

Revisiting Kermack and McKendrick

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1 Kermack's and McKendrick's Epidemic Models

It is well known that Kermack and McKendrick were most important pioneers in the field of mathematical epidemiology. Between World War I and II, they published a series of papers about deterministic structured models for the spread of infectious diseases, which have been so far referred by many authors again and again as an important origin of idea. Nevertheless, in my opinion, possibility and implications of their epidemic models have been so far not necessarily fully examined.

The first paper published in 1927 was especially famous among researchers, in which they developed, what we call, SIR (susceptible-infected-removed) epidemic model with duration dependent (variable) infectivity, that is, the infection rate depends on the duration in the infected and infectious status and the infection happens only one time in the life of host individual. If the infectivity is assumed to be constant, this structured SIR model is reduced to the well known ordinary differential equation model. Even now, unfortunately most people keep referring to the simplest ODE case of Kermack's and McKendrick's SIR epidemic model as if it were the only Kermack and McKendrick model. But this leads a historical misunderstanding, and should stop (Diekmann, Heesterbeek and Metz 1995). But reexamination of Kermack's and McKendrick's structured SIR model has been started by Metz (1978) and Diekmann (1977) (see also Metz and Diekmann 1986, Iannelli 1995). The importance of this kind of structured SIR model is now widely recognized, since it provides a model for epidemic with long incubation period and variable infectivity such as HIV/AIDS epidemic (Thieme and Castillo-Chavez 1993). During the past two decades SIR-type epidemic models have been well studied and extended to various kind of epidemic-demographic situations (Anderson and May 1991).

On the other hand, as far as I know, Kermack's and McKendrick's general complex models developed in two papers written in 1932 and 1933 have been still neglected. In those papers they have proposed a kind of *duration-dependent* epidemic model, where the transmission rate depends on both duration of infected host (*disease-age*) and duration of susceptible host. The total population is decomposed into three compartments, the never infected, infected and recovered. The host population is structured by duration variable in each status, but the chronological age is neglected. We call this model as *variable susceptibility model*, since the infection rate from infecteds to recovered population depends on not only the disease-age but also the duration variable of recovered host. That

is, in this model, recovered individuals can be reinfected repeatedly, and their reinfection probability depend on how long it takes since the last infection. Kermack and McKendrick concentrated to the problem of endemicity of this model, that is, they examined conditions under which existence and uniqueness of the endemic steady state can be established.

Why so far has their variable susceptibility model been paid less attention and neglected ? Though one reason would be that their model was too complex to be analyzed without computer, another important reason would be that they did not answer the question what kind of real epidemic could be well described by this type of model and whether it is worth while studying this complex model. However, today we can recognize that their idea of variable susceptibility is very much important, since their formulation is so flexible that we can take into account the genetic change of virus or the variation of host immunity structure. There exists at least two main reasons that the host immunity will decay though time, one possibility is that there is a natural decay of host immunity, another reason is the antigenic change in virus. The second reason is now becoming more and more important, because we are confronting with difficulty to control epidemic in which by the genetic changes in virus the vaccination and the host immunity becomes less effective. The evolutionary mechanism would be one of most important factors which reemerge infectious diseases.

In this short note, we reformulate Kermack's and McKendrick's variable susceptibility model by using modern mathematical expressions, and prove an existence and uniqueness result for the endemic steady state. Subsequently we discuss its applications to evolutionary epidemic model.

2 Variable susceptibility model

Here we formulate the variable susceptibility model as an initial-boundary value problem for McKendrick partial differential equation system, which would be useful to make the mathematical essence of the model clear.

Let $s_0(t, \tau)$ be the density of never infected population (susceptible population, which is also called as *virgin* population in the terminology of Kermack and McKendrick) at time t and duration τ . Let $i(t, \tau)$ be the density of infected and infectious population at time t and duration (disease-age) τ and let $s(t, \tau)$ be the density of recovered population (partially susceptible population) at time t and duration τ . Let μ denotes the natural death rate, $b(t)$ the birth rate at time t , $v(\tau)$ the recovery rate at disease-age τ , $\gamma_1(\tau)\gamma_2(\zeta)$ the infection rate from infected individual at disease-age ζ to recovered host at duration τ . For the transmission rate, we adopt the following intuitively reasonable assumption:

Assumption 2.1 $\gamma_1(\tau)$ is a bounded, nonnegative, monotone non-decreasing function, and the infection rate from infecteds at disease-age ζ to never infected individuals is given

by $\gamma_1(\infty)\gamma_2(\zeta)$.

That is, $\gamma_2(\zeta)$ reflects the variable infectivity of infected individual and $\gamma_1(\tau)$ denotes the variable susceptibility of recovered individual. Since it could be assumed that there is no correlation between those two forces, the transmission rate is assumed to be given by the proportionate mixing assumption.

Then the variable susceptibility model is formulated as follows:

$$\frac{\partial s_0(t, \tau)}{\partial t} + \frac{\partial s_0(t, \tau)}{\partial \tau} = -\mu s_0(t, \tau) - s_0(t, \tau) \gamma_1(\infty) \int_0^\infty \gamma_2(\zeta) i(t, \zeta) d\zeta, \quad (2.1)$$

$$\frac{\partial s(t, \tau)}{\partial t} + \frac{\partial s(t, \tau)}{\partial \tau} = -\mu s(t, \tau) - s(t, \tau) \gamma_1(\tau) \int_0^\infty \gamma_2(\zeta) i(t, \zeta) d\zeta, \quad (2.2)$$

$$\frac{\partial i(t, \tau)}{\partial t} + \frac{\partial i(t, \tau)}{\partial \tau} = -(\mu + \delta + v(\tau)) i(t, \tau), \quad (2.3)$$

$$s_0(t, 0) = b(t) \quad (2.4)$$

$$s(t, 0) = \int_0^\infty v(\tau) i(t, \tau) d\tau \quad (2.5)$$

$$i(t, 0) = \int_0^\infty \{ \gamma_1(\infty) s_0(t, \tau) + \gamma_1(\tau) s(t, \tau) \} d\tau \int_0^\infty \gamma_2(\zeta) i(t, \zeta) d\zeta, \quad (2.6)$$

Let $N(t)$ be the total size of host population as

$$N(t) := \int_0^\infty s_0(t, \tau) d\tau + \int_0^\infty s(t, \tau) d\tau + \int_0^\infty i(t, \tau) d\tau. \quad (2.7)$$

Then it follows that

$$N'(t) = b(t) - \mu N(t) - \delta I(t), \quad (2.8)$$

where $I(t) := \int_0^\infty i(t, \tau) d\tau$. In the following we mainly consider a simple case that $b(t) = b = \text{const.}$ and $\delta = 0$. Therefore without loss of generality we can assume in advance that the total size of population is constant $N = b/\mu$. If an initial condition is added to (2.1)-(2.6), the existence and uniqueness result for this system could be established by semigroup method developed by Webb (1985).

3 The problem of endemicity

Papers written in the 1930s, Kermack and McKendrick were mainly concerned with the problem of endemicity for the variable susceptibility model under various kind of conditions. Since their treatment of that problem was not necessarily rigorous and their mathematical expressions were difficult to follow for modern readers, we here try to give a new formulation and a clear proof for the existence and uniqueness result for the endemic steady state of the variable susceptibility model under simple conditions.

Let $(s_0^*(\tau), s^*(\tau), i^*(\tau))$ be the steady state for system (2.1)-(2.6). Then we have

$$i^*(\tau) = i^*(0)\Gamma(\tau), \quad (3.1)$$

$$s_0^*(\tau) = be^{-\mu\tau - i^*(0)\langle \gamma_2, \Gamma \rangle \gamma_1(\infty)\tau} \quad (3.2)$$

$$s^*(\tau) = i^*(0)\langle v, \Gamma \rangle e^{-\mu\tau - i^*(0)\langle \gamma_2, \Gamma \rangle \int_0^\tau \gamma_1(\sigma) d\sigma} \quad (3.3)$$

where $\langle u, v \rangle := \int_0^\infty u(x)v(x)dx$ and $\Gamma(\tau)$ is the survival rate of the infected hosts given by

$$\Gamma(\tau) := e^{-\mu\tau - \int_0^\tau v(\sigma) d\sigma}$$

Then corresponding to $i^*(0) = 0$, there exists a disease-free steady state as

$$(s_0^*(\tau), s^*(\tau), i^*(\tau)) = (be^{-\mu\tau}, 0, 0) \quad (3.4)$$

In the initial invasion phase at the disease-free steady state, the number of newly infected individuals per unit time, denoted by $B(t)$, is described by the linearized equation (renewal integral equation) as follows:

$$B(t) = N\gamma_1(\infty) \int_0^t \gamma_2(\zeta)\Gamma(\zeta)B(t-\zeta)d\zeta + N\gamma_1(\infty) \int_t^\infty \frac{\gamma_2(\zeta)\Gamma(\zeta)}{\Gamma(\zeta-t)} i(0, \zeta-t)d\zeta. \quad (3.5)$$

Then we know that the basic reproduction number for this epidemic system is defined by

$$R_0 = N\gamma_1(\infty) \int_0^\infty \gamma_2(\zeta)\Gamma(\zeta)d\zeta. \quad (3.6)$$

It is easily seen from $i(t, 0) \leq B(t)$ that the following stability result holds:

Proposition 3.1 *If $R_0 < 1$, then the disease-free steady state is globally asymptotically stable.*

Next in order to investigate existence and uniqueness of endemic steady state, we prepare the following technical lemma, which was essentially observed by Kermack and McKendrick:

Lemma 3.2 *If $i^*(0) \neq 0$, it follows that*

$$\int_0^\infty s_0^*(\tau)d\tau = \frac{1 - \langle v, \Gamma \rangle (1 - \mu\Phi(i^*(0)))}{\gamma_1(\infty)\langle \gamma_2, \Gamma \rangle}, \quad (3.7)$$

where

$$\Phi(x) := \int_0^\infty e^{-\mu\tau - x\langle \gamma_2, \Gamma \rangle \int_0^\tau \gamma_1(\sigma) d\sigma} d\tau. \quad (3.8)$$

Proof. We can observe that

$$\frac{b}{\mu} = \int_0^\infty s_0^*(\tau)d\tau + \int_0^\infty s^*(\tau)d\tau + \int_0^\infty i^*(\tau)d\tau \quad (3.9)$$

$$= \frac{b}{\mu + \langle \gamma_2, \Gamma \rangle \gamma_1(\infty) i^*(0)} + i^*(0) \langle v, \Gamma \rangle \Phi(i^*(0)) + i^*(0) \|\Gamma\|$$

where $\|u\| := \int_0^\infty u(x) dx$. If $i^*(0) \neq 0$, we can solve the above equation for b , hence we obtain that

$$b = \frac{\mu + \langle \gamma_2, \Gamma \rangle \gamma_1(\infty) i^*(0)}{\langle \gamma_2, \Gamma \rangle \gamma_1(\infty)} \mu \{ \|\Gamma\| + \langle v, \Gamma \rangle \Phi(i^*(0)) \} \quad (3.10)$$

If we note that

$$\mu \|\Gamma\| = 1 - \langle v, \Gamma \rangle, \quad \int_0^\infty s_0^*(\tau) d\tau = \frac{b}{\mu + \langle \gamma_2, \Gamma \rangle \gamma_1(\infty) i^*(0)},$$

then we arrive at the expression (3.7). \square

It follows from (3.7) and (3.9) that

$$N = \frac{1 - \langle v, \Gamma \rangle}{\langle \gamma_2, \Gamma \rangle \gamma_1(\infty)} \quad (3.11)$$

$$+ \frac{\langle v, \Gamma \rangle}{\langle \gamma_2, \Gamma \rangle \gamma_1(\infty)} \Phi(i^*(0)) \{ \mu + i^*(0) \langle \gamma_2, \Gamma \rangle \gamma_1(\infty) \} + i^*(0) \|\Gamma\|.$$

Now we define a function $F(x)$ by

$$F(x) := \frac{1 - \langle v, \Gamma \rangle}{\langle \gamma_2, \Gamma \rangle \gamma_1(\infty)} + \frac{\langle v, \Gamma \rangle}{\langle \gamma_2, \Gamma \rangle \gamma_1(\infty)} G(x) + x \|\Gamma\|, \quad (3.12)$$

where $G(x)$ is defined by

$$G(x) := \Phi(x) \{ \mu + x \langle \gamma_2, \Gamma \rangle \gamma_1(\infty) \}. \quad (3.13)$$

Then we know that if the equation $F(x) = N$ has a positive solution $x^* \in (0, N/\|\Gamma\|]$, the endemic steady state is given by (3.1)-(3.3) with $i^*(0) = x^*$. Since $F(x)$ is a continuous function and it is easy to see that $F(0) = \frac{N}{R_0}$ and $F(\frac{N}{\|\Gamma\|}) > N$. Therefore we can conclude that

Proposition 3.3 *If $R_0 > 1$, there exists at least one endemic steady state.*

Note that we here do not need to assume the monotonicity of $\gamma_1(\tau)$ to show the above existence theorem of endemic steady state. On the other hand, if we adopt the Assumption 1.1 and improve the original proof by Kermack and McKendrick, we can show the uniqueness result as follows:

Proposition 3.4 *Under the Assumption 1.1, there exists a unique endemic steady state.*

Proof. It is sufficient to show that under the Assumption 1.1, $F(x)$ is monotone increasing for $x \in (0, N/\|\Gamma\|]$. Integrating by parts, we can observe that

$$\mu\Phi(x) = 1 - x \langle \gamma_2, \Gamma \rangle \int_0^\infty \gamma_1(\tau) e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle \int_0^\tau \gamma_1(\sigma) d\sigma} d\tau.$$

Then we have

$$G(x) = 1 + x \langle \gamma_2, \Gamma \rangle \int_0^\infty (\gamma_1(\infty) - \gamma_1(\tau)) e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle \int_0^\tau \gamma_1(\sigma) d\sigma} d\tau. \quad (3.14)$$

Here we can assume without loss of generality that there exists a number $\tau_0 \geq 0$ such that $\gamma_1(\tau) = 0$ for $\tau \in [0, \tau_0]$ and $\gamma_0(\tau) > 0$ for $\tau > \tau_0$. That is, the recovered individuals can keep a complete immunity for the time interval $[0, \tau_0]$. Let $h > 0$ be an arbitrary small number. Then we have

$$\begin{aligned} & \int_0^\infty (\gamma_1(\infty) - \gamma_1(\tau)) e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle \int_0^\tau \gamma_1(\sigma) d\sigma} d\tau \\ &= \left\{ \int_0^{a_0} + \int_{a_0}^{a_0+h} + \int_{a_0+h}^\infty \right\} (\gamma_1(\infty) - \gamma_1(\tau)) e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle \int_0^\tau \gamma_1(\sigma) d\sigma} d\tau. \end{aligned}$$

Then in (3.14) we can calculate the integral as follows:

$$J_1(x) := x \langle \gamma_2, \Gamma \rangle \int_0^{a_0} \gamma_1(\infty) e^{-\mu\tau} d\tau = \gamma(\infty) x \langle \gamma_2, \Gamma \rangle \frac{1 - e^{-\mu a_0}}{\mu},$$

$$J_2(x) := x \langle \gamma_2, \Gamma \rangle \int_{a_0}^{a_0+h} (\gamma_1(\infty) - \gamma_1(\tau)) e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle \int_{a_0}^\tau \gamma_1(\sigma) d\sigma} d\tau,$$

$$J_3(x) := x \langle \gamma_2, \Gamma \rangle \int_{a_0+h}^\infty (\gamma_1(\infty) - \gamma_1(\tau)) e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle \int_{a_0}^\tau \gamma_1(\sigma) d\sigma} d\tau$$

$$= - \int_{a_0+h}^\infty \frac{\gamma_1(\infty) - \gamma_1(\tau)}{\gamma_1(\tau)} e^{-\mu\tau} \frac{\partial}{\partial \tau} e^{-x \langle \gamma_2, \Gamma \rangle \int_{a_0}^\tau \gamma_1(\sigma) d\sigma} d\tau$$

$$= \frac{\gamma_1(\infty) - \gamma_1(a_0 + h)}{\gamma_1(a_0 + h)} e^{-\mu(a_0+h) - x \langle \gamma_2, \Gamma \rangle \int_{a_0}^{a_0+h} \gamma_1(\sigma) d\sigma} + H(x),$$

where $H(x)$ is define as

$$H(x) := \int_{a_0+h}^\infty \frac{\partial}{\partial \tau} \left\{ \frac{\gamma_1(\infty) - \gamma_1(\tau)}{\gamma_1(\tau)} e^{-\mu\tau} \right\} e^{-x \langle \gamma_2, \Gamma \rangle \int_0^\tau \gamma_1(\sigma) d\sigma} d\tau.$$

It follows from the monotonicity of $\gamma_1(\tau)$ that

$$\frac{\partial}{\partial \tau} \left\{ \frac{\gamma_1(\infty) - \gamma_1(\tau)}{\gamma_1(\tau)} e^{-\mu\tau} \right\} \leq 0.$$

Then we have $H'(x) \geq 0$. Observe that

$$F'(x) = \frac{\langle v, \Gamma \rangle}{\langle \gamma_2, \Gamma \rangle \gamma_1(\infty)} (J'_1(x) + J'_2(x) + J'_3(x)) + \| \Gamma \|$$

$$\begin{aligned}
&= \|\Gamma\| + \langle v, \Gamma \rangle \frac{1 - e^{-\mu a_0}}{\mu} + \frac{\langle v, \Gamma \rangle}{\gamma_1(\infty)} \int_{a_0}^{a_0+h} (\gamma_1(\infty) - \gamma(\tau)) e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle} \int_{a_0}^{\tau} \gamma_1(\sigma) d\sigma d\tau \\
&\quad - \frac{x \langle v, \Gamma \rangle \langle \gamma_2, \Gamma \rangle}{\gamma_1(\infty)} \int_{a_0}^{a_0+h} (\gamma_1(\infty) - \gamma(\tau)) \left\{ \int_{a_0}^{\tau} \gamma_1(\sigma) d\sigma \right\} e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle} \int_{a_0}^{\tau} \gamma_1(\sigma) d\sigma d\tau \\
&\quad + \frac{\langle v, \Gamma \rangle}{\gamma_1(\infty) \langle \gamma_2, \Gamma \rangle} \\
&\quad \times \left\{ -\frac{\gamma_1(\infty) - \gamma_1(a_0 + h)}{\gamma_1(a_0 + h)} \langle \gamma_2, \Gamma \rangle \left[\int_{a_0}^{a_0+h} \gamma_1(\sigma) d\sigma \right] e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle} \int_{a_0}^{a_0+h} \gamma_1(\sigma) d\sigma + H'(x) \right\}.
\end{aligned}$$

The minus parts of the above expression can be estimated as follows:

$$\begin{aligned}
&\left| \frac{x \langle v, \Gamma \rangle \langle \gamma_2, \Gamma \rangle}{\gamma_1(\infty)} \int_{a_0}^{a_0+h} (\gamma_1(\infty) - \gamma(\tau)) \left\{ \int_{a_0}^{\tau} \gamma_1(\sigma) d\sigma \right\} e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle} \int_{a_0}^{\tau} \gamma_1(\sigma) d\sigma d\tau \right| \\
&\leq \frac{N \langle v, \Gamma \rangle \langle \gamma_2, \Gamma \rangle}{\|\Gamma\| \gamma_1(\infty)} \gamma_1(\infty)^2 \frac{h^2}{2}, \\
&\left| -\frac{\gamma_1(\infty) - \gamma_1(a_0 + h)}{\gamma_1(a_0 + h)} \langle \gamma_2, \Gamma \rangle \left[\int_{a_0}^{a_0+h} \gamma_1(\sigma) d\sigma \right] e^{-\mu\tau - x \langle \gamma_2, \Gamma \rangle} \int_{a_0}^{a_0+h} \gamma_1(\sigma) d\sigma \right| \\
&\leq \langle v, \Gamma \rangle h.
\end{aligned}$$

Therefore if we choose a $h > 0$ small enough in advance, we can conclude that $F'(x) \geq 0$, hence that $F(x)$ is a monotone non-decreasing function. Thus the endemic steady state exists uniquely. \square

4 Discussion: Toward Evolutionary Epidemic Model

As is pointed out above, the variable susceptibility model could be a very useful tool to take into account the effect of changes in the host immunity structure or the antigenic change of virus. As an example, let us consider the Pease's influenza model (1987).

In the type A influenza epidemic, genetic changes in the virus are thought to play an important role in causing recurrent epidemic. The virus changes genetically, and hence immunologically from one epidemic to the next. Therefore a descendant virus strain can infect hosts who are immune to the progenitor strain diseases, and hence reinvade communities that recently suffered an epidemic of the progenitor strain. It is also observed that the more a virus has changed genetically from its progenitor, the more easily it will be able to reinfect a host that is immune to its progenitor.

In order to formulate the influenza model, Pease makes three major biological assumptions: First the probability of reinfection is a monotone increasing function of the number

of amino acid substitutions between the immunizing and challenge virus strains. In fact Pease's original assumption is that the probability is proportional to the number of amino acid substitutions, but we assume that the infection rate is upper bounded, since the arbitrarily large susceptibilities seem unrealistic as Pease pointed out. Second, only one virus strain circulates in a human community at any one time. Third, random drift, and not frequency-dependent selection by the host, causes amino acid substitutions to occur in the influenza virus. Random drift occurs continually and causes gradual changes in the virus antigens, thereby genetic changes in the pathogen from epidemic to epidemic cause previously immune hosts to become susceptible.

Under the above assumptions, the Pease model is formulated as follows: Let $I(t)$ be the number of infected hosts at time t and let $S(t, a)$ be the density of uninfected hosts, so that $\int_{a_0}^{a_1} S(t, a) da$ is the number of uninfected hosts that were last infected by a virus which differed by more than a_0 and less than a_1 amino acid substitution from the virus strain prevailing at time t . We assume that the number of amino acid substitution is a continuous variable, and it is causing the antigenic drift in the virus strain. Then the Pease's evolutionary epidemic model is formulated by the following integrodifferential equations:

$$\frac{\partial S(t, a)}{\partial t} + k \frac{\partial S(t, a)}{\partial a} = -\gamma(a)S(t, a)I(t), \quad (4.1)$$

$$\frac{dI(t)}{dt} = -vI(t) + I(t) \int_0^\infty \gamma(a)S(t, a)da, \quad (4.2)$$

$$kS(t, 0) = vI(t), \quad (4.3)$$

where v is the rate at which infected hosts recover, k is the (constant) rate at which amino acid substitutions occur in the virus population and $\gamma(a)$ specifies how amino acid substitutions affect the probability of reinfection. Though the Pease model does not consider the never infected population and neglect the demography, it is easily observed that it is a special case of the variable susceptibility model with constant recovery rate.

The analysis of Pease model suggests that there exists a correlation between the prevalence at the endemic steady state and its stability, and the recurrent outbreak (periodic solution) could be produced by the evolutionary mechanism, that is, the decay of host immunity by the antigenic drift of the type A virus. Though in the rigorous sense, the question whether the sustained oscillation can be realized for realistic value of the prevalence is still open (Inaba 1998, 1999), those observations suggest potential abilities of the variable susceptibility model.

For the general variable susceptibility model, under appropriate conditions we can establish the endemic threshold criteria, that is, the basic reproduction number R_0 is less than one, the infected population will be eradicated through time, otherwise R_0 is greater than the unity, there exists unique endemic steady state. But up to now there are no results for stability of the endemic steady state. Moreover, even in the full model (2.1)-(2.6), there

are many neglected factors, for example, the chronological age, the disease induced death rate, vaccination term, etc. To analyze the model including those factors will be difficult but important future challenge. That is, we can say that the possibilities of Kermack's and McKendrick's models have not yet been exhausted, which is the reason why we still have to continue to revisit Kermack and McKendrick again and again, though even more than 60 years have passed since their work.

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