# PRION PROLIFERATION WITH UNBOUNDED POLYMERIZATION RATES

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Abstract. A model for prion replication is studied. We prove global existence of weak solutions for unbounded polymerization and degradation rates. For bounded degradation rates, the solutions are shown to be classical.

## 1. Introduction

Prions are widely regarded as the infectious agent causing fatal diseases known as TSE's including BSE of cattle, Creutzfeld-Jakob and Kuru of human, and Scrapie of sheep. Despite apparently lacking DNA and RNA, prions seem to be capable of proliferation. The probably by now leading theory for replication is called *nucleated polymerization*, according to which the infectious prions are thought to be a polymer form, called $PrP^{Sc}$, of a normal protein $PrP^{C}$. This polymer form can build bonds involving several thousands of monomer units by attaching non-infectious $PrP^{C}$ monomers and converting them to the infectious form. Prions are very stable but, nevertheless, can split into smaller polymers. Usually, this produces again two infectious $PrP^{Sc}$ polymers. However, if at least one part falls below a critical size $y_0 > 0$, it is assumed that this part instantaneously degenerates into $PrP^{C}$ monomers. We refer to [5], [6], [7], [10] and the references therein for more detailed information about the biological background and, in particular, for the mechanism of nucleated polymerization.

Here we consider a mathematical model for nucleated polymerization that has recently been introduced in [5]. According to this model, the biological processes of coagulation and splitting can be described by a coupled system consisting of an ordinary differential equation for the number of $PrP^{C}$ monomers $v(t) \geq 0$ and a partial differential equation for the density distribution function $u(t,y) \geq 0$ for $PrP^{Sc}$ polymers of size $y > y_0$. The equations read as

$$\dot{v} = \lambda - \gamma v - v \int_{y_0}^{\infty} \tau(y)\, u(t,y)\, \mathrm{d}y + 2 \int_{y_0}^{\infty} u(t,y)\, \beta(y) \int_0^{y_0} y'\, \kappa(y',y)\, \mathrm{d}y' \mathrm{d}y \quad (1)$$

and

$$\dot{u} + v(t)\, \partial_y \big(\tau(y) u(y)\big) = -\big(\mu(y) + \beta(y)\big)\, u(y) + 2 \int_y^{\infty} \beta(y')\, \kappa(y,y')\, u(y')\, \mathrm{d}y' \quad (2)$$

for $y \in Y := (y_0, \infty)$, which are supplemented with the initial conditions

$$v(0) = v^0 \,, \quad u(0,y) = u^0(y) \,, \quad y \in Y \,, \quad (3)$$

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and the boundary condition

$$u(t,y_0) \;=\; 0 \ , \quad t>0 \ . \tag{4}$$

The right hand side of the linear ode for $v$ takes into account that, on the one hand, the number of monomers is increased by a constant background source $\lambda$ or if a $PrP^{Sc}$ polymer of any size $y>y_0$ decays at a rate $\beta(y)$ into at least one daughter polymer of size $y'\le y_0$, which is assumed to degenerate immediately into monomers. The probability (density) for this event is denoted by $\kappa(y',y)$. On the other hand, the number of $PrP^C$ monomers decreases by metabolic degradation, which is accounted for by the term $-\gamma v$, and if any monomer is attached to a $PrP^{Sc}$ polymer of size $y>y_0$ at a rate $\tau(y)$.
The pde for $u$ involves a transport term $v(t)\partial_y(\tau(y)u(y))$ on the left hand side due to polymerization, while the right hand side reflects that polymers of size $y>y_0$ either disappear by metabolic degradation with rate $\mu(y)$ or by splitting with rate $\beta(y)$, or that they can be produced as the result of the decay of a larger polymer.

The equations above have been investigated in [4], [5], [9] assuming that the kernels have the particular form

$$\tau\;\equiv\;const \ , \quad \mu\;\equiv\;const \ , \quad \beta(y)\;=\;\beta\, y \ , \quad \kappa(y',y)\;=\;\frac{1}{y} \ . \tag{5}$$

If $U(t)$ denotes the number of all $PrP^{Sc}$ polymers and $P(t)$ the number of all $PrP^C$ monomers forming those polymers, that is, if

$$U(t):=\int_Y u(t,y)\,\mathrm{d}y \ , \quad P(t):=\int_Y y\,u(t,y)\,\mathrm{d}y \ ,$$

we notice that (5) leads to the closed system of ode's

$$\dot v \;=\; \lambda-\gamma\, v-\tau\, v\, U\;+\;\beta\, y_0^2\, U \ , \tag{6}$$

$$\dot U \;=\; \beta\, P\;-\;\mu\, U\;-\;2\,\beta\, y_0\, U \ , \tag{7}$$

$$\dot P \;=\; \tau\, v\, U\;-\;\mu\, P\;-\;\beta\, y_0^2\, U \ , \tag{8}$$

which is uniquely globally solvable. Thus, in this case, (1) and (2) are no longer coupled since $v(t)$ is known for all times $t\ge 0$. Moreover, as observed in [5], there exists a disease-free steady state and a disease steady state for the ode-problem (6)-(8) and the original pde-problem (1), (2) as well. We point out that in the general case, that is, if the kernels are not exactly of the form (5), existence of a non-trivial (disease) steady state is not known so far.

In [5] the asymptotic behavior of the ode system (6)-(8) is investigated assuming (5). In particular, global stability of the disease-free steady state and local stability of the disease steady state is shown depending on the involved parameters. The result concerning the non-trivial steady state has subsequently been improved in [9] to global stability. Using the method of characteristics combined with semigroup theory, equation (2) with data as in (5) has been solved in [4]. In addition, it is shown that the solution converges towards the disease-free or the disease steady state depending on whether or not there holds

$$y_0\beta+\mu>\sqrt{\frac{\lambda\beta\tau}{\gamma}} \ . \tag{9}$$

Recently, equations (1)-(4) have been studied in [11] without assuming (5). There existence and uniqueness of global classical solutions is shown provided the polymerization rate $\tau$ is independent of polymer size, the degradation rates $\mu$ and $\beta$ are arbitrary bounded functions, and the probability density satisfies the natural constraints

$$\kappa(y',y)=\kappa(y-y',y)\ , \quad y>y_0\ , \quad 0<y'<y\ , \tag{10}$$

meaning binary splitting of polymers, and

$$\int_0^y \kappa(y',y)\,\mathrm{d}y' \;=\; 1\ , \quad y>y_0\ . \tag{11}$$

Let us point out here that (10) and (11) imply

$$2\int_0^y y'\,\kappa(y',y)\,\mathrm{d}y' \;=\; y\ , \quad y>y_0\ ,$$

i.e. splitting conserves the number of monomers.
In [11] also global weak solutions have been shown to exist for $\mu$ and $\beta$ unbounded. In both situations it has been proved that the disease-free steady state $(v,u)=(\lambda/\gamma,0)$ is globally asymptotically stable under some additional growth assumptions.

The novelty of this paper is to take into consideration non-constant, even unbounded polymerization rates $\tau$. The mathematically convenient assumption of constant polymerization rate is often explained biologically by the linear appearance of scrapie-associated $PrP^{Sc}$ polymers when observed using an electron microscope. Obviously, the model becomes mathematically more tractable when assuming a constant polymerization rate [6, 7]. However, as pointed out in [6], assuming $\tau$ constant is plausible for linear polymers, but not for globular aggregates since the polymers may have another geometry on other levels. Therefore, our aim is to establish existence for the equations involving a varying polymerization rate $\tau$.

In the next section 2, we state our main results. The first statement is about the existence and uniqueness of classical solutions, whose proof is sketched in section 3. Based on this result, we then show in section 4 how we can obtain existence of weak solutions using a compactness argument. Finally, section 5 is dedicated to asymptotical stability of the disease-free steady state.

## 2. Main Results

Clearly, the positive cone $L_1^+$ of $L_1 := L_1(Y, y\mathrm{d}y)$ is a reasonable state space for the population density $u$, since it allows to account for the biologically important quantities of all $PrP^{Sc}$ polymers and all $PrP^C$ monomers forming those polymers, respectively.

For $\mu$ and $\beta$ bounded we can proof the existence and uniqueness of global classical solutions that propagate with finite speed.

**Theorem 2.1.** *Suppose that $\mu,\beta\in L_\infty^+(Y)$, that $\kappa$ is a non-negative measurable function satisfying* (10), (11) *and that*

$$\tau\in C^1([y_0,\infty)) \quad \textit{with} \quad 0<\tau(y)\le\tau^*\,y\ , \quad y\ge y_0\ . \tag{12}$$

*Then, given any $v^0>0$ and any $u^0\in L_1^+$ with $\partial_y(\tau u^0)\in L_1$ and $u^0(y_0)=0$, there exists a unique global classical solution $(v,u)$ to* (1)-(4) *such that $v\in C^1(\mathbb{R}^+)$, $v(t)>0$ for $t\geq 0$, and $u\in C^1(\mathbb{R}^+,L_1)$ with $\partial_y(\tau u)\in C(\mathbb{R}^+,L_1)$ and $u(t)\in L_1^+$ for $t\geq 0$.*
*In addition, if $\tau'$ is bounded and* $\operatorname{supp} u^0\subset[y_0,S_0]$ *for some $S_0>y_0$, then also* $\operatorname{supp} u(t)\subset[y_0,S(t)]$, *$t\geq 0$, where $S$ is the global solution to $\dot S=v\tau(S)$, $t>0$, with $S(0)=S_0$.*

From a biological point of view, the assumption of a bounded splitting rate $\beta$ does not seem to be appropriate. We therefore would like to weaken the assumptions on $\beta$ and $\mu$ to also allow for unbounded degradation rates. To do so we introduce the notion of weak solutions.

In the following we mean by $L_{1,\mathsf{w}}(Y)$ the space $L_1(Y):=L_1(Y,\mathrm{d}y)$ equipped with its weak topology. Moreover, we denote by

$$Q[u](y)\;:=\;-\big(\mu(y)+\beta(y)\big)\,u(y)\;+\;2\int_y^\infty\beta(y')\,\kappa(y,y')\,u(y')\,\mathrm{d}y'\ ,\quad \text{a.e. } y\in Y\ ,$$

the right hand side of (2).

**Definition 2.2.** *Given $v^0>0$ and $u^0\in L_1^+$, we call $(v,u)$ a global weak solution to* (1)-(4) *if*

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

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

(iii) *for all $t>0$ and $\varphi\in W_\infty^1(Y)$ there holds $Q[u]\in L_1((0,t)\times Y)$ and*

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

We point out that for a weak solution $(v,u)$ the function $u$ *a priori* is time continuous merely in the weak topology of $L_1(Y)$. But arguments similar to [2, sect. II.1, II.2] show that $u$ actually belongs to $C(\mathbb{R}^+,L_1(Y))$ provided that $\tau$ satisfies (12) and has a bounded derivative.

To prove existence of weak solutions in the sense of Definition 2.2 we assume that

$$\begin{cases}\text{there exists } \alpha\geq 1 \text{ and } \varrho\in L_\infty^+(Y) \text{ such that}\\ \varrho(y)\to 0 \text{ as } y\to\infty \text{ and } \mu(y)+\beta(y)\leq\varrho(y)y^\alpha,\ \text{a.e. } y\in Y\ .\end{cases}\tag{13}$$

Furthermore, we require that $\kappa$ satisfies (10), (11) and the technical condition

$$\begin{cases}\text{given } R>y_0 \text{ and } \varepsilon>0 \text{ there exists } \delta>0 \text{ such that}\\ \displaystyle\sup_{\substack{\mathcal{E}\subset(y_0,R)\\|\mathcal{E}|\leq\delta}}\ \operatorname*{ess-sup}_{y\in Y}\ \frac{\beta(y)}{y^\alpha}\int_{y_0}^y\mathbf{1}_{\mathcal{E}}(y')\,\kappa(y',y)\,\mathrm{d}y'\ \leq\ \varepsilon\ ,\end{cases}\tag{14}$$

where $\mathbf{1}_{\mathcal{E}}$ denotes the indicator function of a measurable set $\mathcal{E}\subset Y$ and $|\mathcal{E}|$ its Lebesgue measure. We suppose that the polymerization rate $\tau$ satisfies (12) and that, in the case $\alpha=1$,

$$\tau(y)\leq\varrho(y)y\ ,\quad \text{a.e. } y\in Y\ .\tag{15}$$

Based on Theorem 2.1 we can prove existence of weak solutions employing a compactness argument.

**Theorem 2.3.** *Suppose* (13)-(14) *and* (12) *with* (15) *if* $\alpha = 1$. *Given any* $v^0 > 0$ *and any* $u^0 \in L_1^+(Y, y^\alpha \mathrm{d}y)$, *problem* (1)-(4) *admits at least one global weak solution* $(v, u)$. *Moreover,* $u$ *belongs to* $L_{\infty,loc}(\mathbb{R}^+, L_1(Y, y^\alpha \mathrm{d}y))$.
*In addition, if* $\tau'$ *is bounded and* $\mathrm{supp}\, u^0 \subset [y_0, S_0]$ *for some* $S_0 > y_0$, *then also* $\mathrm{supp}\, u(t) \subset [y_0, S(t)]$, $t \geq 0$, *where* $S$ *is the global solution to* $\dot{S} = v\tau(S)$, $t > 0$, *with* $S(0) = S_0$.

To conclude, we mention the analogue to the stability result of [11] for the disease-free steady state $(v, u) = (\lambda/\gamma, 0)$. For this purpose, we suppose that either

$$\begin{cases} \mu, \beta \in L_\infty^+(Y) \text{ and} \\ v^0 > 0\ ,\ \ u^0 \in L_1^+ \text{ with } \partial_y(\tau u^0) \in L_1 \text{ and } u^0(y_0) = 0\ , \end{cases} \tag{16}$$

or

$$\begin{cases} (13),\ (14) \text{ hold and} \\ v^0 > 0\ ,\ \ u^0 \in L_1^+(Y, y^\alpha \mathrm{d}y)\ . \end{cases} \tag{17}$$

Furthermore, in both cases we assume that $\tau \in C^1([y_0, \infty))$ with

$$0 < \tau_* \leq \tau(y) \leq \tau^* < \infty\ , \quad y \in Y\ , \tag{18}$$

and that

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

We then introduce constants $\varepsilon_k, \delta_k$ such that

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

for $k = 0, 1$, assuming at least $\varepsilon_1 < \infty$. In the following we suppose that $\underline{\mu} \wedge \delta_0 > 0$, where

$$\underline{\mu}\ :=\ \operatorname*{ess\text{-}inf}_{y\in Y} \mu(y)\ ,$$

and that

$$\frac{1}{2d_0}\left(\underline{\mu}\ +\ 2\,\delta_0\right)\ >\ \frac{\lambda(\tau^*)^2}{2\gamma\tau_*}\ +\ \frac{\varepsilon_1\tau^*}{\tau_*}\ -\ 2\,\delta_1\ +\ \frac{2d_0\delta_1\big(\varepsilon_1\tau^*/\tau_* - \delta_1\big)}{\underline{\mu} + 2\delta_0}\ . \tag{19}$$

As the next theorem shows, the disease-free steady state is globally asymptotically stable.

**Theorem 2.4.** *Suppose* (10), (11), (18) *and* (16) *or* (17). *Moreover, let* (19) *be satisfied. Denote by* $(v, u)$ *either the classical solution provided by Theorem 2.1 if* (16) *holds, or the weak solution provided by Theorem 2.3 if* (17) *holds. Then, for each* $\varepsilon > 0$ *there is* $\delta > 0$ *such that*

$$|v(t) - \lambda/\gamma|\ +\ \|u(t)\|_{L_1}\ \leq\ \varepsilon\ , \quad t \geq 0\ ,$$

*whenever*

$$|v^0 - \lambda/\gamma|\ +\ \|u^0\|_{L_1}\ \leq\ \delta\ .$$

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

$$\big(v(t), u(t)\big) \longrightarrow (\lambda/\gamma, 0) \quad \text{in} \quad \mathbb{R} \times L_1(Y, y^\sigma \mathrm{d}y) \quad \text{as} \quad t \longrightarrow \infty$$

*for each* $\sigma < 1$.

We point out that the assumptions of Theorem 2.4 are equivalent to (9) in the case that the data are as in (5). Indeed, in this case we may take $d_0 = \beta/\mu$, $\delta_0 := \beta y_0$ and $\varepsilon_1 := \delta_1 := \beta y_0^2/2$.

## 3. Proof of Theorem 2.1

We merely give a sketch of the proof of Theorem 2.1 since the argumentation follows closely the lines of [11, Thm.3.1].

We define a diffeomorphism $\Phi : Y \to (0,\infty)$ by virtue of

$$\Phi(y) := \int_{y_0}^{y} \frac{\mathrm{d}y'}{\tau(y')} \ , \quad y \in Y \ , \tag{20}$$

and observe that

$$\Phi^{-1}\big(\Phi(y)+t\big) \ \le\ y\, e^{t\tau^*} \ , \quad y > y_0 \ , \quad t \ge 0 \ ,$$

due to (12). Given $f \in L_1$ we set

$$\big(W(t)f\big)(y) := \mathbf{1}_{[t,\infty)}\big(\Phi(y)\big)\,\frac{\tau\big(\Phi^{-1}(\Phi(y)-t)\big)}{\tau(y)}\, f\big(\Phi^{-1}(\Phi(y){-}t)\big) \ , \quad y \in Y \ , \quad t \ge 0 \ .$$

It is not difficult to check that $\{W(t)\,;\, t \ge 0\}$ is a strongly continuous positive semigroup on $L_1$ satisfying

$$\|W(t)\|_{\mathcal{L}(L_1)} \le e^{\tau^* t} \ , \quad t \ge 0 \ .$$

For the corresponding generator $-A$ there holds

$$Au \,=\, \partial_y(\tau u) \ , \quad u \in D(A) = \{f \in L_1\,;\, \partial_y(\tau f) \in L_1 \,,\, f(y_0) = 0\} \ .$$

Recall then that $Q$ is a bounded and linear operator on $L_1$ due to $\mu, \beta \in L_\infty(Y)$. Therefore, given $T > 0$, $R > 1$ and defining $\mathbb{A}_v(t) := v(t)A - Q$ for

$$v \in \mathcal{V}_{T,R} := \big\{v \in C^1([0,T])\,;\, R^{-1} \le v(t) \le \|v\|_{C^1([0,T])} \le R\big\} \ ,$$

it follows from [8, §5.2] that $\big(-\mathbb{A}_v(t)\big)_{t\in[0,T]}$ generates a unique evolution system $U_v(t,s)$, $0 \le s \le t \le T$, in $L_1$ with

$$\|U_v(t,s)\|_{\mathcal{L}(L_1)} \le e^{\omega(t-s)} \ , \quad 0 \le s \le t \le T \ , \quad v \in \mathcal{V}_{T,R} \ , \tag{21}$$

for some $\omega := \omega(T,R) > 0$. Moreover, following the lines of the proof of [8, Thm.5.4.6] we infer that the differentiability of $v \in \mathcal{V}_{T,R}$ ensures that $U_v(t,s)$ maps $D(A)$ continuously into itself and we may assume that

$$\|U_v(t,s)\|_{\mathcal{L}(D(A))} \le \omega \ , \quad 0 \le s \le t \le T \ , \quad v \in \mathcal{V}_{T,R} \ . \tag{22}$$

In addition, for $0 \le s \le t \le T$ and $v, w \in \mathcal{V}_{T,R}$, we have

$$\|U_v(t,s) - U_w(t,s)\|_{\mathcal{L}(D(A),L_1)} \le \omega\,(t-s)\,\|v-w\|_{C([0,T])} \ . \tag{23}$$

For details we refer to the proof of [11, Prop.2.2].

We choose $T > 0$ and $S^{-1} > 0$ sufficiently small and we denote by $v_{\bar u} \in C^1([0,T])$ the unique solution to (1) with $u$ replaced by

$$\bar u \in X_T \,:=\, \big\{w \in C([0,T], L_1^+)\,;\, \|w(t)\|_{L_1} \le S \,,\, t \in [0,T]\big\} \ .$$

There exists $R := R(S) > 1$ such that $v_{\bar u} \in \mathcal{V}_{T,R}$ whenever $\bar u \in X_T$. We then observe that, since $u^0 \in D(A)$,

$$\Lambda(\bar u)(t) \,:=\, U_{v_{\bar u}}(t,0)\,u^0 \ , \quad t \in [0,T] \ , \quad \bar u \in X_T \ ,$$

defines the unique solution in $C([0,T],D(A))\cap C^1([0,T],L_1)$ to the problem

$$\dot u\,+\,\mathbb{A}_{v_{\bar u}}(t)\,u\,=\,0\;,\quad t\in[0,T]\;,\qquad u(0)\,=\,u^0\;.$$

Furthermore, (21)-(23) ensure that $\Lambda: X_T\to X_T$ is a contraction and hence has a fixed point. This proves existence and uniqueness of a maximal solution $(v,u)$ to (1)-(4) on an interval $J$ with properties as stated in Theorem 2.1. As in the proof of [11, Thm.3.1] the identity

$$\dot v(t)\,+\,\frac{\mathrm{d}}{\mathrm{d}t}\int_{y_0}^\infty y\,u(t,y)\,\mathrm{d}y\,=\,\lambda\,-\,\gamma\,v(t)\,-\,\int_{y_0}^\infty y\,\mu(y)\,u(t,y)\,\mathrm{d}y\;,\quad t\in J\;,\quad(24)$$

and (1) warrant the existence of $R>1$ such that $R^{-1}\le v(t)\le\|v\|_{C^1(J)}\le R$ for $t\in J$. According to (22) this implies

$$\|U_v(t,s)\|_{\mathcal{L}(D(A))}\le c(J)\;,\quad 0\le s\le t\in J\;,$$

whence $J=\mathbb{R}^+$ since $\|u(t)\|_{D(A)}$ remains bounded (see the proof of [11, Thm.3.1]). In order to prove finite speed of propagation we first recall that $\dot S=v\tau(S)$, $t>0$, $S(0)=S_0$ has, thanks to [1, Satz 5.1], a global solution given by

$$S(t)\,=\,\phi^{-1}\left(\int_0^t v(s)\,\mathrm{d}s\right)\;,\quad\text{where}\quad\phi(y)\,:=\,\int_{S_0}^y\frac{\mathrm{d}z}{\tau(z)}\;.$$

Next, we define $P\in C^1(\mathbb{R}^+,L_1(Y))$ by

$$P(t,y):=\int_y^\infty u(t,y')\,\mathrm{d}y'\;,\quad y\in Y\;,\quad t\ge 0\;,$$

and notice that (2) implies

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\int_{S(t)}^\infty P(t,y)\,\mathrm{d}y&=v(t)\,\tau\big(S(t)\big)\,P\big(t,S(t)\big)\,+\,v(t)\int_{S(t)}^\infty\tau'(y)\,P(t,y)\,\mathrm{d}y\\&\quad-\,\dot S(t)\,P\big(t,S(t)\big)\,+\,\int_{S(t)}^\infty\int_y^\infty Q[u(s)](y')\,\mathrm{d}y'\,\mathrm{d}y\\&\le\,\|\tau'\|_\infty\,v(t)\int_{S(t)}^\infty P(t,y)\,\mathrm{d}y\,+\,\|\beta\|_\infty\int_{S(t)}^\infty P(t,y)\,\mathrm{d}y\;.\end{aligned}$$

Owing to

$$\int_{S(0)}^\infty P(0,y)\,\mathrm{d}y\,=\,0$$

we infer

$$\int_{S(t)}^\infty P(t,y)\,\mathrm{d}y=0\;,\quad t\ge 0\;.$$

This completes the proof of Theorem 2.1.

## 4. Proof of Theorem 2.3

In order to prove Theorem 2.3 we need the following auxiliary result. As in section 3 we use the notation $-A=-\partial_y(\tau\cdot)$ and denote by $W(t)$, $t\ge 0$, the corresponding semigroup on $L_1(Y)$.

**Lemma 4.1.** *Suppose $\tau$ satisfies* (12) *and, given $v\in C([0,T],\mathbb{R}^+)$, let $U_{A_v}(t,s)$, $0\le s\le t\le T$, denote the unique evolution system in $L_1(Y)$ for*

$$-A_v(t):=-v(t)A\ ,\quad 0\le t\le T\ .$$

*For $S>y_0$ and $\delta>0$, put*

$$\lambda_S(\delta):=\tau^*\,S\sup_{\substack{\mathcal{E}\subset(y_0,S)\\ |\mathcal{E}|\le\delta}}\int_{\mathcal{E}}\frac{\mathrm{d}z}{\tau(z)}\ .$$

*Then there holds*

$$\sup_{\substack{\mathcal{E}\subset(y_0,S)\\ |\mathcal{E}|\le\delta}}\int_{\mathcal{E}}U_{A_v}(t,s)\,f\ \mathrm{d}y\ \le\ \sup_{\substack{\mathcal{F}\subset(y_0,S)\\ |\mathcal{F}|\le\lambda_S(\delta)}}\int_{\mathcal{F}}f\ \mathrm{d}y$$

*for any $f\in L_1^+(Y)$ and $0\le s\le t\le T$.*

*Proof.* Given any measurable subset $\mathcal{E}$ of $(y_0,S)$ and any $f\in L_1(Y)$ we notice that

$$\begin{aligned}\int_{\mathcal{E}}W(t)f\,\mathrm{d}y&=\int_{\Phi^{-1}(t)}^{\infty}\mathbf{1}_{\mathcal{E}}(y)\frac{\tau\big(\Phi^{-1}(\Phi(y)-t)\big)}{\tau(y)}f\big(\Phi^{-1}(\Phi(y)-t)\big)\,\mathrm{d}y\\&=\int_{y_0}^{\infty}\mathbf{1}_{\Phi^{-1}((\Phi(\mathcal{E})-t)\cap(0,\infty))}(y)\,f(y)\,\mathrm{d}y\ ,\end{aligned}$$

with $\Phi$ as in (20). Clearly, $\Phi^{-1}\big((\Phi(\mathcal{E})-t)\cap(0,\infty)\big)\subset(y_0,S)$ and thus, due to (12),

$$\big|\Phi^{-1}\big((\Phi(\mathcal{E})-t)\cap(0,\infty)\big)\big|\ \le\ \lambda_S(\delta)$$

since the Lebesgue measure is invariant under translations. Observing that the unique evolution system to $\big(-A_v(t)\big)_{t\in[0,T]}$ is given by

$$U_{A_v}(t,s)\ =\ W\left(\int_s^t v(r)\mathrm{d}r\right)\ ,\quad 0\le s\le t\le T\ ,$$

the assertion follows. □

Now we turn to the proof of Theorem 2.3. We rather briefly sketch it and point out the necessary modifications to [11, Thm.4.3] .

First, let $u_n^0\in\mathcal{D}^+(Y)$ be such that $u_n^0\to u^0$ in $L_1(Y,y^\alpha\mathrm{d}y)$. Put $\mu_n:=\min\{\mu,n\}$, $\beta_n:=\min\{\beta,n\}$. We denote by

$$(v_n,u_n)\in C(\mathbb{R}^+,\mathbb{R}^+\times D(A))\cap C^1(\mathbb{R}^+,\mathbb{R}\times L_1)$$

the classical solution to (1)-(4) provided by Theorem 2.1, where $(u^0,\beta,\mu)$ is replaced by $(u_n^0,\beta_n,\mu_n)$. From the corresponding identity (24) we obtain, for $T>0$ fixed,

$$v_n(t)+\|u_n(t)\|_{L_1}\le c_0(T)\ ,\quad t\in[0,T]\ ,\quad n\ge1\ . \tag{25}$$

Moreover, since by (10) and (11)

$$2\int_{y_0}^{y}(y')^\alpha\,\kappa(y',y)\,\mathrm{d}y'\ \le\ y^\alpha\ ,\quad y>y_0\ ,$$

we infer from (2) and (12)

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\int_{y_0}^{\infty}y^\alpha\,u_n(t,y)\,\mathrm{d}y\ &\le\ \alpha\,v_n(t)\int_{y_0}^{\infty}y^{\alpha-1}\,\tau(y)\,u_n(t,y)\,\mathrm{d}y\\&\le\ c(T)\int_{y_0}^{\infty}y^\alpha\,u_n(t,y)\,\mathrm{d}y\ ,\end{aligned}$$

whence

$$\|u_n(t)\|_{L_1(Y,y^\alpha \mathrm{d}y)} \le c(T)\ , \quad t\in[0,T]\ , \quad n\ge 1\ , \tag{26}$$

with $c(T)$ being independent of $n$. Using (13), (25) and (26) we easily derive from equation (1)

$$\max_{t\in[0,T]} |\dot v_n(t)| \,\le\, c(T)\ , \quad n\ge 1\ .$$

Therefore, the sequence $(v_n)$ is relatively compact in $C([0,T])$ due to the Arzelà-Ascoli theorem.

We then claim that the set $\{u_n(t)\,;\, n\ge 1\,,\, t\in[0,T]\}$ is relatively compact in $L_{1,\mathsf{w}}(Y)$. Indeed, from (25) it follows

$$\lim_{R\to\infty}\ \sup_{\substack{n\ge 1\\ t\in[0,T]}} \int_R^\infty u_n(t,y)\,\mathrm{d}y \,=\, 0\ . \tag{27}$$

Writing the solution $u_n$ in the form

$$u_n(t) \,=\, U_{A_{v_n}}(t,0)\,u_n^0 + \int_0^t U_{A_{v_n}}(t,s)\,Q_n[u_n(s)]\,\mathrm{d}s\ , \quad t\in[0,T]\ ,$$

with $U_{A_{v_n}}$ denoting the evolution system corresponding to $\big(-v_n(t)A\big)_{t\in[0,T]}$, we obtain from Lemma 4.1, for $R>y_0$ and $\delta>0$,

$$\begin{aligned}\int_{\mathcal E} u_n(t,y)\,\mathrm{d}y \,&\le\, \int_{\mathcal E\cap(y_0,R)} u_n(t,y)\,\mathrm{d}y \,+\, \int_R^\infty u_n(t,y)\,\mathrm{d}y\\ &\le\, \sup_{\substack{\mathcal F\subset(y_0,R)\\ |\mathcal F|\le\lambda_R(\delta)}} \int_{\mathcal F} u_n^0(y)\,\mathrm{d}y\\ &\quad + 2\int_0^t \sup_{\substack{\mathcal F\subset(y_0,R)\\ |\mathcal F|\le\lambda_R(\delta)}} \int_{y_0}^\infty u_n(s,y)\,\beta_n(y)\int_{y_0}^y \mathbf{1}_{\mathcal F}(y')\,\kappa(y',y)\,\mathrm{d}y'\,\mathrm{d}y\,\mathrm{d}s\\ &\quad + \frac{1}{R}\,\|u_n(t)\|_{L_1}\ ,\end{aligned}$$

where $\mathcal E$ is any measurable subset of $Y$ with measure $|\mathcal E|\le\delta$. Hence, (13), (14), (26), and the fact that $\lambda_R(\delta)\to 0$ as $\delta\to 0^+$ imply

$$\lim_{|\mathcal E|\to 0}\ \sup_{\substack{n\ge 1\\ t\in[0,T]}} \int_{\mathcal E} u_n(t,y)\,\mathrm{d}y \,=\, 0\ ,$$

what entails the claimed compactness of $\{u_n(t)\,;\, n\ge 1\,,\, t\in[0,T]\}$ in $L_{1,\mathsf{w}}(Y)$ by invoking the Dunford-Pettis theorem (cf. [3, Thm.4.21.2]). Next, (25)-(27) guarantee that the set $\{u_n\,;\, n\ge 1\}$ is equicontinuous in $L_{1,\mathsf{w}}(Y)$ at every $t\in[0,T]$ (see the proof of [11, Thm.4.3]). It thus follows from a variant of the Arzelà-Ascoli theorem [12, Thm.1.3.2] that we may extract a subsequence (not relabeled) and $(v,u)$ such that

$$(v_n,u_n)\to(v,u) \quad \text{in} \quad C(\mathbb{R}^+,\mathbb{R}\times L_{1,\mathsf{w}}(Y))\ . \tag{28}$$

It remains to show that $(v,u)$ is a weak solution to (1)-(4). But due to (13), (26), and (12) combined with (15) in the case $\alpha=1$, we may apply [11, Lem.4.2] and see that $(v,u)$ satisfies (iii) of Definition 2.2. We also derive from the just cited lemma that $v$ is continuously differentiable and solves (i) of Definition 2.2.

Finally, finite speed of propagation follows from Theorem 2.1 since we may choose the sequence $(u_n^0) \subset \mathcal{D}^+(Y)$ such that $\operatorname{supp} u_n^0 \subset [y_0, S_0]$ (see [11, Cor.4.4]). Thus the proof of Theorem 2.3 is complete.

## 5. Proof of Theorem 2.4

The proof of Theorem 2.4 is based on the observation that, as in the proof of [11, Lem.5.1], condition (19) ensures the existence of constants $a, b > 0$ such that the function

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

defines a Lyapunov function satisfying

$$F(v,u)(t) + p\int_0^t\int_{y_0}^\infty u(s,y)\,\mathrm{d}y\,\mathrm{d}s \le F(v^0,u^0)\ , \quad t \ge 0\ , \tag{29}$$

for some $p > 0$. For the classical solution $(v, u)$ this follows directly by differentiating $F(v, u)$, while for the case of the weak solution we use inequality (29) for the approximating sequence $(v_n, u_n)$ of the proof of Theorem 2.3 and show that it is still true in the limit $n \to \infty$. Due to the definition of $F$, this already proves the stability statement of Theorem 2.4. If $\beta(y) \le By$, then (2) and (29) imply

$$\|u(t+h)\|_{L_1(Y)} - \|u(t)\|_{L_1(Y)} \le c\,h\ , \quad t\,,\,h > 0\ ,$$

and

$$\int_0^\infty \|u(s)\|_{L_1(Y)}\,\mathrm{d}s \le \frac{1}{p}\,F(v^0,u^0)\ .$$

Taking into account that

$$\|u(t)\|_{L_1} \le \frac{1}{a}\,F(v^0,u^0)\ , \quad t \ge 0\ ,$$

by (29), we conclude from the above inequalities that

$$u(t) \to 0 \quad \text{in} \quad L_1(Y, y^\sigma \mathrm{d}y) \quad \text{as} \quad t \to \infty$$

for each $\sigma < 1$. This then also implies $v(t) \to \lambda/\gamma$ as $t \to \infty$, hence the statement of Theorem 2.4.

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## References

[1] H. Amann. *Gewöhnliche Differentialgleichungen.* (de Gruyter 1995)
[2] R.J. DiPerna, P.L. Lions. *Ordinary differential equations, transport theory and Sobolev spaces.* Invent. Math. **98** (1989), 511-547.
[3] R.E. Edwards. *Functional analysis. Theory and applications.* Dover Publ., New York 1995.
[4] H. Engler, J. Prüss, G. Webb. *Analysis of a model for the dynamics of prions II.* J. Math. Anal. Appl. **324** (2006), 98-117.
[5] M. Greer, L. Pujo-Menjouet, G. Webb. *A mathematical analysis of the dynamics of prion proliferation.* To appear in: J. Theor. Biol.
[6] J. Masel, V. Jansen, M. Nowak. *Quantifying the kinetic parameters of prion replication.* Bio. Chem. **77** (1999), 139-152.

[7] M. Nowak, D. Krakauer, A. Klug, R. May. *Prion infection dynamics.* Integrative Biology. **1** (1998), 3-15.

[8] A. Pazy. *Semigroups of linear operators and applications to partial differential equations.* Springer, Berlin, New York, Heidelberg 1983.

[9] J. Prüss, L. Pujo-Menjouet, G. Webb, R. Zacher. *Analysis of a model for the dynamics of prions.* Discrete Contin. Dyn. Syst. Ser. B **6** (2006), no. 1, 225–235 (electronic).

[10] S.B. Prusiner. *Novel proteinaceous invectious particles cause scrapie.* Science **216** (1986), 136-144.

[11] G. Simonett, C. Walker. *On the solvability of a mathematical model for prion proliferation.* J. Math. Anal. Appl. **324** (2006), 580-603.

[12] I.I. Vrabie. *Compactness methods for nonlinear evolutions.* $2^{nd}$ edition. Longman, London 1995.

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