Global Stability for an SEIR Epidemiological Model with Varying Infectivity and Infinite Delay

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GLOBAL STABILITY FOR AN SEIR EPIDEMIOLOGICAL MODEL WITH VARYING INFECTIVITY AND INFINITE DELAY

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ABSTRACT. A recent paper (Math. Biosci. and Eng. (2008) 5:389-402) presented an SEIR model using an infinite delay to account for varying infectivity. The analysis in that paper did not resolve the global dynamics for $R_0 > 1$. Here, we show that the endemic equilibrium is globally stable for $R_0 > 1$. The proof uses a Lyapunov functional that includes an integral over all previous states.

1. Introduction. A recent paper [16] presented an SEIR model for an infectious disease that included infection-age structure to allow for varying infectivity. The incidence is of mass action type, but because of the varying infectivity, has the form $\beta S(t) \int_0^\infty k(a)i(t,a)da$. Nevertheless, the authors gave a thorough analysis leaving out only the elusive global stability of the endemic equilibrium.

That issue is resolved in this paper using a Lyapunov functional related to the type of Lyapunov function used for ordinary differential equation (ODE) ecological models [3, 4] in the 1980s and used more recently for ODE epidemiological models [6, 10, 11, 12, 13, 14, 15]. In [5], an ODE model of arbitrary dimension that includes varying infectivity is studied using the same type of Lyapunov function. For each of these models, the Lyapunov function is a sum of terms of the form $f(y) = y - 1 - \ln y$, where $y$ is a variable of the system. The model studied in this paper has infinite delay, and so it is necessary to include in the Lyapunov functional a term that integrates over all previous states.

We now provide a brief outline of the paper. In Section 2 we describe the equations that are to be studied. Section 3 includes results by Röst and Wu from [16], providing the context in which this paper is to be read. Many of these results are then used in Section 4 where the global stability of the endemic equilibrium is shown — the key result of this paper.

2. Model equations. A population is divided into classes: susceptible, exposed, infectious, and recovered, denoted by $S$, $E$, $I$, and $R$, respectively. The infectious class is structured by age of infection (i.e. time since entry into class $I$). The density of individuals with infection-age $a$ at time $t$ is given by $i(t,a)$ with $I(t) = \int_0^\infty i(t,a)da$.  

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Constant recruitment into \( S \) is given by \( \Lambda \). Incidence is of mass action type with baseline coefficient \( \beta \). The relative infectivity of individuals of infection-age \( a \) is \( k(a) \), where \( k \) is an integrable function taking values in the interval \([0, 1]\). The natural death rate is \( d \), the disease-related death rate is \( r \), the average latency period is \( 1/\mu \) and the average period of infectivity is \( 1/r \).

The original model equations [16] are

\[
\begin{align*}
\frac{dS(t)}{dt} &= \Lambda - \beta S(t) \int_0^\infty k(a)i(t,a)da - dS(t) \\
\frac{dE(t)}{dt} &= \beta S(t) \int_0^\infty k(a)i(t,a)da - (\mu + d)E(t) \\
\frac{dI(t)}{dt} &= \mu E(t) - (d + \delta + r)I(t) \\
\frac{dR(t)}{dt} &= rI(t) - dR(t)
\end{align*}
\]

and

\[
\left( \frac{\partial}{\partial t} + \frac{\partial}{\partial a} \right) i(t,a) = -(d + \delta + r)i(t,a)
\]

with the boundary condition

\[ i(t,0) = \mu E(t). \]

Solving (2) gives

\[ i(t,a) = \mu e^{-(d+\delta+r)a}E(t-a). \]

This allows equation (1) to be rewritten as

\[
\begin{align*}
\frac{dS(t)}{dt} &= \Lambda - \mu \beta S(t) \int_0^\infty k(a)e^{-(d+\delta+r)a}E(t-a)da - dS(t) \\
\frac{dE(t)}{dt} &= \mu \beta S(t) \int_0^\infty k(a)e^{-(d+\delta+r)a}E(t-a)da - (\mu + d)E(t),
\end{align*}
\]

where the equations for \( \frac{dR}{dt} \) and \( \frac{dI}{dt} \) are omitted because they decouple.

In order to specify the initial conditions for (3), we introduce the following notation. Given a non-negative function \( E \) defined on the interval \([-\infty, T]\), for any \( t \leq T \) we define the function \( E_\theta : \mathbb{R}_{\leq 0} \to \mathbb{R}_{\geq 0} \) by \( E_\theta(\theta) = E(t + \theta) \) for \( \theta \leq 0 \).

For equation (1), the initial condition would specify \( S(0), E(0), R(0) \geq 0 \) and \( i(0, \cdot) : \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0} \). For equation (3), an equation with infinite delay, the initial condition must specify \( S(0) \geq 0 \) and \( E_0 : \mathbb{R}_{\leq 0} \to \mathbb{R}_{\geq 0} \).

Due to the infinite delay, it is necessary to determine an appropriate phase space. For any \( \Delta \in (0, d + \delta + r) \), let

\[
C_\Delta = \{ \varphi : \mathbb{R}_{\leq 0} \to \mathbb{R} \text{ such that } \varphi(\theta)e^{\Delta \theta} \text{ is bounded and uniformly continuous} \}
\]

and

\[
Y_\Delta = \{ \varphi \in C_\Delta : \varphi(\theta) \geq 0 \text{ for all } \theta \leq 0 \}.
\]

Define the norm on \( C_\Delta \) and \( Y_\Delta \) by

\[ ||\varphi|| = \sup_{\theta \leq 0} |\varphi(\theta)e^{\Delta \theta}|. \]

It follows immediately that \( \varphi(0) \leq ||\varphi||. \)

Fixing \( \Delta \in (0, d + \delta + r) \), we take the phase space for equation (3) to be \( \mathbb{R}_{\geq 0} \times Y_\Delta \). Any initial condition \((S(0), E_0) \in \mathbb{R}_{\geq 0} \times Y_\Delta \) gives a solution \((S(t), E_t)\) that remains
in the phase space for all time. Furthermore, if \((S(t), E(t))\) is bounded for \(t \geq 0\), then the positive orbit \(\Gamma_+ = \{(S(t), E(t)) : t \geq 0\}\) has compact closure in \(\mathbb{R}_{\geq 0} \times Y_{\Delta}\).

Relevant developments of infinite delay equations, including determining the phase space, can be found in [1, 8, 9] and references found therein.

3. Previous results. In their paper, the authors of [16] give a thorough analysis of equation (3). They find the equilibria, calculate the basic reproduction number \(R_0\) and show that the system is point dissipative. The disease-free equilibrium is shown to be globally stable for \(R_0 < 1\). For \(R_0 > 1\) the disease-free equilibrium is unstable, there is a unique endemic equilibrium, which is locally asymptotically stable, and the system is permanent. They also do a final size calculation.

All that remains to complete the analysis is to determine the global behaviour for \(R_0 > 1\). This is done in Section 4 of this paper, where it is shown that the endemic equilibrium is globally stable for \(R_0 > 1\). In preparation for that, we now give results from [16].

**Theorem 3.1.** Equation (3) is point dissipative. That is, there exists \(M > 0\) such that for each solution of (3) there is a \(T > 0\) such that \(S(t) \leq M\) and \(\|E(t)\| \leq M\) for all \(t \geq T\).

Note that \(\|E(t)\| \leq M\) implies \(E(t) \leq M\).

The basic reproduction number \([2]\) for the model is

\[
R_0 = \frac{\beta \Lambda \mu}{d(\mu + d)} \int_0^\infty k(a)e^{-(d+\delta+r)a}da.
\]

For all values of the parameters, there is a disease-free equilibrium \(P_0 = (S_0, 0)\) where \(S_0 = \Lambda/d\). For \(R_0 \leq 1\), \(P_0\) is the only equilibrium. For \(R_0 > 1\), there is a unique endemic equilibrium \(P^* = (S^*, E^*)\) where

\[
S^* = \frac{S_0}{R_0} = \frac{\Lambda}{dR_0} \quad \text{and} \quad E^* = \frac{\Lambda}{\mu + d} \left(1 - \frac{1}{R_0}\right).
\]

Note that while we write an equilibrium of (3) as a point \((\bar{S}, \bar{E})\) \(\in \mathbb{R}^2\), more formally, an equilibrium point is a point \((\bar{S}, \bar{E})\) \(\in \mathbb{R}_{\geq 0} \times Y_{\Delta}\) satisfying \(\bar{S} = S\) and \(\bar{E}(\theta) = E\) for all \(\theta \leq 0\). The equilibrium solution is given by \((S(t), E(t)) = (\bar{S}, \bar{E})\) \(\in \mathbb{R}_{\geq 0} \times Y_{\Delta}\) for each \(t\). Related to this is an equilibrium of (1) for which \(S(t), E(t), I(t)\) and \(R(t)\) are constant functions and for which \(i(t, a) = \tilde{i}(a) = \mu E e^{-(d+\delta+r)a}\) is independent of time \(t\).

**Theorem 3.2.** If \(R_0 < 1\), then all solutions converge to the disease-free equilibrium, which is locally asymptotically stable.

As with many finite dimensional models, if \(R_0\) is larger than one, then the disease-free equilibrium attracts disease-free states and repels states for which disease is present. Let \(\bar{a} = \inf \{a : \int_0^\infty k(\sigma)d\sigma = 0\}\). For a system with a truly infinite delay, we have \(\bar{a} = \infty\), whereas, for a system with a bounded distributed delay, we have \(0 < \bar{a} < \infty\).

For a state \((\bar{S}, \bar{E})\) \(\in \mathbb{R}_{\geq 0} \times Y_{\Delta}\), we say that **disease is present** if \(\bar{E}(-a) > 0\) for some \(a \in [0, \bar{a})\). Recall that elements of \(Y_{\Delta}\) are continuous. Thus, if \(\bar{E}\) is positive at some point, then \(\bar{E}\) is positive on an interval about that point. If disease is present for \((\bar{S}, \bar{E})\), then the solution of (3) with initial condition \((\bar{S}, \bar{E})\) will satisfy \(E(t) > 0\) for some \(t > 0\). If \(\bar{E}\) does not satisfy the given condition (i.e. \(\bar{E}(-a) = 0\) for all
Theorem 3.3. Suppose $R_0 > 1$. Then the disease-free equilibrium is unstable and the endemic equilibrium is locally asymptotically stable. Furthermore, the system is persistent; that is, there exists $\eta > 0$ such that for any solution for which the disease is initially present, we have

$$\liminf_{t \to \infty} S(t) \geq \eta \quad \text{and} \quad \liminf_{t \to \infty} E(t) \geq \eta.$$ 

Remark 1. In [16], it is implicitly understood that $\bar{a} = \infty$ meaning that the system has a true infinite delay. However, for a bounded distributed delay, which gives $\bar{a} < \infty$, the proofs in [16] still hold, as do the new results of this paper.

4. Global stability for $R_0 > 1$. Let $X(t) = (S(t), E_t)$ be a solution of equation (3) for which disease is initially present. It is shown in the proof of Theorem 6.1 of [16] that the semi-flow induced by equation (3) has properties that imply the existence of a global compact attractor (see Theorem 3.4.6 of [7]). Combined with Theorem 3.1 and Theorem 3.3, it follows that the $\omega$-limit set $\Omega$ of $X$ is non-empty, compact, and invariant. It follows that $\Omega$ is the union of orbits of equation (3). That is, if $(\tilde{S}, \tilde{E}) \in \mathbb{R}_{\geq 0} \times Y_{\Delta}$ is an omega limit point of $X$, then there is a solution through $(\tilde{S}, \tilde{E})$ such that every point on the solution is in $\Omega$.

Lemma 4.1. Suppose $R_0 > 1$ and $Z(t) = (\phi(t), \varphi_t)$ is a solution to equation (3) that lies in $\Omega$. Then $\eta - \epsilon \leq \phi(t) \leq M$ and $\eta - \varphi(t) \leq M$ for all $t \in \mathbb{R}$.

Proof. Fix $\epsilon > 0$ and $T \in \mathbb{R}$, and let $Z = Z(T) = (\phi(T), \varphi_T)$. Then $Z \in \Omega$ is an omega limit point of $X$. Thus, there exists a sequence $\{t_n\}$ that increases to infinity such that $X(t_n) \to Z$.

Then $S(t_n) \to \phi(T)$. By Theorem 3.1 and Theorem 3.3, we have $\eta - \epsilon \leq S(t_n) \leq M$ for large $n$, and so the same inequalities apply to $\phi(T)$. Also, $0 \leq |E(t_n) - \varphi(T)| \leq |E(t_n) - \varphi_T|$, which goes to 0 as $n \to \infty$. Thus, since $\eta - \epsilon \leq E(t_n) \leq M$ for large enough $n$, the same is true for $\varphi(T)$.

Because the choice of $T$ was arbitrary, as was the choice of $\epsilon > 0$, the desired result follows for all $t \in \mathbb{R}$. \qed

Theorem 4.2. Suppose $R_0 > 1$ and $Z(t) = (\phi(t), \varphi_t)$ is a solution to equation (3) that lies in $\Omega$. Then $Z$ converges to the endemic equilibrium; that is,

$$\lim_{t \to \infty} (\phi(t), \varphi(t)) = (S^*, E^*).$$

Proof. We begin by normalizing. Let $s(t) = \phi(t)/S^*$, $x(t) = \varphi(t)/E^*$ and $x_t = \varphi_t/E^*$. Then

$$\frac{ds(t)}{dt} = \Lambda - \mu S^* s(t) \int_0^\infty k(a)e^{-(d+\delta+r)a}x(t-a)da - ds(t)
$$

$$\frac{dx(t)}{dt} = \mu S^* s(t) \int_0^\infty k(a)e^{-(d+\delta+r)a}x(t-a)da - (\mu + d)x(t).$$

\begin{equation}
\tag{4}
\end{equation}
The endemic equilibrium for (4) is \( p^* = (s^*, x^*) = (1, 1) \). Thus, by evaluating both sides of (4) at \( p^* \), we have

\[
0 = \frac{\Lambda}{S^*} - \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} da - d
\]

\[
0 = \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} da - (\mu + d).
\]

Let

\[
f(y) = y - 1 - \ln y,
\]

and let

\[
U_s(t) = f(s(t))
\]

\[
U_x(t) = \alpha_x f(x(t))
\]

\[
U_+(t) = \int_0^\infty \alpha(a)f(x(t-a)) da,
\]

where

\[
\alpha_x = \frac{E_x^*}{S^*} \quad \text{and} \quad \alpha(a) = \mu \beta S^* \int_a^\infty k(\sigma)e^{-(d+\delta+r)\sigma} d\sigma.
\]

We will study the behaviour of the Lyapunov functional

\[
U(t) = U_s + U_x + U_+.
\]

We note that \( \alpha_x \) is positive, as is \( \alpha(a) \) for each \( a \in [0, \bar{a}] \). The function \( f \) has domain \( \mathbb{R}_{\geq 0} \) and range \( \mathbb{R}_{\geq 0} \). We also note that \( f \) has only one extreme value, which is the global minimum: \( f(1) = 0 \). Thus, \( U(t) \geq 0 \) with equality if and only if \( s(t) = x(t) = 1 \) and \( x(t-a) = 1 \) for almost all \( a \in [0, \bar{a}] \). Lemma 4.1 implies \( U \) is well-defined; that is, \( U_+ \) is finite for all \( t \).

For clarity, we calculate the derivatives of each of \( U_s, U_x \) and \( U_+ \) separately and then combine them to get \( \frac{dU}{dt} \). Also, instances of \( s(t) \) and \( x(t) \) will be written as \( s \) and \( x \), respectively.

\[
\frac{dU_s}{dt} = \left(1 - \frac{1}{s}\right) \frac{ds}{dt}
\]

\[
= \frac{s-1}{s} \left( \frac{\Lambda}{S^*} - \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} x(t-a) da - ds \right).
\]

Subtracting the right-hand side of the first equation of (5) gives

\[
\frac{dU_s}{dt} = \frac{s-1}{s} \left( \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} (1 - sx(t-a)) da + d (1-s) \right)
\]

\[
= -d \frac{(s-1)^2}{s} + \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} \left(1 - sx(t-a) - \frac{1}{s} + x(t-a) \right) da.
\]

In calculating \( \frac{dU_x}{dt} \), we use the second equation of (5) to replace \( \mu + d \) with the integral, obtaining

\[
\frac{dU_x}{dt} = \alpha_x \left(1 - \frac{1}{x}\right) \left( \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} x(t-a) da - (\mu + d)x \right)
\]

\[
= \frac{E^*}{S^*} \left(1 - \frac{1}{x}\right) \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} (sx(t-a) - x) da
\]

\[
= \mu \beta S^* \int_0^\infty k(a)e^{-(d+\delta+r)a} \left( sx(t-a) - x - \frac{sx(t-a)}{x}+1 \right) da.
\]
We now calculate the derivative of $U_+(t)$.

$$\frac{dU_+}{dt} = \frac{d}{dt} \int_0^\infty \alpha(a)f(x(t-a))da$$

$$= \int_0^\infty \frac{d}{da} \alpha(a)f(x(t-a))da$$

$$= -\int_0^\infty \alpha(a)\frac{d}{da}f(x(t-a))da.$$ 

Using integration by parts, we get

$$\frac{dU_+}{dt} = -\alpha(a)f(x(t-a))|_0^\infty + \int_0^\infty \frac{d}{da} \alpha(a)f(x(t-a))da.$$

By Lemma 4.1, since the solution $Z(t)$ is in the omega limit set $\Omega$, we have $\frac{dZ}{dt} \leq x(t)$ for all $t \in \mathbb{R}$. Thus, $f(x(t-a))$ is bounded above and below. Then, noting that $0 \leq \alpha(a) = \mu_\beta E^* \int_0^{\infty} k(\sigma)e^{-(d+\delta+r+\sigma)d\sigma} \leq \mu_\beta E^* \int_0^{\infty} e^{-(d+\delta+r+\sigma)d\sigma} = \frac{\mu_\beta E^*}{(d+\delta+r)} e^{-(d+\delta+r)a} \rightarrow 0$, it follows that $\lim_{a \rightarrow \infty} \alpha(a)f(x(t-a)) = 0$. Also, at $a = 0$ we get $\alpha(a)f(x(t-a)) = \alpha(0)f(x(t))$, and so

$$\frac{dU_+}{dt} = \alpha(0)f(x(t)) + \int_0^\infty \frac{d}{da} \alpha(a)f(x(t-a))da.$$

Filling in for $\alpha(0)$, evaluating the derivative $\frac{d}{da}\alpha(a) = -\mu_\beta E^*k(a)e^{-(d+\delta+r)a}$, and then combining the two resulting integrals gives

$$\frac{dU_+}{dt} = \mu_\beta E^* \int_0^\infty k(a)e^{-(d+\delta+r)a} \left( f(x(t)) - f(x(t-a)) \right)da$$

$$= \mu_\beta E^* \int_0^\infty k(a)e^{-(d+\delta+r)a} \left( x - \ln x - x(t-a) + \ln x(t-a) \right)da.$$

Adding equations (6), (7), and (8), we obtain

$$\frac{dU}{dt} = -d\frac{(s-1)^2}{s} - \mu_\beta E^* \int_0^\infty k(a)e^{-(d+\delta+r)a}C(a)da,$$

where

$$C(a) = -2 + \frac{1}{s} + \frac{sx(t-a)}{x} + \ln x - \ln x(t-a)$$

$$= \left( \frac{1}{s} - 1 + \ln s \right) + \left( \frac{sx(t-a)}{x} - 1 - (ln s + \ln x(t-a) - \ln x) \right)$$

$$= \frac{1}{s} + f \left( \frac{sx(t-a)}{x} \right)$$

$$\geq 0.$$ 

Thus, $\frac{dU}{dt} \leq 0$ with equality if and only if $s(t) = 1$ and $x(t-a)/x(t) = 1$ for almost all $a \in [0, \bar{a})$. It follows that $U(t)$ is a non-increasing function that is bounded below by zero, and therefore $\lim_{t \rightarrow \infty} U(t)$ exists.

Next, we show that $\lim_{t \rightarrow \infty} s(t) = 1$. To do this, we first note that $\frac{dU}{dt} \leq -g(t)$ for $g(t) = d\frac{(s-1)^2}{s}$. Suppose that $s(t)$ does not converge to 1. Then there exist $\epsilon > 0$ and a sequence $\{t_n\}$ that increases to infinity such that $g(t_n) \geq \epsilon$ for each $n$. Note that the bounds on $Z$ given by Lemma 4.1 imply that the derivative $\frac{dU}{dt}$ is bounded, and so there exists $\tau > 0$ such that $g(t) \geq \frac{\epsilon}{4}$ for $t \in I_n = (t_n - \tau, t_n + \tau)$. Then, we have $\frac{dU}{dt} \leq -\frac{\epsilon}{4}$ for all $t \in \cup I_n$, which is a set of infinite measure. Hence,
$U$ decreases to $-\infty$, which contradicts the fact that $U$ is bounded below. Thus, $s(t)$ must converge to 1.

Finally, we show that $\lim_{t \to \infty} x(t) = 1$. To do this, let $y(t) = s(t) + \alpha x(t)$. Then

$$\frac{dy}{dt} = \frac{ds}{dt} + \alpha \frac{dx}{dt} = \frac{\Lambda}{S^*} - ds - \alpha_x (\mu + d)x$$

$$= \frac{\Lambda}{S^*} + \mu s - (\mu + d)y$$

Since $s(t)$ converges to 1, this is an asymptotically autonomous ordinary differential equation for which solutions of the limiting equation go to a hyperbolic equilibrium. Thus, $\lim_{t \to \infty} y(t) = \lim_{t \to \infty} \left( \frac{\Lambda}{S^*} + \mu \right)$. Using (5), it follows that $\lim_{t \to \infty} x(t) = \lim_{t \to \infty} \left( y(t) - s(t) \right) = 1$.

Since $\lim_{t \to \infty} (s(t), x(t)) = (1, 1)$, it follows that $\lim_{t \to \infty} (\phi(t), \varphi(t)) = (S^*, E^*)$, completing the proof.

**Theorem 4.3.** If $R_0 > 1$, then all solutions of equation (3) for which the disease is initially present converge to the endemic equilibrium; that is,

$$\lim_{t \to \infty} (S(t), E(t)) = (S^*, E^*).$$

**Proof.** Let $Z(t)$ be a solution in $\Omega$, the omega limit set of $X$. By Theorem 4.2, $Z(t)$ converges to the endemic equilibrium $P^*$. Since $\Omega$ is closed, we have $P^* \in \Omega$ and so $X$ gets arbitrarily close to $P^*$. By Theorem 3.3, $P^*$ is locally asymptotically stable and therefore $X$ converges to $P^*$.

We note that the results here include systems with bounded distributed delay.

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