ANALYSIS OF A MODEL FOR THE DYNAMICS OF PRIONS II

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Abstract

A new mathematical model for the dynamics of prion proliferation involving an ordinary differential equation coupled with a partial integro-differential equation is analyzed, continuing the work in [9]. We show the well-posedness of this problem in its natural phase space $Z_+ := \mathbb{R}_+ \times L_1^+((x_0,\infty); xdx)$, i.e. there is a unique global semiflow on Z_+ associated to the problem.

A theorem of threshold type is derived for this model which is typical for mathematical epidemics. If a certain combination of kinetic parameters is below or at the threshold, there is a unique steady state, the disease-free equilibrium, which is globally asymptotically stable in Z_+; above the threshold it is unstable, and there is another unique steady state, the disease equilibrium, which inherits that property.

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1. Introduction and Main Results

In this paper we continue our analysis, begun in [9], of a recent model describing the proliferation of prions. This model has been introduced in Greer, Pujo-Menjouet and Webb [4], based on the works of Masel, Jansen and Nowak [6], Nowak, Krakauer, Klug and May [7] and others. For comprehensive explanations and discussions of the model and the relevant biochemical literature we refer to [4]. Here we only give a very short description of the model.

Prions are proteins that are believed to be responsible for certain diseases like BSE and the Creutzfeld-Jacob disease. There are two basic forms of prions of interest here, the *Prion Protein Cellular* PrP^C and the *Prion Protein Scrapie* PrP^{Sc}. The single molecule proteins PrP^C, also called *monomers* in the sequel, are protease resistent proteins which have a cell protective function and are produced by the body, regularly. On the other hand, the infectious prion PrP^{Sc} is a string-like *polymer* formed of monomeric PrP^C. Above a critical chain length $x_0 > 0$ the polymers are more stable than the PrP^C, and they can grow to chains containing thousands of monomers. PrP^{Sc} has the ability to replicate by splitting, we assume binary splitting here.

So there are three main processes which govern the dynamics of prions in this model.

- growth in length by polymerization with rate $\tau > 0$;
- binary splitting with rate $\beta(x) > 0$, a polymer of length $x > 0$ splits into one of length $0 < y < x$ and one of length $x - y$ with probability $\kappa(y, x)$;
- natural degradation with rate $\gamma > 0$ for the monomers and with rate $\mu(x)$ for the polymers with length x.

The model proposed in [7] further assumes that polymers of length $0 < x \le x_0$ immediately decompose completely into monomers. This reflects the assumption that PrP^{Sc} polymers are unbranched and form a simple α-helix with x_0 monomer units per turn. An α-helix of length less than x_0 is incomplete and thus is much less stable. Denoting the numbers of monomers at time t by $V(t)$ and the density of polymers by $u(t,x)$, we obtain the following model equations.

$$
\begin{aligned}
&\partial_t V(t) = \lambda - \gamma V(t) - \tau V(t) \int_{x_0}^{\infty} u(t,x)dx + 2\int_0^{x_0} x \int_{x_0}^{\infty} \beta(y)\kappa(x,y)u(t,y)dydx \\
&\partial_t u(t,x) + \tau V(t)\partial_x u(t,x) + (\mu(x)+\beta(x))u(t,x) = 2\int_x^{\infty} \beta(y)\kappa(x,y)u(t,y)dy \qquad (1.1)\\
&V(0) = V_0 \ge 0, \quad u(t,x_0) = 0, \quad u(0,x) = u_0(x),
\end{aligned}
$$

where $t \geq 0$ and $x_0 \leq x < \infty$. Here $\lambda > 0$ is a constant background source of monomers. Observe that the splitting function $\kappa(y,x)$ 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 $x \geq x_0$, $y \geq 0$, and $\kappa(y,x) = 0$ if $y > x$ or $x \leq x_0$. Note that these conditions imply

$$2\int_0^x y\kappa(y,x)dy = x, \quad x > 0.$$

In fact,

$$\begin{aligned} 2\int_0^x y\kappa(y,x)dy &= \int_0^x y\kappa(y,x)dy + \int_0^x y\kappa(x-y,x)dy \\ &= \int_0^x y\kappa(y,x)dy + \int_0^x (x-y)\kappa(y,x)dy = x\int_0^x \kappa(y,x)dy = x. \end{aligned}$$

This implies that mass does not change via the splitting process, and by a simple computation we obtain the following relation for the total number of monomers in the system.

$$\frac{d}{dt}[V(t) + \int_{x_0}^\infty xu(t,x)dx] = \lambda - \gamma V(t) - \int_{x_0}^\infty x\mu(x)u(t,x)dx, \quad t \geq 0.$$

In [7] it is further assumed that splitting is equi-distributed (polymer chains are equally likely to split at all locations), and that the rate of splitting is proportional to length. This reflects again the hypothesis that polymers form α-helices and are not folded in more complicated configurations, which would make certain segments of the chain less likely to split than others. Therefore, we make the further assumptions

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

$\beta(x) = \beta x$ is linear, and $\mu(x) \equiv \mu$ constant. Then the model contains only 6 parameters, and can even be reduced to a system of 3 ordinary differential equations. In fact, introduce the new functions

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

representing the total number of polymers, and the total number of monomers in polymers at time t, respectively. Integrating the equation for $u(t,x)$ over $[x_0,\infty)$ we get

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

hence

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

Multiplying the equation for $u(t,x)$ by x, integration yields

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

hence

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

Thus we obtain the following closed model involving only ordinary differential equations.

$$\begin{aligned} \dot{U} &= \beta P - \mu U - 2\beta x_0 U \\ \dot{V} &= \lambda - \gamma V - \tau U V + \beta x_0^2 U \\ \dot{P} &= \tau U V - \mu P - \beta x_0^2 U \end{aligned} \tag{1.2}$$

with initial conditions

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

This way the partial differential equation for the density $u(t,x)$ decouples from the ordinary differential equations. Once the solutions of (1.2) are known, one has to solve only a linear partial integro-differential eqution to obtain $u(t,x)$. The system (1.2) is identical to the "basic virus dynamics model" that is discussed at length in [8].

Concerning the ode-system (1.2) we have the following result from Prüss, Pujo-Menjouet, Webb and Zacher [9].

Theorem 1.1. *Suppose $x_0, \beta, \gamma, \lambda, \mu, \tau > 0$ are given constants. Then the system (1.2) induces a global semiflow on the set $K = \{(U,V,P) \in \mathbb{R}^3 : U, V, P - x_0 U \geq 0\}$. There is precisely one disease free equilibrium $(0, \lambda/\gamma, 0)$ which is globally exponentially stable if and only if $\mu + x_0\beta > \sqrt{\lambda\beta\tau/\gamma}$, and asymptotically stable in case of equality. On the other hand, if $\mu + x_0\beta < \sqrt{\lambda\beta\tau/\gamma}$ there is the unique disease equilibrium*

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

which is globally exponentially stable in $K \setminus [\{0\} \times \mathbb{R}_+ \times \{0\}]$.

It is the purpose of this paper to study the full system (1.1) under the assumptions of equi-distributed splitting, linear splitting rate, and constant rates of degradation.

Since $V(t) + \int_{x_0}^{\infty} x u(t,x) dx$ is the total number of monomers in the system, which should be finite at any time, it seems reasonable to study (1.1) in the standard cone $Z_+ := \mathbb{R}_+ \times L_1^+((x_0,\infty); xdx)$ of the Banach space $Z := \mathbb{R} \times L_1((x_0,\infty); xdx)$. The following theorem summarizes our results.

Theorem 1.2. *Assume equi-distributed splitting with linear splitting rate $\beta(x) = \beta x$ and constant degradation rates γ and $\mu(x) \equiv \mu$. Suppose $\lambda, \tau, \beta, \gamma, \mu, x_0 > 0$. Then (1.1) generates a global semiflow in the natural phase space Z_+. Furthermore,*
(i) if $\lambda\beta\tau/\gamma \leq (\mu + \beta x_0)^2$, then the disease-free equilibrium $\bar{z} = (\lambda/\gamma, 0)$ is globally asymptotically stable in Z_+, and even exponentially in the case of strict inequality;
(ii) if $\lambda\beta\tau/\gamma > (\mu + \beta x_0)^2$, then there is a unique disease equilibrium $z_* = (V_*, u_*)$ which is globally asymptotically stable in $Z_+ \setminus (\mathbb{R}_+ \times \{0\})$. It is given by

$$V_* = \frac{(\mu+\beta x_0)^2}{\beta\tau}, \quad u_*(x) = \frac{2\beta}{\mu\tau} \frac{\lambda\beta\tau - \gamma(\mu+\beta x_0)^2}{(\mu+\beta x_0)(\mu+2\beta x_0)} \Phi\Big(\frac{\beta(x-x_0)}{\mu+\beta x_0}\Big),$$

where $\Phi(r) = (r + r^2/2)\exp(-(r+r^2/2))$.

The remaining part of this paper deals with the proof of this result. Recall that the function $\omega(t) := \tau V(t)$ can be considered as known, by Theorem 1.1, and $\omega(t) \to \omega_\infty$ exponentially, where either $\omega_\infty = \lambda/\gamma$ in the disease-free or $\omega_\infty = (\mu + \beta x_0)^2/\beta$ in the disease case. Hence we have to solve a linear nonautonomous partial integro-differential equation of first order. For this we shall use standard techniques from the theory of C_0-semigroups and we refer to the monograph Arendt, Batty, Hieber and Neubrander [2] as a general reference for the results employed below.

We proceed in four steps. First we study the autonomous case where $\omega \equiv \omega_\infty$. In Section 2 we show that there is a unique C_0-semigroup $T(t) = e^{-Lt}$ associated with the pde-part of (1.1) in $X = L_1((x_0,\infty); xdx)$, which is positive and contractive, and even exponentially stable in the disease-free case. The resolvent of L is shown to be compact in Section 3, hence L has only point spectrum in the closed right half-plane. In the disease case, we further show that 0 is the only eigenvalue of L on the imaginary axis, it is simple and so the ergodic projection $\mathcal{P}$ onto the kernel $N(L)$ of L along the range $R(L)$ of L exists and is rank one. We compute an element $e \in N(L)$ which is positive. A result of Arendt, Batty, Lubich and Phong [2] then shows that $T(t)$ is strongly

ergodic, i.e. $\lim_{t\to\infty} T(t) = \mathcal{P}$ strongly in X. Wellposedness of the nonautonomous problem is proved in Section 4 by means of monotone convergence, it is shown that the evolution operator exists and is bounded. Moreover, bounds for $\partial_x u(t,\cdot)$ in X are derived. Finally, in Section 5 we put together these results to prove Theorem 1.2.

While we assume throughout that $\beta(x) = \beta x$, $\mu(x) = \mu$ (constant), and $y\kappa(x,y) = 1$ for $x < y$, $y > x_0$, $\kappa(x,y) = 0$ elsewhere, our methods extend to versions of (1.1) where these assumptions do not hold. We do not carry out these generalizations since it is not clear which would be biologically reasonable. On the other hand, the equation discussed in this paper

$$\partial_t u(t,x) = -\tau V(t)\partial_x u(t,x) - (\mu+\beta x)u(t,x) + 2\beta\int_x^\infty u(t,y)dy$$

for $x > x_0$, $t > 0$, with initial and boundary data as in (1.1), can be solved with an integral transformation followed by the method of characteristics. Namely, define

$$v(t,x) = \int_x^\infty \int_y^\infty u(t,\xi)\,d\xi\,dy = \int_x^\infty (\xi - x)u(t,\xi)\,d\xi, \quad \partial_x^2 v(t,x) = u(t,x)\,.$$

Then a computation shows that v solves the first order partial differential equation without integral term

$$\partial_t v(t,x) = -\tau V(t)\partial_x v(t,x) - (\mu+\beta x)v(t,x)$$

for $x > x_0$, $t > 0$, with initial data $v(0,x)$ obtained by integrating u_0 twice and boundary data $v(t,x_0) = P(t) - x_0 U(t)$. The equation for v may be solved by the method of characteristics, and u is recovered from $\partial_x^2 v(t,x) = u(t,x)$. The solution depends on the initial data in the region $\{(x,t)\,|\,x > x_0 + \tau\int_0^t V(s)ds\,\}$ and on the boundary data in the complement of this region. Since $V(t)$ always has a positive limit, it is evident that the contribution from the initial data is swept out towards large x-values and decays exponentially, in fact, at a rate like $e^{-\varepsilon t^2}$ for some $\varepsilon > 0$. If the disease-free state is stable, then $(P(t),U(t)) \to (0,0)$ as $t\to\infty$, which implies that the solution u converges to zero also in the region where it depends on the boundary data. In the case of a positive disease equilibrium, $P(t) - x_0U(t)$ has a positive limit as $t\to\infty$, which determine the limiting equilibrium distribution u_* given in Theorem 1.2. This method breaks down if $\beta(\cdot)$, $\mu(\cdot)$, or $\kappa(\cdot,\cdot)$ have more complicated forms, as the reader will readily confirm.

2. The Linear Automomous Problem

2.1. **Functional Analytic Setting.** We consider the problem

$$\begin{aligned} \partial_t u(t,x) + \omega\partial_x u(t,x) + (\mu+\beta x)u(t,x) &= 2\beta\int_x^\infty u(t,y)dy, \\ u(0,x) = u_0(x), \quad u(t,x_0) &= 0, \quad t>0,\ x>x_0. \end{aligned} \tag{2.1}$$

Set $w(t,x) = u(t,x+x_0)$, $x \ge 0$. Then this problem becomes the following one on $\mathbb{R}_+$.

$$\begin{aligned} \partial_t w(t,x) + \omega\partial_x w(t,x) + (\mu_0+\beta x)w(t,x) &= 2\beta\int_x^\infty w(t,y)dy, \\ w(0,x) = g(x) := u_0(x+x_0), \quad w(t,0) &= 0, \quad t>0,\ x>0. \end{aligned} \tag{2.2}$$

Here we have set $\mu_0 = \mu + \beta x_0$. ω plays the role of τV at ∞, i.e.

$$\omega = \tau V(\infty) = \lambda\tau/\gamma$$

in the disease-free case or

$$\omega = \tau V(\infty) = (\mu+\beta x_0)^2/\beta = \mu_0^2/\beta$$

in the disease case.

We want to study (2.2) in the basic space $X = L_1(\mathbb{R}_+;(a+x)dx)$, where we choose as the norm

$$||w|| = a|w|_1 + |xw|_1,$$

with $a > 0$ to be determined later. We define two linear operators in X by means of

$$Au(x) = \omega u'(x) + (\mu_0+\beta x)u(x), \quad x\in\mathbb{R}_+,$$

with domain

$$D(A) = \{u \in W_1^1(\mathbb{R}_+) \cap X : \ x^2 u \in L_1(\mathbb{R}_+), xu'(x) \in L_1(\mathbb{R}_+), \ u(0) = 0\},$$

and

$$Bu(x) = 2\beta \int_x^\infty u(y)dy, \quad D(B) = D(A).$$

Both operators are well-defined and linear, B will be considered as a perturbation of A.

2.2. **m-Accretivity of A.** We have

$$\begin{aligned} \int_0^\infty Au \operatorname{sgn} u dx &= \omega \int_0^\infty |u|' dx + \mu_0 |u|_1 + \beta |xu|_1 \\ &= \mu_0 |u|_1 + \beta |xu|_1, \end{aligned}$$

and

$$\begin{aligned} \int_0^\infty Au \operatorname{sgn} u x dx &= \omega \int_0^\infty |u|' x dx + \mu_0 |xu|_1 + \beta |x^2 u|_1 \\ &= -\omega |u|_1 + \mu_0 |xu|_1 + \beta |x^2 u|_1. \end{aligned}$$

Employing the bracket in L_1 this implies

$$[Au, u]_+ \geq (a\mu_0 - \omega)|u|_1 + (a\beta + \mu_0)|xu|_1 \geq \eta ||u||,$$

for some $\eta > 0$ provided $\mu_0 > \omega/a$. Hence for such a, A is strictly accretive, in particular closable.

Next we compute the resolvent of A. The equation $(\lambda + A)u = f$ is equivalent to solving the ode

$$\lambda u(x) + \omega u'(x) + (\mu_0 + \beta x)u(x) = f(x), \quad x > 0, \tag{2.3}$$

with initial condition $u(0) = 0$. Therefore we obtain

$$u = (\lambda + A)^{-1} f(x) = \frac{1}{\omega} \int_0^x \exp -[(\lambda + \mu_0)(x - y)/\omega + \beta(x^2 - y^2)/2\omega] f(y) dy.$$

If $f \in L_1(\mathbb{R}_+)$ then on easily obtains the estimate

$$|u|_1 \leq |f|_1/(\lambda + \mu_0).$$

If also $xf \in L_1(\mathbb{R}_+)$ then

$$\begin{aligned} |x^2 u(x)| &\leq \frac{1}{\omega} \int_0^x e^{-(\lambda+\mu_0)(x-y)/\omega} (x^2 - y^2) e^{-\beta(x^2-y^2)/2\omega)} |f(y)| dy \\ &+ \frac{1}{\omega} \int_0^x y e^{-\beta(x-y)2y/2\omega} y |f(y)| dy, \end{aligned}$$

hence

$$|x^2 u|_1 \leq \frac{1}{\omega} \frac{\omega}{\lambda + \mu_0} \frac{2\omega}{\beta e} |f|_1 + \frac{1}{\omega} \frac{\omega}{\beta^2} |xf|_1.$$

This shows that $x^2 u \in L_1(\mathbb{R}_+)$, hence $xu \in L_1(\mathbb{R}_+)$, and then by equation (2.3) also $u' \in L_1(\mathbb{R}_+)$ as well as $xu' \in L_1(\mathbb{R}_+)$, i.e. $u \in D(A)$. This shows that A is m-accretive.

As a consequence we note that $-A$ generates a C_0-semigroup in X which is also positive and strictly contractive, hence exponentially stable.

2.3. **Accretivity of $A - B$.** We have

$$|\int_x^\infty u(x)dx|_1 \leq |xu|_1, \quad |x \int_x^\infty u(x)dx|_1 \leq \frac{1}{2}|x^2 u|_1,$$

and therefore

$$\int_0^\infty (Au - Bu) \operatorname{sgn}(u) dx \geq \mu_0 |u|_1 + \beta |xu|_1 - 2\beta |xu|_1,$$

as well as

$$\int_0^\infty (Au - Bu) \operatorname{sgn}(u) x dx \geq -\omega |u|_1 + \mu_0 |xu|_1.$$

This yields

$$[(A-B)u,u]_+ \geq (\mu_0 a-\omega)|u|_1+(\mu_0-\beta a)|xu|_1 \geq 0,$$

for all $u \in D(A)$, provided $\mu_0 a \geq \omega$ and $\mu_0 \geq \beta a$. Such a choice of $a>0$ is possible if and only if the condition $\omega/\mu_0 \leq \mu_0/\beta$ is met, i.e. if and only if

$$\omega \leq \mu_0^2/\beta$$

holds true. Now in the disease-free case we have $\omega = \lambda\tau/\gamma$, while in the disease case $\omega = \mu_0^2/\beta$; then $a = \mu_0/\beta$. Thus $A-B$ will be strictly accretive in the disease-free case while it will be accretive only in the disease case. In the first case, the decay rate can easily be estimated not to be smaller than $\mu_0 - \sqrt{\lambda\beta\tau/\gamma}$.

2.4. **Density of the Range of $A-B$.** Let $f \in L_1(\mathbb{R}_+;(a+x)dx)$ be given and assume $f \geq 0$. Set $u_1 = (1+A)^{-1}f$ and define the sequence u_n inductively by means of

$$u_{n+1} = u_1 + (1+A)^{-1}Bu_n.$$

Then $u_1 \geq 0$, and $u_2 - u_1 = (1+A)^{-1}Bu_1 \geq 0$, hence by induction $u_{n+1} \geq u_n$ pointwise, since B is positive. This shows that the sequence of functions u_n is nonnegative and increasing pointwise. Moreover,

$$\omega u_n' + (1+\mu_0+\beta x)u_n = f + 2\beta\int_x^\infty u_{n-1}(y)dy \leq f + 2\beta\int_x^\infty u_n(y)dy,$$

which implies

$$(1+\mu_0)|u_n|_1 + \beta|xu_n|_1 \leq |f|_1 + 2\beta|xu_n|_1,$$

and

$$-\omega|u_n|_1 + (1+\mu_0)|xu_n|_1 + \beta^2|x^2u_n|_1 \leq |xf|_1 + \beta|x^2u_n|_1.$$

Choosing a as above this yields an a priori bound for the sequence (u_n)

$$||u_n|| = a|u_n|_1 + |xu_n| \leq C||f||,$$

and therefore we may conclude by the monotone convergence theorem $u_n \to u_\infty$ as $n \to \infty$. If in addition $x^2 f \in L_1(\mathbb{R}_+)$ then we obtain in a similar way boundedness of x^2u_n in X. This implies $(1+A-B)u_n = f + B(u_{n-1}-u_n) \to f$ in X as $n \to \infty$, hence $u_\infty \in D(\overline{A-B})$ and $u_\infty = (1+\overline{A-B})^{-1}f$. Since $L_1 = L_1^+ - L_1^+$ we may conclude $R(1+\overline{A-B}) = X$, i.e. the closure of $A-B$ is m-accretive.

Remark 2.1. The above proof shows that the resolvent of $\overline{A-B}$ is positive, hence the semigroup generated by this operator will be as as well.

2.5. **Irreducibility.** Suppose $f \in X$ is nonnegative and u solves

$$\omega u' + (\lambda+\mu_0+\beta x)u = f + 2\beta\int_x^\infty u(y)dy, \quad x \geq 0,$$

with initial value $u(0)=0$. If $f \not\equiv 0$ then let $x_1 := \inf \operatorname{supp} f$. We have

$$u(x) = \frac{1}{\omega}\int_0^x \exp -[(\lambda+\mu_0)(x-y)/\omega + \beta(x^2-y^2)/2\omega][f(y)+Bu(y)]dy.$$

Since we already know $u(x) \geq 0$, this formula implies $u(x) > 0$ for all $x > x_1$. But then $\int_x^\infty u(y)dy > 0$ for all $x \geq 0$, and so so $u(x) > 0$ for all $x > 0$. This proves the irreducibility of the semigroup generated by $\overline{A-B}$.

2.6. $A-B$ **is not Closed.** Unfortunately, the sum $A-B$ is not closed. We show this by the following example.

Example 2.2. Set $u=\chi/x^3$ where χ denotes a cut-off function which is 0 on $[0,1]$ and 1 on $[2,\infty)$. Then $u, u'u, xu \in L_1(\mathbb{R}_+)$, but $x^2u \notin L_1(\mathbb{R}_+)$, and $u(0)=0$. On the other hand,

$$\begin{aligned} f(x) &:= \omega u'(x)+(\lambda+\mu_0+\beta x)u(x)-2\beta\int_x^\infty u(y)dy \\ &= \omega\chi'/x^3-3\omega\chi/x^4+(\lambda+\mu_0)\chi/x^3+\beta\chi/x^2-2\beta\int_x^\infty \chi(y)dy/y^3 \end{aligned}$$

Since

$$\begin{aligned} &\chi(x)/x^2-2\int_x^\infty \chi(y)dy/y^3=\chi(x)/x^2+\chi(y)/y^2|_x^\infty-\int_x^\infty \chi'(y)dy/y^2 \\ =\ &-\int_x^\infty \chi'(y)dy/y^2, \end{aligned}$$

we obtain

$$f=\omega\chi'(x)/x^3-3\omega\chi(x)/x^4+(\lambda+\mu_0)\chi(x)/x^3-\beta\int_x^\infty \chi'(y)dy/y^2.$$

Obviously, f as well as xf belong to $L_1(\mathbb{R}_+)$, so $A-B$ with domain $D(A)$ is not closed.

2.7. **Summary.** Let us summarize what we have shown so far.

Theorem 2.3. *Suppose $\beta\omega\le\mu_0^2$. Then problem (2.2) is well-posed in $X=L_1(\mathbb{R}_+;(a+x)dx)$ and admits an associated C_0-semigroup $T(t)=e^{-Lt}$ which is positive. If a is chosen from the interval $a\in[\omega/\mu_0,\mu_0/\beta]$ then $T(t)$ is nonexpansive.*

In the strictly disease free case $\omega=\lambda\tau/\gamma<\mu_0^2/\beta$, the semigroup $T(t)$ is exponentially stable with type $\omega_0(T)\le-\mu_0+\sqrt{\lambda\beta\tau/\gamma}<0$.

3. Asymptotic Behavior of the Autonomous Problem

3.1. **Compactness.** Set $L=\overline{A-B}$. Since L is m-accretive in $X=L_1(\mathbb{R}_+;(a+x)dx)$, the spectrum $\sigma(L)$ is contained in the closed right halfplane. We want to show that the resolvent of L is compact. For this purpose we derive another representation of $(\lambda+L)^{-1}$ for $\lambda>0$. Let $f\in X$ and set $u=(\lambda+L)^{-1}f$. Then we obtain

$$u=(\lambda+A)^{-1}f+(\lambda+A)^{-1}Bu,$$

and

$$\begin{aligned} (\lambda+A)^{-1}Bu &= 2\beta(\lambda+A)^{-1}[\int_x^\infty u(y)dy] \\ &= \frac{2\beta}{\omega}\int_0^x e^{-(\lambda+\mu_0)(x-y)/\omega}e^{-\beta(x^2-y^2)/2\omega}[\int_y^\infty u(r)dr]dy \\ &= \frac{2\beta}{\omega}\int_x^\infty u(r)[\int_0^x e^{-(\lambda+\mu_0)(x-y)/\omega}e^{-\beta(x^2-y^2)/2\omega}dy]dr \\ &+ \frac{2\beta}{\omega}\int_0^x u(r)[\int_0^r e^{-(\lambda+\mu_0)(x-y)/\omega}e^{-\beta(x^2-y^2)/2\omega}dy]dr \\ &= k_\lambda(x)\int_x^\infty u(r)dr+\omega(\lambda+A)^{-1}[k_\lambda u], \end{aligned}$$

where

$$k_\lambda(x)=\frac{2\beta}{\omega}\int_0^x e^{-(\lambda+\mu_0)(x-y)/\omega}e^{-\beta(x^2-y^2)/2\omega}dy.$$

Note that

$$0\le k_\lambda(x)\le\frac{2\beta}{\omega}\int_0^x e^{-(\lambda+\mu_0)(x-y)/\omega}dy\le\frac{2\beta}{\lambda+\mu_0},$$

i.e. $k_\lambda \in L_\infty(\mathbb{R}_+)$. We thus have the identity

$$u(x) - k_\lambda(x)\int_x^\infty u(y)dy = (\lambda + A)^{-1}f(x) + \omega(\lambda + A)^{-1}[k_\lambda u] =: g(x),$$

and $u(0) = 0$. We may solve this equation for u to the result

$$u(x) = g(x) - k_\lambda(x)\int_0^x \exp\left(-\int_y^x k_\lambda(r)dr\right) g(y)dy + k_\lambda(x)\exp\left(-\int_0^x k_\lambda(s)ds\right) < q_\lambda|f >,$$

where

$$< q_\lambda, f >:= \frac{1}{(\lambda+\mu_0)^2 - \omega\beta}((\lambda+\mu_0)\int_0^\infty f(s)ds + \beta\int_0^\infty sf(s)ds)\,.$$

This way we have the representation

$$(\lambda+L)^{-1}f = (1-R_\lambda)(\lambda+A)^{-1}[1+\omega k_\lambda(\lambda+L)^{-1}]f + k_\lambda(x)\exp\left(-\int_0^x k_\lambda(s)ds\right) < q_\lambda|f >, \tag{3.1}$$

with

$$(R_\lambda g)(x) = k_\lambda(x)\int_0^x \exp\left(-\int_y^x k_\lambda(r)dr\right) g(y)dy.$$

Next $D(A)$ embeds compactly into X, hence $(\lambda + A)^{-1}$ is compact. From boundedness of k_λ we may then conclude that $(\lambda + L)^{-1}$ is compact, as soon as we know that the Volterra operator R_λ is bounded in X.

To prove the latter we estimate as follows

$$\begin{aligned}
||R_\lambda g|| &= \int_0^\infty (a+x)k_\lambda(x)|\int_0^x \exp\left(-\int_y^x k_\lambda(r)dr\right) g(y)dy|dx \\
&\le \int_0^\infty |g(y)|[\int_y^\infty (a+x)k_\lambda(x)\exp\left(-\int_y^x k_\lambda(r)dr\right)dx]dy \\
&= \int_0^\infty |g(y)|[(a+y) + \int_y^\infty \exp\left(-\int_y^x k_\lambda(r)dr\right)dx]dy \\
&\le C_\lambda\int_0^\infty |g(y)|(a+y)dy = C_\lambda||g||,
\end{aligned}$$

as we show now.

$$\begin{aligned}
k_\lambda(x) &= \frac{2\beta}{\omega}\int_0^x e^{-(\lambda+\mu_0)(x-y)/\omega}e^{-\beta(x^2-y^2)/2\omega}dy \\
&\ge \frac{2\beta}{\omega}\int_0^x e^{-(\lambda+\mu_0)y/\omega}e^{-\beta xy/\omega}dy \\
&= \frac{2\beta}{\lambda+\mu_0+\beta x}(1 - e^{-(\lambda+\mu_0+\beta x)x/\omega}) \\
&\ge \frac{2\beta}{\lambda+\mu_0+\beta x}\cdot\frac{(\lambda+\mu_0+\beta x)x/\omega}{1+(\lambda+\mu_0+\beta x)x/\omega)} \\
&= \frac{2\beta x}{\omega + (\lambda+\mu+\beta x)x},
\end{aligned}$$

by the elementary inequality $1 - e^{-x} \ge x/(1+x)$. This implies

$$\begin{aligned}
\int_y^x k_\lambda(r)dr &\ge 2\beta\int_y^x rdr/(\omega + (\lambda+\mu_0+\beta r)r \\
&= \int_y^x \frac{2\beta r + \lambda + \mu_0}{\omega + (\lambda+\mu_0)r + \beta r^2}dr - (\lambda+\mu_0)\int_y^x \frac{dr}{\omega + (\lambda+\mu_0)r + \beta r^2} \\
&\ge \log\frac{\omega + (\lambda+\mu_0)x + \beta x^2}{\omega + (\lambda+\mu_0)y + \beta y^2} - c_\lambda,
\end{aligned}$$

since the second integral is bounded. This estimate finally yields

$$\int_y^\infty \exp\left(-\int_y^x k_\lambda(r)dr\right)dx \le e^{c_\lambda}\int_y^\infty \frac{\omega+(\lambda+\mu_0)y+\beta y^2}{\omega+(\lambda+\mu_0)x+\beta x^2}dx \le C_\lambda(a+y).$$

This completes the proof of compactness of the resolvent of L.

3.2. **Ergodicity.** Since the resolvent of L is compact we know that the spectrum of L consists only of eigenvalues of finite multiplicity, these are poles of the resolvent of L. By accretivity of L we have the inequality $|(\lambda+L)^{-1}|_{\mathcal{B}(X)} \le 1/\mathrm{Re}\lambda$, $\mathrm{Re}\lambda > 0$, hence the resolvent can only have poles of first order on the imaginary axis. This shows that all eigenvalues on the imaginary axis are semisimple. Compactness of the resolvent implies also that the range of $\lambda + L$ is closed, for each $\lambda \in \mathbb{C}$. In particular, we have the direct sum decomposition $X = N(L) \oplus R(L)$, i.e. ergodicity in the sense of Abel.

Now we concentrate on the disease equilibrium which means $a = \mu_0/\beta$ and $\omega = \mu_0^2/\beta$. A function $e(x)$ belongs to the kernel of L if

$$\omega e'(x) + (\mu_0+\beta x)e(x) - 2\beta\int_x^\infty e(y)dy = 0, \quad x > 0,\ e(0) = 0,$$

or equivalently

$$e''(x) + \frac{\beta}{\mu_0}(1+\frac{\beta}{\mu_0}x)e'(x) + 3\frac{\beta^2}{\mu_0^2}e(x) = 0, \quad x > 0,\ e(0) = 0.$$

The scaling $e(x) = v(\beta x/\mu_0)$ reduces this problem to

$$v''(z) + (1+z)v'(z) + 3v(z) = 0, \quad z > 0,\ v(0) = 0.$$

By the initial condition $v(0) = 0$, this shows that the kernel of L can be only one-dimensional, and a simple computation yields that

$$v(z) = (z + z^2/2)e^{-(z+z^2/2)}, \quad z > 0,$$

is a solution. Therefore $N(L) = \mathrm{span}\{e\}$, with $e(x) = (\beta/\mu_0)^2 v(\beta x/\mu_0)$, and another simple computation yields

$$\int_0^\infty (a+x)e(x)dx = 1.$$

Since L is Fredholm with index zero, the kernel $N(L^*)$ of the dual of L has also a one-dimensional kernel which are the constant functions. The ergodic projection $\mathcal{P}$ onto the kernel of L along the range of L is then given by

$$\mathcal{P}u(x) = [\int_0^\infty (a+x)u(x)dx]e(x) =< u|e^* > e(x), \quad x > 0. \tag{3.2}$$

Suppose there are no other eigenvalues of L on the imaginary axis. Then L^* also has no other eigenvalues on the imaginary axis, and then by the theorem of Arendt, Batty, Lubich and Phong we may conclude that

$$e^{-Lt}u \to \mathcal{P}u \quad \text{as } t \to \infty, \text{ for each } u \in X,$$

i.e. the semigroup generated by $-L$ is strongly ergodic.

We show now that there are in fact no eigenvalues other than 0 on the imaginary axis. Suppose on the contrary that

$$i\rho u(x) + \omega u'(x) + (\mu_0+\beta x)u(x) = 2\beta\int_x^\infty u(y)dy, \quad x > 0,\ u(0) = 0,$$

$u \neq 0$. Multiplying this equation with $\bar{u}/|u|$, taking real parts, and integrating over $\mathbb{R}_+$ we obtain

$$\mu_0|u|_1 + \beta|xu|_1 = 2\beta\mathrm{Re}\int_0^\infty u(x)\int_0^x \bar{u}(y)/|u(y)|dydx \le 2\beta|xu|_1, \tag{3.3}$$

and similarly, multiplying with $x\bar{u}(x)/|u(x)|$ we get

$$-\omega|u|_1 + \mu_0|xu|_1 + \beta|x^2u|_1 = 2\beta\mathrm{Re}\int_0^\infty u(x)\int_0^x y\bar{u}(y)/|u(y)|dydx \le \beta|x^2u|_1. \tag{3.4}$$

Multiplying the first inequality with $a = \mu_0/\beta$ and adding the second we arrive at a contradiction if at least one of the inequalities (3.3), (3.4) is strict. Hence we must have

$$\mathrm{Re}\int_0^\infty u(x)\int_0^x \bar{u}(y)/|u(y)|dydx = |xu|_1,$$

which implies with $\arg u(x) = \theta(x)$

$$x \equiv \mathrm{Re}\int_0^x e^{i(\theta(x)-\theta(y))}dy = \frac{1}{2}\frac{d}{dx}|\int_0^x e^{i\theta(y)}dy|^2,$$

or equivalently

$$|\int_0^x e^{i\theta(y)}dy|^2 = x^2, \quad x > 0.$$

But this is only possible if $\theta(y)$ is constant, w.l.o.g. we may assume $\theta = 0$ i.e. $u(x)$ is nonnegative, which in turn yields $\rho = 0$ since $u \neq 0$ by assumption.

3.3. **Summary.** Let us summarize what we have shown in this section.

Theorem 3.1. *Assume the disease case $\omega = \mu_0^2/\beta$, $a = \mu_0/\beta$. The the semigroup $T(t) = e^{-Lt}$ is strongly ergodic, it converges strongly to the projection $\mathcal{P}$ onto the kernel $N(L)$ of L along its range $R(L)$. The kernel is one-dimensional and spanned by $e(x) = (\beta/\mu_0)^2\Phi(\beta x/\mu_0)$, where $\Phi(z) = (z + z^2/2)e^{-(z+z^2/2)}$, and the projection $\mathcal{P}$ is given by*

$$\mathcal{P}u(x) = [\int_0^\infty (a+y)u(y)dy]e(x) =< e^*|u > e(x), \quad x > 0,\ u \in X.$$

Remark. We do not know whether the ergodicity is exponential since it is not clear that the type of the semigroup e^{-Lt} restricted to $R(L)$ is negative.

4. Well-posedness of the Non-Autonomous Evolution

4.1. **The Trivial Evolution.** Let $\omega \in C(\mathbb{R}_+)$ be positive, such that $0 < \omega_\infty = \lim_{t\to\infty}\omega(t)$ exists, and assume $\omega(\cdot) - \omega_\infty \in L_1(\mathbb{R}_+)$. Let

$$\omega_+ = \max_{s\geq 0}\omega(s) \quad \text{and} \quad \omega_- = \min_{s\geq 0}\omega(s),$$

and note that $\omega_+ \geq \omega_- > 0$. We are particularly interested in the cases $\omega_\infty = \lambda\tau/\gamma$, the disease-free case, and $\omega_\infty = \mu_0^2/\beta$, the disease case. We want to show that the nonautonomous problem is well-posed in $X = L_1(\mathbb{R}_+; (a+x)dx)$. We begin with the problem

$$\begin{aligned} \partial_t u(t,x) + \omega(t)\partial_x u(t,x) + (\mu_0 + \beta x)u(t,x) = 0, \quad x > 0, t > s \geq 0 \\ u(s,x) = g(x), \quad u(t,0) = 0, \quad t > s \geq 0, x > 0. \end{aligned} \tag{4.1}$$

The method of characteristics yields easily the evolution operator $U_0(t,s)$ for this problem. It is given by

$$[U_0(t,s)g](x) = u(t,x) = g(x - \int_s^t \omega(\tau)d\tau)e^{-\phi(t,s,x)}, \tag{4.2}$$

$$\phi(t,s,x) = \mu_0(t-s) + \beta(t-s)(x - \int_s^t \omega(\tau)d\tau) + \beta\int_s^t (t-\tau)\omega(\tau)d\tau,$$

if we extend g trivially to $\mathbb{R}$. We obviously have the estimate $|U_0(t,s)|_{\mathcal{B}(X)} \leq e^{-\mu_0(t-s)}$, and $u(t,x)$ is a strong solution in X if the initial function g belongs to D defined by

$$D := \{g \in L_1(\mathbb{R}_+) :\ x^2 g, g', xg' \in L_1(\mathbb{R}_+), g(0) = 0\}.$$

We also need the solution of

$$\begin{aligned} \partial_t u(t,x) + \omega(t)\partial_x u(t,x) + (\mu_0 + \beta x)u(t,x) = 0, \quad x > 0, t > s \geq 0 \\ u(s,x) = 0, \quad u(t,0) = h(t), \quad t > s \geq 0, x > 0. \end{aligned} \tag{4.3}$$

Again the method of characteristics applies and yields with $K(t,x)=\int_{\rho(t,x)}^t(r-\rho(t,x))\omega(r)dr$ the formula

$$[V_0(t,s)h](x)=u(t,x)=h(\rho(t,x))e^{-[\mu_0(t-\rho(t,x)+\beta x(t-\rho(t,x))-\beta K(t,x)]},$$

for $x<\int_s^t\omega(r)dr$, and zero elsewhere, where the function $\rho(t,x)$ is defined by the equation

$$x=\int_\rho^t\omega(r)dr; \tag{4.4}$$

note that this equation has a unique solution $\rho(t,x)\in(s,t)$, since $\omega(r)\geq\omega_-\,>0$ for all $r\geq 0$, by assumption, and $x<\int_s^t\omega(r)dr$. Observe that with $K_0(t,s)=\int_s^t\omega(r)dr$ we have

$$\begin{aligned}
&\int_0^\infty(a+x)[V_0(t,s)h](x)dx\leq|h|_\infty\int_0^{K_0(t,s)}(a+x)e^{-\mu_0(t-\rho(t,x))}dx\\
&\leq|h|_\infty\int_s^t(a+\int_\sigma^t\omega(r)dr)e^{-\mu_0(t-\sigma)}\omega(\rho(t,x))d\sigma\\
&\leq|h|_\infty\omega_+\int_0^{t-s}(a+\omega_+\sigma)e^{-\mu_0\sigma}d\sigma\leq C|h|_\infty,
\end{aligned}$$

by the variable transformation $\sigma=\rho(t,x)$. Thus the part coming from a nontrivial bounded boundary value h is bounded in X.

4.2. **Well-posedness for the Full Problem.** Let us now consider the full problem, i.e.

$$\begin{aligned}
\partial_t u(t,x)+\omega(t)\partial_x u(t,x)+(\mu_0+\beta x)u(t,x)&=2\beta\int_x^\infty u(t,y)dy,\\
u(s,x)=g(x),\quad u(t,0)=0,\quad t>s\geq 0,\ x>0.&
\end{aligned}\tag{4.5}$$

Since the standard cone in X is reproducing, i.e. $L_1=L_1^+-L_1^+$, we may restrict attention to nonnegative initial functions g. We define the sequence u_n inductively by

$$u_1(t):=U_0(t,s)g,\quad u_{n+1}(t)=u_1(t)+\int_s^t U_0(t,r)Bu_n(r)dr,\quad t\geq s\geq 0.$$

Since $U_0(t,s)$ is positive the functions u_n are as well, and $u_2(t)\geq u_1(t)$ since B is positive. Inductively we obtain with

$$u_{n+1}(t)-u_n(t)=\int_s^t U_0(t,r)B(u_n(r)-u_{n-1}(r))dr,\quad t\geq s\geq 0,$$

that the functions u_n are pointwise increasing w.r.t. $n\in\mathbb{N}$.

Suppose that $g\in D$. Then u_n is a strong solution of

$$\begin{aligned}
\partial_t u_n(t,x)+\omega(t)\partial_x u_n(t,x)+(\mu_0+\beta x)u_n(t,x)&=2\beta\int_x^\infty u_{n-1}(t,y)dy\\
&\leq 2\beta\int_x^\infty u_n(t,y)dy,\quad x>0,t>s\geq 0\\
u(s,x)=g(x),\quad u(t,0)=0,\quad t>s\geq 0,x>0,&
\end{aligned}$$

i.e. u_n is a strong lower solution of (4.5). Multiplying the equation with x^i and integrating over $\mathbb{R}_+$ this yields with $z_i(t)=|x^iu_n(t)|_1$

$$\partial_t z_0(t)+\mu_0 z_0(t)+\beta z_1(t)\leq 2\beta z_1(t),$$

for $i=0$, and for $i=1$

$$\partial_t z_1(t)-\omega(t)z_0(t)+\mu_0 z_1(t)+\beta z_2(t)\leq\beta z_2(t).$$

Setting $z(t)=(z_0(t),z_1(t))^T$, $b(t)=(0,(\omega(t)-\omega_\infty)z_0(t))^T$, and defining G by the 2×2-matrix with entries $-\mu_0,\beta,\omega_\infty,-\mu_0$, this inequality becomes

$$\partial_t z(t)\leq Gz(t)+b(t),\quad t\geq s\geq 0.$$

The eigenvalues of G are given by $\lambda_\pm = -\mu_0 \pm \sqrt{\beta\omega_\infty}$ which are both nonpositive if $\beta\omega_\infty \le \mu_0^2$, which is true in both, the disease-free and the disease case. Since e^{Gt} is positive we may conclude

$$z(t) \le e^{G(t-s)}z(s) + \int_s^t e^{G(t-r)}b(r)dr.$$

Boundedness of e^{Gt} then implies an inequality of the form

$$|z(t)| \le C + C\int_s^t |\omega(r) - \omega_\infty||z(r)|dr, \quad t \ge s \ge 0,$$

which implies boundedness of $z(t)$ on $[s,\infty)$ since $(\omega(\cdot) - \omega_\infty) \in L_1(\mathbb{R}_+)$ by assumption. Note that the constant C depends only on the parameters $\mu_0, \beta, \omega_\infty$ and on $||g||$.

Therefore the functions $u_n(t)$ are bounded in X uniformly in t and n. By monotone convergence we may conclude $u_n(t) \to u(t)$ in X for each $t \ge s$. Since B is positive, $Bu_n \to Bu$ in $L_1(\mathbb{R}_+)$ as well, and then also

$$u(t) = U_0(t,s)g + \int_s^t U_0(t,r)Bu(r)dr, \quad t \ge s \ge 0, \tag{4.6}$$

at least in $L_1(\mathbb{R}_+)$. A density argument finally shows that this conclusion is valid for all initial data $g \in X$.

Remark. It is not clear that solutions of (4.6) are unique. The reason for this is that B is unbounded. Therefore we need another definition of mild solution.

Definition. *Let $f \in L_{1,loc}(R_+; X)$.*
(i) We call a function $u \in C(\mathbb{R}_+; X)$ strong solution of

$$\partial_t u(t,x) + \omega(t)\partial_x u(t,x) + (\mu_0 + \beta x)u(t,x) = 2\beta\int_x^\infty u(t,y)dy + f(t,x),$$
$$u(s,x) = g(x), \quad u(t,0) = 0, \quad t > s \ge 0, x > 0. \tag{4.7}$$

if $u \in C^1(\mathbb{R}_+; X) \cap C(\mathbb{R}_+; D)$ and (4.7) is valid pointwise.
(ii) We call a function $u \in C(\mathbb{R}_+; X)$ mild solution of (4.7) if there are $f_n \in L_{1,loc}(R_+; X)$ and strong solutions u_n of (4.7) such that $u_n \to u$ and $f_n \to f$ as $n \to \infty$, in X, uniformly on compact intervals.

Suppose that $g \in D$ has compact support. Then each iteration $u_n(t)$ has also compact support, namely

$$\operatorname{supp} u_n(t) \subset \operatorname{supp} g + \omega_+[0,t],$$

for each $n \in \mathbb{N}$. Therefore each function $u_n(t)$ is a strong solution of (4.7) with inhomogeneity $f_n(t) = B(u_{n-1}(t) - u_n(t))$. This proves that the limit $u(t)$ is a mild solution. Approximation then shows that (4.5) has at least one mild solution, for each initial value $g \in X$.

Uniqueness of mild solutions can be obtained as follows. If u is a strong solution of (4.7) then the equation yields as above the inequality

$$\partial_t||u(t)|| \le \omega_+||u(t)|| + ||f(t)||, \quad t > 0,$$

hence

$$||u(t)|| \le e^{\omega_+(t-s)}||g|| + \int_s^t e^{\omega_+(t-r)}||f(r)||dr.$$

By approximation this inequality is also valid for mild solutions, hence $u \equiv 0$ in case $f \equiv g = 0$. Thus mild solutions are unique and of course they satisfy the integral equation (4.6).

4.3. **Summary.** We have proved the following result about well-posedness of (4.5)

Theorem 4.1. *Suppose $\omega \in C(\mathbb{R}_+)$ is a given strictly positive function, such that $\omega_\infty = \lim_{t\to\infty}\omega(t) > 0$ exists and $\omega(\cdot) - \omega_\infty \in L_1(\mathbb{R}_+)$. Then (4.5) is well-posed in the sense of the definition given above. There exists a unique evolution operator $U(t,s)$ in X generated by (4.5), which is bounded in X, uniformly in $0 \le s \le t < \infty$, and positive. Moreover, (4.5) has finite speed of propagation with maximum speed less than $\omega_+ = \sup_{t\ge 0}\omega(t)$.*

4.4. **Higher Order Bounds.** Consider an initial function $g \in C_0^\infty(0,\infty)$. Then u_1 is smooth as well and has compact support for each $t \geq s$. Then the same holds true for u_2, hence by induction for all u_n. Setting $v_n = \partial_x u_n$ we have the following problem for v_n.

$$\begin{aligned} &\partial_t v_n + \omega(t)\partial_x v_n + (\mu_0 + \beta x)v_n = -\beta[u_n + 2u_{n-1}], \\ &v_n(s,x) = g'(x), \quad v_n(t,0) = \psi_n(t), \quad t > s \geq 0, x > 0 \end{aligned} \tag{4.8}$$

where $\psi_n(t) = \frac{2\beta}{\omega(t)}|u_{n-1}(t)|_1$. This implies

$$\partial_x u_n(t) = v_n(t) = U_0(t,s)g' - \beta \int_s^t U_0(t,r)[u_n(r) + 2u_{n-1}(r)]dr + w_n(t), \quad t \geq s \geq 0,$$

with

$$w_n(t) = 2\beta V_0(t,s)[|u_{n-1}(\cdot)|_1/\omega(\cdot)].$$

Uniform boundedness of u_n in X and exponential stability of the evolution operator $U_0(t,s)$ in X then implies boundedness of $\partial_x u_n$ in X. Passing to the limit we get

$$\partial_x u(t) = U_0(t,s)g' - 3\beta \int_s^t U_0(t,r)u(r)dr + w(t), \quad t \geq s \geq 0,$$

where

$$w(t,x) = 2\beta V_0(t,s)[|u(\cdot)|_1/\omega(\cdot)].$$

This yields $\partial_x u \in C_b([s,\infty); X)$. The last identity was proven for $g \in C_0^\infty(0,\infty)$, but via density can be extended to $g \in D$.

5. Convergence

We are now ready to prove the main result on convergence. Let us first look at the disease-free case. Then with $A(t)$, B, defined as in section 2, and $L(t) = \overline{A(t) - B}$, we know that $L(t)$ is strictly accretive for large times t if the parameter a is chosen in $a \in (\lambda\tau/\gamma\mu_0, \mu_0/\beta)$. This proves exponential stability of the trivial solution in the disease-free case, with decay rate at least $\mu_0 - \sqrt{\lambda\beta\tau/\gamma}$.

Suppose we have a solution u of the nonautonomous problem in the disease case such that $\partial_x u(t)$ is bounded in X. Then we may write

$$\begin{aligned} &\partial_t u + \omega_\infty \partial_x u + (\mu_0 + \beta x)u - 2\beta \int_x^\infty u(t,y)dy = (\omega_\infty - \omega(t))\partial_x u, \\ &u(0,x) = g(x), \quad u(t,0) = 0, \quad t > 0, x > 0. \end{aligned} \tag{5.1}$$

Therefore we obtain the identity

$$u(t) = e^{-Lt}g + \int_0^t e^{-L(t-r)}(\omega_\infty - \omega(r))\partial_x u(r))dr, \quad t \geq 0.$$

We know from Section 9 that e^{-Lt} converges strongly in X to the ergodic projection $\mathcal{P}$. On the other hand, the scalar function $\omega(\cdot) - \omega_\infty$ belongs to $L_1(\mathbb{R}_+)$ by assumption. This then implies

$$u(t) \to u_\infty \in R(\mathcal{P}).$$

Thus we have convergence in X to a unique element for all nonnegative solutions with initial values in D. Since the evolution operator associated with (4.5) is bounded in X, this convergence extends to all initial values $u_0 \in X$.

Returning now to the system (1.1), we may compute the limit u_∞. For this purpose recall that $U(t) = \int_{x_0}^\infty u(t,x)dx \to U_\infty$ and $P(t) = \int_{x_0}^\infty u(t,x)xdx \to P_\infty$. This implies

$$u_\infty = \lim_{t\to\infty} \mathcal{P}u(t) = \lim_{t\to\infty}[aU(t) + P(t) - x_0 U(t)]e = [\mu U_\infty/\beta + P_\infty]e.$$

Note that u_∞ is independent of the initial values V_0 and u_0.

This completes the proof of Theorem 1.2.

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