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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

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

This allows equation (1) to be rewritten as

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

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 $t \leq T$ we define the function $E_t : \mathbb{R}_{\leq 0} \rightarrow \mathbb{R}_{\geq 0}$ by $E_t(\theta) = E(t + \theta)$ for $\theta \leq 0$.

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

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

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

and

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

Define the norm on C_Δ and Y_Δ 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 \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

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

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 $(\tilde{S}, \tilde{E}) \in \mathbb{R}_{\geq 0} \times Y_\Delta$ satisfying $\tilde{S} = \bar{S}$ and $\tilde{E}(\theta) = \bar{E}$ for all $\theta \leq 0$. The equilibrium solution is given by $(S(t), E_t) = (\tilde{S}, \tilde{E}) \in \mathbb{R}_{\geq 0} \times Y_\Delta$ 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 $i(t, a) = \bar{i}(a) = \mu\bar{E}e^{-(d+\delta+r)a}$ 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 $\tilde{a} = \inf \{a : \int_a^\infty k(\sigma)d\sigma = 0\}$. For a system with a truly infinite delay, we have $\tilde{a} = \infty$, whereas, for a system with a bounded distributed delay, we have $0 < \tilde{a} < \infty$.

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

$a \in [0, \tilde{a})$, 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*

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

Remark 1. In [16], it is implicitly understood that $\tilde{a} = \infty$ meaning that the system has a true infinite delay. However, for a bounded distributed delay, which gives $\tilde{a} < \infty$, 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 $(\tilde{S}, \tilde{E}) \in \mathbb{R}_{\geq 0} \times Y_\Delta$ 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 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 $\tilde{Z} = Z(T) = (\phi(T), \varphi_T)$. Then $\tilde{Z} \in \Omega$ is an omega limit point of X . Thus, there exists a sequence $\{t_n\}$ that increases to infinity such that $X(t_n) \rightarrow \tilde{Z}$.

Then $S(t_n) \rightarrow \phi(T)$. 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 $n \rightarrow \infty$. 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 $t \in \mathbb{R}$. \square

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,*

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

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

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

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

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

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

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

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 $a \in [0, \tilde{a})$. 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 $a \in [0, \tilde{a})$. 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.

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

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

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

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

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

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

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

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

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

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

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

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 $a \in [0, \tilde{a})$. 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 $\frac{dU}{dt} \leq -g(t) \leq 0$ 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 $\lim_{t \rightarrow \infty} x(t) = 1$. 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, $\lim_{t \rightarrow \infty} y(t) = \frac{1}{\mu + d} \left(\frac{\Lambda}{S^*} + \mu \right)$. Using (5), it follows that $\lim_{t \rightarrow \infty} x(t) = \lim_{t \rightarrow \infty} \frac{1}{\alpha_x} (y(t) - s(t)) = 1$.

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

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,*

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

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^* . \square

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

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