro-differential equation in (2.1) to obtain the density with respect to fibril length $u(t,x)$. The full PDE-system (2.1), which contains also the dynamics of the fibril density $u(t,x)$, is analyzed in [13] and [54]. Our goal is to analyze the global behavior of the solution of (2.2) in the cone $U \geq 0$, $V \geq 0$, $P \geq x_0 U$. We prove the following result concerning the qualitative behavior of the system (2.2)

Theorem 2.1.1 *Suppose* $x_0, \beta, \gamma, \lambda, \mu, \tau > 0$. *The system (2.2) induce a global semi-flow on the se* $K = \{(U,V,P) \in \mathbb{R}^3 : U, V, P - x_0 U \geq 0\}$. *There is precisely one disease-free equilibrium* $(0, \lambda/\gamma, 0)$ *which is globally asymptotically stable if and only if* $\mu + x_0\beta \geq \sqrt{\lambda\beta\tau/\gamma}$. *On the other hand, if* $\mu + x_0\beta < \sqrt{\lambda\beta\tau/\gamma}$, *then there is a unique disease equilibrium*

$$\left(\frac{(\mu + \beta x_0)^2}{\beta\tau}, \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\tau\mu(\mu + \beta x_0)}, \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\tau\mu\beta} \right),$$

which is globally asymptotically stable in $K \backslash \{0\} \times \mathbb{R}_+ \times \{0\}$.

This result shows that the solutions of (2.2) exhibit the typical behavior of epidemic models. Let $R_0 = \lambda\beta\tau/\gamma(\mu+\beta x_0)^2$, which is the number of secondary infections produced on average by one infectious prion. If $R_0 \leq 1$, then the disease dies out and the disease-free equilibrium is globally asymtotically stable. If $R_0 > 1$, a unique nontrivial steady state, the disease equilibrium, bifurcates from the trivial one and subsumes the global asymptotic stability. Thus, for $R_0 > 1$, the disease persists and exhibits strong stability properties.

2.2 A general three compartment model of infection dynamics

As general references for the theoretical results employed below we refer to the monographs of Amann [2] or Chicone [7]. We first transform the model of prion proliferation (2.2) to the following more general system:

$$\begin{cases} \dot{x} = z - \xi x, \\ \\ \dot{y} = \sigma - \rho y - xy + \delta x, \\ \\ \dot{z} = xy - z. \end{cases} \tag{2.3}$$

with initial conditions

$$x(0) = x_0 \geq 0, \quad y(0) = y_0 \geq 0, \quad z(0) = z_0 \geq 0.$$

We prove the following theorem for (2.3).

Theorem 2.2.1 *Suppose $\xi > 0$, $\sigma > 0$, $\rho > 0$ and $\delta \in [0, \xi)$. The system (2.3) induce a global semiflow on the set $\mathbb{R}^3_+$. there exists precisely one (disease-free) equilibrium $(0, \sigma/\rho, 0)$ globally asymptotically stable, if and only if $\sigma \leq \xi\rho$. On the other hand, if $\sigma > \xi\rho$ there is one additional (disease) equilibrium $(\sigma - \xi\rho/\xi - \delta, \xi, \xi\sigma - \xi\rho/\xi - \delta)$ which is globally asymptotically stable in $\mathbb{R}^3_+ \backslash \{0\} \times \mathbb{R}_+ \times \{0\}$*

Theorem 2.1.1 is proved by Theorem 2.2.1, with (2.2) converted to (2.3) as follows: First to work in the standard positive cone $\mathbb{R}^3_+$, we replace the variable P by $W = P - x_0 U$ (the feasible values of P and U satisfy $P \geq x_0 U$, since the minimum value for P is $x_0 U$). This gives the system

$$x_0 \dot{U} = \beta x_0 W - (-\mu + 2\beta x_0) U,$$

$$\dot{V} = \lambda - \gamma V - \frac{\tau}{x_0} x_0 V U + \beta x_0^2 U$$

$$\dot{P} = \frac{\tau}{x_0} x_0 V U - (\mu + \beta x_0) W$$

with initial values $U(0) = u_0 \geq 0$, $V(0) = V_0 \geq 0$, $W(0) = W_0 = P - x_0 U_0 \geq 0$.
Next, perform a scaling of the variables by setting

$$x_0 U(t) = a x(\alpha t), \quad V(t) = b y(\alpha t), \quad W(t) = c z(\alpha t).$$

with $\alpha = \mu + \beta x_0$, $a = (\mu + \beta x_0) x_0 / \tau$, $b = c = (\mu + \beta x_0)^2 / \beta\tau$, we obtain the system (2.3) with $\xi = 1$, $\sigma = \lambda\beta\tau/(\mu + \beta x_0)^3 > 0$, $\rho = \gamma/(\mu + \beta x_0) > 0$, $\delta = (\beta x_0/(\mu + \beta x_0))^2 \in (0, 1)$.
The model (2.3) also admits an interpretation for SEIS epidemics. Consider the populations of susceptibles $S(t)$ (individuals capable of acquiring the disease), exposed $E(t)$ (infected individuals who are not yet contagious), and infectious $I(t)$ (infected individuals who are capable of transmitting the disease to susceptibles). We assume a constant influx of susceptibles $\lambda > 0$ and natural death rate $\gamma > 0$ of susceptibles. Susceptibles enter the exposed class at a rate proportional to the product of the susceptible and infectious populations with rate constant τ . Exposed individuals enter the infectious class with rate α or are otherwise removed with rate β. Infectious individuals return to the susceptible class with rate β or are otherwise removed with rate ν. Thus, infectious individuals either die, recover with permanent immunity, or recover with no immunity. The equations of

the model are

$$\begin{cases} \dot{S} = \lambda - \gamma S - \tau IS + \beta I \\ \\ \dot{E} = \tau IS - (\alpha + \mu)E, \\ \\ \dot{I} = \alpha E - (\beta + \nu)I. \end{cases} \tag{2.4}$$

Theorem 2.2.2 *Suppose $\lambda, \gamma, \tau, \beta, \alpha, \mu, \nu > 0$. The system (2.4) induces a global semi-flow in R^3_+. Let $R_0 = \frac{\alpha\lambda\tau}{\gamma(\alpha+\mu)(\beta+\nu)}$. There is precisely one disease-free equilibrium $\overline{S} = \lambda/\gamma; \overline{E} = 0; \overline{I} = 0$, which is globally asymptotically stable if and only if $R_0 \leq 1$.*
On the other hand, if $R_0 > 1$, then there is a unique disease equilibrium

$$\overline{S} = \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\mu\tau(\mu + 2\beta x_0)^2} \quad \overline{E} = \frac{(\mu + \beta x_0)^2}{\beta\tau} \quad \overline{I} = \frac{\lambda\beta\tau - \gamma(\mu + \beta x_0)^2}{\beta\mu\tau},$$

which is globally asymptotically stable in $R^3_+ \backslash R_+ \times \{0\} \times \{0\}$.

The conversion of (2.4) to (2.3) is accomplished as follows: Set $x(t) = \frac{\tau}{\alpha+\mu} I(\frac{t}{\alpha+\mu})$, $y(t) = \frac{\alpha\tau}{(\alpha+\mu)^2} S(\frac{t}{\alpha+\mu})$, $z(t) = \frac{\alpha\tau}{(\alpha+\mu)^2} E(\frac{t}{\alpha+\mu})$, $\xi = \frac{\beta+\nu}{\alpha+\mu}$, $\sigma = \frac{\alpha\tau\lambda}{(\alpha+\mu)^3}$, $\rho = \frac{\gamma}{\alpha+\mu}$, $\delta = \frac{\alpha\beta}{(\alpha+\mu)^2}$. Note that $\delta < \xi$. For the SEIS model (2.4) $R_0 = \frac{\alpha\lambda\tau}{\gamma(\alpha+\mu)(\beta+\nu)} = \frac{\sigma}{\xi\rho}$ is the number of secondary infections produced by a single infectious individual.

SEIS models have been studied extensively, and many results are known ([4], [5], [8], [14], [15], [18], [23], [24], [25], [27], [29], [30], [35], [36],[37] , [38], [40], [52], [56],[59]). In [36] the global stability of the disease equilibrium was established for a SEIRS model with constant total population size, which reduces to a SEIS model similar to (2.4) as the parameter for transition from I to R tends to infinity. In [14] the global stability of the disease equilibrium was established for a model similar to (2.4), but with more restrictive loss rates.

The model (2.4) can also be interpretated in terms of viral-host cell interactions (Bonhoeffer et al. [3] and May and Nowak [41]). Consider the populations of virus $V(t)$, uninfected host cells $T(t)$, and infected host cells $T^*(t)$ in an infected host at time t.

Virus is produced at a rate proportional to the population of infected cells with rate constant α and loss rate ν. There is a constant source λ and normal loss rate γ of uninfected cells, an additional loss of uninfected cells (and gain of infected cells) proportional to the product of infected cells and virus with rate constant τ , and virus-stimulated production of uninfected cells at a rate β. Infected cells have loss rate μ. The equations of this model are

$$\begin{aligned} \dot{V} &= \alpha T^* - \nu V, \\ \dot{T} &= \lambda - \gamma T - \tau V T + \beta V, \\ \dot{T}^* &= \tau V T - \mu T^* \end{aligned} \tag{2.5}$$

Theorem 2.2.3 *Suppose* $\alpha, \nu, \lambda, \tau, \mu > 0$ *and* $\alpha\beta < \mu\nu$. *The system (2.5) induces a global semifow in* R^3_+. *Let* $R_0 = \frac{\alpha\lambda\tau}{\gamma\mu\nu}$. *There is precisely one disease-free equilibrium* $\overline{V} = 0; \overline{T} = \lambda/\gamma; \overline{T}^* = 0$, *which is globally asymptotically stable if and only if* $R_0 \leq 1$. *On the other hand, if* $R_0 > 1$, *then there is a unique disease equilibrium*

$$\overline{V} = \frac{\alpha\lambda\tau - \gamma\mu\nu}{\tau(\mu\nu - \alpha\beta)} \quad \overline{T} = \frac{\mu\nu}{\tau} \quad \overline{T} = \frac{\nu(\alpha\lambda\tau - \gamma\mu\nu)}{\tau\alpha(\mu\nu - \alpha\beta)}.$$

which is globally asymptotically stable in $R^3_+ \backslash [\{0\} \times \mathrm{I\!R}_+ \times \{0\}]$.

The conversion of (2.5) to (2.3) is accomplished as follows: Set $x(t) = \frac{\tau}{\mu} V(\frac{t}{\mu})$, $y(t) = \frac{\alpha\tau}{\mu^2} T(\frac{t}{\mu})$, $z(t) = \frac{\alpha\tau}{\mu^2} T^*(\frac{t}{\mu})$, $\xi = \frac{\nu}{\mu}$, $\sigma = \frac{\alpha\tau\lambda}{\mu^3}$, $\rho = \frac{\gamma}{\mu}$, $\delta = \frac{\alpha\beta}{\mu^2}$. The condition $\delta < \xi$ requires $\alpha\beta < \mu\nu$. For the virus-host cell dynamics model (2.5) $R_0 = \frac{\alpha\lambda\tau}{\gamma\mu\nu} = \frac{\sigma}{\xi\rho}$ is the number of secondary host cell infections from a single infected host cell. In the case that $\beta = 0$ the global asymptotics of system (2.5) have been analyzed by Korobeinikov [27], [28], by transforming (2.5) to an equivalent SEIR model with constant host population size. The system (2.5) (with$\beta = 0$) has been used extensively in modeling the within-host dynamics of HIV infection (Perelson et al. [44], Perelson and Nelson [45], Gilchrist et al. [16]).

2.3 Proof of the theorems

2.3.1 Global well-posedness

Since the right hand sides of (2.3) are polymers, this system generates a local flow in $\mathbb{R}^3$. Recall that an ode-system $\dot{u} = f(u)$ on $\mathbb{R}^n$ is called quasi-positive if

$$u \geq 0, \qquad u_k = 0 \Rightarrow f_k(u) \geq 0,$$

is valid for all $k = 1, 2, ..., n$.

System (2.3) obviously is quasi-positive, hence solutions with nonnegative initial data $(x_0, y_0, z_0) \in \mathbb{R}^3_+$ stay in the standard cone $\mathbb{R}^3_+$ for all $t > 0$. From the three equations we get

$$\phi = \frac{\xi + \delta}{2\xi} x + y + z$$

and

$$\dot{\phi} = \sigma - \rho y - \frac{\xi - \delta}{2} x - \frac{\xi - \delta}{2\xi} z \leq \sigma - \epsilon\phi,$$

where $\epsilon = \min \left\{ \rho, \frac{\xi - \delta}{2}, \frac{\xi - \delta}{2\xi} \right\}$. Hence we obtain the bound

$$0 \leq \phi(t) \leq \frac{\sigma}{\epsilon} + \phi(0) e^{-\epsilon t},$$

whenever $(x_0, y_0, z_0) \in \mathbb{R}^3_+$ and $t \geq 0$. This implies boundedness of the solutions, hence global existence for all $t \geq 0$, which shows that the system (2.3) induce global semiflow in $\mathbb{R}^3_+$.

2.3.2 Global asymptotic stability of the trivial equilibrium

Suppose $\sigma \leq \xi\rho$, by means of a Lyapunov function we show that in this case the trivial equilibrium is globally asymptotically stable in $\mathbb{R}^3_+$. For this purpose we set:

$$\Phi(x, y, z) = \frac{1}{2}(y - \overline{y})^2 + (2\xi - \delta - \overline{y})(x + z).$$

Then for $\sigma = \rho\overline{y}$,

$$\begin{aligned} \dot{\Phi} &= \frac{\partial \Phi}{\partial x}\frac{dx}{dt} + \frac{\partial \Phi}{\partial y}\frac{dy}{dt} + \frac{\partial \Phi}{\partial z}\frac{dz}{dt} \\ &= -\rho(y - \overline{y})^2 + x(-(y - \xi)^2 - (\xi - \frac{\sigma}{\rho})(\xi - \delta)) \leq 0 \end{aligned}$$

Thus Φ is a Lyapunov function for (2.3) in $\mathbb{R}^3_+$ if $\sigma \leq \xi\rho$. Further, in this case we have $\dot{\Phi} = 0$ only if $y = \overline{y} = \sigma/\rho$ and $x = 0$. Now the only invariant subset of the set $y = \overline{y}$ is the disease free steady state, hence it is globally asymptotically stable in $\mathbb{R}^3_+$.

2.3.3 Steady states

Observe that the set $\{(x, y, z) \in \mathbb{R}^3_+ : x = z = 0\}$ is an invariant subset of (2.3). Thus, the system trivializes to the single equation

$$\dot{y} = \sigma - \rho y, \qquad y(0) = y_0,$$

which admits the single steady state $\overline{y} = \sigma/\rho$. Further, $\overline{y}$ is globally asymptotically stable in the set $\{(x, y, z) \in \mathbb{R}^3_+ : x = z = 0\}$. Hence the system (2.3) has the steady state $(0, \sigma/\rho, 0)$ which we call the trivial or disease free equilibrium.

A simple computation shows that the system admits another steady state, namely, (x^*, y^*, z^*), where $x^* = (\sigma - \xi\rho)(\xi - \delta)$, $y^* = \xi$ and $z^* = \xi x^*$. We call this steady state the nontrivial or disease equilibrium. Note that this steady state is only biologically relevant if it lies in $\mathbb{R}^3_+$ which means that the condition $\sigma \geq \xi\rho$ must hold. At the critical value $\sigma = \xi\rho$ this

steady state bifurcates from the trivial one via a simple transcritical bifurcation.
To examine the local exponential asymptotic stability properties of these equilibria we compute their linearizations. At the trivial equilibrium we obtain the linearization

$$A = \begin{bmatrix} -\xi & 0 & 1 \\ \delta - \sigma/\rho & -\rho & 0 \\ \sigma/\rho & 0 & -1 \end{bmatrix}.$$

The eigenvalues of this matrix are

$$z_{1,2} = \frac{-1-\xi \pm \sqrt{(1-\xi)^2 + 4\sigma/\rho}}{2}, \qquad z_3 = -\rho$$

It is easily seen that all three eigenvalues are negative, if $\sigma < \xi\rho$. By the principle of linearized stability we thus see that the trivial equilibrium is locally exonentially asymptotically stable if $\overline{y} = \sigma/\rho < \xi$, which is precisely the case when the disease equilibrium has no biological relevance.
For the linearization at the disease equilibrium we get

$$A = \begin{bmatrix} -\xi & 0 & 1 \\ \delta - \xi & -\rho - x^* & 0 \\ \xi & x^* & -1 \end{bmatrix}$$

where $x^* = (\sigma - \xi\rho)/(\xi - \delta) > 0$. The characteristic polynomial of this matrix is given by

$$p(z) = det(zI - A) = z^3 + a_1 z^2 + a_2 z + a_3,$$

$$a_1 = 1 + \xi + \frac{\sigma - \delta\rho}{\xi - \delta} \quad a_2 = \frac{(1+\xi)(\sigma - \delta\rho)}{\xi - \delta} \quad a_3 = \sigma - \xi\rho.$$

Since $a_1 a_2 > (1+\xi)(\sigma - \delta\rho) > a_3$, the Ruth-Hurwitz criterion implies that all roots of p have negative real parts, which shows that the disease equilibrium is locally exponentially asymptotically stable if it is biologically meaningful, i.e. if $\sigma > \xi\rho$.

2.3.4 Global asymptotic stability of the disease equilibrium

Consider now the case $\sigma > \xi\rho$. It is convenient to translate the equation to the disease equilibrium. We set $u = x - x^*$, $v = y - y^*$, $w = z - z^*$ where $(x^*, y^*, z^*) = (\frac{\sigma - \xi\rho}{\xi - \delta}, \xi, \xi\frac{\sigma - \xi\rho}{\xi - \delta})$, and obtain the following new system:

$$\begin{cases} \dot{u} &= w - \xi u \\ \\ \dot{v} &= -v(\rho + u) - u(\xi - \delta) \\ \\ \dot{w} &= xv + \xi u - w. \end{cases} \tag{2.6}$$

we compute the derivatives of the following function which are well-know in the theory of epidemics. For $x > 0, y > 0, z > 0$,

$$\begin{aligned} \frac{d}{dt}(u - x^* \ln(x/x^*)) &= \frac{\dot{x}}{x}(x - x^*) \\ \\ &= z - \xi x - \frac{z}{x}x^* + \xi x^* \\ \frac{d}{dt}(v - y^* \ln(y/y^*)) &= \frac{\dot{y}}{y}(y - y^*) \\ \\ &= \frac{-\rho}{y}v^2 + \delta\frac{uv}{y} - xy + \xi x - \frac{\xi^2 x^*}{y} + \xi x, \\ \frac{d}{dt}(w - z^* \ln(z/z^*)) &= \frac{\dot{z}}{z}(z - z^*) \\ \\ &= xy - z - \frac{xy}{z}z^* + z^*. \end{aligned}$$

Summing these equations, we obtain the Lyapunov function

$$\begin{aligned} &\Psi_0(x, y, z) = (u - x^* \ln(x/x^*)) + (v - y^* \ln(y/y^*)) + (w - z^* \ln(z/z^*)), \\ &\dot{\Psi}_0(x, y, z) = -\frac{\rho}{y}v^2 + \delta\frac{uv}{y} - x^*[\frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi]. \end{aligned}$$

Observe that $\psi_0(x,y,z)$ approaches infinity at the boundary of the positive octant of $\mathbb{R}^3$. To remove the second term in $\psi_0(x,y,z)$, which does not have a negative sign, we consider the modified Lyapunov function

$$\Psi = \Psi_0 + \frac{\delta}{\xi - \delta}(v - \xi \ln y),$$

Note that $\psi(x,y,z)$ approaches infinity at the boundary of the positive actant of $\mathbb{R}^3$ and is bounded below. For this function we obtain

$$\begin{aligned}
\dot{\Psi} &= -\frac{\rho}{y}v^2 + \frac{\delta uv}{y} - x^*\left(\frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi\right) - \frac{\delta}{\xi - \delta}(v(\rho + x) + u(\xi - \delta))\frac{v}{y} \\
&= -\frac{v^2}{y}(\rho + \frac{\delta(\rho + x)}{\xi - \delta}) - x^*\left(\frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi\right) \\
&= -\frac{\xi\rho + \delta x}{y(\xi - \delta)}v^2 - x^*(\frac{z}{x} + \frac{\xi^2}{y} + \frac{xy\xi}{z} - 3\xi).
\end{aligned}$$

Now the first term is obviously nonpositive. Concerning the second term note that $x^* > 0$ in the disease case. Set $a = z/x > 0$, $b = \xi^2/y > 0$ and consider $\phi(a,b) = a + b + \frac{\xi^3}{ab} - 3\xi$ on $(0,\infty)^2$. Clearly this function is strictly positive for $a + b \geq 3\xi$ and for $ab \leq \xi^2/3$, but $\phi(\xi,\xi) = 0$. Therefore it has an absolute minimum in $(0,\infty)^2$. Computing the derivatives of ϕ one finds that $(a,b) = (\xi,\xi)$ is the unique absolute minimum. Therefore we see that for all values of $\sigma > \xi\rho$ and $\delta \in [0,\xi)$ the function ψ is a Lyapunov function for the system (2.3), and $\dot{\psi} = 0$ if and only if $y = \xi$ and $z = \xi x$ hold. Looking at the equation for v we obtain in case $y = \xi$, *i.e.* $v = 0$

$$\dot{v} = -(\xi - \delta)u \neq 0$$

unless $u = 0$ *i.e.* $x = x^*$. Thus the only invariant set contained in the set $\dot{\psi} = 0$ is the disease equilibrium $(x^*, y^*, z^*) = (x^*, \xi, \xi x^*)$, hence La Salle's theorem implies convergence of the solutions to this equilibrium, for all initial values not in the set $\{0\} \times \mathbb{R}_+ \times \{0\}$. This shows that the disease equilibrium is globally asymptotically stable in $\mathbb{R}^3_+ \setminus \{0\} \times$

$\mathbb{R}_+ \times \{0\}$. If the initial data is in $\{0\} \times \mathbb{R}_+ \times \{0\}$, then the solution obviously converges to the disease free equilibrium.

Thus, Theorem 2.1.1 and 2.2.1 are proved. The results of Theorem 2.2.2 are applicable to the models (2.2), (2.4) and (2.5), since each can be converted to model (2.3). Thus, for each of these models of infectious disease, there is a threshhold value R_0, dependent on the specific model parameters, such that if $R_0 \leq 1$, then all solutions converege to the unique disease-free equilibrium, and if $R_0 > 1$, then all solutions converege to the unique disease-endemic equilibrium.

2.4 Conclusion

Understanding prion dynamics under different experimental conditions is of importance (not exclusively) for the laboratory biologists involved in dealing with one of the most devastating existing pathology. In this work we took on to study the comportment of prion model's solutions, where there is a threshold value R_0, dependent on the model parameters, such that if $R_0 \leq 1$, then all solutions converege to the unique disease-free equilibrium, and if $R_0 > 1$, then all solutions converege to the unique disease-endemic equilibrium.

Chapter 3

MATHEMATICAL MODEL FOR PRION PROLIFERATION

3.1 Introduction

The present chapter aims to investigate mathematically a model that describes the dynamics of prion proliferation.

Denoting the number of PrP^C monomers at time $t \geq 0$ by $v(t) \geq 0$ and introducing a population density $u = u(t, y) \geq 0$ for the infectious PrP^{Sc} polymers at time $t \geq 0$ and size y greater than the minimum length $y_0 > 0$, the interaction of the PrP^C monomers and the PrP^{Sc} polymers can be described by the coupled system consisting of the ordinary differential equation

$$v'(t) = \lambda - \gamma v(t) - \tau v(t) \int_{x_0}^{\infty} u(t,x)dx + 2 \int_{0}^{x_0} x \int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(t,y)dydx, \tag{3.1}$$

and the partial differential equation

$$\partial_t u(t,x) + \tau v(t)\partial_x u(t,x) + (\mu(x) + \beta(x))u(t,x) = 2 \int_{x}^{\infty} \beta(y)\kappa(x,y)u(t,y)dy, \tag{3.2}$$

for $y \in (y_0, \infty)$ subject to the boundary condition

$$u(t, y_0) = 0, \qquad t > 0 \tag{3.3}$$

These equations are supplemented with the initial conditions

$$v(0) = v^0, \qquad u(0, y) = u^0(y), \qquad y \in (y_0, \infty). \tag{3.4}$$

Equation (3.1) includes a source term $\lambda \geq 0$, while the term $-\gamma v(t)$, with $\gamma \geq 0$, takes into account metabolic degradation of monomers. The constant $\tau > 0$ denotes the polymerization rate. Moreover, $\beta(y) \geq 0$ is the length-dependent fragmentation rate of polymers of size $y > y_0$, and $\kappa(y', y)$ is the probability of a polymer of size $y > y_0$ splitting into two pieces $y' < y$ and $y - y' < y$. The transport term $\tau v(t)\partial_y u(t, y)$ in equation (3.2) accounts for the loss of polymers of size y due to lengthening. A loss of polymers according to metabolic degradation is reflected by the term $\mu(y)u(y)$. Finally, the terms involving β on the right hand side of equation (3.2) represent the loss and gain of PrP^{Sc} polymers caused by splitting. For a more detailed explanation of each process we refer to [19], [20] and the references therein.

Let us point out that (3.1), (3.2) is a coupled system of non-linear, non-local equations. In order to solve this equations we employ Kato's theory for hyperbolic evolution equations. That is, given a function v with appropriate regularity properties, we construct an evolution system for the partial differential equation (3.2). We should remark that in the absence of the kernel operator on the right hand side of (3.2), an evolution system can readily be obtained by using the method of characteristics.

It should also be pointed out that equations (3.1), (3.2) can be handled as an abstract quasilinear hyperbolic system in order to obtain local existence, see for instance [[43], §6.4]. However, this approach does not seem to yield optimal results for equations (3.1), (3.2).

Before outlining the contents of this chapter, we summarize the present-state of knowledge on the above model. It seems that only kernels of the form

$$\mu \equiv \text{const} \quad \beta(y) = \beta y \quad \kappa(y', y) = \frac{1}{y} \tag{3.5}$$

have been considered so far. This choice of kernels leads to a closed system of ordinary differential equations for v and

$$U(t) = \int_{x_0}^{\infty} u(t,y)dy \quad \text{and} \qquad P(t) = \int_{x_0}^{\infty} yu(t,y)dy.$$

Indeed, (3.1) reduces to

$$\dot{V} = \lambda - \gamma V - \tau V U + \beta y_0^2 U \tag{3.6}$$

and integrating (3.2) yields the equations

$$\dot{U} = -\mu U + \beta P - 2\beta y_0 U \tag{3.7}$$

$$\dot{P} = \tau V U - \mu P - \beta y_0^2 U \tag{3.8}$$

which, together with (3.6), are uniquely globally solvable. In addition, it has been shown in [20] that the disease-free steady state $(v, U, P) = (\lambda/\gamma, 0, 0)$ for the equations (3.6)-(3.8) is globally stable provided

$$\beta y_0 + \mu > \sqrt{\frac{\beta\lambda\tau}{\gamma}}. \tag{3.9}$$

If one reverses the strict inequality sign in (3.9) it has also been proved in [20] that there exists a prion disease steady state which is locally asymptotically stable. These results have been improved in chapter 2 in that the disease-free steady state is globally asymptotically stable also for an equality sign in (3.9) and in that the disease steady state is even globally asymptotically stable for (3.9) with a reversed strict inequality sign.

Observe that the solvability of (3.6)-(3.8) implies that the original equations (3.1), (3.2) are no longer coupled since v is completely determined for all $t \geq 0$. Hence, as shown in [13], the partial differential equation (3.2) (with kernels as in (3.5)) can be solved for $u = u(t, y)$ by using the method of characteristics combined with semigroup theory. Moreover, it has also been shown in [13] that u converges either to the disease free state or to the disease steady state according to whether or not (3.9) holds.

Our aim is to consider quite general kernels, merely assuming suitable growth conditions. More precisely, after collecting some auxiliary results in section 2, we show in section 3 that (3.1)-(3.4) is globally well-posed provided μ and β are bounded, see Theorem 3.4. The basic idea is to solve equation (3.1) for a fixed, suitable function $\overline{u}$ and then to substitute the obtained solution $v_{\overline{u}}$ into equation (3.2). Using Kato's theory for hyperbolic evolution equations, we solve then equation (3.2) in order to obtain a classical solution $u_{\overline{u}}$. A fixed point argument for the map $\overline{u} \to u_{\overline{u}}$ yields then local existence and uniqueness of a solution pair (v, u) for (3.1)-(3.4). Suitable a priori estimates guarantee global existence. A weak formulation of (3.2) allows then to extend in section 4 the existence results to unbounded kernels by using a weak compactness method, see Theorem 3.4.1. We also prove finite speed of propagation for the weak (and classical) solutions to (3.2). Finally, in section 5 we show that the disease-free steady state is globally asymptotically stable provided some suitable lower and upper bounds for the splitting kernels are available. We refer to Theorem 3.5.1 for a precise statement.

Clearly, the method described above does not yield uniqueness of weak solutions. This issue will be the topic of future work [33].

3.2 Preliminaries

In the following, we set $Y := (y_0, \infty)$ and assume that

$$\mu, \beta \in L^+_\infty(Y), \tag{3.10}$$

where $L_\infty^+(Y)$ stands for the positive cone in $L_\infty(Y)$. We also assume that $\kappa \geq 0$ is measurable on $K := \{(y', y); y_0 < y < \infty, 0 < y' < y\}$ and satisfies

$$\kappa(y', y) = \kappa(y - y', y), \qquad (y', y) \in K. \tag{3.11}$$

which means binary splitting. Moreover, we suppose the number of monomer units to be preserved during splitting, that is

$$2\int_0^y y'\kappa(y', y)dy' = y, \qquad \text{a.e.} \quad y \in Y. \tag{3.12}$$

Furthermore, let

$$\tau > 0, \quad \text{and } \lambda, \gamma \geq 0. \tag{3.13}$$

It is easy to check that (3.11) and (3.12) imply

$$\int_0^y \kappa(y', y)dy' = 1, \qquad a.e. \quad y \in Y. \tag{3.14}$$

Observe that the natural constraints (3.11) and (3.12) hold if κ is of self-similar form

$$\kappa(y', y) = \frac{1}{y}\kappa_0\left(\frac{y'}{y}\right), \quad y > y_0, \quad 0 < y' < y, \tag{3.15}$$

where κ_0 is a non-negative integrable function defined on $(0, 1)$ such that

$$\kappa_0(y) = \kappa_0(1 - y), \quad y \in (0, 1) \quad \int_0^1 \kappa_0(y)dy = 1. \tag{3.16}$$

This allows to capture κ in (3.5) by taking $\kappa_0 \equiv 1$. Also note that the operator L, given by

$$L[u](y) := -(\mu(y) + \beta(y))u(y) + 2\int_y^\infty \beta(y')\kappa(y, y')u(y')dy', \qquad a.e.\ y \in Y \tag{3.17}$$

defines a linear and bounded operator from $L_1(Y, ydy)$ into itself according to (3.10)-(3.12) and that

$$\begin{aligned}\int_{y_0}^{\infty} \varphi(y)L[u](y)dy = & -\int_{y_0}^{\infty} \varphi(y)\mu(y)u(y)dy \\ & + \int_{y_0}^{\infty} u(y)\beta(y)\left(-\varphi(y) + 2\int_{y_0}^{y} \varphi(y')\kappa(y', y)dy'\right)\end{aligned} \tag{3.18}$$

for $u \in L_1(Y, ydy)$ and a suitable test function φ. We then put

$$E_0 := L_1(Y, ydy) \qquad \text{and } E_1 := W_1^1(Y, ydy) := cl_{W_1^1(Y,ydy)}\mathcal{D}(Y),$$

where $\mathcal{D}(Y)$ denotes the space of all test functions on Y . By E_0^+ we mean the positive cone in E_0 and $E_1^+ := E_1 \cap E_0^+$. Finally, given any interval J and any function $v : J \to R^+$, we define

$$\mathbb{A}_v(t)u := \tau v(t)\partial_y u - L[u], \qquad u \in E_1, \qquad t \in J. \tag{3.19}$$

Lemma 3.2.1 *The operator $-A$, defined as*

$$A\varphi := \partial_y\varphi, \varphi \in E_1, \tag{3.20}$$

generates a strongly continuous semigroup $\{e^{-tA}; t \geq 0\}$ on E_0. It is given by

$$[e^{-tA}\varphi](y) = \begin{cases} \varphi(y-t), & y > y_0 + t, \qquad t \geq 0 \\ 0, & y_0 < y \leq y_0 + t, \end{cases} \tag{3.21}$$

and satisfies

$$\|e^{-tA}\|_{\mathcal{L}(E_0)} \leq e^{t/y_0}, \qquad t \geq 0. \tag{3.22}$$

Proof: Clearly, (3.21) defines a strongly continuous semigroup on E_0 satisfying

$$\|e^{-tA}\varphi\|_{E_0} \leq \left(1 + \frac{t}{y_0}\right)\|\varphi\|_{E_0} \leq e^{t/y_0}\|\varphi\|_{E_0}, \qquad t \geq 0,$$

for $\varphi \in E_0$, whence (3.22). It thus remains to show that its generator $-A$ is indeed given by (3.20). Note that Lebesgue's theorem guarantees that the test functions are contained in the domain of A and that

$$A\varphi = \partial_y \varphi, \qquad \varphi \in \mathcal{D}(Y). \tag{3.23}$$

Since (3.21) is a right translation, $\mathcal{D}(Y)$ is invariant under e^{-tA} and therefore is a core for A. In particular, $\mathcal{D}(Y)$ is dense in the domain of A, which, together with (3.23), easily yields (3.20). $\square$ In the sequel, we set $J_T := [0,T]$ for $T > 0$ and, given $R > 1$, we define

$$\mathcal{V}_{T,R} := \{v \in C^1(J_T); R^{-1} \leq v(t) \leq \|v\|_{C_1(J_T)} \leq R\}. \tag{3.24}$$

Recall then that the operator $\mathbb{A}_v(t)$ has been defined in (3.19).

Proposition 3.2.1 *Fix $R > 1$, $T_0 > 0$ and let $0 < T \leq T_0$. Then $(\mathbb{A}_v(t))_{t\in[0,T]}$ generates for each $v \in \mathcal{V}_{T,R}$ a unique evolution system $U_v(t,s)$, $0 \leq s \leq t \leq T$, in E_0, and there exists a constant $\omega_0 := \omega_0(T_0, R) > 0$ such that*

$$\|U_v(t,s)\|_{\mathcal{L}(E_0)} \leq e^{\omega_0(t-s)}, \qquad 0 \leq s \leq t \leq T, \qquad v \in \mathcal{V}_{T,R} \tag{3.25}$$

and

$$\|U_v(t,s)\|_{\mathcal{L}(E_1)} \leq \omega_0, \qquad 0 \leq s \leq t \leq T, v \in \mathcal{V}_{T,R}\ . \tag{3.26}$$

Moreover, for $v, w \in \mathcal{V}_{T,R}$ it holds that

$$\|U_v(t,s) - U_w(t,s)\|_{\mathcal{L}(E_1,E_0)} \leq \omega_0(t-s)\|v - w\|_{C(J_T)}\ , \quad 0 \leq s \leq t \leq T. \tag{3.27}$$

Proof: Since L is a bounded operator on E_0, Lemma and a well-known perturbation result (see [[43], Thm.3.1.1]) ensure that, for any fixed $v \in \mathcal{V}_{T,R}$ and any $s \in J_T$, $-\mathbb{A}_v(s)$

generates a strongly continuous semigroup on E_0 with

$$\|e^{-t\mathbb{A}_v(s)}\|_{\mathcal{L}(E_0)} \leq e^{\widetilde{\omega}t}, \qquad t \geq 0, \tag{3.28}$$

where $\widetilde{\omega} := \tau R y_0^{-1} + \|L\|_{\mathcal{L}(E0)}$. Hence, putting $\omega := \widetilde{\omega} + 1$ it follows that $\{\mathbb{A}_v(t)\}_{t\in J_T}$ is stable in the sense of [[43], §5.2] for each $v \in \mathcal{V}_{T,R}$. Next, given any $t \in J_T$, the definition $Q_v(t) := \omega + \mathbb{A}_v(t)$ yields an isomorphism from E_1 onto E_0 satisfying

$$\|Q_v(t)\|_{\mathcal{L}(E_1,E_0)} \leq \omega + \tau R + \|L\|_{\mathcal{L}(E_0)}, \qquad t \in J_T, \qquad v \in \mathcal{V}_{T,R}. \tag{3.29}$$

Moreover, for $u \in E_1$,

$$Q_v(\cdot)u \in C^1(J_T, E_0) \quad \text{ with } \dot{Q}_v(t)u := \frac{d}{dt}Q_v(t)u = \tau\dot{v}(t)\partial_y u.$$

Therefore, assumptions (H_1), $(H_2)^+$, (H_3) of [[43], §5] hold, thus implying that there indeed exists a unique evolution system $U_v(t,s)$, $0 \leq s \leq t \leq T$, in E_0 for each $v \in \mathcal{V}_{T,R}$, which, in addition, satisfies statements $(E_1) - (E_5)$ of [[43], §5]. In particular, (3.25) holds (with ω_0 replaced by $\widetilde{\omega}$).

We now refer to the proof of [[43], Thm.5.4.6]: The evolution system $U_v(t,s)$ can be written as

$$U_v(t,s) = Q_v(t)^{-1}W_v(t,s)Q_v(s), \qquad 0 \leq s \leq t \leq T, \tag{3.30}$$

where $W_v(t,s) \in \mathcal{L}(E_0)$ satisfies

$$W_v(t,s)u = U_v(t,s)u + \int_s^t W_v(t,r)C_v(r)U_v(r,s)u dr$$

for $0 \leq s \leq t \leq T$ and $u \in E_0$ with

$$C_v(t) := \dot{Q}_v(t)Q_v(t)^{-1} \in \mathcal{L}(E_0), \qquad t \in J_T.$$

We then claim that there is a constant $c_0(R) > 0$ such that

$$\|Q_v(t)^{-1}\|_{\mathcal{L}(E_0,E_1)} \leq c_0(R), \qquad t \in J_T, \qquad v \in \mathcal{V}_{T,R}. \tag{3.31}$$

Indeed, (3.28) implies

$$\|Q_v(t)-1\|_{\mathcal{L}(E_0)} \leq 1, \qquad t \in J_T,$$

and therefore, for $u \in E_0$ and $t \in J_T$,

$$\begin{aligned}
\|Q_v(t)^{-1}u\|_{E_1} &= \|Q_v(t)^{-1}u\|_{E_0} + \|\partial_y Q_v(t)^{-1}u\|_{E_0} \\
&\leq \|u\|_{E_0} + \frac{1}{\tau v(t)}\|u - (\omega - L)Q_v(t)^{-1}u\|_{E_0} \\
&\leq (1 + R/\tau(1 + \omega + \|L\|_{\mathcal{L}(E_0)}))\|u\|_{E_0},
\end{aligned}$$

whence (3.31). Consequently, we have

$$\begin{aligned}
\|C_v(t)\|_{\mathcal{L}(E_0)} &\leq \|\dot{Q}_v(t)\|_{\mathcal{L}(E_1,E_0)}\|Q_v(t)^{-1}\|_{\mathcal{L}(E_0,E_1)} \\
&\leq \tau\|\dot{v}\|_{C(J_T)}c_0(R) \leq c_0'(R)
\end{aligned}$$

for $t \in J_T$ and $v \in \mathcal{V}_{T,R}$. From the proof of [[43], Lem.5.4.5] (see in particular equation (4.11) therein) and from (3.25) it thus follows that there exists a constant $c(T_0, R) > 0$ such that

$$\|W_v(t,s)\|_{\mathcal{L}(E_0)} \leq c(T_0, R), \qquad 0 \leq s \leq t \leq T, \qquad v \in \mathcal{V}_{T,R}. \tag{3.32}$$

Applying estimates (3.29), (3.31), and (3.32) to (3.30) we conclude that (3.26) is true. Finally, let $v, w \in \mathcal{V}_{T,R}$ and $u \in E_1$ be arbitrary. Then, for $0 \leq s < t \leq T$,

$$N := [\sigma \mapsto U_v(t,\sigma)U_w(\sigma,s)u] \in C^1((s,t),E_0) \cap C([s,t],E_1)$$

by $(E_2) - (E_5)$ in [[43], §5] with

$$\dot{N}(\sigma) = U_v(t,\sigma)(\mathbb{A}_v(\sigma) - \mathbb{A}_w(\sigma))U_w(\sigma,s)u.$$

Therefore, (3.25) and (3.26) yield

$$\begin{aligned}\|U_w(t,s)u - U_v(t,s)u\|_{E_0} &\leq \int_s^t \|U_v(t,\sigma)\|_{\mathcal{L}(E_0)} \|\mathbb{A}_v(\sigma) - \mathbb{A}_w(\sigma)\|_{\mathcal{L}(E_1,E_0)} \|U_w(\sigma,s)\|_{\mathcal{L}(E_1)} d\sigma \|u\|_{E_1} \\ &\leq c(T_0,R)(t-s)\|v-w\|_{C(J_T)}\|u\|_{E_1}\end{aligned}$$

for $0 \leq s \leq t \leq T$, hence statement (3.27) holds. □

Remark 3.2.1 *As observed in the previous proof, the evolution system $U_v(t,s)$, $0 \leq s \leq t \leq T$, corresponding to $v \in \mathcal{V}_{T,R}$ satisfies $(E_1) - (E_5)$ in [9, §5]. In particular, we have for $u_0 \in E_1$ that*

$$[t \mapsto U_v(t,0)u^0] \in C^1(J_T, E_0) \cap C(J_T, E_1).$$

The existence of weak solutions will require the following auxiliary result.

Lemma 3.2.2 *For $v \in C(J_T)$ with $v(t) \geq 0$ put $A_v(t) := \tau v(t)\partial_y$, $t \in J_T$, and let $U_{A_v}(t,s)$, $0 \leq s \leq t \leq T$, be the corresponding evolution system in $L_1(Y)$. Then, for any $\delta > 0$, it holds that*

$$\sup_{|\varepsilon|\leq\delta} \int_\varepsilon U_{A_v}(t,s)\varphi dy \leq \sup_{|\varepsilon|\leq\delta} \int_\varepsilon \varphi dy, \qquad 0 \leq s \leq t \leq T, \quad \varphi \in L_1^+(Y),$$

the supremum being taken over all measurable sets $\varepsilon \subset Y$.

Proof: Noticing that $-\partial y$ with domain $W_1^1(Y)$ generates a strongly continuous positive semigroup of contractions on $L_1(Y)$ given as in (3.21), it follows that

$$\|e^{-tA_v(s)}\|_{\mathcal{L}(L_1(Y))} \leq 1, \qquad \|e^{-tA_v(s)}\|_{\mathcal{L}(W_1^1(Y))} \leq 1, \qquad t \geq 0, \qquad s \in J_T.$$

Hence, the corresponding evolution system $U_{A_v}(t,s)$, $0 \leq s \leq t \leq T$, in $L_1(Y)$ is well-defined according to [[43], Thm.5.2.2, Thm.5.3.1]. Let then $\varepsilon \subset Y$ be any measurable subset of Y with measure $|\varepsilon| \leq \delta$ and choose $\varphi \in L_1^+(Y)$. Denoting by χs the characteristic function on a set S, we have

$$\int_{\mathcal{E}} [e^{-tA_v(s)}\varphi](y)dy = \int_{y_0}^{\infty} \chi_{\{-t\tau v(s)+\varepsilon\}}(y)\varphi(y)dy \leq \sup_{|\varepsilon'|\leq\delta} \int_{\varepsilon'} \varphi(y)dy$$

for $s \in J_T$ and $t \geq 0$. From equations (3.5) and (3.15) in [[43], §5] we thus deduce

$$\int_{\varepsilon} U_{A_v}(t,s)\varphi dy \leq \sup_{|\varepsilon'|\leq\delta} \varphi dy, \qquad 0 \leq s \leq t \leq T,$$

and the assertion follows. □

3.3 Classical solutions

In this section we show that problem (3.1)-(3.4) is globally well-posed for bounded kernels μ and β. In order to do this, let us denote by $|\cdot|_1$ the norm in $L_1(Y)$ and put

$$g(u) := 2\int_{y_0}^{\infty} u(y)\beta(y)\int_0^{y_0} y'\kappa(y',y)dy'dy.$$

Defining L by (3.17) and $A_v(t)$ by (3.19), we may rewrite (3.1)-(3.4) as

$$\dot{v} = \lambda - \gamma v - \tau v|u|_1 + g(u), \quad t > 0, \qquad v(0) = v^0, \tag{3.33}$$

provided $u \geq 0$, and

$$\dot{u} + \mathbb{A}_v(t)u = 0, \qquad t > 0, \qquad u(0) = u^0. \tag{3.34}$$

Theorem 3.3.1 *Suppose (3.10)-(3.13) hold. Then, given any $v^0 > 0$ and $u^0 \in E_1^+$, problem (3.33), (3.34) possesses a unique global classical solution (v,u) such that $v \in C^1(\mathrm{I\!R}^+)$, $v(t) > 0$ for $t > 0$, and $u \in C^1(\mathrm{I\!R}^+, E_0) \cap C(\mathrm{I\!R}^+, E_1^+)$.*

Proof: (i) We first prove that, for any $S > 0$, there exists $T := T(S) \in (0,1]$ such that (3.33), (3.34) possesses a unique solution (v,u) on J_T with regularity properties as stated in the theorem, provided that $(v^0,u^0) \in \mathbb{R}^+ \times E_1^+$ satisfies

$$S^{-1} \leq v^0 \qquad \text{and} \qquad v^0 + \|u^0\|_{E_1} \leq S. \tag{3.35}$$

In the following, we denote by $c(S) > 0$ a generic constant depending on S but not on $T \in (0,1]$. Let us then define the complete metric space

$$X_T := \{u \in C(J_T, E_0^+); \|u(t)\|_{E_0} \leq S+1, t \in J_T\},$$

and let us choose $\overline{u} \in X_T$ arbitrarily. Then, since $g(\overline{u})$, $|\overline{u}| \in C(J_T)$ due to (3.12), it follows that (3.33), with u replaced by $\overline{u}$, admits a unique solution $v_{\overline{u}} \in C^1(J_T)$. Clearly,

$$\begin{aligned} v_{\overline{u}}(t) \quad = \quad & e^{-\gamma t - \tau \int_0^t |\overline{u}(\sigma)|_1 d\sigma} v^0 \\ & + \int_0^t e^{-\gamma(t-s) - \tau \int_s^t |\overline{u}(\sigma)|_1 d\sigma} (\lambda + g(\overline{u}(s)))ds \end{aligned}$$

for $t \in J_T$, hence

$$v_{\overline{u}}(t) \geq e^{\gamma t - \tau/y0(S+1)t} v^0 \geq c(S), \qquad 0 \leq t \leq T \leq 1. \tag{3.36}$$

Moreover, since $v^0 \leq S$ and $g(\overline{u}(t)) \leq \|\beta\|_\infty (S+1)$ for $t \in J_T$, we deduce

$$v_{\overline{u}}(t) \geq c(S), \qquad t \in J_T, \tag{3.37}$$

from which it follows

$$-c(S) \leq -(\gamma + \tau|\overline{u}(t)|_1) v_{\overline{u}}(t) \leq \dot{v}_{\overline{u}}(t) \leq \lambda + g(\overline{u}(t)) \leq c(S), \quad t \in J_T. \tag{3.38}$$

Therefore, (3.36)-(3.38) entail the existence of $R := R(S) > 1$, depending on $S > 0$ but not on $T \in (0,1]$, such that $v_{\overline{u}} \in \mathcal{V}_{T,R}$ whenever $\overline{u} \in X_T$, where $\mathcal{V}_{T,R}$ is given by (3.24).

Furthermore, we readily derive from the explicit representation of $v_{\overline{u}}$ and the linearity of g that

$$|v_{\overline{u}_1}(t) - v_{\overline{u}_2}(t)| \leq c(S)\|\overline{u}_1 - \overline{u}_2\|_{X_T}, \qquad 0 \leq t \leq T \leq 1, \qquad \overline{u}_1, \overline{u}_2 \in X_T. \tag{3.39}$$

Let $U_{v_{\overline{u}}}(t,s)$, $0 \leq s \leq t \leq T$, denote the unique evolution system in E_0 corresponding to $\{A_{v_{\overline{u}}}(t)\}_{t\in J_T}$ and by $\omega_0 = \omega_0(1, R(S))$ the constant occurring in Proposition 3.2.1. Defining

$$\Lambda(\overline{u})(t) := U_{v_{\overline{u}}}(t,0)u^0, \qquad t \in J_T, \qquad \overline{u} \in X_T,$$

we obtain by Remark 3.2.1 the unique solution in $C(J_T, E_1) \cap C^1(J_T, E_0)$ to

$$\dot{u} + \mathbb{A}_{v_{\overline{u}}}(t)u = 0, \qquad t > 0, \qquad u(0) = u^0.$$

Next we show that $\Lambda : X_T \to X_T$ is a contraction, which, consequently, would imply our first claim. Provided $T := T(S) \in (0, 1]$ is chosen sufficiently small, we deduce from (3.25) that, for $\overline{u} \in X_T$ and $t \in J_T$,

$$\|\Lambda(\overline{u})(t)\|_{E_0} \leq e^{\omega_0 T}\|u^0\|_{E_0} \leq S + 1,$$

and (3.27) and (3.39) ensure for $\overline{u}_1, \overline{u}_2 \in X_T$ and $t \in J_T$

$$\|\Lambda(\overline{u}_1)(t) - \Lambda(\overline{u}_2)(t)\|_{E_0} \leq \omega_0 T\|v_{\overline{u}_1} - v_{\overline{u}_2}\|_{C(J_T)}\|u_0\|_{E_1} \leq \frac{1}{2}\|\overline{u}_1 - \overline{u}_2\|_{X_T}.$$

In order to prove that $\Lambda(\overline{u})(t)$ is non-negative observe that $\Lambda(\overline{u})$ also solves

$$\dot{u} + (A_{v_{\overline{u}}}(t) + r)u = L[u] + ru =: B(u), \qquad t > 0, \qquad u(0) = u^0,$$

with $r := \|\mu + \beta\|_\infty$ and $A_{v_{\overline{u}}}(t) := \tau v_{\overline{u}}(t)\partial_y$. Then $B(u) \in E_0^+$ for $u \in E_0^+$. Since Lemma 3.2 ensures that $-A_{v_{\overline{u}}}(s)$ generates a positive semigroup on E_0, it readily follows from the proof of [[43], Thm.5.3.1] that the evolution system $\widetilde{U}(t,s)$ generated by $\{A_{v_{\overline{u}}}(t) + r\}_{t\in J_T}$

is positive. Defining then

$$F(w)(t) := \widetilde{U}(t,0)u^0 + \int_0^t \widetilde{U}(t,s)B(w(s))ds$$

one shows that F is a contraction from a suitable closed ball in $C([0,\widetilde{T}],E_0)$, containing u^0, into itself provided $\widetilde{T} \in (0,T]$ is sufficiently small. Hence, putting

$$u_0 := u^0, u_{n+1} := F(u_n), \qquad n \in \mathbb{N},$$

we obtain a sequence in $C([0,\widetilde{T}],E_0^+)$ that converges to $\Lambda(\widetilde{u})|_{[0,\widetilde{T}]}$. This shows that

$$T^\star := \sup\{T' \in (0,T]; \Lambda(\overline{u})(t) \in E_0^+, \qquad 0 \le t \le T'\} \ge \widetilde{T}.$$

Assuming $T^\star < T$, a repetition of the above arguments with u^0 replaced by $\Lambda(\widetilde{u})(T^\star) \in E_1^+$ would lead to a contradiction. Thus $T^\star = T$, which entails that $\Lambda : X_T \to X_T$ is indeed a contraction.

(ii) It follows from part (i) that (3.33), (3.34) admits a unique maximal solution

$$(v,u) \in C(J, \mathbb{R}^+ \times E_1^+) \cap C^1(J, \mathbb{R} \times E_0),$$

where J is open in $\mathbb{R}^+$. We claim that, if $t^+ := \sup J < \infty$, then

$$\underline{\lim}_{t \nearrow t^+} v(t) = 0 \qquad \text{or} \qquad \overline{\lim}_{t \nearrow t^+} (v(t) + \|u(t)\|_{E_1} = \infty. \tag{3.40}$$

Suppose to the contrary that there are $t_j \nearrow t^+ < \infty$ and $S > 0$ such that

$$v(t_j) \ge S^{-1} \qquad \text{and } v(t_j) + \|u(t_j)\|_{E_1} \le S.$$

Let $T(S) > 0$ be the corresponding constant from part (i) and fix $t_N > t^+ - T(S)$. Then we may choose $(v(t_N), u(t_N)) \in \mathbb{R}^+\ 0 \times E_1^+$ as initial value and deduce that the solution

(v, u) can be extended to a solution on $[0, t_N + T(S)]$, contradicting its maximality.
(iii) We now show that (3.40) does not occur in finite time. Observe that (3.12) and (3.18) imply

$$\dot{v}(t) + \frac{d}{dt}\int_{y_0}^{\infty} yu(t,y)dy = \lambda - \gamma v(t) - \int_{y_0}^{\infty} y\mu(y)u(t,y)dy, \qquad t \in J, \tag{3.41}$$

hence

$$v(t) + \|u(t)\|_{E_0} \le v^0 + \|u^0\|_{E_0} + \lambda t, \qquad t \in J. \tag{3.42}$$

Suppose now that $t^+ < \infty$. Then (3.42) entails that

$$\dot{v}(t) \le \lambda + g(u(t)) \le \lambda + \|\beta\|_\infty \|u(t)\|_{E_0} \le c(t^+), \qquad t \in J,$$

and

$$\dot{v}(t) \ge -\gamma v(t) - \tau |u(t)|_1 v(t) \ge -c(t^+), \qquad t \in J.$$

Therefore

$$\|v\|_{C^1(J)} \le c(t^+) \tag{3.43}$$

and

$$v(t) \ge e{-}(\gamma + \tau|u(t)|_1)tv^0 \ge e^{-(\gamma+\tau c(t^+))t^+} v^0 > 0, \qquad t \in J. \tag{3.44}$$

Taking (3.26) into account, we derive from (3.43), (3.44) that the evolution system $U_v(t,s)$ satisfies

$$\|U_v(t,s)\|_{\mathcal{L}(E_1)} \le c(t^+), \qquad 0 \le s \le t < t^+.$$

But then

$$\|u(t)\|_{E_1} = \|U_v(t,0)u^0\|_{E_1} \le c(t^+)\|u^0\|_{E_1}, t \in J, \tag{3.45}$$

thus (3.40) cannot be true in view of (3.43) - (3.45). This contradiction proves that the solution (v, u) exists for all times, hence the assertion follows. □ If

(v, u) denotes the solution to (3.1)-(3.4) provided by Theorem 3.4, the next proposition shows that u propagates with finite speed. The proof is adapted from the proof of [[31], Thm.2.6].

Proposition 3.3.1 *Suppose (3.10)-(3.13) hold. For $v^0 > 0$ and $u^0 \in E_1^+$ let (v, u) denote the unique global classical solution to (3.1)-(3.4). If $\text{supp} u^0 \subset [y_0, S_0]$ for some $S_0 > y_0$, then $\text{supp} u(t) \subset [y_0, S(t)]$, $t \geq 0$, where*

$$S(t) := S_0 + \tau \int_0^t v(s)ds, \qquad t \geq 0.$$

Proof: Define $P \in C^1(\mathbb{R}^+, L_1(Y))$ by

$$P(t, y) := \int_y^\infty u(t, y')dy', \qquad y \in Y, \qquad t \geq 0.$$

Then, since

$$\frac{d}{dt}P(t, y) = \int_y^\infty \dot{u}(t, y')dy' = \tau v(t)u(t, y) + \int_y^\infty L[u(t)](y')dy',$$

we derive from (3.2) and (3.14)

$$\begin{aligned}
\frac{d}{dt}\int_{S(t)}^\infty P(t, y)dy &= \int_{S(t)}^\infty \frac{d}{dt}P(t, y)dy - S'(t)P(t, S(t)) \\
&= \int_{S(t)}^\infty \int_y^\infty L[u(t)](y')dy'dy \\
&\leq 2\int_{S(t)}^\infty \int_y^\infty \int_{y'}^\infty \beta(y'')\kappa(y', y'')u(t, y'')dy''dy'dy \\
&= 2\int_{S(t)}^\infty \int_y^\infty \beta(y'')u(t, y'') \int_y^{y''} \kappa(y', y'')dy'dy''dy \\
&\leq 2\|\beta\|_\infty \int_{S(t)}^\infty P(t, y)dy,
\end{aligned}$$

which implies

$$\int_{S(t)}^\infty P(t, y)dy \leq e^{2\|\beta\|_\infty t} \int_{S_0}^\infty \int_y^\infty u^0(y')dy'dy = 0, \qquad t \geq 0.$$

Hence $u(t,y) = 0$ for $y \in (S(t), \infty)$ and $t \geq 0$. $\square$

Remark 3.3.1 *Note that if $\mu(y) \geq \underline{\mu} > 0$ for a.e. $y \in Y$ and $\gamma > 0$, then (3.41) entails*

$$v(t) + \int_{y_0}^{\infty} y u(t,y)dy \leq \frac{\lambda}{\nu} + e^{-\nu t}\left(v^0 + \|u^0\|_{E_0} - \frac{\lambda}{\nu}\right), \qquad t \geq 0, \tag{3.46}$$

where $\nu := \min\{\underline{\mu}, \gamma\} > 0$. In particular,

$$\int_0^t v(s)ds \leq \frac{\lambda t}{\nu} + \frac{1}{\nu}(1 - e^{-\nu t}\left(v^0 + \|u^0\|_{E_0} - \frac{\lambda}{\nu}\right), \qquad t \geq 0. \tag{3.47}$$

3.4 Weak solutions

The aim of this section is to relax condition (3.10) and to prove existence of weak solutions for unbounded kernels μ and β. More precisely, instead of (3.10) we assume in the following that

$$\begin{cases} \text{there exists } \alpha \geq 1 \quad \text{ and } \quad \varrho \in L_\infty^+(Y) \quad \text{ such that} \\ \varrho(y) \to 0 \text{ as } y \to \infty \text{ and } \mu(y) + \beta(y) \leq \varrho(y) y^\alpha, \ a.e.\ y \in Y. \end{cases} \tag{3.48}$$

In addition, we require that

$$\begin{cases} \text{for each } \varepsilon > 0 \quad \text{ there exists } \quad \delta > 0 \quad \text{ such that} \\ \sup_{|\varepsilon| \leq \delta} \dfrac{\beta(y)}{y^\alpha} \displaystyle\int_{y_0}^{y} \chi\varepsilon(y')\kappa(y',y)dy' \leq \varepsilon, \ a.e.\ y \in Y, \end{cases} \tag{3.49}$$

the supremum being taken over all measurable subsets ε in Y with measure $|\varepsilon| \leq \delta$. Observe that if κ is subject to the self-similar form (3.15), (3.16), then

$$\lim_{|\varepsilon| \to 0} \text{ess-sup}_{y > y_0} \int_{y_0}^{y} \mathbf{1}_\varepsilon(y')\kappa(y',y)dy' = \lim_{|\varepsilon| \to 0} \text{ess-sup}_{y > y_0} \int_{y_0/y}^{1} \mathbf{1}_{\frac{1}{y}\varepsilon}(y')\kappa_0(y')dy' = 0$$

due to $y_0 > 0$ and the integrability of κ_0, so (3.49) automatically holds by (3.48).
In the following we denote by $L_{1,w}(Y)$ the space $L_1(Y)$ equipped with its weak topology.

Definition 3.4.1 *Given $v^0 > 0$ and $u^0 \in L_1^+(Y, ydy)$, we call (v,u) a (global) weak solution to (3.1)-(3.4) if*

(i) $g(u) \in C(\mathbb{R}^+)$,

(ii) $v \in C^1(\mathbb{R}^+)$ *is a non-negative solution to (3.1),*

(iii) $u \in C(\mathbb{R}^+, L_{1,w}(Y)) \cap L_{\infty,loc}(\mathbb{R}^+, L_1^+(Y, ydy))$,

(iv) for all $t > 0$ and $\varphi \in W_\infty^1(Y)$ it holds that $L[u] \in L_1((0,t) \times Y)$ and

$$\int_{y_0}^{\infty} \varphi(y)u(t,y)dy - \tau \int_0^t v(s) \int_{y_0}^{\infty} \varphi'(y)u(s,y)dyds$$
$$= \int_{y_0}^{\infty} \varphi(y)u^0(y)dy + \int_0^t \int_{y_0}^{\infty} \varphi(y)L[u(s)](y)dyds.$$

We first need the following auxiliary result.

Lemma 3.4.1 *Suppose that h_n and h are measurable functions on Y such that $h_n \to h$ a.e. and let $u_n \to u$ in $L_{1,w}^+(Y)$.*

(i) If $\|h_n\|_\infty \leq c$, then $h_n u_n \to hu$ in $L_{1,w}(Y)$.

(ii) If ϱ and α are as in (3.48) and if $|h_n(y)| \leq \varrho(y)y^\alpha$ for a.e. $y \in Y$ and

$$\int_{y_0}^{\infty} y^\alpha u_n(y)dy \leq c, \qquad n \in \mathbb{N},$$

then $h_n u_n \to hu$ in $L_{1,w}(Y)$.

Proof: In case that Y is a finite interval, a proof of (i) is implicitly contained in [[55],Lem.4.1] (a detailed proof can also be found in [[58], App.]). The case of unbounded Y is a slight modification thereof. Statement (ii) can be shown along the lines of [[32], App.A, Cor.4.1]. First note that the assumptions imply $|h(y)| \leq \varrho(y)y^\alpha$, a.e. $y \in Y$, and

$$\int_{y_0}^{\infty} y^\alpha u(y)dy \leq c.$$

Putting $\overline{u}_n(y) := \varrho(y)y^\alpha u_n(y)$ and $\overline{u}(y) := \varrho(y)y^\alpha u(y)$ we obtain for $\varphi \in L_\infty(Y)$ and $R > y_0$

$$\left|\int_{y_0}^{\infty} \varphi(y)\left(\overline{u}_n(y) - \overline{u}(y)\right)dy\right| \leq \left|\int_{y_0}^{R} \varphi(y)\varrho(y)y^\alpha\left(\overline{u}_n(y) - \overline{u}(y)\right)dy\right|$$

$$+2c\|\varphi\|_\infty\|\varrho\|_{L_\infty(R,\infty)}.$$

Taking first the lim sup as $n \to \infty$ on both sides and letting then $R \to \infty$, we conclude from (3.48) that $\overline{u}_n \to \overline{u}$ in $L_{1,w}(Y)$. Therefore, it follows from (i) that the right hand side of the estimate

$$\begin{aligned}\left|\int_{y_0}^{\infty} \varphi(y)\left(h_n(y)u_n(y) - h(y)u(y)\right)dy\right| \leq &\left|\int_{y_0}^{\infty} \varphi(y)\left(\varrho(y)y^\alpha\right)^{-1}\left(h_n(y) - h(y)\right)\overline{u}_n(y)dy\right| \\ &+\left|\int_{y_0}^{\infty} \varphi(y)\left(\varrho(y)y^\alpha\right)^{-1}h(y)\left(\overline{u}_n(y) - \overline{u}(y)\right)dy\right|\end{aligned}$$

converges to 0, leading to the assertion. □ Now we are in a position to relax the

boundedness assumptions on μ and β and also the assumption on u^0 can be weakened.

Theorem 3.4.1 *Suppose that (3.11)-(3.13) and (3.48), (3.49) hold. Then, given any* $v^0 > 0$ *and* $u^0 \in L_1^+(Y, y^\alpha dy)$*, problem (3.1)-(3.4) admits at least one global weak solution* (v, u)*. In addition,* u *belongs to* $L_{\infty,loc}(\mathbb{R}^+, L_1(Y, y^\alpha dy))$*.*

Proof: (i) Let $u_n^0 \in D^+(Y)$ be such that $u_n^0 \to u^0$ in $L_1(Y, y^\alpha dy)$. We define $\mu_n := \min\{\mu, n\}$ and $\beta_n := \min\{\beta, n\}$. Observe that μ_n, β_n also satisfy (3.48) and (3.49). Then Theorem guarantees the existence of

$$(v_n, u_n) \in C(\mathbb{R}^+, \mathbb{R}^+ \times E_1^+) \cap C^1(\mathbb{R}^+, \mathbb{R} \cap E_0)$$

satisfying

$$\dot{v}_n = \lambda - \gamma v_n - \tau v_n |u_n|_1 + g_n(u_n), \qquad t > 0, \qquad v_n(0) = v^0, \tag{3.50}$$

and

$$\partial_t u_n + \tau v_n(t) \partial_y u_n = L_n[u_n], \qquad t > 0, \qquad u_n(0) = u_n^0, \tag{3.51}$$

where

$$g_n(u) := 2 \int_{y_0}^{\infty} u(y) \beta_n(y) \int_0^{y_0} y' \kappa(y', y) dy' dy$$

and

$$L_n[u](y) := -(\mu_n(y) + \beta_n(y)) u(y) + 2 \int_y^{\infty} \beta_n(y') \kappa(y, y') u(y') dy'.$$

Let $T > 0$ be arbitrary. According to (3.42) there exists $c_0(T) > 0$ independent of $n \geq 1$ such that

$$v_n(t) + \|u_n(t)\|_{E_0} \leq c_0(T), \qquad t \in J_T, \qquad n \geq 1. \tag{3.52}$$

Moreover, we claim that

$$\|u_n(t)\|_{L_1(Y, y^\alpha dy)} \leq c_0(T), \qquad t \in J_T, \qquad n \geq 1. \tag{3.53}$$

For, recall that $u_n(t)$ has compact support due to Proposition . Hence, we may test (3.51) by y^α and obtain

$$\begin{aligned}
\frac{d}{dt} \int_{y_0}^{\infty} y^\alpha u_n(t, y) dy &= \alpha \tau v_n(t) \int_{y_0}^{\infty} y^{\alpha - 1} u_n(t, y) dy \\
&\quad - \int_{y_0}^{\infty} y^\alpha (\mu_n(y) + \beta_n(y)) u_n(t, y) dy \\
&\quad + 2 \int_{y_0}^{\infty} u_n(t, y) \beta_n(y) \int_{y_0}^{y} (y')^\alpha \kappa(y', y) dy' dy \\
&\leq \alpha \tau v_n(t) \int_{y_0}^{\infty} y^{(\alpha - 1)} u_n(t, y) dy
\end{aligned}$$

for $t \geq 0$, since (3.12) ensures

$$2\int_{y_0}^{y} (y')^{\alpha}\kappa(y',y)dy' \leq y^{\alpha}, \qquad \text{a.e. } y > y_0.$$

Therefore, Gronwall's inequality and estimate (3.52) yield (3.53). In particular, combining (3.53), (3.48) and (3.14) we deduce

$$g_n(u_n(t)) \leq 2y_0\|\varrho\|_\infty \|u_n(t)\|_{L_1(Y,y^\alpha dy)} \leq c(T), \qquad t \in J_T, \qquad n \geq 1.$$

(ii) It follows from (3.1) and the estimate on $g_n(u_n(t))$ that

$$|v_n(t) - v_n(s)| \leq c(T)|t-s|, \qquad t,s \in J_T, \qquad n \geq 1,$$

where $c(T) > 0$ is independent of $n \geq 1$. Taking (3.52) into account, the Arzelà-Ascoli theorem warrants that the sequence (v_n) is relatively compact in $C(J_T)$.
(iii) We show that (u_n) is relatively sequentially compact in $C(J_T, L_{1,w}(Y))$. According to a variant of the Arzelà-Ascoli theorem (see [[57], Thm.1.3.2]) we merely have to check that the set $\{u_n(t); n \geq 1\}$ is relatively compact in $L_{1,w}(Y)$ for every $t \in J_T$ and that the set $\{u_n; n \geq 1\}$ is equicontinuous in $L_{1,w}(Y)$ at every $t \in J_T$.
First observe that (3.52) entails

$$\lim_{R\to\infty} \sup_{n\geq 1 t\in J_T} \int_R^\infty u_n(t,y)dy = 0. \tag{3.54}$$

Let $U_{v_n}(t,s)$ denote the evolution system in $L_1(Y)$ corresponding to the operator $A_{v_n}(t) := \tau v_n(t)\partial_y$. Then

$$u_n(t) = U_{v_n}(t,0)u_n^0 + \int_0^t U_{v_n}(t,s)L_n[u_n(s)]ds, t \in J_T.$$

Consequently, given $\delta > 0$, Lemma and the positivity of $u_n(t)$ imply that

$$\begin{aligned}
\sup_{|\varepsilon|\le\delta} \int_\varepsilon u_n(t,y)dy \ &\le\ \sup_{|\varepsilon|\le\delta} \int_\varepsilon u_n^0(y)dy \\
&+2\int_0^t \sup_{|\varepsilon|\le\delta} \int_{y_0}^\infty u_n(s,y)\beta_n(y) \int_{y_0}^y \chi\varepsilon(y')\kappa(y',y)dy'dyds.
\end{aligned}$$

Since $u_n^0 \to u^0$ in $L_1(Y, y^\alpha dy)$ and in view of (3.49) and (3.53), we conclude that

$$\lim_{|\varepsilon|\to 0} \sup_{n\ge 1_{t\in J_T}} \int_\varepsilon u_n(t,y)dy = 0. \tag{3.55}$$

From (3.52), (3.54), (3.55) and the Dunford-Pettis theorem (cf. [[10], Thm.4.21.2]) we derive that $\{u_n(t); t\in J_T, n\ge 1\}$ is relatively compact in $L_{1,w}(Y)$.
Now let $\varphi \in D(Y)$ be arbitrary. Testing (3.51) by φ, we infer

$$\begin{aligned}
\left|\int_{y_0} \varphi(y)[u_n(t,y)-u_n(s,y)]dy\right| \ &\le\ \tau\int_s^t v_n(\sigma)\int_{y_0}^\infty |\varphi'(y)|u_n(\sigma,y)dyd\sigma \\
&+\int_s^t\int_{y_0}^\infty |\varphi(y)|(\mu_n(y)+\beta_n(y))u_n(\sigma,y)dyd\sigma \\
&+2\int_s^t\int_{y_0}^\infty u_n(\sigma,y)\beta_n(y)\int_{y_0}^y |\varphi(y')|\kappa(y',y)dy'dyd\sigma
\end{aligned}$$

for $0\le s\le t\le T$. Hence, from (3.14), (3.48), (3.52) and (3.53),

$$\left|\int_{y_0}^\infty \varphi(y)[u_n(t,y)-u_n(s,y)]dy\right| \le c(T,\varphi)|t-s|, \qquad t,s\in J_T. \tag{3.56}$$

For $\varphi\in L_\infty(Y)$ let $\varphi_j \to D(Y)$ be such that $\varphi_j\to\varphi$ a.e. and $\|\varphi_j\|_\infty \le \|\varphi\|_\infty$, (see [1,p.131f]). Given $\varepsilon>0$ it follows from (3.54), from the fact that $\{u_n(t); t\in J_T, n\ge 1\}$ is relatively compact in $L_{1,w}(Y)$, and from Egorov's theorem that there are $R > y_0$, a measurable subset ε of (y_0, R) and $j\in \mathbb{N}$ such that

$$\int_R^\infty u_n(t,y)dy + \int_\varepsilon u_n(t,y)dy \le \frac{\varepsilon}{12\|\varphi\|_\infty}, \qquad t\in J_T, \quad n\ge 1,$$

and

$$\|\varphi - \varphi_j\|_{L_\infty((y_0,R)\ \varepsilon)} \leq \frac{\varepsilon}{6c_0(T)},$$

where $c_0(T) > 0$ stems from (3.52). Therefore, (3.56) yields

$$\begin{aligned}
\left|\int_{y_0}^{\infty} \varphi(y)[u_n(t,y) - u_n(s,y)]dy\right| \leq\ & \|\varphi - \varphi_j\|_{L_\infty((y_0,R)\ \varepsilon)} (|u_n(t)|_1 + |u_n(s)|_1) \\
& + (\|\varphi\|_\infty + \|\varphi_j\|_\infty) \int_\varepsilon (u_n(t,y) + u_n(s,y))dy \\
& + (\|\varphi\|_\infty + \|\varphi_j\|_\infty) \int_R^\infty (u_n(t,y) + u_n(s,y))dy \\
& + c(T,\varphi_j)|t-s| \\
\leq\ & \varepsilon + c(T,\varphi_j)|t-s|
\end{aligned}$$

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

$$\lim_{s\to t} \sup_{n\geq 1} \left|\int_{y_0}^{\infty} \varphi(y)[u_n(t,y) - u_n(s,y)]dy\right| = 0,$$

hence $u_n; n \geq 1$ is equicontinuous in $L_{1,w}(Y)$ at every $t \to J_T$.

(iv) Since now (v_n, u_n) is relatively weakly compact in $C(J_T, \mathbb{R} \times L_{1,w}(Y))$ for each $T > 0$, we may choose a subsequence (again denoted by $((v_n, u_n))_{n\in\mathbb{N}}$) and a function $(v, u) \in C(\mathbb{R}^+, \mathbb{R} \times L_{1,w}(Y))$ such that

$$(v_n, u_n) \to (v, u) \text{ in } C(J_T, \mathbb{R} \times L_{1,w}(Y)) \tag{3.57}$$

for each $T > 0$.

(v) We then claim that (v, u) is a weak solution to (3.1)-(3.4). Evidently, it holds that $(v(t), u(t)) \in \mathbb{R}^+ \times L_1^+(Y)$ for $t > 0$ since $(v_n(t), u_n(t)) \in \mathbb{R}^+ \times L_1^+(Y)$. We fix again $T > 0$. Then (3.57) and (3.53) imply

$$\|u(t)\|_{L_1(Y, y^\alpha dy)} \leq c_0(T), \qquad t \in J_T, \tag{3.58}$$

in particular, we have $u \in L_{\infty,loc}(\mathbb{R}^+ L_1(Y, y^\alpha dy))$. Let $\varphi \in W^1_\infty(Y)$ be arbitrary. Clearly, (3.57) yields

$$\lim_{n\to\infty} \int_{y_0}^\infty \varphi(y) u_n(t,y)dy = \int_{y_0}^\infty \varphi(y)u(t,y)dy, \qquad t \in J_T. \tag{3.59}$$

Moreover, writing

$$\begin{aligned} \left| \int_0^t v(s) \int_{y_0}^\infty \varphi'(y)u(s,y)dyds - \int_0^t v_n(s) \int_{y_0}^\infty \varphi'(y)u_n(s,y)dyds \right| \\ \leq \int_0^t |v(s) - v_n(s)| \int_{y_0}^\infty |\varphi'(y)| u(s,y)dyds \\ + \int_0^t v_n(s) \left| \int_{y_0}^\infty \varphi'(y)[u(s,y) - u_n(s,y)]dy \right| ds \end{aligned}$$

for $t \in J_T$, we infer from (3.57), (3.52) and Lebesgue's theorem that, for $t \in J_T$,

$$\lim_{n\to\infty} \int_0^t v_n(s) \int_{y_0}^\infty \varphi'(y)u_n(s,y)dyds = \int_0^t v(s) \int_{y_0}^\infty \varphi'(y)u(s,y)dyds. \tag{3.60}$$

In addition, since $\mu_n(y) + \beta_n(y) \leq \varrho(y)y^\alpha$ for a.e. $y \in Y$, we conclude from Lemma 3.4.1 (ii), (3.53), (3.57) and Lebesgue's theorem that

$$\begin{aligned} \lim_{n\to\infty} \int_0^t \int_{y_0}^\infty \varphi(y) \left(\mu_n(y) + \beta_n(y)\right) u_n(s,y)dyds \\ = \int_0^t \int_{y_0}^\infty \varphi(y) \left(\mu(y) + \beta(y)\right) u(s,y)dyds \end{aligned}$$

as well as

$$\begin{aligned} \lim_{n\to\infty} \int_0^t \int_{y_0}^\infty \varphi(y) \int_y^\infty u_n(s,y')\beta_n(y')\kappa(y,y')dy'dyds \\ = \int_0^t \int_{y_0}^\infty \varphi(y) \int_y^\infty u(s,y')\beta(y')\kappa(y,y')dy'dyds, \end{aligned}$$

where we use Fubini's theorem for the second limit. Therefore,

$$\lim_{n\to\infty} \int_0^t \int_{y_0}^\infty \varphi(y) L_n[u_n(s)]dyds = \int_0^t \int_{y_0}^\infty \varphi(y) L[u(s)]dyds. \tag{3.61}$$

Now, since (v_n, u_n) is a weak solution to (3.1)-(3.4), we derive from (3.59)-(3.61) that u indeed satisfies part (iv) of Definition 3.4.1. Next, it follows from Lemma 3.4.1(ii), similarly as above, that

$$\lim_{n\to\infty} g_n(u_n(t)) = g(u(t)), \qquad t \in J_T,$$

and also

$$\lim_{n\to\infty} \int_0^t |u_n(s)|_1 ds = \int_0^t |u(s)|_1 ds, \qquad t \in J_T.$$

Consequently, (3.50) yields

$$v(t) = e^{-\gamma t - \tau \int_0^t |u(\sigma)|_1 d\sigma} v^0 + \int_0^t e^{-\gamma(t-s) - \tau \int_s^t |u(\sigma)|_1 d\sigma} \left(\lambda + g(u(s))\right) ds$$

for $t \in J_T$. But since $u \in C(\mathbb{R}^+, L_{1,w}(Y))$, Lemma 3.4.1(ii) and (3.58) warrant that $g(u) \in C(J_T)$. In addition, $|u|_1 \in C(J_T)$, so we deduce that $v \in C^1(J_T)$ solves (3.1). This proves the theorem. $\square$ Also the weak solution propagates with finite speed as shown in the next corollary.

Corollary 3.4.1 *Suppose (3.11)-(3.13), (3.48), (3.49). If $v^0 > 0$ and if $u^0 \in L_1^+(Y, y^\alpha dy)$ is such that supp$u^0 \subset [y_0, S_0]$, then the weak solution (v, u) provided by Theorem 3.4.1 satisfies supp$u(t) \subset [y_0, S(t)]$ for $t \geq 0$, where*

$$S(t) := S_0 + \tau \int_0^t v(s) ds, \qquad t \geq 0.$$

Proof: We may choose the sequence $(u_n^0) \subset D^+(Y)$ in the proof of Theorem 3.4.1 such that supp$u_n^0 \subset (y_0, S_0)$. Then Proposition 3.4 ensures that the approximating sequence $((v_n, u_n))_{n\in\mathbb{N}}$ given in (3.50), (3.51) satisfies supp$u_n(t) \subset [y_0, S_n(t)]$ for $t \geq 0$, where

$$S_n(t) := S_0 + \tau \int_0^t v_n(s) ds, \qquad t \geq 0, \qquad n \geq 1.$$

Evidently, $lim_{n\to\infty}S_n(t) = S(t)$ and

$$\int_{S(t)}^{\infty} u(t,y)dy = \lim_{n\to\infty}\int_{S_n(t)}^{\infty} u_n(t,y)dy = 0$$

by (3.57) and Lemma 3.4.1(i), thus supp$u(t) \subset [y_0, S(t)]$ for $t \geq 0$. □

Remark 3.4.1 *In addition to (3.11)-(3.13), (3.48), (3.49) suppose that* $\mu(y) \geq \underline{\mu} > 0$ *for a.e.* $y \in Y$ *and that* $\gamma > 0$*. Then the weak solution* (v,u) *also satisfies the estimates (3.46) and (3.47). Indeed, (3.46) follows immediately from the corresponding estimate for* (v_n, u_n) *and (3.57).*

3.5 Stability of the disease free steady state

This section is devoted to the investigation of stability properties of the disease-free steady state $(v,u) = (\lambda/\gamma, 0)$ of (3.1),(3.2).

In the sequel, we always assume that (3.11)-(3.13) are satisfied with $\gamma > 0$ and that either

$$\begin{cases} (3.10) \text{ holds },\\ v^0 > 0, \qquad u^0 \in E_1^+, \end{cases} \tag{3.62}$$

or

$$\begin{cases} (3.48), (3.49) \text{ hold},\\ v^0 > 0, \qquad u^0 \in L_1^+(Y, y^\alpha dy). \end{cases} \tag{3.63}$$

Then we denote by (v,u) either the classical solution provided by Theorem 3.4 if (3.62) holds, or the weak solution provided by Theorem 3.4.1 if (3.63) holds.

We assume that

$$d_0 := \text{ess-sup}_{y\in Y}\frac{\beta(y)}{y\mu(y)} \in (0,\infty),$$

and introduce ε_k, δ_k such that

$$0 \leq \delta_k \leq \beta(y)\int_0^{y_0}(y')^k\kappa(y',y)dy' \leq \varepsilon_k, \qquad \text{a.e.} \quad y \in Y,$$

for $k = 0, 1$, assuming at least ε_1 to be finite. In the following we suppose that

$$\underline{\mu} := \text{ess-inf}_{y \in Y} \mu(y) > 0, \tag{3.64}$$

and

$$\frac{1}{2d_0}(\underline{\mu} + 2\delta_0) > \frac{\tau\lambda}{2\gamma} + \varepsilon_1 - 2\delta_1 + \frac{2d_0\delta_1(\varepsilon_1 - \delta_1)}{\underline{\mu} + 2\delta_0}. \tag{3.65}$$

Given the assumptions above we can construct a Lyapunov function as follows.

Lemma 3.5.1 *Suppose (3.62) or (3.63) and that (3.64) and (3.65) are satisfied. Then there are constants $a, b, p, q > 0$ such that for*

$$F(v, u) := \left(v - \frac{\lambda}{\gamma}\right)^2 + a \int_{y_0}^{\infty} y u(y) dy + b \int_{y_0}^{\infty} u(y) dy,$$

there holds

$$F(v, u)(t) + p \int_0^t \int_{y_0}^{\infty} u(s, y) dy ds + q \int_0^t \int_{y_0}^{\infty} y u(s, y) dy ds \leq F(v^0, u^0),$$

for each $t \geq 0$, where (v, u) is either the classical solution or the weak solution constructed in Theorem 3.4 or Theorem 3.4.1, respectively.

Proof: Defining

$$A := \frac{\tau}{2}(\underline{\mu} + 2\delta_0) > 0, \qquad B := 2\delta_1 - \varepsilon_1 - \frac{\tau\lambda}{2\gamma}, C := 4\delta_1(\varepsilon_1 - \delta_1) \geq 0$$

and $d := \tau d_0/4$, (3.65) can be recast as

$$\frac{A}{4d} > -B + \frac{Cd}{A}.$$

Therefore, with

$$b := \frac{A}{4d^2} + \frac{C}{A} > \frac{C}{A} \geq 0$$

we have $bd < B + \sqrt{Ab - C}$, hence

$$0 < \frac{4}{\tau} bd < a < \frac{4}{\tau}\left(B + \sqrt{Ab - C}\right) \qquad \text{and} \ \frac{4}{\tau}\left(B + \sqrt{Ab - C}\right) < a \tag{3.66}$$

for $a := 2/\tau(\max bd, B - \sqrt{Ab - C} + B + \sqrt{Ab - C})$. We set

$$R := b(\underline{\mu} + 2\delta_0) + \frac{4\lambda\delta_1}{\gamma} - \frac{\tau\lambda^2}{2\gamma^2} - \frac{2\varepsilon_1^2}{\tau} - \frac{2\lambda\varepsilon_1}{\gamma}$$

and notice that $0 < Ab - C = B^2 + \tau R/2$, hence $p := -\tau a^2/8 + Ba + R > 0$ by (3.66). Since (3.66) also warrants that $d_0 < a/b$, we infer from (3.64) the existence of $q > 0$ such that

$$\text{ess-sup}_{y \in Y} \frac{\beta(y)}{y\mu(y)} + \frac{q}{b} \text{ess-sup}_{y \in Y} \frac{1}{\mu(y)} < \frac{a}{b}. \tag{3.67}$$

Now, in the case of the classical solution one can show directly that

$$\frac{d}{dt} F(v,u)(t) \leq -p|u(t)|_1 - q \int_{y_0}^{\infty} u(t,y) y dy, \qquad t \geq 0,$$

using estimates very close to the subsequent ones. We hence focus on the case of weak solutions. Let (v_n, u_n) be the approximations of (v,u) corresponding to the data $(v^0, u_n^0, \beta_n, \mu_n)$ as in the proof of Theorem 3.4.1 . Then it follows from (3.12), (3.14) and (3.18) that

$$\begin{aligned} \frac{d}{dt} F(v_n, u_n) \ &= \ -2\gamma \left(v_n - \frac{\lambda}{\gamma}\right)^2 - 2\tau v_n^2 |u_n|_1 + \frac{2\tau\lambda}{\gamma} v_n |u_n|_1 \\ &\quad +4\left(v_n - \frac{\lambda}{\gamma}\right) \int_{y_0}^{\infty} u_n(t)\beta_n(y) \int_0^{y_0} y' \kappa(y', y) dy' dy \\ &\quad + a\tau v_n |u_n|_1 - a \int_{y_0}^{\infty} y\mu_n(y) u_n(y) dy \\ &\quad -2a \int_{y_0}^{\infty} u_n(t)\beta_n(y) \int_0^{y_0} y'\kappa(y', y) dy' dy \\ &\quad -b \int_{y_0}^{\infty} y\mu_n(y) u_n(y) dy \\ &\quad +b \int_{y_0}^{\infty} u_n(y)\beta n(y) \left(1 - 2\int_0^{y_0} \kappa(y', y) dy'\right) dy. \end{aligned}$$

Recalling that $\underline{\mu} > 0$ and $\varepsilon_1 < \infty$, integration of the above equality yields (for $n > \underline{\mu}$)

$$\begin{aligned} F(v_n, u_n)(t) &+ \int_0^t |u_n(s)|_1 (2\tau v_n(s)^2 + b\underline{\mu}) ds \\ &+ \int_0^t \int_{y_0}^\infty u_n(s,y)\beta_n(y) \left[\left(\frac{4\lambda}{\gamma} + 2a \right) \int_0^{y_0} y'\kappa(y',y)dy' + 2b \int_0^{y_0} \kappa(y',y)dy' \right] dyds \\ &+ a \int_0^t \int_{y_0}^\infty y\mu_n(y)u_n(s,y)dyds \\ &\le F(v^0, u_n^0) + b \int_0^t \int_{y_0}^\infty u_n(s,y)\beta_n(y)dyds + \int_0^t |u_n(s)|_1 v_n(s)ds \left(\frac{2\tau\lambda}{\gamma} + a\tau + 4\varepsilon_1 \right). \end{aligned} \tag{3.68}$$

Observe then that (3.57) ensures

$$F(v,u)(t) \le \overline{\lim_{n\to\infty}} F(v_n, u_n)(t), \qquad t \ge 0. \tag{3.69}$$

Next, (3.57) and Lebesgue's theorem imply

$$\lim_{n\to\infty} \int_0^t |u_n(s)|_1 v_n(s) ds = \int_0^t |u(s)|_1 v(s) ds, \qquad t \ge 0. \tag{3.70}$$

As in (3.61) one shows that

$$\begin{aligned} \lim_{n\to\infty} \int_0^t \int_{y_0}^\infty u_n(s,y)\beta_n(y) \int_0^{y_0} (y')^k \kappa(y',y)dy'dyds \\ = \int_0^t \int_{y_0}^\infty u(s,y)\beta(y) \int_0^{y_0} (y')^k \kappa(y',y)dy'dyds \end{aligned} \tag{3.71}$$

for $k = 0, 1$. Owing to Lemma 3.4.1, (3.48), (3.52) and (3.57) we may apply Lebesgue's theorem to conclude

$$\begin{aligned} \lim_{n\to\infty} \int_0^t \int_{y_0}^\infty \chi_{(y_0,R)}(y) u_n(s,y)\mu_n(y) y dyds \\ = \int_0^t \int_{y_0}^\infty \chi_{(y_0,R)}(y) u(s,y)\mu(y) y dyds \end{aligned}$$

for each $R > y_0$, hence

$$\int_0^t \int_{y_0}^{\infty} u(s,y)\mu(y)ydyds \le \overline{\lim_{n\to\infty}} \int_0^t \int_{y_0}^{\infty} u_n(s,y)\mu_n(y)ydyds. \tag{3.72}$$

Thus, in view of (3.69)-(3.72) we may pass to the limit in (3.68) to deduce that this inequality is still true if we replace (v_n, u_n) by (v, u) and $(\beta n, \mu n)$ by (β, μ), respectively. Rearranging the terms and using the definition of δ_k we derive

$$\begin{aligned} F(v,u)(t) + \int_0^t |u(s)|_1 \left\{ 2\tau v(s)^2 - \left(\frac{2\tau\lambda}{\gamma} + a\tau + 4\varepsilon_1 \right) v(s) + b(\underline{\mu} + 2\delta_0) + \left(\frac{2\lambda}{\gamma} + 2a \right) \delta_1 \right\} ds \\ + \int_0^t \int_{y_0}^{\infty} (ay\mu(y) - b\beta(y))u(s,y)dyds \\ \le F(v^0, u^0) \end{aligned}$$

for each $t \ge 0$. Minimizing the quadratic function in the curly brackets and observing then that $p > 0$ is a lower bound, the assertion follows from (3.67). □

Remark 3.5.1 *In the case of rates subject to (3.5) it has already been observed in [4] that the function F defined in Lemma 3.5.1 is a Lyapunov function.*

The next theorem shows that the disease-free steady state is asymptotically stable.

Theorem 3.5.1 *Suppose (3.62) or (3.63) is satisfied and that (3.64), (3.65) hold. Then, given $\varepsilon > 0$ there exists $\delta > 0$ such that*

$$|v(t) - \lambda/\gamma| + \|u(t)\|_{E_0} \le \varepsilon, \qquad t \ge 0,$$

whenever

$$|v^0 - \lambda/\gamma| + \|u^0\|_{E_0} \le \delta,$$

where (v,u) is either the classical solution or the weak solution constructed in Theorem 3.4 or Theorem 3.4.1, respectively.

Moreover, if $\beta(y) \leq By$ for a.e. $y \in Y$ and some $B > 0$, then

$$(v(t), u(t)) \to (\lambda/\gamma, 0) \quad \textit{in} \quad \mathbb{R} \times L_1(Y, y^\alpha dy) \quad \textit{as} \quad t \to \infty$$

for each $\sigma < 1$ and any initial value (v^0, u^0) subject to (3.62) or (3.63).

Proof: Defining F as in Lemma 3.5.1, the first statement readily follows from the fact that $F(v,u)(t) \leq F(v^0, u^0)$ for $t \geq 0$. Next, Lemma 3.5.1 also ensures that

$$\|u(t)\|_{L_1(Y,ydy)} \leq \frac{1}{a} F(v^0, u^0), \qquad t \geq 0. \tag{3.73}$$

Furthermore, by definition of a weak solution we have

$$|u(t)|_1 = |u^0|_1 + \int_0^t \int_{y_0}^\infty L[u(s)](y)dyds, \qquad t \geq 0,$$

from which we infer that

$$\begin{aligned} \frac{1}{h}(|u(t+h)|_1 - |u(t)|_1) &= \frac{1}{h}\int_t^{t+h} \int_{y_0}^\infty L[u(s)](y)dyds \\ &\leq \frac{1}{h}\int_t^{t+h} \int_{y_0}^\infty u(s,y)\beta(y)dyds \\ &\leq B \sup_{s\geq 0} \|u(s)\|_{L_1(Y,ydy)}, \end{aligned}$$

for $t \geq 0$ and $h > 0$. Thus, (3.73) yields

$$|u(t+h)|_1 - |u(t)|_1 \leq ch, \qquad t, h > 0. \tag{3.74}$$

Lemma 3.5.1 also ensures that

$$\int_0^\infty |u(s)|_1 ds \leq \frac{1}{p} F(v^0, u^0). \tag{3.75}$$

Combining (3.74) and (3.75) we conclude that $lim_{t\to\infty}|u(t)|_1 = 0$, which, together with (3.73), warrants that for each $\sigma < 1$

$$u(t) \to 0 \quad \text{in} \quad L_1(Y, y^\alpha dy) \quad \text{as} \quad t \to \infty. \tag{3.76}$$

Finally, since $\varepsilon_1 < \infty$ both $g(u(t))$ and $|u(t)|_1$ tend to 0 as $t \to \infty$ due to (3.76). Since $v \in C^1(\mathbb{R}^+)$ solves (3.1), it is easy to check that $v(t)$ converges to λ/γ. □ The result above can be improved in the case of classical solutions as follows.

Corollary 3.5.1 *Suppose (3.62), (3.64), and (3.65) hold. Then the classical solution (v, u) corresponding to $v^0 > 0$ and $u^0 \in E_1^+$ satisfies*

$$(v, u) \to (\lambda/\gamma, 0) \quad \textit{in} \quad \mathbb{R} \times L_1(Y, ydy) \quad \textit{as} \quad t \to \infty.$$

Proof: Set

$$Q(t) := \int_{y_0}^{\infty} yu(t, y)dy \geq 0, \qquad t \geq 0.$$

Then $Q \in C^1(\mathbb{R}^+)$ according to Theorem 3.4. From Lemma 3.5.1 it follows that

$$Q(t) + \int_0^\infty Q(s)ds \leq c, \qquad t \geq 0. \tag{3.77}$$

In addition, $v(t) \leq c$ for each $t \geq 0$, whence

$$\dot{Q}(t) \leq \tau v(t)|u(t)|_1 \leq c, \qquad t \geq 0. \tag{3.78}$$

Consequently, we deduce $lim_{t\to\infty}Q(t) = 0$ from (3.77) and (3.78). □

Remarks 3.5.1 *(a) As was pointed out in the introduction, equations (3.1), (3.2) are no longer coupled in case the rates are subject to (3.5), since v is then completely determined for all $t \geq 0$. In this case the results in [3] yield a semiflow in the natural phase space $\mathbb{R}^+ \times L_1^+(Y, ydy)$, whereas Theorem 3.4.1 guarantees existence of weak* *solutions only for initial values* $(v^0, u^0) \in \mathbb{R}^+ \times L_1^+(Y, y^\alpha dy)$ *with* $\alpha > 1$. *However, in this particular case it can be easily verified that the function* (v, u) *in (3.57) satisfies Definition 3.4.1 for any initial value* $(v^0, u^0) \in \mathbb{R}^+ \times L_1^+(Y, ydy)$, *provided one takes test functions* $\varphi \in W_\infty^1(Y)$ *with compact support. For this one should note that* $\lim_{y\to\infty} \varrho(y) = 0$ *is merely required for step (v) in the proof of Theorem 3.4.1.*

(b) *If the kernels are of the form (3.5), then we may take* $d_0 = \beta/\mu$, $\delta_0 := \beta y_0$ *and* $\varepsilon_1 := \delta_1 := \beta y_0^2/2$, *so (3.65) is equivalent to (3.9). We should like to point out that in this case the authors in [3] prove that the disease-free steady state is globally exponentially stable in* $\mathbb{R}^+ \times L_1^+(Y, ydy)$, *and asymptotically stable if* $\beta y_0 + \mu = \sqrt{\beta\lambda\tau/\gamma}$.

(c) *If the rates are subject to (3.5) it has already been observed in [4] that system (3.1)-(3.2) admits also a non-trivial (disease) steady state, provided the inequality in (3.9) is reversed. It is shown in [3] that this steady state is again globally asymptotically stable in* $R^+ \times L_1^+(Y, ydy)$. *For general rates as in the present work, existence of other equilibria besides* $(\lambda/\gamma, 0)$ *is an open problem.*

Chapter 4

EXISTENCE RESULTS FOR PRION DISEASE MODEL WITH IMPULSE EFFECTS

4.1 Introduction

In this chapter we consider a model describing prion polymerization, our model is inspired from those of Webb and collaborators (see [19], [49]), it is constituted by a differential equation modeling the evolution of PrP^c and partial differential equation describing the PrP^{sc} evolution. With perturbations represented by impulse effects, which could be the protein produced naturally by the organism discretely in order to fill the gap in monomers polymerized, or the protein administered to mice during laboratory experiments. More specifically we consider the following system

$$\begin{cases} v'(t) = \lambda - \gamma v(t) - \tau v(t) \displaystyle\int_{x_0}^{\infty} u(t,x)dx \\ \qquad +2 \displaystyle\int_0^{x_0} x \int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(t,y)dydx, \ t \neq t_i, \quad i = 1,2,\ldots, \\ v(t_i^+) - v(t_i^-) = \lambda_i, \quad \lambda_i > 0, \quad i = 1,2,\ldots, \\ \partial_t u(t,x) + \tau v(t)\partial_x u(t,x) + (\mu(x) + \beta(x))u(t,x) \\ \qquad = 2 \displaystyle\int_x^{\infty} \beta(y)\kappa(x,y)u(t,y)dy, \end{cases} \tag{4.1}$$

for $t \geq 0$, $x \in [x_0, +\infty)$ and fixed $x_0 > 0$.

The aim of this work is investigating mathematically existence, uniqueness and positivity of solutions of (4.1).

4.2 Preliminaries

Let $(X, \|\cdot\|)$ be a separable Banach space, $J = [0,b]$ an interval in $\mathbf{R}$ and $C(J,X)$ the Banach space of all continuous and bounded functions from J into X with the norm

$$\|y\|_\infty = \sup\{\|y(t)\|\colon\ t \in J\}.$$

$L(X)$ refers to the Banach space of linear bounded operators from X to X with the norm

$$\|N\|_{L(X)} = \sup\{\|N(y)\|\colon\ \|y\| = 1\}.$$

A function $y\colon J \to X$ is called measurable provided, for every open subset $V \subset X$, the set $y^{-1}(V) = \{t \in J\colon\ y(t) \in V\}$ is Lebesgue measurable. A measurable function $y\colon J \to X$ is Bochner integrable if $\|y\|$ is Lebesgue integrable. For properties of the Bochner integral see Yosida [60]. In what follows $L^1(J,X)$ denotes the Banach space of functions $y\colon\ J \longrightarrow X$, which are Bochner integrable with the norm

$$|y|_1 = \int_0^b \|y(t)\| dt.$$

Definition 4.2.1 *A family of operators* $\{U(t,s)\}_{t\geq s} \subset L(X)$ *with* $t,s \in \mathbf{R}$ *or* $t,s \in \mathbf{R}_+$, *is called an evolution family if it satisfies the conditions:*

(i) $U(t,r) = U(t,s) \circ U(s,r), \quad$ *for* $t \geq s \geq r$.

(ii) $U(t,t) = I$, *here* I *denotes the identity operator in* X.

(iii) for each $x \in X$, *the function* $(t,s) \to U(t,s)x$ *is continuous for* $t \geq s$.

In what follows, for the family $\{A(t), t \in J\}$ of closed densely defined linear unbounded operators on the Banach space X, we assume that it satisfies the following assumptions (see [12], [43]).

(i) The domain $D = D(A(t))$ is independent of t and is dense in X.

(ii) For $t \geq 0$, the resolvent $R(\xi, A(t)) = (\xi I - A(t))^{-1}$ exists for all ξ with $Re\ \xi \leq 0$ and there is a constant M independent of ξ and t, such that

$$\|R(\xi, A(t))\|_{L(X)} \leq M(1 + |\xi|)^{-1} \text{ for } Re\ \xi \leq 0.$$

(iii) There exist constants $R_0 > 0$ and $0 < \alpha \leq 1$ such that

$$\|(A(t) - A(s))A^{-1}(\theta)\|_{L(X)} \leq R_0|t - \theta|^{\alpha} \text{ for } t, s, \theta \in J.$$

(iv) The mapping $(s, b] \ni t \to U(t,s) \in L(X)$ is continuous with respect to the uniform operator topology of $L(X)$. Moreover, this continuity is uniform with respect to s lying in sets bounded away from t, i.e. as long as $t - s \geq \alpha_*$ for any fixed $\alpha_* > 0$.

Definition 4.2.2 *The solution operator $U(t,s)$ is called exponentially bounded if there are constants $Z(U) > 0$ and $\omega \geq 0$ such that*

$$\|U(t,s)\|_{L(X)} \leq Z(U)e^{-\omega(t-s)} \text{ for } t,s \geq 0.$$

More details on evolution families can be found in Engel and Nagel [12] and Pazy [43].
Consider the following problem

$$\begin{cases} u'(t) + v(t)Au(t) + Bu(t) = f(t,u(t)), & t \in J := [0,b], \\ u(0) = u_0, \end{cases} \tag{4.2}$$

where $u_0 \in \mathbf{R}$, $u \in X$, $v : J \to \mathbf{R}$ is a continuous function except on a finite set $\{t_i\}_{1 \leq i \leq p} \subset J$, $p \in \mathbb{N}$ with $\lim_{t \to t_i^-} v(t)$, $\lim_{t \to t_i^+} v(t)$ exist, $v(t_i^-) = v(t)$, $f : J \times X \to X$ is a given function, A generates a strongly continuous semigroup $\{T(t)\}$ in X satisfying $\|T(t)\|_{L(X)} \leq Me^{\omega t}$ with $M \geq 1$, $\omega \in \mathbf{R}$ and B is a linear bounded operator.
Let $A_v(t) = v(t)A + B$. Since A generates a C_0-semigroup and B is bounded, a well-known perturbation result (see [43], Thm 3.1.1) ensures that, for any $s \in J$, $A_v(t)$ generates a strongly continuous semigroup on X.
Then (4.2) becomes

$$\begin{cases} u'(t) + A_v(t)u(t) = f(t,u(t)), & t \in J, \\ u(0) = u_0. \end{cases} \tag{4.3}$$

Let $U_v(t,s)$ for $0 \leq s < t \leq b$, be the evolution system generated by $\{A_v(t)\}_{t \in J}$, then

$$\|U_v(t,s)\|_{L(X)} \leq Me^{\omega(t-s)}, \tag{4.4}$$

where $M > 1$, $\omega \in \mathbf{R}$ and $0 \leq s < t \leq b$.

Definition 4.2.3 *$u \in C(J,X)$ is a mild solution of (4.3) if*

$$u(t) = U_v(t,0)u_0 + \int_0^t U_v(t,s)f(s,u(s))ds, \qquad t \in J. \tag{4.5}$$

Theorem 4.2.1 *(Nonlinear Alternative [17]). Let X be a Banach space with $C \subset X$ closed and convex. Assume Ω is a relatively open subset of C with $0 \in \Omega$ and $G : \overline{\Omega} \to C$ is a compact map. Then either*

(i) G has a fixed point in $\overline{\Omega}$, or

(ii) there is a point $u \in \partial\Omega$ and $\sigma \in (0,1)$ with $u = \sigma G(u)$.

4.3 Existence results

Theorem 4.3.1 *Assume that f is a continuous function and there exists $h \in L^1(J, \mathbf{R}_+)$ such that*

$$\|f(t,u_1) - f(t,u_2)\| \leq h(t)\|u_1 - u_2\|, \qquad \forall u_1, u_2 \in X, \ a.e. \ t \in J.$$

Then (4.3) has a unique mild solution.

Proof: Consider the following map $N : C(J,X) \to C(J,X)$ defined by

$$(Nu)(t) = U_v(t,0)u_0 + \int_0^t U_v(t,s)f(s,u(s))ds, \quad t \in J, \tag{4.6}$$

clearly the fixed points of N are mild solutions of the problem (4.3).
Let $K = \sup\{Me^{\omega(t-s)}, 0 \leq s < t \leq b\}$, then $\|U_v(t,s)\|_{L(X)} \leq K$ for $0 \leq s \leq t \leq b$.
For $u \in C(J,X)$, let $\|u\|_1 = \sup_{t\in[0,b]}\{\exp\left(-\rho\int_0^t h^*(s)ds\right)\|u(t)\|\}$ and $\rho > 1$, where

$$h^*(t) = Kh(t), \quad t \in J.$$

Let $u_1, u_2 \in C(J,X)$ for all $t \in J$, we have

$$\begin{aligned}
\|(Nu_1)(t) - (Nu_2)(t)\| &\leq \int_0^t \|U_v(t,s)\|_{L(X)} \|f(s,u_1(s)) - f(s,u_2(s))\| ds \\
&\leq \int_0^t Kh(s)\|u_1(s) - u_2(s)\| ds \\
&\leq \frac{1}{\rho}\int_0^t \rho h^*(s) e^{\rho \int_0^s h^*(r)dr} ds \|u_1 - u_2\|_1 \\
&= \frac{1}{\rho}\int_0^t \left[e^{\rho \int_0^s h^*(r)dr} \right]' ds \|u_1 - u_2\|_1 \\
&\leq \frac{1}{\rho} e^{\rho \int_0^t h^*(s)ds} \|u_1 - u_2\|_1.
\end{aligned}$$

Therefore

$$e^{-\rho \int_0^t h^*(s)ds} \|(Nu_1)(t) - (Nu_2)(t)\| \leq \frac{1}{\rho}\|u_1 - u_2\|_1.$$

Hence

$$\|Nu_1 - Nu_2\|_1 \leq \frac{1}{\rho}\|u_1 - u_2\|_1, \text{ for all } u_1, u_2 \in C(J,X).$$

Hence N is a contraction, and then from Banach theorem of contraction [17], N has a unique solution which is a solution of the problem (4.3). □

Theorem 4.3.2 *Suppose that the following hypotheses are satisfied:*

($\mathcal{H}_1$) f is a continuous function.

($\mathcal{H}_2$) $U_v(t,s)$ is compact for $t - s > 0$ and since U_v is exponentially bounded then there exist $K_0 > 0$ such that $\|U_v(t,s)\|_{L(X)} \leq K_0$ for $t - s > 0$.

($\mathcal{H}_3$) There exist a continuous nondecreasing function $\psi : [0,\infty) \to [0,\infty)$ and $p \in L^1(J, \mathbf{R}_+)$ such that

$$\|f(t,y)\| \leq p(t)\psi(\|y\|), \quad t \in J, \quad y \in X$$

and

$$K_0 \int_0^b p(s)ds < \int_{K_0\|u_0\|}^{+\infty} \frac{dx}{\psi(x)}.$$

Then the problem (4.3) has at least one mild solution.

Proof: The solutions of the problem (4.3) are the fixed points of N defined by (4.6). In order to apply the nonlinear alternative of Leray-Schauder type, we first show that N is completely continuous. The proof will be given in several steps.

- *Step 1:* N sends bounded sets into bounded sets in $C(J, X)$.

  For each $t \in J$ and $u \in \overline{B}(0, r)$, we have

$$\begin{aligned} \|(Nu)(t)\| &\leq \|u_0\|\|U_v(t,0)\|_{L(X)} + \int_0^t \|U_v(t,s)\|_{L(X)}\|f(s,u(s))\|ds, \\ &\leq K_0\|u_0\| + K_0 \int_0^t p(s)\psi(\|u(s)\|)ds, \\ &\leq K_0\|u_0\| + K_0|p|_1\psi(r) := l \end{aligned}$$

- *Step 2:* N maps bounded sets into equicontinuous sets.

  Let $t_1, t_2 \in J$ such that $t_1 < t_2$ and $u \in \overline{B}(0, r)$, we have

$$\begin{aligned} \|(Nu)(t_2) - (Nu)(t_1)\| \quad \leq \quad & \|u_0\|\|U_v(t_2,0) - U_v(t_1,0)\|_{L(X)} \\ & + \int_{t_1}^{t_2} \|U_v(t_2,s)\|_{L(X)}\|f(s,u(s))\|ds \\ & \int_0^{t_1} \|U_v(t_2,s) - U_v(t_1,s)\|_{L(X)}\|f(s,u(s))\|ds. \end{aligned}$$

  Then

$$\begin{aligned} \|(Nu)(t_2) - (Nu)(t_1)\| \quad \leq \quad & \|u_0\|\|U_v(t_2,0) - U_v(t_1,0)\|_{L(X)} \\ & + \int_{t_1}^{t_2} \|U_v(t_2,s)\|_{L(X)}p(s)\psi(r)ds \\ & + \int_0^{t_1} \|U_v(t_2,s) - U_v(t_1,s)\|_{L(X)}p(s)\psi(r)ds. \end{aligned}$$

  From the compactness of U_v, we have $\|U_v(t_2,s) - U_v(t_1,s)\|_{L(X)} \to 0$ when $t_1 \to t_2$, hence $\|(Nu)(t_2) - (Nu)(t_1)\| \to 0$ when $t_1 \to t_2$.

Now, we show that $H(t) = \{(Nu)(t),\ u \in \overline{B}(0,r)\}$ is a precompact set in X. Let $0 < t \leq b$ and $0 < \epsilon < t$, for $u \in \overline{B}(0,r)$ we put

$$\begin{aligned}(N_\epsilon u)(t) \quad &:= U_v(t,0)u_0 + \int_0^{t-\epsilon} U_v(t,s)f(s,u(s))ds \\ &= U_v(t,t-\epsilon)\left(U(t-\epsilon,0)u_0 + \int_0^{t-\epsilon} U_v(t-\epsilon,s)f(s,u(s))ds\right)\end{aligned}$$

Since $U(t,t-\epsilon)$ is compact for every $\epsilon > 0$ the set

$$\begin{aligned}H_\epsilon(t) \quad &= \quad \{(N_\epsilon u)(t) :\ u \in \overline{B}(0,r)\} \\ &= \quad U_v(t,t-\epsilon)\times \\ &\qquad \{U(t-\epsilon,0)u_0 + \int_0^{t-\epsilon} U_v(t-\epsilon,s)f(s,u(s))ds : u \in \overline{B}(0,r)\}\end{aligned}$$

is precompact in X. Moreover for every $u \in \overline{B}(0,r)$ we have

$$\|(Nu)(t) - (N_\epsilon u)(t)\| \quad \leq \quad K\int_{t-\epsilon}^{t} p(s)\psi(r)ds$$

which tends to 0 as $\epsilon \to 0$. Therefore, there are precompact sets arbitrarily closed to the set $H(t)$. Then $H(t)$ is precompact in X. It is clear that $H(0) = \{u_0\}$ is precompact in X. Hence for each $t \in [0,b]$ the set $H(t)$ is precompact in X.

- *Step 3:* N is continuous.

  Let $(u_n)_{n\in\mathbb{N}}$ be a sequence such that $u_n \to u$ in $C(J,X)$. Then there exist $r > 0$ such that $\|u_n\|_\infty \leq r$ for all $n \in \mathbb{N}$ and $\|u\|_\infty \leq r$. We have

$$\|(Nu_n)(t) - (Nu)(t)\| \leq \int_0^b \|U_v(t,s)\|_{L(X)}\|f(s,u_n(s)) - f(s,u(s))\|ds,$$

then

$$\|(Nu_n)(t) - (Nu)(t)\| \leq K_0\int_0^b \|f(s,u_n(s)) - f(s,u(s))\|ds.$$

From the continuity of f, we have

$$\|Nu_n - Nu\|_\infty \leq bK_0\|f(\cdot, u_n(\cdot)) - f(\cdot, u(\cdot))\|_\infty \to 0 \text{ as } n \to \infty,$$

then N is continuous.

- *Step 4: A priori* estimates.

  Now, we show that there exists a constant $M_0 > 0$ such that $\|u\|_\infty \leq M_0$ where u is a solution of the problem (4.3).

  Let u be a solution of (2.2) for $t \in J$, we have

$$\begin{aligned}\|u(t)\| &\leq \|u_0\|\|U_v(t,0)\|_{L(X)} + \int_0^t \|U_v(t,s)\|_{L(X)}\|f(s,u(s))\|ds, \\ &\leq K_0\|u_0\| + K_0\int_0^t p(s)\psi(\|u(s)\|)ds.\end{aligned}$$

  Then

$$\|u\|_\infty \leq \Gamma^{-1}(K_0\int_0^b p(s)ds),$$

  where $\Gamma(z) = \displaystyle\int_{K_0\|u_0\|}^z \frac{dx}{\psi(x)}$.

Let $\mathcal{V} = \{u \in C(J,X) : \|u\|_\infty < M_0 + 1\}$. As a consequence of steps 1 to 4 and together with the Ascoli-Arzela theorem [17], we conclude that the map $N : \overline{\mathcal{V}} \to X$ is completely continuous.

From the choice of $\mathcal{V}$ there is no $u \in \partial\mathcal{V}$ such that $u = \sigma Nu$ for any $\sigma \in (0,1)$. As a consequence of the nonlinear alternative of Leray-Schauder (theorem 4.2.1) we deduce that there exist $u \in \overline{\mathcal{V}}$, such that $N(u) = u$ is a fixed point of N which is a mild solution of the problem (4.3). □

4.4 Application to prion disease model

Consider the prion disease model given by (4.1) for $t \in J := [0, b]$.

The variables and parameters of the model are

- $v(t)$ is the number of PrP^c monomers at time t,
- $u(t, x)$ is the density of PrP^{sc} polymers of length x at time t,
- x_0 is the lower bound for polymer length (that is polymers have length x with $x_0 < x < \infty$),
- λ is the source rate for PrP^c monomers produced continuously,
- λ_i is the number of monomers PrP^c produced discretely at time t_i,
- γ is the metabolic degradation rate for PrP^c,
- τ is the rate associated with lengthening of PrP^{sc} polymers by attaching to and converting PrP^c monomers,
- $\beta(x)$ is length-dependent rate of polymer breakage,
- $\kappa(x, y)$ is the probability, when a polymer of length y breaks, that one of the two resulting polymers has length x,
- $\mu(x)$ is the length-dependent metabolic degradation rate of PrP^{sc} polymers having length x.

The kernel $\kappa(y, x)$ should satisfy the following properties:

$$\kappa(y, x) \geq 0, \quad \kappa(y, x) = \kappa(x - y, x), \quad \int_0^x \kappa(y, x)dy = 1,$$

for all $x \geq x_0, y \geq 0$,

$$\begin{aligned} \kappa(y, x) &= 1/x, && \text{if} \quad x > x_0 \quad \text{and} \quad 0 < y < x. \\ \kappa(y, x) &= 0, && \text{elsewhere.} \end{aligned}$$

We consider the case where $\beta(x) \equiv \beta$ and $\mu(x) \equiv \mu$ are constant. Then for $t \in J$, $x \in Y := [x_0, +\infty)$, $u^0 \in D$ and $u \in L^1(Y)$, we may rewrite (1.1) as

$$\begin{cases} v'(t) = \lambda - \gamma v(t) - \tau v(t)|u|_1 + \beta x_0^2 |\kappa u|_1, & t \neq t_i, \\ v(t_i^+) - v(t_i) = \lambda_i, \quad \lambda_i > 0, \quad i \in \mathbb{N}^*, \\ v(0) = v^0, \end{cases} \tag{4.7}$$

and

$$\begin{cases} \partial_t u(t,x) + \tau v(t) \partial_x u(t,x) + (\mu + \beta) u(t,x) = 2\beta \int_x^\infty \kappa(x,y) u(y) dy, \\ u(t, x_0) = 0, \quad u(0,x) = u^0(x), \end{cases} \tag{4.8}$$

where $|u|_1 = \int_{x_0}^\infty |u(y)| dy$.

Set $D := \{u^0 \in L^1(Y) \cap W^{1,1}(\mathbf{R}) : x^2 u^0, (u^0)', x(u^0)' \in L^1(Y), u^0(x) = 0 \text{ for } x \leq x_0\}$.

Let $J_i = (t_i, t_{i+1})$, $i = 0, \ldots, p$, and v_i be the restriction of a function y to J_i.

Consider the following spaces

$PC = \{y\colon\ J \to X,\ v_i \in C(J_i, X),\ i = 0, \ldots, p,$ such that $v(t_i^-)$ and $y(t_i^+)$ exist and satisfy $v(t_k^-) = v(t_k)$ for $i = 0, \ldots, p\}$ with the norm $\|v\|_{PC} = \max\{\|v_k\|_\infty,\ i = 0, \ldots, p\}$, $PC^1(J, \mathbf{R}) = \{v \in PC : v \in C^1(J_i, \mathbf{R}), \exists v'(t_i^+), v'(t_i^-), i = 1, \ldots, p\}$ with the norm $\|v\|_{PC^1} = \max\{\|v\|_{PC}, \|v'\|_{PC}\}$ and $X := L^1(Y; (a+x)dx)$ where $a > 0$, with the norm defined by $\|y\|_X = a|y|_1 + |xy|_1$.

Then $(PC, \|\cdot\|_{PC})$, $(PC^1, \|\cdot\|_{PC^1})$ and $(X, \|\cdot\|_X)$ are Banach spaces.

For $\overline{u} \in C(J, X)$, the solution of (4.1) is given by

$$\begin{aligned} v_{\overline{u}}(t) &= \sum_{0 < t_j \leq t \leq b} \lambda_j e^{\left(-\gamma(t - t_j) - \tau \int_{t_j}^t |\overline{u}(s)|_1 ds\right)} + v^0 e^{\left(-\gamma t - \tau \int_0^t |\overline{u}(s)|_1 ds\right)} \\ &\quad + \beta x_0^2 \int_0^t |\kappa \overline{u}(s)|_1 e^{\left(-\gamma(t-s) - \tau \int_s^t |\overline{u}(\sigma)|_1 d\sigma\right)} ds + \lambda \left(\frac{1 - e^{-(\gamma+\tau)t}}{\gamma + \tau} \right). \end{aligned}$$

Let $v = v_{\overline{u}}$, the problem (4.8) is written as in (4.3) with

$$A_{v_{\overline{u}}}(t) = v_{\overline{u}}(t) \partial_x u(x) + (\mu + \beta) u(x), \qquad \text{for } x \in Y, \quad t \in J$$

and

$$f(t,u(t,x)) = 2\beta \int_x^{\infty} \kappa(x,y)u(t,y)dy, \quad \text{with} \qquad f: J\times X \to X.$$

Then for $(s,t)\in\Delta := \{(t,s)\in J^2, t\geq s\}$, the evolution problem for (4.8) is given by (see [13])

$$\left[U_{v_{\overline{u}}}(t,s)u^0\right](x) = u^0\left(x - \textstyle\int_s^t v_{\overline{u}}(\sigma)d\sigma\right)e^{-\phi(t,s)}, \tag{4.9}$$

where $\phi(t,s) = (\mu+\beta)(t-s)$.

Lemma 4.4.1 *The two parameter family linear operators $U_{v_{\overline{u}}}(t,s)$ is an exponentially bounded evolution semi-group system.*

Proof: $U_{v_{\overline{u}}}$ is an exponentially bounded evolution semi-group system if the following conditions are satisfied:

- $U_{v_{\overline{u}}}(s,s) = I$, $U_{v_{\overline{u}}}(t,r)U_{v_{\overline{u}}}(r,s) = U_{v_{\overline{u}}}(t,s)$, for $(s,r,t)\in J^3$ with $s\leq r\leq t$.
- $\|U_{v_{\overline{u}}}(t,s)\|_{L(X)} \leq K_* e^{-(\mu+\beta)(t-s)}$ for $(s,t)\in\Delta$ and some $K_*>0$.
- $(t,s)\to U_{v_{\overline{u}}}(t,s)$ is strongly continuous for $(s,t)\in\Delta$.

(i) Let us show that $U_{v_{\overline{u}}}(s,s) = I$, we have

$$\left[U_{v_{\overline{u}}}(s,s)u^0\right](x) = u^0\left(x - \int_s^s v_{\overline{u}}(\sigma)d\sigma\right)e^{-\phi(s,s)}$$

with $\phi(s,s) = (\mu+\beta)(s-s) = 0$, hence
$\left[U_{v_{\overline{u}}}(s,s)u^0\right](x) = u^0\left(x - \int_s^s v_{\overline{u}}(\tau)d\tau\right)e^0 = u^0(x) = (Iu^0)(x)$, then $U_{v_{\overline{u}}}(s,s) = I$.
Now, let us show that $U_{v_{\overline{u}}}(t,r)U_{v_{\overline{u}}}(r,s) = U_{v_{\overline{u}}}(t,s)$. We have

$$\begin{aligned}
\left[U_{v_{\overline{u}}}(t,r)U_{v_{\overline{u}}}(r,s)\right]u^0(x) &= U_{v_{\overline{u}}}(t,r)\left[U_{v_{\overline{u}}}(r,s)u^0\right](x) \\
&= U_{v_{\overline{u}}}(t,r)u^0(x - \int_s^r v_{\overline{u}}(\sigma)d\sigma)e^{-\phi(r,s)} \\
&= u^0(x - \int_s^r v_{\overline{u}}(\sigma)d\sigma - \int_r^t v_{\overline{u}}(\sigma)d\sigma)\times \\
&\quad e^{-\phi(r,s)-\phi(t,r)} \\
&= u^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)e^{-\phi(t,s)},
\end{aligned}$$

then

$$[U_{v_{\overline{u}}}(t,r)U_{v_{\overline{u}}}(r,s)]\, u^0(x) = U_v(t,s)u^0(x).$$

(ii) Let $u^0 \in D$, $x \in Y$ and $(t,s) \in \Delta$, we get

$$\|(U_{v_{\overline{u}}}(t,s)u^0)\|_X = \int_{x_0}^{\infty} u^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)e^{-\phi(t,s)}(a+x)dx.$$

Since $(U_{v_{\overline{u}}}(t,s)u^0)(x) = 0$ for $x - \int_s^t v_{\overline{u}}(\sigma)d\sigma \le x_0$ and $(U_{v_{\overline{u}}}(t,s)u^0)(x) = u^0\left(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma\right)e^{-\phi(t,s)}$ for $x - \int_s^t v_{\overline{u}}(\sigma)d\sigma > x_0$, we obtain

$$\begin{aligned}
\|(U_{v_{\overline{u}}}(t,s)u^0)\|_X \;\; &\le \;\; e^{-(\mu+\beta)(t-s)}\Big[a\int_{x_0}^{\infty} u^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)dx \\
&\quad + \int_{x_0}^{\infty} xu^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)dx\Big] \\
&\le \;\; e^{-(\mu+\beta)(t-s)}\Big[a\int_{x_0-\int_s^t v_{\overline{u}}(\sigma)d\sigma}^{\infty} u^0(y)dy \\
&\quad + \int_{x_0-\int_s^t v_{\overline{u}}(\sigma)d\sigma}^{\infty} yu^0(y)dy \\
&\quad + \int_{x_0-\int_s^t v_{\overline{u}}(\sigma)d\sigma}^{\infty} (\int_s^t v_{\overline{u}}(\sigma)d\sigma)u^0(y)dy\Big].
\end{aligned}$$

Since $0 \le \int_0^b v_{\overline{u}}(\sigma)d\sigma < \infty$ there exists $M_* \ge 0$ such that $\int_0^b v_{\overline{u}}(\sigma)d\sigma \le M_* a$. Then, we get

$$\begin{aligned}
\|(U_{v_{\overline{u}}}(t,s)u^0)\|_X \;\; &\le e^{-(\mu+\beta)(t-s)}\Big[a\int_{x_0}^{\infty} u^0(y)dy + \int_{x_0}^{\infty} yu^0(y)dy \\
&\quad + \int_{x_0}^{\infty} M_* a u^0(y)dy\Big] \\
&\le (M_*+1)e^{-(\mu+\beta)(t-s)}\int_{x_0}^{\infty}(a+y)u^0(y)dy.
\end{aligned}$$

Hence

$$\|(U_{v_{\overline{u}}}(t,s)u^0)\|_X \le (M_*+1)e^{-(\mu+\beta)(t-s)}\|u^0\|_X.$$

We obtain

$$\|U_{v_{\overline{u}}}(t,s)\|_{L(X)} \leq (M_* + 1)e^{-(\mu+\beta)(t-s)}.$$

(iii) Continuity of $U_{v_{\overline{u}}}$.

Let $u^0 \in D$ and $(t,s) \in \Delta$, then

$$\begin{aligned}
\|U_{v_{\overline{u}}}(t,s)u^0 - u^0\|_X &\leq a\int_{x_0}^{\infty} |(U_{v_{\overline{u}}}(t,s)u^0)(x) - u^0(x)|dx \\
&\quad + \int_{x_0}^{\infty} |x((U_{v_{\overline{u}}}(t,s)u^0)(x) - u^0(x))|dx \\
&\leq a\int_{x_0}^{\infty} |u^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)e^{-\phi(t,s)} - u^0(x)|dx \\
&\quad + \int_{x_0}^{\infty} |x(u^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)e^{-\phi(t,s)} - u^0(x))|dx.
\end{aligned}$$

Using the fact that $u^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)e^{-\phi(t,s)} \to u^0(x)$ as $s \to t$ and $xu^0(x - \int_s^t v_{\overline{u}}(\sigma)d\sigma)e^{-\phi(t,s)} \to xu^0(x)$ as $s \to t$. The Lebesgue dominated convergence theorem implies that $\|(U_{v_{\overline{u}}}(t,s)u^0) - u^0\|_X \to 0$ as $s \to t$.

□

Then for $v = v_{\overline{u}}$ the solution of (4.8) is given by

$$u(t) = U_{v_{\overline{u}}}(t,0)u^0 + \int_0^t U_{v_{\overline{u}}}(t,s)f(s,u(s))ds. \tag{4.10}$$

Theorem 4.4.1 *The problem (4.8) has a unique mild solution $u \in C(J,X)$.*

Proof: To have existence and uniqueness of solution of (4.10), we have to verify the conditions of theorem 4.3.1.

In fact, let $u_1, u_2 \in X$ then for $t \in J$ and $x \geq x_0$, we have

$$\begin{aligned}
\|f(t,u_1) - f(t,u_2)\|_X &\leq \int_{x_0}^{\infty} 2\beta \left| \int_x^{\infty} \kappa(x,y)(u_1(y) - u_2(y))dy \right| (a+x)dx \\
&\leq 2\beta \int_{x_0}^{\infty} |u_1(y) - u_2(y)|dy \int_{x_0}^{y} \kappa(x,y)(a+x)dx \\
&\leq 2\beta \int_{x_0}^{\infty} |u_1(y) - u_2(y)| \frac{(ay + \frac{y^2}{2})}{y} dy \\
&\leq 2\beta \int_{x_0}^{\infty} |u_1(y) - u_2(y)|(a+y)dy \\
&\leq 2\beta \|u_1 - u_2\|_X .
\end{aligned}$$

Hence from the theorem 4.3.1 the problem (4.8) has a unique mild solution in X given by (4.10). □

Theorem 4.4.2 *For $v^0 > 0$ and $u^0 \in X$, the problem (4.7) and (4.8) has a unique global positive solution $(v,u) \in PC^1(J, \mathbf{R}) \times C(J,X)$.*

Proof: Let $\overline{u}_1,\ \overline{u}_2 \in C(J,X)$, from the explicit representation of $v_{\overline{u}}$ we have

$$\begin{aligned}
|v_{\overline{u}_1}(t) - v_{\overline{u}_2}(t)| \quad \leq \quad & \sum_{0 \leq t_j \leq t} \lambda_j \left| e^{(-\tau \int_{t_j}^t |\overline{u}_1(s)|_1 ds)} - e^{(-\tau \int_{t_j}^t |\overline{u}_2(s)|_1 ds)} \right| \\
& + v^0 \left| e^{(-\tau \int_0^t |\overline{u}_1(s)|_1 ds)} - e^{(-\tau \int_0^t |\overline{u}_2(s)|_1 ds)} \right| \\
& + \beta x_0^2 \int_0^t \left| |\kappa \overline{u}_1(s)|_1 e^{(-\tau \int_s^t |\overline{u}_1(\sigma)|_1 d\sigma)} - |\kappa \overline{u}_2(s)|_1 e^{(-\tau \int_s^t |\overline{u}_2(\sigma)|_1 d\sigma)} \right| ds \\
\leq \quad & \sum_{0 \leq t_j \leq t} \lambda_j \left| \tau \int_{t_j}^t (|\overline{u}_1(s)|_1 - |\overline{u}_2(s)|_1) ds \right| + v^0 \left| \tau \int_0^t (|\overline{u}_1(s)|_1 - |\overline{u}_2(s)|_1) ds \right| \\
& + \beta \tau x_0 t \|\overline{u}_1 - \overline{u}_2\|_{\infty} \\
\leq \quad & b\tau \left(\sum_{0 \leq t_j \leq t} \lambda_j + v^0 + \beta x_0 \right) \|\overline{u}_1 - \overline{u}_2\|_{\infty} .
\end{aligned}$$

Let $\Lambda(\overline{u})(t) = U_{v_{\overline{u}}}(t,0)u^0$, for $t \in J$ and $\overline{u} \in C(J,X)$.
Next we show that $\Lambda : C(J,X) \to C(J,X)$ is a contraction, which would imply existence and uniqueness of the solution of (4.7) and (4.10).
In fact, for $\overline{u}_1,\ \overline{u}_2 \in C(J,X)$ and $t \in J$, we have

$$\begin{aligned}
\int_{x_0}^{\infty}(\Lambda(\overline{u}_1)(t)-\Lambda(\overline{u}_2)(t))(x)(a+x)dx &= e^{-\phi(t,0)}\int_{x_0}^{\infty}(u^0(x-\int_0^t v_{\overline{u}_1}(\sigma)d\sigma)\\
&\quad -u^0(x-v_{\overline{u}_2}(\sigma)d\sigma))(a+x)dx\\
&= e^{-\phi(t,0)}\int_{x_0-\int_0^t v_{\overline{u}_1}(\sigma)d\sigma}^{\infty} u^0(x)(a+x+\int_0^t v_{\overline{u}_1}(\sigma)d\sigma)dx\\
&\quad -e^{-\phi(t,0)}\int_{x_0-\int_0^t v_{\overline{u}_2}(\sigma)d\sigma}^{\infty} u^0(x)(a+x+\int_0^t v_{\overline{u}_2}(\sigma)d\sigma)dx\\
&= e^{-\phi(t,0)}\int_{x_0}^{\infty} u^0(y)(\int_0^t(v_{\overline{u}_1}(\sigma)-v_{\overline{u}_2}(\sigma)d\sigma))dy.
\end{aligned}$$

Thus

$$\|\Lambda(\overline{u}_1)(t)-\Lambda(\overline{u}_2)(t)\|_X \le \left|u^0\right|_1 b^2\tau\left(\sum_{0\le t_j\le t}\lambda_j+v^0+\beta x_0\right)\|\overline{u}_1-\overline{u}_2\|_\infty .$$

Hence Λ is a contraction for $|u^0|_1\left(\sum_{0\le t_j\le b}\lambda_j+v^0+\beta x_0\right)<\dfrac{1}{b^2\tau}$.

Now, we prove the existence and uniqueness of solution for (4.7) and (4.8). Let $r>0$ such that $u^0\in B(0,r)\subset X$, then there exists $K>0$ such that

$$\|U_{v_u}(t,s)\|\le K \quad \text{for all } u\in B(0,r).$$

Let $u\in C(J,X)$ such that $u(t)=U_{v_u}(t,0)u^0+\int_0^t U_{v_u}(t,s)f(s,u(s))ds,\ t\in J$ and $u(t)\in B(0,r),\ t\in J$, then

$$\begin{aligned}
\|u(t)\|_X &\le |u^0|_1K+K\int_0^t\|f(s,u(s))\|_X ds\\
&\le |u^0|_1K+2\beta K\int_0^t\|u(s)\|_X ds\\
&\le |u^0|_1K+2\beta Kbr.
\end{aligned}$$

Assume that $|u^0|_1K+2\beta Kbr\le r$. Set $C=\{u\in C(J,X):\ \|u\|_\infty\le r\}$. Now, we show that $N:C\to C$ has a unique fixed point.

Let $u_1, u_2 \in C$, thus

$$\begin{aligned}
\|(Nu_1)(t) - (Nu_2)(t)\|_X &\leq \|\Lambda(u_1)(t) - \Lambda(u_2)(t)\|_X \\
&\quad + \int_0^t \|U_{v_{u_1}}(t,s) f(s, u_1(s)) - U_{v_{u_2}} f(s, u_2(s))\|_X ds \\
&\leq \|\Lambda(u_1)(t) - \Lambda(u_2)(t)\|_X \\
&\quad + K \int_0^t \|f(s, u_1(s)) - f(s, u_2(s))\|_X ds \\
&\quad + \int_0^t \|U_{v_{u_1}}(t,s) - U_{v_{u_2}}(t,s)\|_{B(X)} \|f(s, u_2(s))\|_X ds \\
&\leq \|\Lambda(u_1)(t) - \Lambda(u_2)(t)\|_X \\
&\quad + K \int_0^t 2\beta \|u_1(s) - u_2(s)\|_X ds \\
&\quad + \int_0^t \frac{2\beta r}{x_0} \|U_{v_{u_1}}(t,s) - U_{v_{u_2}}(t,s)\|_{B(X)} ds \\
&\leq \|\Lambda(u_1)(t) - \Lambda(u_2)(t)\|_X \\
&\quad + \frac{2K\beta}{\mu} \int_0^t e^{\mu s} ds \|u_1 - u_2\|_* ds \\
&\quad + \frac{2\beta r}{x_0 \mu} \int_0^t e^{\mu s} ds \|u_1 - u_2\|_* \\
&\leq e^{\mu t}\left(c + \frac{2\beta(K x_0 + r)}{x_0 \mu}\right) \|u_1 - u_2\|_*
\end{aligned}$$

where$\|u\|_* = \sup_{t \in J} e^{-\mu t} \|u(t)\|_X$, $c = |u^0|_1 b^2 \tau \left(\sum_{0 \leq t_j \leq t} \lambda_j + v^0 + \beta x_0 \right)$ and $\mu > 0$ large enough such that $C_0 = c + \frac{2\beta(Kx_0 + r)}{x_0 \mu} < 1$. Hence $\|Nu_1 - Nu_2\|_* \leq C_0 \|u_1 - u_2\|_*$.
To prove the positivity of the solution of (4.8), we proceed by induction.
Put $u_1(t) = U_v(t, 0) u^0$, and for $n \geq 1$

$$u_{n+1}(t) = u_1(t) + \int_s^t U_v(t,s) f(s, u_n(s)) ds, \quad t \geq 0.$$

We have $u_1 \geq 0$. Suppose that u_n is positive, and we show that u_{n+1} is positive. In fact, from the positivity of $U_v(\cdot, \cdot)$ and u_n we deduce that u_{n+1} is positive. By induction, we conclude that $u_n \geq 0$, $\forall n \in \mathbb{N}$. Finally we obtain $u = \lim_{n \to \infty} u_n \geq 0$. $\square$

4.5 Concluding remarks

In this work we have considered an impulsive mathematical model for a prion diseases, where the production of prion is subject to perturbations caused by discontinuous production prion in order to fill the gap in PrP^c monomers polymerized. We have obtained the existence, uniqueness and positivity of the solution for condition on the amplitude of initial values u^0 and v^0. The results obtained for bounded interval J need to be extended to $\mathbf{R}_+$ to study global existence and stability. The discrete perturbations may be in the polymers caused by external interaction, for example laboratory experiments. It would be interesting to consider the case of non constant β and μ depending on the polymer length x using adequate approaches.

CONCLUSIONS

The main work of this thesis is the impulsive model for prion diseases given in chapter four, we can give some remarks on the results obtained. The existence result obtained is local and it is important to obtain global results on the positive real line, which gives the possibility to study the stability of the system with respect to its parameters. It is interesting to show the approach given in chapter two from [13] which consists to transform the problem under study in a system of ordinary differential equations, concerning the impulsive model it becomes a system of impulsive differential equations to analyze and study, this should give some interesting conclusions for the initial system and the phenomenon. We can also apply impulse effects to other models from the literature, some parameters are constants in the model but it should be interesting to follow the dynamics of the diseases when some them are not constant. Generally, when mathematical models are studied simulations are needed to have a complete analysis of the problem under study, so we could plane to do some simulations in future.

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الملخص:

في هذه الأطروحة درسنا بعض النماذج الرياضية لأمراض متعلقة ببروتينات بريون، قمنا بدراسة رياضية لجملة معدلتين مكونة من معادلة تفاضلية و معادلة ذات تفاضلات جزئية، المعادلة الأولى نموذج لتطور وحدات بروتينات بريون، أما المعادلة الثانية فهي تصف كيفية تطور البوليميرات المتكونة من تلاصق البروتينات أو بوليميرات لتكون بوليميرات أطول من الأولى، أو تنكسر لتكون اخرى أقصر من المنكسرة.

Le résumé

Dans cette thèse nous avons étudié quelques modèles mathématiques modélisant l'évolution des maladies à PRION, mathématiquement parlant, nous avons étudié l'existence de solutions d'un système constitué d'une équation différentielle, modélisant l'évolution des monomères de la protéine du PRION, et d'une équation aux dérivées partielles, modélisant l'évolution des polymères résultant de la polymérisation des protéines PRION.

Abstract

In this thesis we have studied some mathematical models describing the evolution of PRION diseases, we have studied mathematicaly the existence of solutions of a system constituted by differential equation and partial differential equation, the first equation describes the evolution of PRION monomers and the second one describes the evolution of polymers constituted by PRION monomers.