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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 $\mathcal{R}_0 > 1$. Here, we show that the endemic equilibrium is globally stable for $\mathcal{R}_0 > 1$. 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 Λ. Incidence is of mass action type with baseline coefficient β. 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

$$\begin{aligned}\frac{dS(t)}{dt} &= \Lambda - \beta S(t)\int_0^\infty k(a)i(t,a)da - dS(t)\\ \frac{dE(t)}{dt} &= \beta S(t)\int_0^\infty k(a)i(t,a)da - (\mu+d)E(t)\\ \frac{dI(t)}{dt} &= \mu E(t) - (d+\delta+r)I(t)\\ \frac{dR(t)}{dt} &= rI(t) - dR(t)\end{aligned} \tag{1}$$

and

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)i(t,a) = -(d+\delta+r)i(t,a) \tag{2}$$

with the boundary condition

$$i(t,0) = \mu E(t).$$

Solving (2) gives

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

This allows equation (1) to be rewritten as

$$\begin{aligned}\frac{dS(t)}{dt} &= \Lambda - \mu\beta S(t)\int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a}E(t-a)da - dS(t)\\ \frac{dE(t)}{dt} &= \mu\beta S(t)\int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a}E(t-a)da - (\mu+d)E(t),\end{aligned} \tag{3}$$

where the equations for $\frac{dI}{dt}$ and $\frac{dR}{dt}$ 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 $t\le T$ we define the function $E_t:\mathbb{R}_{\le 0}\to\mathbb{R}_{\ge 0}$ by $E_t(\theta)=E(t+\theta)$ for $\theta\le 0$.

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

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

$$C_\Delta = \left\{\varphi:\mathbb{R}_{\le 0}\to\mathbb{R} \text{ such that } \varphi(\theta)\mathrm{e}^{\Delta\theta} \text{ is bounded and uniformly continuous}\right\}$$

and

$$Y_\Delta = \{\varphi\in C_\Delta : \varphi(\theta)\ge 0 \text{ for all } \theta\le 0\}.$$

Define the norm on C_Δ and Y_Δ by

$$\|\varphi\| = \sup_{\theta\le 0}\left|\varphi(\theta)\mathrm{e}^{\Delta\theta}\right|.$$

It follows immediately that $\varphi(0)\le\|\varphi\|$.

Fixing $\Delta\in(0,d+\delta+r)$, we take the phase space for equation (3) to be $\mathbb{R}_{\ge 0}\times Y_\Delta$. Any initial condition $(S(0),E_0)\in\mathbb{R}_{\ge 0}\times Y_\Delta$ 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 $\mathcal{R}_0$ and show that the system is point dissipative. The disease-free equilibrium is shown to be globally stable for $\mathcal{R}_0 < 1$. For $\mathcal{R}_0 > 1$ 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 $\mathcal{R}_0 > 1$. This is done in Section 4 of this paper, where it is shown that the endemic equilibrium is globally stable for $\mathcal{R}_0 > 1$. 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

$$\mathcal{R}_0 = \frac{\beta\Lambda\mu}{d(\mu + d)} \int_0^\infty k(a) \mathrm{e}^{-(d+\delta+r)a} da.$$

For all values of the parameters, there is a disease-free equilibrium $P_0 = (S_0, 0)$ where $S_0 = \Lambda/d$. For $\mathcal{R}_0 \leq 1$, P_0 is the only equilibrium. For $\mathcal{R}_0 > 1$, there is a unique endemic equilibrium $P^* = (S^*, E^*)$ where

$$S^* = \frac{S_0}{\mathcal{R}_0} = \frac{\Lambda}{d\mathcal{R}_0} \quad \text{and} \quad E^* = \frac{\Lambda}{\mu + d}\left(1 - \frac{1}{\mathcal{R}_0}\right).$$

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 $(\widetilde{S}, \widetilde{E}) \in \mathbb{R}_{\geq 0} \times Y_\Delta$ satisfying $\widetilde{S} = \bar{S}$ and $\widetilde{E}(\theta) = \bar{E}$ for all $\theta \leq 0$. The equilibrium solution is given by $(S(t), E_t) = (\widetilde{S}, \widetilde{E}) \in \mathbb{R}_{\geq 0} \times Y_\Delta$ 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 $i(t, a) = \bar{i}(a) = \mu\bar{E}\mathrm{e}^{-(d+\delta+r)a}$ is independent of time t.

Theorem 3.2. *If $\mathcal{R}_0 < 1$, then all solutions converge to the disease-free equilibrium, which is locally asymptotically stable.*

As with many finite dimensional models, if $\mathcal{R}_0$ is larger than one, then the disease-free equilibrium attracts disease-free states and repels states for which disease is present. Let $\widetilde{a} = \inf\left\{a : \int_a^\infty k(\sigma) d\sigma = 0\right\}$. For a system with a truly infinite delay, we have $\widetilde{a} = \infty$, whereas, for a system with a bounded distributed delay, we have $0 < \widetilde{a} < \infty$.

For a state $(\widetilde{S}, \widetilde{E}) \in \mathbb{R}_{\geq 0} \times Y_\Delta$, we say that *disease is present* if $\widetilde{E}(-a) > 0$ for some $a \in [0, \widetilde{a})$. Recall that elements of Y_Δ are continuous. Thus, if $\widetilde{E}$ is positive at some point, then $\widetilde{E}$ is positive on an interval about that point. If disease is present for $(\widetilde{S}, \widetilde{E})$, then the solution of (3) with initial condition $(\widetilde{S}, \widetilde{E})$ will satisfy $E(t) > 0$ for some $t > 0$. If $\widetilde{E}$ does not satisfy the given condition (i.e. $\widetilde{E}(-a) = 0$ for all

$a \in [0, \widetilde{a})$), then the solution of (3) will have $E(t)$ identically zero for $t \geq 0$, and will converge to P_0. For a solution for which disease is present for the initial condition, we say the *disease is initially present.*

Theorem 3.3. *Suppose $\mathcal{R}_0 > 1$. 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*

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

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

4. Global stability for $\mathcal{R}_0 > 1$.

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 ω-limit set Ω of X is non-empty, compact, and invariant. It follows that Ω is the union of orbits of equation (3). That is, if $(\widetilde{S}, \widetilde{E}) \in \mathbb{R}_{\geq 0} \times Y_\Delta$ is an omega limit point of X, then there is a solution through $(\widetilde{S}, \widetilde{E})$ such that every point on the solution is in Ω.

Lemma 4.1. *Suppose $\mathcal{R}_0 > 1$ and $Z(t) = (\phi(t), \varphi_t)$ is a solution to equation (3) that lies in Ω. Then $\eta \leq \phi(t) \leq M$ and $\eta \leq \varphi(t) \leq M$ for all $t \in \mathbb{R}$.*

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

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 $t \in \mathbb{R}$. ☐

Theorem 4.2. *Suppose $\mathcal{R}_0 > 1$ and $Z(t) = (\phi(t), \varphi_t)$ is a solution to equation (3) that lies in Ω. 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

$$\begin{aligned} \frac{ds(t)}{dt} &= \frac{\Lambda}{S^*} - \mu\beta E^* s(t) \int_0^\infty k(a) \mathrm{e}^{-(d+\delta+r)a} x(t-a)da - ds(t) \\ \frac{dx(t)}{dt} &= \mu\beta S^* s(t) \int_0^\infty k(a) \mathrm{e}^{-(d+\delta+r)a} x(t-a)da - (\mu+d)x(t). \end{aligned} \tag{4}$$

The endemic equilibrium for (4) is $p^* = (s^*, x^*) = (1, 1)$. Thus, by evaluating both sides of (4) at p^*, we have

$$
\begin{aligned}
0 &= \frac{\Lambda}{S^*} - \mu\beta E^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} da - d \\
0 &= \mu\beta S^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} da - (\mu + d).
\end{aligned}
\tag{5}
$$

Let

$$f(y) = y - 1 - \ln y,$$

and let

$$
\begin{aligned}
U_s(t) &= f(s(t)) \\
U_x(t) &= \alpha_x f(x(t)) \\
U_+(t) &= \int_0^\infty \alpha(a) f(x(t-a)) da,
\end{aligned}
$$

where

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

We will study the behaviour of the Lyapunov functional

$$U(t) = U_s + U_x + U_+.$$

We note that α_x is positive, as is $\alpha(a)$ for each $a \in [0, \widetilde{a})$. The function f has domain $\mathbb{R}_{>0}$ 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 $a \in [0, \widetilde{a})$. 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.

$$
\begin{aligned}
\frac{dU_s}{dt} &= \left(1 - \frac{1}{s}\right) \frac{ds}{dt} \\
&= \frac{s-1}{s} \left(\frac{\Lambda}{S^*} - \mu\beta E^* s \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} x(t-a) da - ds \right).
\end{aligned}
$$

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

$$
\begin{aligned}
\frac{dU_s}{dt} &= \frac{s-1}{s} \left(\mu\beta E^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} \left(1 - sx(t-a)\right) da + d\left(1 - s\right) \right) \\
&= -d\frac{(s-1)^2}{s} + \mu\beta E^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} \left(1 - sx(t-a) - \frac{1}{s} + x(t-a) \right) da.
\end{aligned}
\tag{6}
$$

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

$$
\begin{aligned}
\frac{dU_x}{dt} &= \alpha_x \left(1 - \frac{1}{x}\right) \left(\mu\beta S^* s \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} x(t-a) da - (\mu + d)x \right) \\
&= \frac{E^*}{S^*} \left(1 - \frac{1}{x}\right) \mu\beta S^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} \left(sx(t-a) - x\right) da \\
&= \mu\beta E^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a} \left(sx(t-a) - x - \frac{sx(t-a)}{x} + 1 \right) da.
\end{aligned}
\tag{7}
$$

We now calculate the derivative of $U_+(t)$.

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

Using integration by parts, we get

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

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

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

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

$$\begin{aligned}\frac{dU_+}{dt} &= \mu\beta E^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a}\big(f(x(t)) - f(x(t-a))\big)da\\ &= \mu\beta E^* \int_0^\infty k(a)\mathrm{e}^{-(d+\delta+r)a}\big(x - \ln x - x(t-a) + \ln x(t-a)\big)da.\end{aligned} \tag{8}$$

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

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

where

$$\begin{aligned}C(a) &= -2 + \frac{1}{s} + \frac{sx(t-a)}{x} + \ln x - \ln x(t-a)\\ &= \left(\frac{1}{s} - 1 + \ln s\right) + \left(\frac{sx(t-a)}{x} - 1 - (\ln s + \ln x(t-a) - \ln x)\right)\\ &= f\left(\frac{1}{s}\right) + f\left(\frac{sx(t-a)}{x}\right)\\ &\geq 0.\end{aligned}$$

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 $a \in [0, \widetilde{a})$. It follows that $U(t)$ is a non-increasing function that is bounded below by zero, and therefore $\lim_{t\to\infty} U(t)$ exists.

Next, we show that $\lim_{t\to\infty} s(t) = 1$. To do this, we first note that $\frac{dU}{dt} \leq -g(t) \leq 0$ where $g(t) = d\frac{(s(t)-1)^2}{s(t)}$. 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 $\frac{ds}{dt}$ is bounded, and so there exists $\tau > 0$ such that $g(t) \geq \frac{\epsilon}{2}$ for $t \in I_n = (t_n - \tau, t_n + \tau)$. Then, we have $\frac{dU}{dt} \leq -\frac{\epsilon}{2}$ 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 $y(t) = s(t) + \alpha_x x(t)$. Then

$$\begin{aligned}\frac{dy}{dt} &= \frac{ds}{dt} + \alpha_x \frac{dx}{dt} \\ &= \frac{\Lambda}{S^*} - ds - \alpha_x(\mu + d)x \\ &= \frac{\Lambda}{S^*} + \mu s - (\mu + d)y\end{aligned}$$

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, $\lim_{t\to\infty} y(t) = \frac{1}{\mu+d}\left(\frac{\Lambda}{S^*} + \mu\right)$. Using (5), it follows that $\lim_{t\to\infty} x(t) = \lim_{t\to\infty} \frac{1}{\alpha_x}\left(y(t) - s(t)\right) = 1$.

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 $\mathcal{R}_0 > 1$, 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 Ω, the omega limit set of X. By Theorem 4.2, $Z(t)$ converges to the endemic equilibrium P^*. Since Ω 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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