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AGE OF INFECTION IN EPIDEMIOLOGY MODELS

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Abstract. Disease transmission models in which infectivity depends on the time since infection are of importance in studying such diseases as HIV/AIDS. They also provide a means of unifying models with exposed stages or temporary immunity. We formulate a general age of infection model and carry out a partial analysis. There are open questions in the analysis of the characteristic equation at an endemic equilibrium.

1. Introduction

The 1927 epidemic model of Kermack and McKendrick [4] is considerably more general than what is usually called the Kermack-McKendrick epidemic model. The general model described by Kermack and McKendrick included a dependence of infectivity on the time since becoming infected (age of infection). The 1932 and 1933 models of Kermack and McKendrick [5, 6], which incorporated births and deaths, did not include this dependence. Curiously, while age of infection models have not played a role in studies of epidemics, they are very important in studies of HIV/AIDS. Since HIV/AIDS acts on a very long time scale it is essential to include demographic effects (recruitment into and departure from a population of sexually active individuals). Also, the infectivity of HIV-positive people is high for a relatively short time after becoming infected, then very low for a long period, possibly several years, and then high shortly before developing into full-blown AIDS. Thus, the age of infection for models described by Kermack and McKendrick for epidemics but not for endemic situations, have become important in endemic situations.

We will describe a general age of infection model which includes demographic effects and carry out a partial analysis. There are many unsolved problems in the analysis, centered on the analysis of the characteristic equation at an endemic equilibrium.

2. The Basic SI^*R Model

We let $S(t)$ denote the number of suceptibles at time t and $R(t)$ the number of members recovered with immunity, as is standard in compartmental epidemiological models. However, instead of using $I(t)$ to denote the number of infective members

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at time t we let $I^*(t)$ denote the number of infected (but not necessarily infective) members and let $\phi(t)$ be the total infectivity at time t.

We make the following assumptions:

(1) The population has a birth rate $\Lambda(N)$, and a natural death rate μ giving a carrying capacity K such that $\Lambda(K) = \mu K, \Lambda'(K) < \mu$.
(2) An average infected member makes $C(N)$ contacts in unit time of which S/N are with susceptible. We define $\beta(N) = C(N)/N$ and it is reasonable to assume that $\beta'(N) \le 0, C'(N) \ge 0$.
(3) $B(\tau)$ is the fraction of infected individuals remaining infective if alive when infection age is τ and $B_\mu(\tau) = e^{-\mu\tau}B(\tau)$ is the fraction of infected ones remaining alive and infected when infection age is τ. Let $\hat{B_\mu}(0) = \int_0^\infty B_\mu(\tau)d\tau$
(4) A fraction f of infected members recovers with immunity and a fraction $(1-f)$ dies of disease.
(5) $\pi(\tau)$ with $0 \le \pi(\tau) \le 1$ is the infectivity at infection age τ; let $A(\tau) = \pi(\tau)B(\tau), A_\mu(\tau) = \pi(\tau)B_\mu(\tau), \hat{A_\mu}(0) = \int_0^\infty A_\mu(\tau)d\tau$.

We let $i_0(t)$ be the number of new infected individuals at time t, $i(t,\tau)$ be the number of infected individuals at time t with infection age τ. Then

$$\begin{gathered} i(t,\tau) = i_0(t-\tau)B_\mu(\tau), \quad 0 \le \tau \le t \\ i_0(t) = S\beta(N)\phi(t) \end{gathered}$$

and

$$\begin{aligned} S' &= \Lambda(N) - \mu S - \beta(N)S\phi \\ I^*(t) &= \int_0^\infty i(t,\tau)d\tau \\ &= \int_0^\infty i_0(t-\tau)B_\mu(\tau)d\tau \\ &= \int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)B_\mu(\tau)d\tau \\ \phi(t) &= \int_0^\infty i_0(t-\tau)A_\mu(\tau)d\tau \\ &= \int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)A_\mu(\tau)d\tau \end{aligned}$$

Differentiation of the equation for I^* shows that the rate of recovery plus the rate of disease death is

$$-\int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)e^{-\mu\tau}B'(\tau)d\tau$$

Thus the SI^*R model is

$$\begin{aligned} S' &= \Lambda(N) - \mu S - \beta(N)S\phi \\ \phi(t) &= \int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)A_\mu(\tau)d\tau \\ N'(t) &= \Lambda(N) - \mu N + (1-f)\int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)e^{-\mu\tau}B'(\tau)d\tau \end{aligned} \tag{2.1}$$

Since I^* is determined when S, ϕ, N are known we have dropped the equation for I^* from the model, but it will be convenient to recall

$$I^*(t) = \int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)B_\mu(\tau)d\tau$$

If $f = 1$ then $N(t)$ approaches the limit K, the model is asymptotically autonomous and its dimension may be reduced to 2, replacing N by the constant K. We note, for future use, that

$$\hat{B_\mu}(0) = \int_0^\infty e^{-\mu\tau}B(\tau)d\tau \le \int_0^\infty e^{-\mu\tau}d\tau = 1/\mu,$$

so that $0 \le 1 - \mu\hat{B_\mu}(0) \le 1$.

We define $M = (1-f)(1-\mu\hat{B_\mu}(0)$, and $0 \le M \le 1$. We note, however, that if $f = 1$ then $M = 0$. We also have, using integration by parts,

$$-\int_0^\infty e^{-\mu\tau}B'(\tau)d\tau = 1 - \mu\hat{B_\mu}(0) \ge 0$$

If a single infective is introduced into a wholly susceptible population, making $K\beta(K)$ contacts in unit time, the fraction still infective at infection age τ is $B_\mu(\tau)$ and the infectivity at infection age τ is $A_\mu(\tau)$. Thus R_0, the total number of secondary infections caused, is

$$\int_0^\infty K\beta(K)A_\mu(\tau)d\tau = K\beta(K)\hat{A_\mu}(0)\,.$$

3. Exposed periods

One common example of an infection age model is a model with an exposed period, during which individuals have been infected but are not yet infective. Thus we may think of infected susceptible individuals going into an exposed class (E), proceeding from the exposed class to the infective class (I) at rate κE and out of the infective class at rate αI. Exposed members have infectivity 0 and infective members have infectivity 1. Thus $I^* = E + I$ and $\phi = I$.

We let $u(\tau)$ be the fraction of infected members with infection age τ who are not yet infective if alive and $v(\tau)$ the fraction of infected members who are infective if alive. Then the fraction becoming infective at infection age τ if alive is $\kappa u(\tau)$, and we have

$$\begin{aligned} u'(\tau) &= -\kappa u(\tau), \quad u(0) = 1 \\ v'(\tau) &= \kappa u(\tau) - \alpha v(\tau) \quad v(0) = 0\,. \end{aligned} \tag{3.1}$$

The solution of the first of the equations of (3.1) is $u(\tau) = e^{-\kappa\tau}$ and substitution of this into the second equation gives

$$v'(\tau) = \kappa e^{-\kappa\tau} - \alpha v(\tau)$$

When we multiply this equation by the integrating factor $e^{\alpha\tau}$ and integrate, we obtain the solution

$$v(\tau) = \frac{\kappa}{\kappa - \alpha}[e^{-\alpha\tau} - e^{-\kappa\tau}]$$

and this is the term $A_\mu(\tau)$ in the general model. The term $B(\tau)$ is $u(\tau)+v(\tau)$. Thus we have

$$\begin{aligned}
A(\tau) &= \frac{\kappa}{\kappa-\alpha}[e^{-\alpha\tau}-e^{-\kappa\tau}] \\
B(\tau) &= \frac{\kappa}{\kappa-\alpha}e^{-\alpha\tau}-\frac{\alpha}{\kappa-\alpha}e^{-\kappa\tau} \\
e^{-\mu\tau}B'(\tau) &= -\frac{\alpha\kappa}{\kappa-\alpha}[e^{-(\mu+\alpha)\tau}-e^{-(\mu+\kappa)\tau}]
\end{aligned}$$

With these choices and the identifications $I=\phi$, $E=I^*-\phi$, we may verify that the system (2.1) reduces to

$$\begin{aligned}
S' &= \Lambda(N)-\beta(N)SI-\mu S \\
E' &= \beta(N)SI-\kappa E \\
I' &= \kappa E-(\mu+\alpha)I \\
N' &= \Lambda(N)-(1-f)\alpha I-\mu N,
\end{aligned}$$

which is a standard $SEIR$ model.

For some diseases there is an asymptomatic period during which individuals have some infectivity rather than an exposed period. If the infectivity during this period is reduced by a factor ϵ, then the model can be described by the system

$$\begin{aligned}
S' &= \Lambda(N)-\beta(N)S(I+\epsilon E)-\mu S \\
E' &= \beta(N)S(I+\epsilon E)-\kappa E \\
I' &= \kappa E-(\mu+\alpha)I \\
N' &= \Lambda(N)-(1-f)\alpha I-\mu N,
\end{aligned}$$

This may be considered as an age of infection model with the same identifications of the variables and the same choice of $u(\tau), v(\tau)$ but with $A(\tau)=\epsilon u(\tau)+v(\tau)$.

4. Equilibria and the characteristic equation

There is a disease-free equilibrium $S=N=K, \phi=0$ of (2.1). Endemic equilibria are given by

$$\begin{gathered}
S\beta(N)\hat{A}_\mu(0)=1 \\
\Lambda(N)=\mu N+(1-f)(1-\mu\hat{B}_\mu(0))S\beta(N)\phi \\
\Lambda(N)=\mu S+S\phi\beta(N)
\end{gathered}$$

If $f=1$ the third condition gives

$$\phi=\frac{\mu(K-\beta(K)}{\hat{A}_\mu(0)}$$

and there is always an endemic equilibrium. If $f<1$ the second of the equilibrium conditions gives

$$\phi=\frac{\hat{A}_\mu(0)}{M}[\Lambda(N)-\mu N]$$

Now substitution of the first two equilibrium conditions into the third gives an equilibrium condition for N, namely

$$(1-M)\Lambda(N)=\mu N-\frac{\mu M}{\beta(N)\hat{A}_\mu(0)} \tag{4.1}$$

If $R_0 < 1$,

$$C(N)\hat{A_\mu}(0) \le C(K)\hat{A_\mu}(0) = R_0 < 1$$

so that

$$1 - \frac{M}{C(N)\hat{A_\mu}(0)} < 1 - M$$

Then we must have $\Lambda(N) < \mu N$ at equilibrium. However, this would contradict the demographic condition $\Lambda(N) > \mu N, 0 < N < K$. This shows that if $R_0 < 1$ there is no endemic equilibrium.

If $R_0 > 1$ for $N = 0$ the left side of (4.1) is non-negative while the right side is negative. For $N = K$ the left side of (4.1) is $\mu K(1 - M)$ while the right side is

$$\mu K - \frac{M\mu K}{R_0} > \mu K(1 - M)$$

This shows that there is an endemic equilibrium solution for N.

The linearization of (2.1) at an equilibrium (S, N, ϕ) is

$$\begin{aligned} x' &= -[\mu + \phi\beta(N)]x + [\Lambda'(N) - S\phi\beta'(N)]y - S\beta(N)z \\ y' &= [\Lambda'(N) - \mu]y + (1 - f)\int_0^\infty e^{-\mu\tau}B(\tau)[\phi\beta(N)x(t - \tau) \\ &\quad + S\phi\beta'(N)y(t - \tau) + S\beta(N)z(t - \tau)]d\tau \\ z(t) &= \int_0^\infty A_\mu(\tau)[\phi\beta(N)x(t - \tau) + S\phi\beta'(N)y(t - \tau) + S\beta(N)z(t - \tau)]d\tau \end{aligned}$$

The condition that this linearization have solutions which are constant multiples of $e^{-\lambda\tau}$ is that λ satisfies a characteristic equation. The characteristic equation at an equilibrium (S, ϕ, N) is

$$\det \begin{bmatrix} -[\lambda + \mu + \phi\beta(N)] & [\Lambda'(N) - S\phi\beta'(N)] & S\beta(N) \\ -\phi\beta(N)Q(\lambda) & -[\lambda - \Lambda'(N) + \mu] - S\phi\beta'(N)Q(\lambda) & -S\phi\beta(N)Q(\lambda) \\ \phi\beta(N)\hat{A_\mu}(\lambda) & S\phi\beta'(N)\hat{A_\mu}(\lambda) & S\beta(N)\hat{A_\mu}(\lambda) - 1 \end{bmatrix} = 0\,,$$

where

$$\hat{A_\mu}(\lambda) = \int_0^\infty e^{-\lambda\tau}A_\mu(\tau)d\tau\,, \quad \hat{B_\mu}(\lambda) = \int_0^\infty e^{-\lambda\tau}B_\mu(\tau)d\tau\,,$$
$$Q(\lambda) = (1 - f)[1 - (\lambda + \mu)\hat{B_\mu}(\lambda)]\,.$$

This reduces to

$$\begin{aligned} &S\beta(N)\hat{A_\mu}(\lambda) + (1 - f)\phi S\beta'(N)\hat{B_\mu}(\lambda) \\ &= 1 + \frac{f\phi\beta(N)}{\lambda + \mu} + \frac{(1 - f)\phi P}{\lambda + \mu - \Lambda'(N)} \cdot [1 - \Lambda'(N)\hat{B_\mu}(\lambda)] \end{aligned} \tag{4.2}$$

where $P = \beta(N) + S\beta'(N) \ge 0$.

The characteristic equation for a model consisting of a system of ordinary differential equations is a polynomial equation. Now we have a transcendental characteristic equation, but there is a basic theorem that if all roots of the characteristic equation at an equilibrium have negative real part (that is, if $\Re\lambda < 0$, where $\Re$ denotes the real part, for every root λ of the characteristic equation) then the equilibrium is asymptotically stable [9].

At the disease-free equilibrium $S = N = K, \phi = 0$ the characteristic equation is

$$K\beta(K)\hat{A_\mu}(\lambda) = 1\,.$$

Since the absolute value of the left side of this equation is no greater than $K\beta(K)\hat{A_\mu}(0)$ if $\Re\lambda \geq 0$ the disease-free equilibrium is asymptotically stable if and only if

$$R_0 = K\beta(K)\hat{A_\mu}(0) < 1\,.$$

5. The Endemic Equilibrium

In the analysis of the characteristic equation (4.2) it is helpful to make use of the following elementary result:

> If $|P(\lambda)| \leq 1$, $\Re g(\lambda) > 0$ for $\Re\lambda \geq 0$, then all roots of the characteristic equation $P(\lambda) = 1 + g(\lambda)$ satisfies $\Re\lambda < 0$.

To prove this result, we observe that if $\Re\lambda \geq 0$ the left side of the characteristic equation has absolute value at most 1 while the right side has absolute value greater than 1.

If $f = 1$, the characteristic equation reduces to

$$S\beta(N)\hat{A_\mu}(\lambda) = 1 + \frac{\phi\beta(N)}{\lambda + \mu}\,.$$

The term

$$\frac{f\phi\beta(N)}{\lambda + \mu}$$

in (4.2) has positive real part if $\Re\lambda \geq 0$. It follows from the lemma that all roots satisfy $\Re\lambda < 0$, so that the endemic equilibrium is asymptotically stable. Thus all roots of the characteristic equation (4.2) have negative real part if $f = 1$. The analysis if $f < 1$ is more difficult.

The roots of the characteristic equation depend continuously on the parameters of the equation. In order to have a root with $\Re\lambda \geq 0$ there must be parameter values for which either there is a root at "infinity", or there is a root $\lambda = 0$ or there is a pair of pure imaginary roots $\lambda = \pm iy, y > 0$. Since the left side of (4.2) approaches 0 while the right side approaches 1 as $\lambda \to \infty, \Re\lambda \geq 0$, it is not possible for a root to appear at "infinity". For $\lambda = 0$, since $S\beta(N)\hat{A_\mu}(0) = 1$ and $\beta'(N) \leq 0$ the left side of (4.2) is less than 1 at $\lambda = 0$, while the right side is greater than 1 since

$$1 - \Lambda'(N)\hat{B_\mu}(0) > 1 - \Lambda'(N)/\mu > 0$$

if $\Lambda'(N) < \mu$. This shows that $\lambda = 0$ is not a root of (4.2), and therefore that all roots satisfy $\Re\lambda < 0$ unless there is a pair of roots $\lambda = \pm iy, y > 0$. According to the Hopf bifurcation theorem [3] a pair of roots $\lambda = \pm iy, y > 0$ indicates that the system (2.1) has an asymptotically stable periodic solution and there are sustained oscillations of the system.

A somewhat complicated calculation using the fact that since $B_\mu(\tau)$ is monotone non-increasing,

$$\int_0^\infty B_\mu(\tau)\sin y\tau dy \geq 0$$

for $0 \leq y < \infty$ shows that the term

$$\frac{(1-f)\phi P}{\lambda + \mu - \Lambda'(N)} \cdot [1 - \Lambda'(N)\hat{B_\mu}(\lambda)]$$

in (4.2) has positive real part at least if $-\mu \le \Lambda'(N) \le \mu$. Therefore, if $-\mu \le \Lambda'(N) \le \mu$, instability of the endemic equilibrium is possible only if the term

$$(1-f)\phi S\beta'(N)\hat{B_\mu}(iy)$$

in (4.2) has negative real part for some $y > 0$. This is not possible with bilinear incidence, since $\beta'(N) = 0$; thus with bilinear incidence the endemic equilibrium of (2.1) is always asymptotically stable. Since $\beta'(N) \le 0$, instability requires

$$\Re\hat{B_\mu}(iy) = \int_0^\infty B_\mu(\tau)\cos y\tau d\tau < 0$$

for some $y > 0$. If the function $B(\tau)$ is non-increasing and convex, that is, if $B'(\tau) \le 0, B''(\tau) \ge 0$, then it is easy to show using integration by parts that

$$\int_0^\infty B_\mu(\tau)\cos y\tau d\tau \ge 0$$

for $0 < y < \infty$. Thus if $B(\tau)$ is convex, which is satisfied for example, by the choice

$$B(\tau) = e^{-\alpha\tau}$$

the endemic equilibrium of (2.1) is asymptotically stable if $-\mu \le \Lambda'(N) \le \mu$.

There are certainly less restrictive conditions which guarantee asymptotic stability. However, examples have been given of instability, even with $f = 0, \Lambda'(N) = 0$, where constant infectivity would have produced asymptotic stability [1, 7, 8]. These results indicate that concentration of infectivity early in the infected period is conducive to such instability. In these examples, the instability arises because a root of the characteristic equation crosses the imaginary axis as parameters of the model change, giving a pure imaginary root of the characteristic equation. This translates into oscillatory solutions of the model. Thus infectivity which depends on infection age can cause instability and sustained oscillations.

6. An SI^*S Model

To formulate an SI^*S age of infection model we need only take the SI^*R age of infection model (2.1) and move the recovery term from the equation for R (which was not listed explicitly in the model) to the equation for S. We obtain the model

$$\begin{aligned}
S' &= \Lambda(N) - \mu S - \beta(N)S\phi - \\
&= f\int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)e^{-\mu\tau}B'(\tau)d\tau \\
\phi(t) &= \int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)A_\mu(\tau)d\tau \\
N'(t) &= \Lambda(N) - \mu N + (1-f)\int_0^\infty \beta(N(t-\tau))S(t-\tau)\phi(t-\tau)e^{-\mu\tau}B'(\tau)d\tau
\end{aligned} \tag{6.1}$$

Although we will not carry out any analysis of this model, we state that it may be attacked using the same approach as that used for (2.1). It may be shown that if $R_0 = K\beta(K)\hat{A}_\mu(0) < 1$ the disease-free equilibrium is asymptotically stable. If $R_0 > 1$ there is an endemic equilibrium and the characteristic equation at this equilibrium is

$$
\begin{aligned}
&S\beta(N)\hat{A_\mu}(\lambda) + (1-f)\phi S\beta'(N)\hat{B_\mu}(\lambda) \\
&= 1 + f\phi\beta(N)\hat{B_\mu}(\lambda) + \frac{(1-f)\phi P}{\lambda+\mu-\Lambda'(N)} \cdot \left[1-\Lambda'(N)\hat{B_\mu}(\lambda)\right],
\end{aligned}
\tag{6.2}
$$

where $P = \beta(N) + S\beta'(N) \geq 0$.

Many diseases, including most strains of influenza, impart only temporary immunity against reinfection on recovery. Such disease may be described by SI^*S age of infection models, thinking of the infected class I^* as comprised of the infective class I together with the recovered and immune class R. In this way, members of R neither spread or acquire infection. We assume that immunity is lost at a proportional rate κ.

We let $u(\tau)$ be the fraction of infected members with infection age τ who are infective if alive and $v(\tau)$ the fraction of infected members who are not recovered and still immune if alive. Then the fraction becoming immune at infection age τ if alive is $\alpha u(\tau)$, and we have

$$
\begin{aligned}
u'(\tau) &= -\alpha u(\tau), \quad u(0) = 1 \\
v'(\tau) &= \alpha u(\tau) - \kappa v(\tau) \quad v(0) = 0
\end{aligned}
\tag{6.3}
$$

These equations are the same as (3.1) obtained in formulating the $SEIR$ model with α and κ interchanged. Thus we may solve to obtain

$$
\begin{aligned}
u(\tau) &= e^{-\alpha\tau} \\
v(\tau) &= \frac{\alpha}{\kappa-\alpha}[e^{-\alpha\tau} - e^{-\kappa\tau}]
\end{aligned}
$$

We take $B(\tau) = u(\tau) + v(\tau)$, $A(\tau) = u(\tau)$. Then if we define $I = \phi, R = I^* - \phi$, the model (6.1) is equivalent to the system

$$
\begin{aligned}
S' &= \Lambda(N) - \beta(N)SI - \mu S + \kappa R \\
I' &= \beta(N)SI - (\mu+\alpha)I \\
R' &= f\alpha E - (\mu+\kappa)R \\
N' &= \Lambda(N) - (1-f)\alpha I - \mu N,
\end{aligned}
$$

which is a standard $SIRS$ model.

If we assume that, instead of an exponentially distributed immune period, that there is an immune period of fixed length ω we would again obtain $u(\tau) = e^{-\alpha\tau}$, but now we may calculate that

$$
v(\tau) = 1 - e^{-\alpha\tau}, (\tau \leq \omega), \quad v(\tau) = e^{-\alpha\tau}(e^{\alpha\omega} - 1), (\tau > \omega).
$$

To obtain this, we note that

$$
v'(\tau) = \alpha u(\tau), 0 \leq \omega, \quad v'(\tau) = \alpha u(\tau) - \alpha u(\tau - \omega), \tau > \omega
$$

From these we may calculate $A(\tau), B(\tau)$ for an SI^*S model. Since it is known that the endemic equilibrium for an $SIRS$ model with a fixed removed period can be unstable [2], this shows that (6.2) may have roots with non-negative real part and the endemic equilibrium of an SI^*S age of infection model is not necessarily asymptotically stable.

7. Discussion

We have formulated some general age of infection epidemiological models and set up their equilibrium analysis. Compartmental models which include exposed periods, temporary immunity, and other compartments, can be formulated as age of infection models.

The SI^*R age of infection model is actually a special case of the SI^*S age of infection model. We may view the class R as still infected but having no infectivity, so that $v(\tau) = 0$. The underlying idea is that in infection age models we divide the population into members who may become infected and members who can not become infected, either because they are already infected or because they are immune. Thus, we may view the SI^*S model as general. If we could carry out a complete analysis of the corresponding characteristic equation we could use it as the basis of a general theory. However, since the characteristic equation analysis is not yet complete there are many open questions whose answers would provide useful insights into general model behaviour.

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