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Abstract

A simple class of stochastic models for epidemic spread in finite, but large, populations is studied. The purpose is to investigate how assumptions about the distribution of times between primary and secondary infections influences the outcome of the epidemic. Of particular interest is how assumptions of individual variability in infectiousness relates to variability of the epidemic curve. The main concern is the proportion of the population that finally are infected and the time scale at which the epidemic evolves. The theoretical results are illustrated by simulations.

Keywords: Epidemic models, Kermack-McKendrick-model, Epidemic curve, Generation time distribution, Basic reproduction number.

1 Introduction

Epidemics are complex processes. The possibility for an infection to spread in a population is related both to medical-biological properties deciding the interplay by an infectious person and the infectious agent and to social factors involved in contacts between infectious and susceptible individuals. Any mathematical model will at best be an approximation. The usefulness of a model depends on to what extent it helps in understanding interesting features of the spread.

In this paper we will consider assumptions about randomness. It is a common understanding that chance plays an important part in spread of infections. Epidemics in large populations are mass phenomena and we can expect that the influence of chance on overall properties will, due to some form of the theorem of large numbers, even out. If this is the case it is crucial to understand for which properties it is sufficient to consider mean properties and how, in that case, they are related to the stochastic properties of the infectious agent and the population. It is worth pointing out that it is well-known that randomness influences the outcomes of an epidemic even in large populations. An example is that it always is a positive probability that the spread stops early with only a few infected. Another random outcome is the time it takes for an epidemic to grow large.

The assumptions used to build a model have to be considered carefully. They should include features that are related to the phenomena under study. If the aim is, as it normally should be, restricted to a study of a few aspects it is also recommendable that the assumptions are as simple as possible. A consequence is that the model should only use assumptions that are important for the predictions of the model.

In this paper we will use a simple model for the spread of an infection to study the impact of some basic assumptions of how an infectious agent is transmitted. The aim is to describe human-to-human spread of an infection in a large closed population. The model used has a long history and is basically a stochastic version of the Kermack-MacKendrick model (Kermack et al. (1927)) applied to a finite population. It is described in section 2. We will here follow the formulation and terminology of Svensson (2007). There are several treatments of models with similar structure, see e.g. Becker (1993).

The assumptions are related to how many persons an infected person may infect and when secondary infections occur. The times that elapses from a person is infected till he infects other persons plays an important part both in applied and theoretical studies of epidemic spread (see e.g. Fine (2003), Wallinga et al. (2007), Kenah et al (2008), and, Tomba et al. (2010)).

These times enter into the model studied here through the generation time distribution. In section 4 different approaches to assumptions about this distribution are considered.

The epidemic is assumed to start with the introduction of one (newly) infected person into the population. The focus of the study is how the assumptions are reflected in the appearance of the epidemic curve, which describes how many persons in a population that are infected at time t after the infection entered the population.

The appearance of the epidemic curves are analysed using martingale theory in section 5. Simulated epidemic curves are presented and discussed in section 6. We will in particular be concerned with the proportion of the population that finally will be infected and at which time scale the epidemic evolves.

In section 7 we consider non-parametric estimates of basic parameters in the model based on one observed epidemic curve. Since the epidemic curve is based on times of infection that are seldom observed this may seem an unrealistic theoretical exercise. However, the possibilities to estimate the parameters that defines the model shows what can be recovered from an observation and thus also which assumptions has identifiable impacts on the predictions of the model.

2 A simple epidemic model

We will assume that the epidemic takes place in a closed, finite population with n members. At time $t = 0$, one newly infected person enters the population and starts the infectious spread.

The spread is assumed to depend on two, possible random, entities, λ and K. Here λ is a non-negative (random) number that decides the "total amount of infectivity" spread by an infected person, K is a (random) positive measure, with total mass 1, defined on $[0, \infty[$. K describes how the infectiousness is distributed in time. The assumption that K is a random measure implies that it is not the same for all infected individuals. It is chosen (independently for all persons) according to a distribution on all possible measures. Let $K(t) = K([0, t[)$. We will refer to $K(t)$ as the contact distribution function. For simplicity we assume that there exist a density so that

$$K(t) = \int_0^t \kappa(s)ds. \tag{2.1}$$

The functions $\lambda\kappa(t)$ are referred to as infectiousness functions by Becker (1993).

Observe that both λ and K are considered to be random and that they may be dependent. In the following analysis we will tacitly assume that all measures and functions are regular enough to admit operations, e.g. exchange of order of integration, that simplifies calculations.

In the model it is assumed that for a given infectious individual the number of possibly infectious contacts in the interval $I = [a, b[$, after infection, is Poisson distributed with mean $\lambda K(I)$ (conditional on λ and K). The number of all possible infectious contacts taken by one infected individual will follow a mixed Poisson distribution i.e. it is Poisson distributed with the random mean λ.

We will consider epidemics in a finite and closed population. The contacted persons are chosen randomly in the population. An infectious contact results in a secondary case if the contact is taken with a susceptible person, i.e. a person that has not been previously infected.

The basic reproduction number, R_0, is often defined as the mean number of secondary cases to an infected individual in a totally susceptible population. We will in this paper define it as the mean number of possible infectious contacts. In the class of models considered here the two definitions are equivalent. Thus

$$R_0 = \mathrm{E}(\lambda). \tag{2.2}$$

The expectation of random functions $\lambda\kappa$, normalized to have total mass 1 is called **the basic generation time density** i.e.

$$g(t) = \frac{\mathrm{E}(\lambda\kappa(t))}{R_0}. \tag{2.3}$$

We can also define **the basic generation time distribution**

$$G(t) = \int_0^t g(s)ds = \frac{\mathrm{E}(\lambda K(t))}{R_0}. \tag{2.4}$$

The function G measures how large proportion of the infectivity a random infected has emitted at time t after infection.

We will also consider the mean generation time

$$T_0 = \int_0^\infty tg(t)dt. \tag{2.5}$$

Later we will be concerned with the variability of the epidemic process. For this reason we introduce the variance function

$$V(t) = \frac{\mathrm{Var}(\lambda K(t))}{R_0^2}. \tag{2.6}$$

Note that

$$V_0 = V(\infty) = \frac{\mathrm{Var}(\lambda)}{R_0^2} \tag{2.7}$$

is the square of the coefficient of variance of the random variable λ.

3 Models of the generation time density

The generation time density plays an important part in the model. Its role is to explain the times between a primary infection and its secondary infections. We will consider two approaches to motivate assumptions of this density.

3.1 Models with non-random generation time density

A common assumption is that the relative infectivity of an infected persons develops without individual variation. This implies that the function $\kappa(t)$ is constant, i.e.

$$\kappa(t) = g(t), \tag{3.1}$$

The intensity of the Poisson process that generates possible infectious contacts of an infectious person at time t after infection is $\lambda g(t)$ where λ is a random variable.

3.2 Models with latent and infectious times

In SEIR-models it is assumed that an infection is followed by a period, called the latent period, during which the infected person do not transmit the infection. The latent period is then followed by an infectious period. Both the latent and infectious periods may have random individual duration. In this paper we shall, for simplicity, only consider models where the infectivity is assumed to be constant throughout the infectious time.

Let X be the duration of the latent period, Y the duration of the infectious period, and α the infectivity during the infectious period. Then

$$\lambda\kappa(t) = \alpha I(X < t \leq X + Y). \tag{3.2}$$

With this formulation $\lambda = \alpha Y$ is the individual total infectivity, and

$$\kappa(t) = I(X < t \leq X + Y)/Y. \tag{3.3}$$

According to (2.3) the basic generation time density g equals

$$g(t) = \frac{\mathrm{P}(X + Y > t) - \mathrm{P}(X > t)}{\mathrm{E}(Y)} = \frac{\mathrm{P}(X \leq t) - \mathrm{P}(X + Y \leq t)}{\mathrm{E}(Y)}. \tag{3.4}$$

A simple calculation yields that the mean generation time

$$T_0 = \mathrm{E}(X) - \frac{\mathrm{E}(Y^2)}{2\mathrm{E}(Y)}. \tag{3.5}$$

4 Models with a specific basic generation time density

Many important properties of the epidemic curve depend on R_0 and g. As seen in the previous section a given generation time density, g, may be motivated in several ways. An often used assumption is that all individuals spreads the infection according to a non-random function coinciding with g. This is always possible provided that g is a non-negative function with total mass 1.

Another possibility, described in section 3.2, is to derive g as the outcome of a model using latent and infectious times and constant infectivity during the infectious period. In such models g can, according to (3.4), be represented as the difference between two functions which are both either decreasing or increasing.

First observe that if g is a decreasing function there will always exist a model with no latent time and constant infectivity under the infectious time that generates this generation time density. The density of the infectious time equals $-g'(t)/g(0)$.

If g is a non-decreasing function it can always be represented as the difference between two decreasing functions. If furthermore $g(0) = 0$ we can construct an X (i.e. the random latent time), and a Y (i.e. the random infectious time) which gives the basic generation density g. The construction is built on the representation:

$$g(t) = -\int_t^\infty \mathrm{I}(g'(s) > 0)g'(s)ds - \int_t^\infty \mathrm{I}(g'(s) < 0)g'(s)ds. \tag{4.1}$$

If $g(0) = 0$ then $\int_0^\infty \mathrm{I}(g'(s) > 0)g'(s)ds = -\int_0^\infty \mathrm{I}(g'(s) < 0)g'(s)ds$. Let Z be a random variable such that

$$\mathrm{P}(Z > t) = \frac{-\int_t^\infty \mathrm{I}(g'(s) < 0)g'(s)ds}{\int_0^\infty \mathrm{I}(g'(s) > 0)g'(s)ds}, \tag{4.2}$$

and X a random variable such that

$$\mathrm{P}(X > t) = \frac{\int_t^\infty \mathrm{I}(g'(s) > 0) g'(s) ds}{\int_0^\infty \mathrm{I}(g'(s) > 0) g'(s) ds}. \tag{4.3}$$

The random variable Z is stochastically larger than X. Thus there exist a random variable Y such that $Z = X + Y$. We may then regard X as the duration of the latent period and Y as the duration of the infectious period. Here

$$\mathrm{E}(Y) = \frac{1}{\int_0^\infty \mathrm{I}(g'(s) > 0) g'(s) ds}. \tag{4.4}$$

With this construction we cannot be sure that the latent and infectious times are independent. To investigate if and when this is possible we will use arguments involving Laplace transforms.

Let

$$L_g = \int_0^\infty e^{-tr} g(t) dt \tag{4.5}$$

be the Laplace transform of the basic generation density. If we have a model as described in section 3.2 where X and Y are independent then

$$L_g(r) = M(r) \frac{1 - L(r)}{r\mathrm{E}(Y)}, \tag{4.6}$$

where M is the Laplace transform of X, i.e. the latent time, and L is the Laplace transform of Y, i.e. the infectious time.

Now $(1 - L(r))/(r\mathrm{E}(Y))$ is the Laplace transform of a decreasing density function. From this we can conclude that a basic generation time density g can be obtained from a model with independent latent and infectious times if and only if the density g, can be obtained as a convolution between two densities where at least one is decreasing. It is worth observing that there are densities that cannot be represented in this way. This is true e.g. for indecomposable densities. One such example is the Beta-distribution with $m + n < 2$. Such densities cannot be the result of assumptions as in section 3.2 (see e.g. Linnik et al (1977)).

In case L_g can be divided into two components where $\tilde{G}$ is the density of the second decreasing component then the infectious period can be modelled as having the density $-\tilde{G}'(t)/\tilde{G}(0)$ and the latent period having the density of the other component.

There may be several models with independent latent and infectious times that result in the same generation time density. A simple example is if X

is exponential distributed with mean γ and Y is exponentially distributed with mean μ. The same generation time distribution is obtained if X is exponentially distributed with mean μ and Y exponentially distributed with mean γ. Due to the fact that an exponential distribution has a decreasing density for any model where the latent and infectious times are assumed to be independent and the latent time is exponential distributed there exists another model, with independent latent and infectious times where the infectious time is exponential distributed, with the same basic generation time density.

4.1 Two examples

4.1.1 Exponentially distributed latent and infectious times

An often used assumption is that the latent and infectious times are independent and exponential distributed. This may be unrealistic for most known infections but has the advantage that it makes the mathematical calculations rather easy. Assume that the latent time, $X \sim \exp(\gamma)$ and the infectious times $Y \sim \exp(\mu)$. Then

$$g(t) = \frac{\gamma\mu}{\gamma - \mu}(\exp(-\mu t) - \exp(-\gamma t)) \tag{4.7}$$

$$G(t) = 1 - \frac{\gamma}{\gamma - \mu}\exp(-\mu t) + \frac{\mu}{\gamma - \mu}\exp(-\gamma t). \tag{4.8}$$

Observe that the functions are symmetric in γ and μ, and the same generation time density holds if the parameters are interchanged. Together with the value of the basic reproduction number, R_0, the pair (γ, μ) defines the model.

Elementary calculations yield

$$T_0 = \frac{1}{\gamma} + \frac{1}{\mu}. \tag{4.9}$$

The variance function defined by (2.6) will not be symmetric in γ and μ.

$$\begin{aligned} V(t) &= 1 + \frac{2\gamma\mu}{(\gamma - \mu)^2}(\exp(-\mu t) - \exp(-\gamma t)) \\ &\quad -(\frac{\gamma}{\gamma - \mu}\exp(-\mu t) - \frac{\mu}{\gamma - \mu}\exp(-\gamma t))^2 - 2t\frac{\gamma\mu}{\gamma - \mu}\exp(-\mu t). \end{aligned} \tag{4.10}$$

If the values of γ and μ are interchanged $V(t)$ will be larger for all $0 < t < \infty$ if $\mu < \gamma$. Regardless of γ and μ

$$V_0 = 1. \tag{4.11}$$

4.1.2 Gamma-distributed latent and infectious times

Assume that the latent time, X, is Gamma-distributed, $\Gamma(r, \gamma)$ and the infectious time, Y is Gamma-distributed, $\Gamma(s, \gamma)$. This implies that $\mathrm{E}(X) = r/\gamma$ and $\mathrm{E}(Y) = s/\gamma$. The generation time density is given by the simple relation (3.4). This function will have a rather complicated expression. In this model

$$T_0 = \frac{r}{\gamma} + \frac{s+1}{2\gamma}, \tag{4.12}$$

and

$$V_0 = \frac{1}{s}. \tag{4.13}$$

Simple manipulation yields that the same generation time distribution is obtained if Y is exponential distributed with intensity γ and X has the distribution given as an equal mixture of the s Gamma-distributions $\Gamma(r, \gamma)$, $\ldots$, $\Gamma(r + s - 1, \gamma)$. Since the generation time density is the same we also have the same mean generation time, T_0. However the variability is different and in this case

$$V_0 = 1. \tag{4.14}$$

5 The epidemic curve

The epidemic curve is described by a counting process, N, where $N(t)$ is the number of infected individuals up till time t. For the stochastic construction of this counting process and related martingales see appendix A.

Let K_i, $i = 0, \ldots, n$ be a sequence of contact distribution functions and λ_i the corresponding infectivities. Here K_i is the contact distribution function of the i'th infected and K_0 the contact distribution function of the individual which introduce the infection into the population. Let κ_i, $i = 0, \ldots, n$ be the corresponding densities. Now $N(t)$ is a counting process with intensity

$$\eta(t) = (1 - N(t-)/n) \left(\int_0^t \lambda_{N(u)} \kappa_{N(u)}(t-u) dN(u) + \lambda_0 \kappa_0(t) \right). \tag{5.1}$$

By subtracting the integrated intensity from the counting process we obtain a martingale:

$$N(t) - \int_0^t \eta(s) ds. \tag{5.2}$$

Another martingale, which has an essential role in the study of the epidemic is

$$M(t) = \int_0^t \frac{dN(s)}{1 - N(s-)/n} - \int_0^t \lambda_{N(s)} K_{N(s)}(t-s) dN(s) - \lambda_0 K_0(t). \tag{5.3}$$

The first integral is a straight-forward function of the $N(t)$. Observe that the second integral equals the integral of $\int_0^s \lambda_{N(u)} \kappa_{N(u)}(s-u) dN(u)$ between 0 and t.

Considering the quadratic variation process, $[M](t)$ we find that

$$\mathrm{Var}(M(t)) = \mathrm{E}\left(\int_0^t \frac{dN(s)}{(1 - N(s-)/n)^2} \right). \tag{5.4}$$

We will also study the process that arise when the random functions $\lambda_i \kappa_i(s)$ are substituted by their expectations, $R_0 g(t)$, (see the definition (2.3)).

$$Z(t) = \int_0^t \frac{dN(s)}{1 - N(s-)/n} - R_0 \left(\int_0^t G(t-s) dN(s) + G(t) \right). \tag{5.5}$$

In appendix A it is proved that

$$\mathrm{E}(Z(t)) = 0, \tag{5.6}$$

and

$$\mathrm{Var}(Z(t)) = \mathrm{E}\left(\int_0^t \frac{dN(s)}{(1 - N(s-)/n)^2} + R_0^2 (\int_0^t V(t-s) dN(s) + V(t)) \right). \tag{5.7}$$

If $f(s)$ be a non-random continuous function

$$\begin{aligned} M_f(t) &= \int_0^t f(s) \frac{dN(s)}{1 - N(s-)/n} \\ &\quad - \int_0^t f(s) \int_0^s \lambda_{N(s)} \kappa_{N(s)}(s-u) dN(u) ds - \lambda_0 \int_0^t f(s) \kappa_0(s) ds \end{aligned} \tag{5.8}$$

is a martingale with mean 0. With the same substitution as above we obtain the new process

$$\begin{aligned} Z_f(t) &= \int_0^t \frac{f(s)dN(s)}{1-N(s-)/n} \\ &\quad -R_0\left(\int_0^t f(s)\int_0^s g(s-u)dN(u)ds + \int_0^t f(s)g(s)ds\right). \end{aligned} \tag{5.9}$$

In appendix A it is proved that

$$\mathrm{E}(Z_f(t)) = 0. \tag{5.10}$$

We will be interested in processes, $Z_{f_r}(t)$, with $f_r(s) = \exp(-rs)$. We find that

$$\begin{aligned} Z_{f_r}(t) &= \int_0^t \frac{\exp(-rs)dN(s)}{1-N(s-)/n} \\ &\quad -R_0\left(\int_0^t \exp(-ru)H_r(t-u)dN(u) + H_r(t)\right), \end{aligned} \tag{5.11}$$

where

$$H_r(t) = \int_0^t \exp(-rs)g(s)ds. \tag{5.12}$$

We find that

$$H_r(\infty) = \int_0^\infty \exp(-rs)g(s)ds = L_g(r) \tag{5.13}$$

as a function of r is the Laplace transform of the generation time density. Thus

$$\begin{aligned} Z_{f_r}(\infty) &= \int_0^\infty e^{-rt}\frac{dN(t)}{1-N(t-)/n} \\ &\quad -R_0\left(\int_0^\infty e^{-rs}dN(s) + 1\right)L_g(r) \end{aligned} \tag{5.14}$$

Another interesting process is $Z_f(t)$ with $f(s) = s$,

$$\begin{aligned} Z_f(t) &= \int_0^t \frac{s dN(s)}{1 - N(s-)/n} \\ &\quad -R_0 \left(\int_0^t J(t-u)N(u) + \int_0^t uG(t-u)dN(u) + J(t) \right), \end{aligned} \tag{5.15}$$

where

$$J(t) = \int_0^t sg(s)ds. \tag{5.16}$$

Here

$$J(\infty) = \int_0^\infty tg(s)ds = T_0, \tag{5.17}$$

is the mean generation time. It follows that

$$\begin{aligned} Z_f(\infty) &= \int_0^\infty t \frac{dN(t)}{1 - N(t-)/n} \\ &\quad -R_0 \left((N(\infty) + 1)T_0 + \int_0^\infty t dN(t) \right). \end{aligned} \tag{5.18}$$

6 Properties of the epidemic curve

In this section we discuss some elementary properties of the epidemic process modelled as above and study how they are related to the assumptions of the model.

We will focus the interest on epidemics with large outbreaks, i.e., where the infection is spread to an non-negligible positive proportion of the population. There is a positive probability that the epidemic never takes on, i.e. stops with only a few infected persons. Let δ be the probability of a large outbreak. If $L_\lambda(s) = \mathrm{E}(\exp(-\lambda s))$ is the Laplace transform of λ then δ is the largest solution of the equation:

$$1 - \delta = L_\lambda(\delta). \tag{6.1}$$

This follows since the epidemic curve initially behaves like a branching process since then almost all contacts will be taken to susceptible persons. The probability for extinction of a branching process depends on the generating function of the number of offspring (here possible infectious contacts) (see

e.g. Haccou et al (2005)). The generating function equals $L_\lambda(1-s)$. Equation (6.1) always has the solution $\delta = 0$. A positive solution exists if and only if $R_0 > 1$.

Figure 6 gives examples of epidemic curves corresponding to large outbreaks. The curves are generated by simulating outcomes of an epidemic model. The generation time density used is of the kind described in section 4.1.1 with the latent time exponentially distributed with mean 1 and the infectious time exponentially distributed with mean 2. The expected lengths of the periods roughly corresponds to what is assumed in studies of the spread of influenza if the time unit is days. The simulations are made with the basic reproduction number, $R_0 = 2$. The epidemic curves differ but they share some features. In the initial phase the epidemics increases at an exponential rate and finally the curves level out by approaching approximately the same level.

We denote the proportion of the population that is infected through the epidemic by $\hat{\pi} = N(\infty)/n$. A well-known relation (see Andersson et al (2000)) is

$$-\ln(1-\hat{\pi}) - R_0\hat{\pi} \to 0, \tag{6.2}$$

as $n \to \infty$.

It should be observed that both the probability of a large outbreak and the final size of a large epidemic only depend on the distribution of λ and not on the basic generation time density. Heuristically, we can understand that these features are not related to time.

In contrast, the speed at which the epidemic grows will depend on the times between primary and secondary infections. At the start the epidemic process can be approximated by a branching process. Such processes have been thoroughly studied and much is known of their probabilistic behaviour. These results may be transferred to the initial behaviour of the epidemic curve.

A basic result is that the epidemic curve increases at exponential rate, i.e., $N(t)$ is in the initial phase proportional to $\exp(rt)$ (see Haccou et al (2005) and Kimmel et al (2002)). A more exact result is that $N(t)$ grows as $W\exp(rt)$ where W is a random variable and r is a constant. The Malthus parameter, r, can be found as the solution to the Euler-Lotka equation:

$$R_0 \int_0^\infty \exp(-rt)g(t)dt = 1. \tag{6.3}$$

Observe that the Malthus parameter depends on both the basic generation time density and on the basic reproduction number, R_0. In the study of epidemics the doubling time of the epidemic, D, i.e. the time it takes for

the number of infected to double, are often used instead of the Malthus parameter. There is a relation between these two numbers,

$$D = \frac{\ln(2)}{r}. \tag{6.4}$$

After the initial phase comes a period in which a non-negative proportion of the population has been infected. During the most intense phase there will be a large number of infectious persons, spreading the infection and a large number of persons still susceptible.

7 Nonparametric estimates

We will consider the possibilities to estimate basic parameters of the model. The estimates will be based on one observation of an entire epidemic curve. If the outbreak stopped with only a small number of infected it would not be possible to obtain any reasonable good estimates. For this reason we will only consider epidemics which grows large. We will use moment estimators suggested by the relation (5.10) based on $Z_f(\infty)$ (see (5.9)) for different choices of f.

7.1 Estimate of R_0

An obvious estimate of the basic reproduction number is the solution to the equation (6.2).

$$\tilde{R}_0 = \frac{-\ln(1-\hat{\pi})}{\hat{\pi}}, \tag{7.1}$$

where $\hat{\pi} = N(\infty)/n$.

Another approach is to use the function $Z(t)$ defined by (5.5) at $t = \infty$ to motivate the moment estimator

$$\hat{R}_0 = \frac{\int_0^\infty \frac{dN(s)}{1-N(s-)/n}}{N(\infty)+1}. \tag{7.2}$$

The two estimates, $\tilde{R}_0$ and $\hat{R}_0$ are asymptotically equivalent since

$$\frac{1}{n}\int_0^t \frac{dN(s)}{1-N(s-)/n} \approx -\ln(1-N(t)/n) \tag{7.3}$$

if $N(t)$ and n are large.

From (5.7) it follows that an estimate of the variance of the estimator is

$$\frac{1}{(N(\infty)+1)^2}\int_0^\infty \frac{dN(s)}{(1-N(s-)/n)^2} + \frac{R_0^2 V_0}{N(\infty)+1}. \tag{7.4}$$

An asymptotically equivalent expression is

$$\frac{1}{n\hat{\pi}}\left(\frac{1}{1-\hat{\pi}} + R_0^2 V_0\right) \tag{7.5}$$

To calculate the variance we will need to know or have an estimate of $R_0^2 V_0 = \mathrm{Var}(\lambda)$.

7.2 Estimates of the generation time distribution and related parameters

We can find an estimate of, $L_g(r)$, i.e. the Laplace transform of the generation time density using the process defined by (5.11). A moment estimator can be derived from the equation (5.14)

$$\hat{L}_g(r) = \frac{\int_0^\infty e^{-rt}\frac{dN(t)}{1-N(t-)/n}}{\hat{R}_0\left(\int_0^\infty e^{-rt}dN(t)+1\right)}. \tag{7.6}$$

This is the same relation that is derived in Kermack et al. (1927).

Since there is a one-to-one relation between a function and its Laplace transform we may find an estimate of g by inverting the estimated Laplace transform. However, it is not trivial to invert the Laplace transform. The inverse uses the entire estimated function and we cannot expect the estimate to be very precise for all r. The estimate for large values of r will mainly depend on the first few times of infections which of course will be very random.

The Malthusian parameter can be estimated with $\hat{r}$, defined by the relation

$$\hat{R}_0\hat{L}_g(\hat{r}) = 1. \tag{7.7}$$

In figure 7.2 it is the intersection between the horizontal line and the estimated function.

7.3 Estimate of T_0

We can use the estimate of the Laplace transform to estimate the mean the generation time distribution. T_0 equals minus the derivative of the Laplace

transform at $r = 0$. An alternative derivation of (an identical estimate) is obtained by using the process defined by (5.15). The moment estimator based on (5.18) is

$$\hat{T}_0 = \frac{\int_0^\infty tdN(t)/(1 - N(t-)/n) - \hat{R}_0 \int_0^\infty tdN(t)}{\int_0^\infty dN(t)/(1 - N(t-)/n)}. \tag{7.8}$$

7.4 Examples of estimation in some simulations

To illustrate the nonparametric estimates of R_0, T_0, and r, 1000 simulations for each of five models where performed. In all cases the population size are $n = 1000$, and the basic reproduction number $R_0 = 2$. The first model assumes that there is no variation in individual infectivity and in models 2–6 different assumptions regarding the latent and infectious periods are made.

Model 1: The generation time distribution is assumed to be non-random, i.e., the same for all individuals and $g(t) = \frac{\gamma\mu}{\gamma-\mu}(\exp(-\mu t) - \exp(\gamma t))$ where $\gamma = 1$ and $\mu = 2$. This generation time density gives $T_0 = 3$ and $r = 0.281$. Since the model is non-random $V_0 = 0$.

Model 2: It is assumed that latent and infectious times, X and Y, are independent, and that X is exponential distributed with mean 1 and Y exponential with mean 2. This results in the same generation time density as in model 1. In this model $V_0 = 1$.

Model 3: It is assumed that latent and infectious times, X and Y, are independent, and that X is exponential distributed with mean 2 and Y exponential with mean 1. This results, as pointed out above, in the same generation time density as in model 2 and consequently in model 1. In this model $V_0 = 1$.

Model 4: It is assumed that latent and infectious times, X and Y, are independent, and that X is $\Gamma(2, 4)$-distributed and Y is $\Gamma(2, 0.6)$-distributed. Some calculations yield that this model gives the same mean generation time, T_0 and the same Malthusian parameter r as the first three models. In this model $V_0 = 1/2$.

Model 5: It is assumed that latent and infectious times, X and Y are independent, and that X is $\Gamma(1, 1)$-distributed, i.e X is exponential distributed with mean 1, and $Y$is $\Gamma(2, 1)$-distributed. In this model $V_0 = 1/2$.

Table 1: Results from 1000 simulations of model 1, with $n = 1000$.

Parameter	True value	mean	sd	mean of estimated sd
R_0	2	1.993	0.0792	0.0774
T_0	3	2.913	0.276	0.285
r	0.281	0.311	0.046	-

Table 2: Results from 1000 simulations of model 2, with $n = 1000$.

Parameter	True value	mean	sd	mean of estimated sd
R_0	2	2.000	0.109	0.106
T_0	3	2.924	0.367	0.388
r	0.281	0.334	0.060	-

Model 6: It is assumed that latent and infectious times, X and Y are independent, and that X is an even mixture of an $\Gamma(1, 1)$-distribution and a $\Gamma(2, 1)$-distribution. Y is is exponential distributed with mean 1. This model has the same basic generation time density as model 5 (see section 4.1.2). In this model $V_0 = 1$.

For each of the 1000 simulated epidemic curves estimates of R_0, T_0, and r were calculated as well as estimates of variances of $\hat{R}_0$ and $\hat{T}_0$. With the exception of the model in which it is assumed that the generation density is non-random the underlying model has to be known in order to estimate the variances of the estimates. The tables give the means of the estimates and their empirical standard deviations. For the basic reproduction number and the mean generation times also the mean of the estimated standard deviations are given. They illustrate that single realizations of an epidemic curve can give valid information of the amount of variation that can be expected. It

Table 3: Results from 1000 simulations of model 3, with $n = 1000$.

Parameter	True value	mean	sd	mean of estimated sd
R_0	2	1.997	0.109	0.106
T_0	3	2.933	0.390	0.389
r	0.281	0.330	0.067	-

Table 4: Results from 1000 simulations of model 4, with $n = 1000$.

Parameter	True value	mean	sd	mean of estimated sd
R_0	2	1.995	0.100	0.093
T_0	3	2.937	0.341	0.344
r	0.281	0.318	0.049	-

Table 5: Results from 1000 simulations of model 5, with $n = 1000$.

Parameter	True value	mean	sd	mean of estimated sd
R_0	2	1.999	0.094	0.093
T_0	2.5	2.440	0.279	0.281
r	0.325	0.372	0.064	-

Table 6: Results from 1000 simulations of model 6, with $n = 1000$.

Parameter	True value	mean	sd	mean of estimated sd
R_0	2	1.999	0.110	0.106
T_0	2.5	2.445	0.320	0.319
r	0.325	0.387	0.075	-

Table 7: Mean ratio between sources of variability in the 1000 simulated epidemics

Model	R_0	T_0
1	0	0
2	0.82	0.84
3	0.82	0.85
4	0.41	0.43
5	0.41	0.44
6	0.82	0.84

is also seen, comparing the results for models 1–3 and models 5 and 6 that models with the same generation time density can generate epidemic curves with different variability.

From the tables it is seen that the estimates of R_0 and T_0 are close to their true values and that the estimates of their precisions made from the individual realizations are close to the variation between realisations. However, the suggested estimate of the Malthusian parameter seems to be biased and tend to overestimate the true value of the parameter.

As is seen in the derivations in appendix B the variability of the estimates comes from two sources. There is one part of the variability that comes, loosely speaking, from the Poisson processes generating the contacts and there is another variability that comes from variation in individual infectious functions. This is clearly illustrated by the expression of the asymptotic variance of the estimate of the basic reproduction number given by (7.5). The first gives approximately the contribution $1/(\pi(1-\pi))$ and the other $R_0^2 V_0/\pi$. If n is large and $R_0 = 2$ equation (6.2) will give $\pi \approx 0.80$.

In table 7 the mean ratio between the two sources of variation for the epidemic curves simulated from models 3–6 are given. For R_0 these ratio should equal $(1-\pi)R_0^2 V_0 \approx 0.8/s$, where s is the value of the shape parameter of the Gamma-distribution for the infectious time.

8 Some remarks

We have studied the behaviour of epidemics simulated from models were the assumptions involve strong stochastic elements. It turns out that some of the most obvious features of the epidemic curve from an epidemic that grows large depend on means. The basic reproduction number and the generation

time density decides the final proportion of infected in the population and the initial rate of increase of the number of infected. Both these entities are derived as means of individual random properties of infected individuals.

The same basic reproduction number and generation time density can be the result of different models. Even if these means are identical the processes are different. In this paper we have illustrated the differences by calculating variability of estimates of R_0 and T_0 for different models. More generally models will differ with respect to the variability around a "mean epidemic curve". It should be possible to study this variability if the generation time density could be estimated with sufficient precision. This could possible be done, more easily, if the models considered are restricted, e.g. by using a parametric model for the contact distribution functions.

Another conclusion from the analysis above is that in some cases variability between different realizations of the same process can be estimated with data from a single realization. This is, of course, due to the fact that a single epidemic curve is the result of a large number of realizations of independent random variables, even if they are not observed individually. However, it is to be expected that there are strong limits to how much one epidemic curve discloses of these variables. This is a question that remains to be studied.

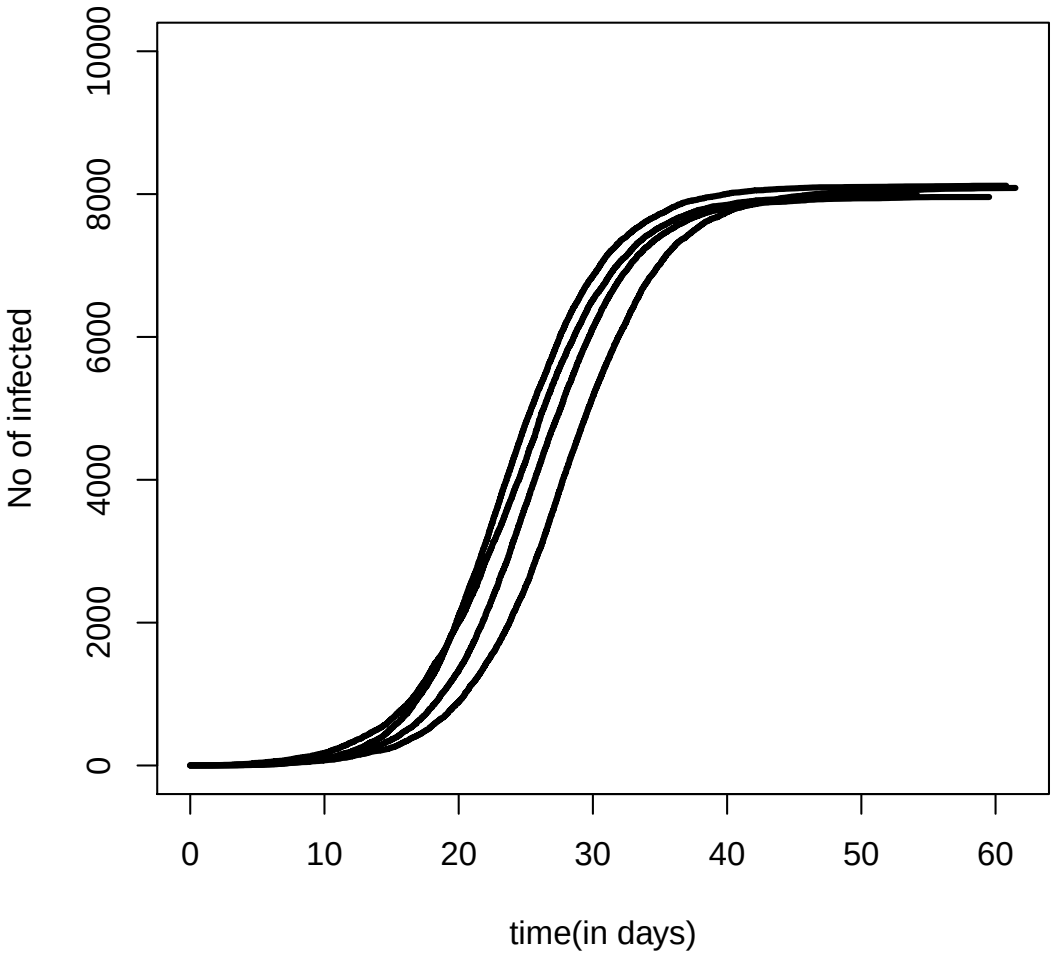

Figure 6.1: Four epidemic curves simulated from the same model. The right end of the curves indicate the last time of infection. The population size is 10,000 and $R_0 = 2$.

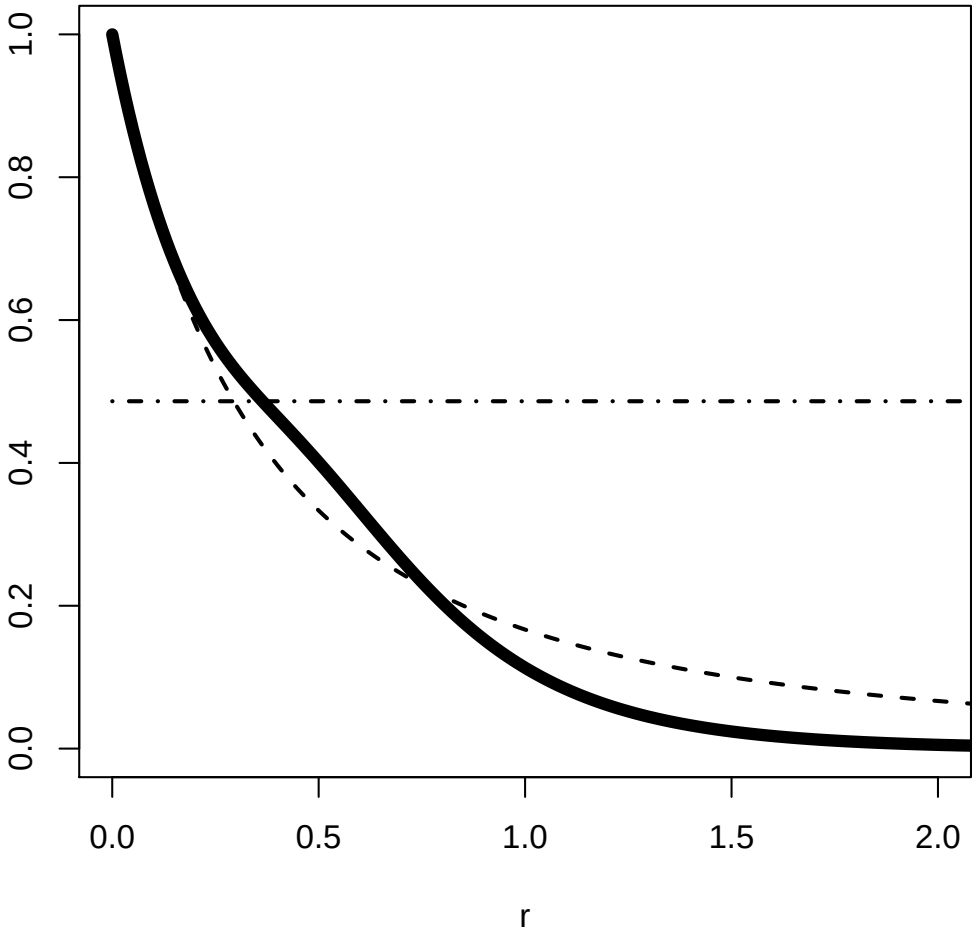

Figure 7.1: Estimated Laplace transforms of the basic generation timed estimated from a simulated epidemic curve. Dashed line is the true transform and the dotted line represents $1/\tilde{R}_0$.

A Appendix A

The processes studied in this paper can be constructed in the following way. The random elements $(\lambda_0, K_0), (\lambda_1, K_1), \ldots, (\lambda_n, K_n)$ are assumed to be measurable relative to $\mathcal{F}_0$. The pairs are assumed to be independent. Here λ_i, $i = 0, \ldots, n$, are non-negative real numbers and K_i, $i = 0, \ldots, n$, are distribution functions with support on $[0, \infty[$, i.e., $K_i(s) = 0$ when $s < 0$. The distributions K_i are assumed to have densities κ_i.

A counting process N is adopted to the filtration $\{\mathcal{F}\}_{t=0}^{\infty}$ and has the predictable intensity function $\eta(t)$ given by (5.1). Let $\tau_1, \ldots, \tau_n$ be the jump times of the process where $\tau_0 = 0$ and $\tau_m = \infty$ if $t > N(\infty)$. Typically the filtration is a history of the process N including the random elements that describes the infectivities of the infected.

It is convenient to use the representation

$$\eta(t) = (1 - N(t-)/n) \sum_{i=0}^{n} \lambda_i \kappa_i (t - \tau_i). \tag{A.1}$$

The martingale M defined by (5.3) can be written as

$$M(t) = \int_0^t \frac{dN(s)}{1 - N(s-)/n} - \sum_{i=0}^{n} \lambda_i K_i (t - \tau_i). \tag{A.2}$$

Let

$$A_i(t) = \lambda_i K_i(t) - R_0 G(t). \tag{A.3}$$

According to the definition (see (2.4)) of the basic generation time distribution, G, we have

$$\mathrm{E}(A_i(t)) = 0. \tag{A.4}$$

It follows that

$$\mathrm{E}(\sum_{i=0}^{n} A_i(t - \tau_i)) = \sum_{i=0}^{n} \mathrm{E}(A_i(t - \tau_i)) = \sum_{i=0}^{n} \mathrm{E}(\mathrm{E}(A_i(t - \tau_i) \mid \tau_i) = 0. \tag{A.5}$$

The process Z defined by (5.5) can be written

$$Z(t) = M(t) - \sum_{i=0}^{n} A_i(t - \tau_i). \tag{A.6}$$

Since $\mathrm{E}(M(t)) = 0$ (5.6) it follows that

$$\mathrm{E}(Z(t)) = 0. \tag{A.7}$$

To find an expression of the variance function of Z we first observe that,

$$\begin{aligned} \mathrm{Var}(\sum_{i=0}^{n} A_i(t-\tau_i)) &= \mathrm{E}\left(\mathrm{Var}\sum_{i=0}^{n} A_i(t-\tau_i) \mid \tau_0,\ldots,\tau_n\right) \\ &= \sum_{i=0}^{n} R_0^2 \mathrm{E}\left(V(t-\tau_i)\right) \\ &= R_0^2\left(\mathrm{E}\left(\int_0^t V(t-u)dN(u)\right) + V(t)\right), \end{aligned} \tag{A.8}$$

where the function V is defined by (2.6).

Also, since $\mathrm{E}(M(t)) = 0$ and

$$\begin{aligned} \mathrm{Cov}(M(t), \sum_{i=0}^{n} A_i(t-\tau_i)) &= \sum_{i=0}^{n} \mathrm{E}(M(t)A_i(t-\tau_i)) \\ &= \sum_{i=0}^{n} \mathrm{E}(\mathrm{E}(M(t)A_i(t-\tau_i) \mid \mathcal{F}_{\tau_i}) \\ &= \sum_{i=0}^{n} \mathrm{E}(M(\tau_i)A_i(t-\tau_i)) = 0. \end{aligned} \tag{A.9}$$

The last sum equals 0 since the martingale M is independent of A_i up till the jump time τ_i.

The martingale M has the quadratic variation

$$[M](t) = \int_0^t \frac{dN(s)}{/(1-N(s-)/n)^2}.$$

Thus (5.7) holds, i.e.

$$\mathrm{Var}(Z(t)) = \mathrm{E}([M](t)) + \mathrm{Var}(\sum_{i=0}^{n} A_i(t-\tau_i)). \tag{A.10}$$

The process Z_f defined by (5.9) can be analysed in a similar way. We can write

$$Z_f(t) = M_f(t) - \sum_{i=0}^{n} B_i(t,\tau_i). \tag{A.11}$$

Here

$$B_i(t,\tau_i) = \int_0^t f(s)\left(\lambda_i\kappa_i(s-\tau_i) - R_0 g(s-\tau_i)\right) ds. \tag{A.12}$$

With arguments analogous to the ones used above we can prove that

$$\mathrm{E}(B_i(t,\tau_i) = \mathrm{E}\left(\mathrm{E}(B_i(t,\tau_i) \mid \tau_i\right) = 0. \tag{A.13}$$

From this follows (5.10), i.e. $\mathrm{E}(Z_f(t)) = 0$. We can also derive an expression of the variance

$$\mathrm{Var}(Z_f(t)) = \mathrm{E}([M_f](t)) + \mathrm{Var}(\sum_{i=0}^{n} B_i(t,\tau_i)). \tag{A.14}$$

B Appendix B

In this appendix we will derive approximate expression for the variances of the nonparametric estimates of R_0 and T_0.

First we discuss estimates of R_0 defined by equation (7.2). We can write

$$\begin{aligned}(N(\infty)+1)\left(\hat{R}_0 - R_0\right) &= \left(\int_0^\infty \frac{dN(t)}{1-N(t-)/n} - \sum_{i=0}^{N(\infty)} \lambda_i\right) \\ &\quad + \left(\sum_{i=0}^{N(\infty)} \lambda_i - (N(\infty)+1)R_0\right)\end{aligned} \tag{B.1}$$

According to (A.10) and (5.7) with $t = \infty$ the variance of this expression can be estimated by

$$\int_0^\infty \frac{dN(t)}{(1-N(t-)/n)^2} + (N(\infty)+1)\mathrm{Var}(\lambda) \tag{B.2}$$

Thus the variance of $\hat{R}_0$ can be approximated by

$$\frac{1}{N(\infty)+1}\left(\frac{\int_0^\infty \frac{dN(t)}{(1-N(t-)/n)^2}}{N(\infty)+1} + \mathrm{Var}(\lambda)\right) \tag{B.3}$$

The discussion of estimates of T_0 will be restricted to the two types of models described in section 3. For the estimator $\hat{T}_0$ defined by (7.8) we obtain

$$\int_0^\infty \frac{dN(t)}{1-N(t-)/n}\left(\hat{T}_0 - T_0\right) = W_1 + W_2 - W_3 - W_4, \tag{B.4}$$

where

$$W_1 = \int_0^\infty \frac{tdN(t)}{1 - N(t-)/n} - \sum_{i=0}^{N(\infty)} \lambda_i \int_0^\infty t\kappa_i(t - \tau_i),$$

$$W_2 = \sum_{i=0}^{N(\infty)} \lambda_i \int_0^\infty t\kappa_i(t - \tau_i) - R_0 \sum_{i=0}^{N(\infty)} \int_0^\infty tg(t - \tau_i),$$

$$W_3 = \left(\int_0^\infty \frac{dN(t)}{1 - N(t-)/n} - \sum_{i=0}^{N(\infty)} \lambda_i \right) \left(\frac{\sum_{i=0}^{N(\infty)} \int_0^\infty tg(t - \tau_i)}{N(\infty) + 1} \right),$$

and

$$W_4 = \left(\sum_{i=0}^{N(\infty)} \lambda_i - (N(\infty) + 1)R_0 \right) \left(\frac{\sum_{i=0}^{N(\infty)} \int_0^\infty tg(t - \tau_i)}{N(\infty) + 1} \right).$$

Let

$$Q = \frac{\sum_{i=0}^{N(\infty)} \int_0^\infty tg(t - \tau_i)}{N(\infty) + 1} = T_0 + \frac{\int_0^\infty tdN(t)}{N(\infty) + 1}. \tag{B.5}$$

If we for the moment treat Q as asymptotically constant as $n \to \infty$ we see that W_1 and W_3 are martingales and W_2 and W_4 conditionally on the jump times only depends on the pairs (λ_i, κ_i). For the same reason as above this implies that $W_1 - W_3$ and $W_2 - W_4$ are uncorrelated. The variance of $W_1 - W_3$ can be estimated by

$$\int_0^\infty \frac{t^2 dN(t)}{(1 - N(t-)/n)^2} + Q^2 \int_0^\infty \frac{dN(t)}{(1 - N(t-)/n)^2} - 2Q \int_0^\infty \frac{tdN(t)}{(1 - N(t-)/n)^2}. \tag{B.6}$$

This will be an estimate of the variance of $\int_0^\infty \frac{dN(t)}{1-N(t-)/n} \left(\hat{T}_0 - T_0 \right)$ if there is no randomness in the pairs (λ_i, κ_i). If this is not the case we have to consider also the variance of $W_2 - W_4$. We will now derive an estimate in the case where we have random and independent latent and infectious times and a constant infectivity during the infectious period. This is the kind of model described in section 3.2. First we find that

$$\lambda_i \int_0^\infty t\kappa_i(t - \tau_i) = \alpha \int_0^\infty t\mathrm{I}(X_i < t - \tau_i < X_i + Y_i)dt = \alpha \left(X_i Y_i + Y_i^2/2 + Y_i \tau_i \right), \tag{B.7}$$

and

$$\lambda_i = \alpha Y_i. \tag{B.8}$$

Thus the variance of $W_2 - W_4$ can be estimated by

$$\alpha^2 \sum_{i=0}^{N(\infty)} \mathrm{Var}(X_i Y_i + Y_i^2/2 + Y_i \tau_i) + Q^2 \mathrm{Var}(Y_i) \\ -2Q\mathrm{Cov}(X_i Y_i + Y_i^2/2 + Y_i \tau_i, Y_i)). \tag{B.9}$$

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