

# Chapter 10

## Distribution Theory, Stochastic Processes and Infectious Disease Modelling

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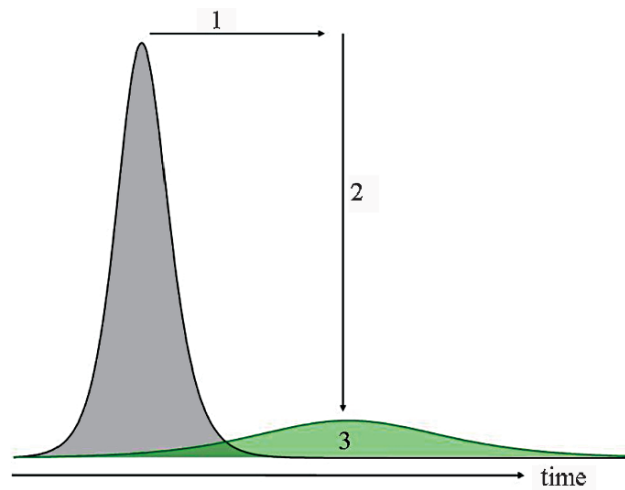
**Abstract** The occurrence of a major outbreak, the shape of the epidemic curves, as well as the final sizes of outbreaks, are realizations of some stochastic events with some *probability distributions*. These distributions are manifested through some *stochastic mechanisms*. This chapter divides a typical outbreak in a closed population into two phases, the initial phase and beyond the initial phase. For the initial phase, this chapter addresses several aspects: the invasion (i.e. the risk of a large outbreak); quantities associated with a small outbreak; and characteristics of a large outbreak. In a large outbreak beyond the initial phase, the focus is on its final size. After a review of distribution theories and stochastic processes, this chapter separately addresses each of these issues by asking questions such as: Are the latent period and/or the infectious period distributions playing any role? What is the role of the contact process for this issue? Is the basic reproduction number  $R_0$  sufficient to address this issue? How many *stochastic mechanisms* may manifest observations that may resemble a power-law distribution, and how much detail is really needed to address this specific issue? etc. This chapter uses distribution theory and stochastic processes to capture the agent–host–environment interface during an outbreak of an infectious disease. With different phases of an outbreak and special issues in mind, modellers need to choose which detailed aspects of the distributions and the stochastic mechanisms need to be included, and which detailed aspects need to be ignored. With these discussions, this chapter provides some syntheses for the concepts and models discussed in some preceding chapters, as well as some food for thought for following chapters on case studies.

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## 10.1 Introduction

This chapter limits the discussions to human–human transmission through direct contacts involving an agent (e.g. virus, bacteria, etc.) in a closed population. The *agent* has biological characteristics. The human *hosts* may differ in susceptibility. The *environment* is where contacts and transmissions take place. One wishes to control the outbreak aimed at preventing a large outbreak from happening. Should it happen, the number of individuals who are infectious at time  $t$  can be approximated by a curve, either symmetrical or slightly negatively skewed, like that illustrated in Fig. 10.1.



**Fig. 10.1** Schematic illustration of the three objectives

Further public health objectives include:

1. Reducing the initial growth of the curve (and delaying the peak)
2. Reducing the peak burden
3. Reducing the final size, defined as the total number of individuals or the proportion of individuals in the population that will be eventually infected by the end of the outbreak.

Brauer [1] (Chap. 2 of this book) discussed the initial growth rate and the maximum value of  $I(t)$  for the number of infectious individuals at time  $t$  in a compartment model. The final size of an outbreak was not only discussed in deterministic compartment models, but also by Allen [2] (Chap. 3 of this book) with respect to stochastic models. These concepts are also embedded in network models introduced by Brauer [3] in Chap. 4 of this book.

## 10.2 A Review of Some Probability Theory and Stochastic Processes

### 10.2.1 Non-negative Random Variables and Their Distributions

#### 10.2.1.1 The Distribution Functions, the Expectation (Mean) and the Variance

Most random variables in this chapter, discrete or continuous, take non-negative values  $X \geq 0$ . The expected (mean) value and variance are denoted by  $E[X]$  and  $var[X]$ . The cumulative distribution function (c.d.f.) is denoted by  $F_X(x) = \Pr\{X < x\}$  satisfying  $F_X(0) = 0$ , monotonically increasing, and  $F_X(\infty) = 1$ . The survivor function is  $\bar{F}_X(x) = 1 - F_X(x) = \Pr\{X \geq x\}$ . The lower case  $f_X(x)$  is used for the probability density function (p.d.f.)  $f_X(x) = -\frac{d}{dx}\bar{F}_X(x) = \lim_{\delta \rightarrow 0} \frac{\Pr\{x \leq X < x+\delta\}}{\delta}$  if  $X$  is absolutely continuous; and for the probability mass function (p.m.f.)  $f_X(x) = \bar{F}_X(x) - \bar{F}_X(x+1) = \Pr\{X = x\}$  if  $X$  is discrete taking values  $x = 0, 1, 2, \dots$ .  $f_X(x)$  satisfies (1)  $f_X(x) > 0$ ; (2)  $\sum_{x=0}^{\infty} f_X(x) = 1$  for discrete and  $\int_0^{\infty} f_X(x)dx = 1$  for continuous random variable  $X$ .

It can be shown that when  $X \geq 0$ ,

$$E[X] = \begin{cases} \sum_{x=0}^{\infty} \bar{F}_X(x), & \text{if } X \text{ discrete,} \\ \int_0^{\infty} \bar{F}_X(x)dx, & \text{if } X \text{ continuous.} \end{cases} \quad (10.1)$$

#### 10.2.1.2 The Probability Generating Function (p.g.f.)

If  $X$  is discrete taking values  $x = 0, 1, 2, \dots$ , the probability generating function, as previously introduced in Allen [2] and Brauer [3], is a mathematical tool to study its distribution. It is defined as

$$G_X(s) = E(s^X) = \sum_{x=0}^{\infty} s^x \Pr\{X = x\}, \quad (10.2)$$

satisfying

$$G_X(0) = \Pr\{X = 0\}, G_X(1) = 1, G'_X(s) > 0, G''_X(s) > 0. \quad (10.3)$$

If the p.m.f.  $f(x) = \Pr\{X = x\}$  is given,  $G_X(s)$  is uniquely defined through (10.2). If  $G_X(s)$  is given, provided that it is a smooth function of  $s$  with higher order of derivatives, then

$$\Pr\{X = x\} = \frac{1}{x!} G_X^{(x)}(0), \quad x = 0, 1, 2, \dots \quad (10.4)$$

where  $G_X^{(x)}(0) = \frac{d^x}{ds^x} G_X(s)|_{s=0}$ , so that the p.m.f.  $f(x)$  can be uniquely generated through  $G_X(s)$ . Calculations of moments and of some probabilities are very easy. The mean and variance of  $X$  are

$$\begin{aligned} E[X] &= G_X'(1), \\ \text{var}[X] &= G_X''(1) + G_X'(1) - (G_X'(1))^2. \end{aligned} \quad (10.5)$$

### 10.2.1.3 The Hazard Function

If  $X$  is continuous, the hazard function,  $h_X(x) \stackrel{\text{def.}}{=} \lim_{\delta \rightarrow 0} \frac{\Pr\{x \leq X < x + \delta | X \geq x\}}{\delta}$  uniquely determines the distribution of  $X$ , through the relationships  $f_X(x) = h_X(x)\bar{F}_X(x)$  and  $\bar{F}_X(x) = \exp(-\int_0^x h_X(u)du)$ . The shape of  $h_X(x)$  can be used to define and classify families of continuous distributions for  $X$ . Some commonly considered candidates are:

1. Constant:  $h_X(x) = \alpha$
2.  $\lim_{x \rightarrow \infty} h_X(x) = \alpha$ , but  $h_X(x)$  is monotone, either increasing or decreasing
3. Monotone with  $\lim_{x \rightarrow \infty} h_X(x) = \begin{cases} \infty, & \text{if increasing} \\ 0, & \text{if decreasing} \end{cases}$
4. Non-monotone:  $h_X(x)$  initially increases to a maximum value and then decreases with  $\lim_{x \rightarrow \infty} h_X(x) = 0$ .

In the first case when  $h_X(x) = \alpha$ ,  $\bar{F}_X(x) = \exp(-\alpha x)$  and  $f_X(x) = \alpha \exp(-\alpha x)$ . This gives the exponential distribution.  $\alpha$  is often called *rate*. If  $X$  represents the infectious period in a Susceptible-Infective-Removed (SIR) model,  $\alpha$  is often referred to as the removal rate. The second equation in (2.1) of Brauer [1] is a special case of a more general equation

$$\begin{aligned} \frac{d}{dt} I(t) &= i(t) - \int_0^t i(s) f_X(t-s) ds \\ &= i(t) - \int_0^t i(s) h_X(t-s) \bar{F}_X(t-s) ds \end{aligned} \quad (10.6)$$

where the special case is  $h_X(x) = \alpha$  and  $\bar{F}_X(x) = \exp(-\alpha x)$  such that  $\frac{d}{dt} I(t) = i(t) - \alpha \int_0^t i(s) e^{-\alpha(t-s)} ds$ . Note that  $I(t) = \int_0^t i(s) e^{-\alpha(t-s)} ds$ , because  $\int_0^t i(s) e^{-\alpha(t-s)} ds = \int_0^t i(s) \Pr\{X > t-s\} ds$  is the number of individuals infected before  $t$  who have not yet been removed. If one further assumes  $i(t) = \beta I(t) S(t)$ , then (10.6) reduces to  $I' = (\beta S - \alpha) I$  which is (2.1) of Brauer [1]. In addition, the exponential distribution has memoryless property:  $\Pr\{X > x+y | X > x\} = \frac{\exp(-\alpha(x+y))}{\exp(-\alpha x)} = \exp(-\alpha y)$ . For  $X$  with exponential distribution, the rate is reciprocal to the mean duration:  $E[X] = \frac{1}{\alpha}$ .

The exponentially distributed infectious period is the underlying assumption in the continuous time Markov chain model in Allen [2].

In the second case  $\lim_{x \rightarrow \infty} h_X(x) = \alpha$ , a commonly used model is the gamma distribution with p.d.f.

$$f_X(x) = \frac{\alpha(\alpha x)^{\kappa-1}}{\Gamma(\kappa)} e^{-\alpha x} \quad (10.7)$$

and survivor function  $\bar{F}_X(x) = \frac{\alpha^\kappa}{\Gamma(\kappa)} \int_x^\infty u^{\kappa-1} e^{-\alpha u} du$ , where  $\alpha$  is a scale parameter.  $\kappa$  is the shape parameter that determines the shape of the hazard function. When  $\kappa > 1$ , the hazard is an increasing function of  $x$  and when  $\kappa < 1$ , a decreasing function of  $x$ . When  $\kappa = 1$ , it is the exponential distribution. It can be shown that for any  $\kappa > 0$ ,  $h_X(x) = \frac{f_X(x)}{\bar{F}_X(x)} \rightarrow \alpha$  as  $x \rightarrow \infty$ .

In the third case, the monotone hazard function satisfies  $\lim_{x \rightarrow \infty} h_X(x) = \infty$ , if increasing, and  $\lim_{x \rightarrow \infty} h_X(x) = 0$ , if decreasing. A common choice is  $h_X(x) = \beta \alpha^\beta x^{\beta-1}$ , a power function of  $x$  such that when  $\beta = 1$ ,  $h_X(x) = \alpha$ ; when  $\beta > 1$ ,  $h_X(x)$  is an increasing function of  $x$  and when  $\beta < 1$ ,  $h_X(x)$  is a decreasing function of  $x$ .  $\beta$  is the shape parameter that determines the shape of the hazard function. The corresponding p.d.f. and the survivor function are  $f_X(x) = \beta \alpha (\alpha x)^{\beta-1} e^{-(\alpha x)^\beta}$  and  $\bar{F}_X(x) = e^{-(\alpha x)^\beta}$ .  $\alpha$  is a scale parameter. This is the Weibull distribution.

Of non-monotone hazard functions that initially increase to a maximum value and then decrease with  $\lim_{x \rightarrow \infty} h(x) = 0$ , there are two commonly used distributions in the literature: the log-normal distribution with p.d.f.  $f_X(x) = \frac{\theta}{x\sqrt{2\pi}} e^{-\frac{\theta^2(\log \alpha x)^2}{2}}$  and the log-logistic distribution with p.d.f.  $f_X(x) = \frac{\alpha\theta(\alpha x)^{\theta-1}}{(1+(\alpha x)^\theta)^2}$ . In both distributions  $\alpha$  is a scale parameter and  $\theta$  is the shape parameter.

Another continuous distribution for  $X$  used in this chapter is the Pareto distribution with hazard function  $h_X(x) = \frac{\alpha\kappa}{1+\alpha x}$  which is monotonically decreasing  $\lim_{x \rightarrow \infty} h_X(x) = 0$ . It has p.d.f.  $f_X(x) = \frac{\kappa\alpha}{(1+\alpha x)^{\kappa+1}}$  and survivor function  $\bar{F}_X(x) = \frac{1}{(1+\alpha x)^\kappa}$ .

### 10.2.1.4 The Laplace Transform

For a non-negative continuous random variable  $X$ , it is sometimes convenient to work with the Laplace transforms

$$\mathcal{L}_X(r) = \int_0^\infty e^{-rx} f_X(x) dx,$$

and its related function  $\mathcal{L}_X^*(r) = \int_0^\infty e^{-rx} \overline{F}_X(x) dx = \frac{1-\mathcal{L}(r)}{r}$ , provided that they exist. As a function of  $r$ , the following statements hold:

- $\lim_{r \rightarrow 0} \mathcal{L}_X^*(r) = \int_0^\infty \overline{F}_X(x) dx = E[X]$
- $\mathcal{L}_X^*(r)$  is monotonically decreasing
- $\lim_{r \rightarrow \infty} \mathcal{L}_X^*(r) = 0$

### 10.2.2 Some Important Discrete Random Variables Representing Count Numbers

#### 10.2.2.1 The Random Number Associated with the Basic Reproduction Number $R_0$

Let us call an *infectious contact* a contact at which transmission takes place [4]. We use the notation  $N$  for a discrete valued random variable, defined as

$N$  = the number of infectious contacts made by an infective individual, throughout its entire infectious period, in a wholly susceptible population.

The expected value of  $N$  is the basic reproduction number  $R_0 = E[N]$ . Uncertainties are captured by  $var[N]$  as well as the probability distribution  $\Pr\{N = x\}$ ,  $x = 0, 1, 2, \dots$ . Some public health questions can be sufficiently addressed by  $R_0 = E[N]$  alone. Some other public health questions can be addressed by the first two moments:  $E[N]$  and  $var[N]$ . For some questions, one needs to know the precise distribution for  $N$ . However, there are many other important public health issues that are not addressed by the distribution  $N$ . The distribution for  $N$  may arise from a combination of the following stochastic mechanisms:

1. The contact network structure and stochastic features that give rise to the contact process
2. The individual (host) properties that determine transmissibility per contact, such as host susceptibility
3. The probability distributions of durations of time-to-events, such as the infectious period.

The same probability distribution  $\Pr\{N = x\}$  can arise from different stochastic mechanisms. For some public health questions, different stochastic mechanisms may give different answers, even if the probability distribution  $\Pr\{N = x\}$  is the same. For some other public health aspects, different distributions for  $\Pr\{N = x\}$  may give the same answer as long as certain aspects of the underlying stochastic mechanisms remain the same.

### 10.2.2.2 Discrete Random Numbers Associated with the *Final Size of an Outbreak*

Calendar time is denoted by  $t$ . At  $t = 0$ , there are  $S_0$  initial susceptible individuals and  $I_0$  initial infectious individuals in a closed population. The population size  $n = S_0 + I_0$ .  $S_0$  and  $I_0$  are fixed integers. Under the assumption  $\frac{S_0}{n} \approx 1$  (i.e.  $S_0$  is very large) and  $\frac{I_0}{n} = \varepsilon \approx 0$  (i.e.  $I_0$  is very small), if infective cases are removed at the end of their infectious period by recovery with immunity, or by complete isolation through intervention, or death, there may be a proportion of susceptible individuals that eventually escape from infection when the outbreak is over. The following pair of quantities are random:

- $S_\infty$  = the total number of susceptible individuals who have escaped from infection in the population
- $Z = n - S_\infty$  = the final size, with a probability distribution  $\Pr\{Z = z\}$ ,  $z = 1, 2, \dots$

Diekmann and Heesterbeek [5] describe the distinction of a *small* outbreak from a *large* outbreak. Using the random variable  $Z$ ,

*Small outbreak.* As  $n \rightarrow \infty$ , the infectious agent produces a handful of cases and the outbreak becomes extinct, such that the expected number of cases,  $E[Z]$ , remains finite. The expected outbreak size as a proportion,  $\frac{E[Z]}{n}$ , is concentrated at zero.

*Large outbreak.* As  $n \rightarrow \infty$ , the final outbreak size as a proportion is a positive quantity, such that the expected final outbreak size number scales linearly with the size of the susceptible population. In other words,  $E[Z] \rightarrow \infty$  but  $\frac{E[Z]}{n} \rightarrow \eta$  where  $\eta$  is a positive quantity,  $0 < \eta < 1$ .

There are occasions that  $E[Z] \rightarrow \infty$  but  $\frac{E[Z]}{n} \rightarrow 0$  (e.g., in the order  $\sim n^{\frac{2}{3}}$ ). In other words, although the final size as a proportion (scaled to the population size  $n$ ) is concentrated at zero, the final outbreak size as absolute numbers can be very large. In this case, the outbreak size is neither small, nor large.

### 10.2.2.3 The Time-to-Extinction of a Small Outbreak

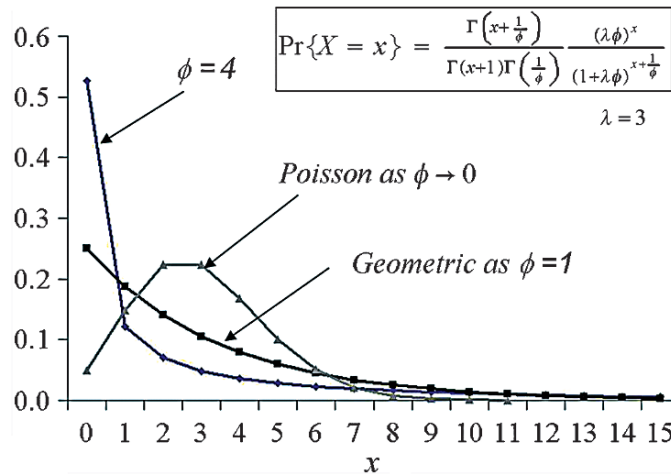
A random variable  $T_g$  is defined as the time to extinction **at** generation  $g = 1, 2, 3, \dots$ , where the event  $\{T_g = g\}$  refers to {no infected case at generation  $g$  and at least one infected case at generation  $g-1$ }. The generation time  $g$  is different from the calendar time  $t$ . In certain situations, observations arising from an outbreak can be identified by generation time.

### 10.2.2.4 Three Commonly Used Discrete Distributions

Allen [2] used p.g.f. to determine the probability of extinction in the context of *branching processes*. Brauer [3] reviewed the use of p.g.f. to characterize and calculate *degree distributions* with respect to the spread of diseases over contact networks. In this chapter, p.g.f. will be used to generate the distributions for  $N$  which is related to the basic reproduction number  $R_0$ , to derive probability distributions for the final size  $\Pr\{Z = z\}$  in small outbreaks, and where possible, to derive the probability  $\Pr\{T_g = g\}$ .

**Table 10.1** Three discrete distributions frequently used in this chapter

	$f_X(x)$	$G_X(s)$	$E[X]$	$var[X]$
Poisson	$\frac{\lambda^x}{x!} e^{-\lambda}$	$e^{-\lambda(1-s)}$	$\lambda$	$\lambda$
Geometric	$\frac{\lambda^x}{(1+\lambda)^{x+1}}$	$\frac{1}{1+\lambda(1-s)}$	$\lambda$	$\lambda^2 + \lambda$
Neg. binomial	$\frac{\Gamma(x+\frac{1}{\phi})}{\Gamma(x+1)\Gamma(\frac{1}{\phi})} \frac{(\lambda\phi)^x}{(1+\lambda\phi)^{x+\frac{1}{\phi}}}$	$\frac{1}{[1+\lambda\phi(1-s)]^{\frac{1}{\phi}}}$	$\lambda$	$\phi\lambda^2 + \lambda$



**Fig. 10.2** Comparing the negative binomial distributions at  $\lambda = 3$

We use the notation  $X$  which could be  $N$ ,  $Z$  or  $T_g$  depending on context. Table 10.1 lists three commonly referred discrete distributions in this chapter. In discrete distributions,  $f_X(x) = F_X(x + 1) - F_X(x)$ . The shapes of  $f_X(x)$  for these distributions are compared in Fig. 10.2. The Poisson distribution is a special case of the negative binomial distribution as  $\phi \rightarrow 0$ ; the geometric distribution is a special case of the negative binomial distribution as  $\phi = 1$ .



### 10.2.3 Continuous Random Variables Representing Time-to-Event Durations

In models involving a sequence of events, one may treat each pair of successive events as an *initiating event* that leads to a *subsequent event* over a random duration  $X \geq 0$ . Durations can be categorized by: (1) the natural history of infectiousness of an infected individual (e.g. latent and infectious periods); (2) the natural history of clinical manifestation (e.g. incubation period and duration of illness); and (3) the reaction time of the public health system (e.g. time to detect an infection or to isolate an infectious individual).

**Table 10.2** Some common durations in infectious disease models

Initiating event	Subsequent event	Duration $X$
Infection of a virus	Becoming infectious	Latent period
Becoming infectious	Removal	Infectious period
Infection of a virus	Onset of symptoms	Incubation period
Infection of a virus	First positive test (diagnosis)	Time to testing
Diagnosis	Starting treatment	Time to treatment
Diagnosis	Isolation	Time to isolation

Models are often developed along the event history based on one or a combination of the three categories. For example, models based on the natural history of infectiousness of an infected host might be a deterministic or stochastic SIR or a Susceptible-Latent-Infective-Removed (SEIR) model, like those discussed in previous chapters.

#### 10.2.3.1 Ordering and Tail Properties of Non-negative Continuous Random Variables

Very often one wants to compare two non-negative random variables  $X_1$  and  $X_2$ , either through some overall summary of their distributions, or through their tail properties. For notational simplicity, we write  $\bar{F}_1(x) = \bar{F}_{X_1}(x)$  and  $\bar{F}_2(x) = \bar{F}_{X_2}(x)$  hereafter.

**Definition 1.**  $X_2$  is longer than  $X_1$  in stochastic order, denoted by  $X_2 \geq_{st} X_1$ , if corresponding survivor functions  $\bar{F}_2(x) \geq \bar{F}_1(x)$  for all  $x$ .

In general,  $\bar{F}_2(x) \geq \bar{F}_1(x) \Rightarrow E[X_2] = \int_0^\infty \bar{F}_2(x) dx \geq E[X_1] = \int_0^\infty \bar{F}_1(x) dx$ . The reverse is not true for non-exponential distributions.

**Definition 2.**  $X_2$  is longer than  $X_1$  in hazard rate order, denoted by  $X_2 \geq_{hr} X_1$ , if corresponding hazard functions  $h_2(x) \leq h_1(x)$ , for all  $x > 0$ .

Note that  $X_2 \geq_{hr} X_1 \Rightarrow X_2 \geq_{st} X_1$ ,

**Definition 3.**  $X_2$  is longer than  $X_1$  in Laplace transform order, denoted by  $X_2 \geq_{\mathcal{L}} X_1$ , if  $\mathcal{L}_2^*(r) = \int_0^\infty e^{-rx} \overline{F}_2(x) dx \geq \mathcal{L}_1^*(r) = \int_0^\infty e^{-rx} \overline{F}_1(x) dx$ .

Note that for the Laplace transforms  $\mathcal{L}_2(r) = \int_0^\infty e^{-rx} f_2(x) dx$  and  $\mathcal{L}_1(r) = \int_0^\infty e^{-rx} f_1(x) dx$ ,  $X_2 \geq_{\mathcal{L}} X_1 \Leftrightarrow \mathcal{L}_2(r) \leq \mathcal{L}_1(r)$  since  $\mathcal{L}_X^*(r) = \frac{1 - \mathcal{L}_X(r)}{r}$ .

In the special case when  $X$  is exponentially distributed, with  $\mu_X = E[X]$ , the hazard function is  $h_X(x) = \frac{1}{\mu_X}$ ; the survivor function is  $\overline{F}_X(x) = e^{-\frac{x}{\mu_X}}$ ; and  $\mathcal{L}_X^*(r) = \frac{\mu_X}{1+r\mu_X}$ . If  $X_2$  and  $X_1$  are both exponentially distributed,  $X_2 \geq_{hr} X_1 \Leftrightarrow X_2 \geq_{st} X_1 \Leftrightarrow X_2 \geq_{\mathcal{L}} X_1 \Leftrightarrow E[X_2] \geq E[X_1]$ . In general,

$$X_2 \geq_{hr} X_1 \Rightarrow X_2 \geq_{st} X_1 \Rightarrow X_2 \geq_{\mathcal{L}} X_1. \tag{10.8}$$

Another stochastic property used in this chapter is the relationship between the hazard function and the tail properties of randomly distributed durations. Denote  $X_s = (X - s | X > s)$  as the *residual life* of a duration  $X$  conditioning on  $X > s$ . If  $X$  stands for the infectious period, then  $X_s$  stands for the time remaining to be infectious, after  $s$  amount of time since the beginning of the infectious period. Thus

$$\Pr\{X_s > x\} = \Pr\{X > s + x | X > s\} = \frac{\overline{F}_X(s+x)}{\overline{F}_X(s)}$$

is the survivor function of  $X_s$ . Given the hazard function  $h_X(x)$ , it can be shown that  $\frac{\overline{F}_X(s+x)}{\overline{F}_X(s)} = \exp\left(-\int_s^{s+x} h_X(u) du\right)$ . This leads to:

1. If  $h_X(x)$  is strictly increasing with  $h_X(x) \rightarrow \infty$ , then  $\frac{\overline{F}_X(s+x)}{\overline{F}_X(s)}$  is a decreasing function of  $s$ ,  $\lim_{s \rightarrow \infty} \frac{\overline{F}_X(s+x)}{\overline{F}_X(s)} = 0$ , for any  $x > 0$ .
2. If there exists  $x_0 \geq 0$  such that for  $x > x_0$ ,  $h_X(x)$  is a decreasing function of  $x$  with  $\lim_{x \rightarrow \infty} h_X(x) = 0$ , then

$$\lim_{s \rightarrow \infty} \frac{\overline{F}_X(s+x)}{\overline{F}_X(s)} = 1, \text{ for any } x > 0. \tag{10.9}$$

The distribution is said to be *heavy tailed* if it satisfies (10.9). Intuitively, if  $X$  ever exceeds a large value, then it is just as likely to exceed any larger value.

3. If  $h_X(x) \rightarrow \alpha$ , the distribution has *exponential tail*

$$\lim_{s \rightarrow \infty} \frac{\overline{F}_X(s+x)}{\overline{F}_X(s)} = e^{-\alpha x}, \text{ for any } x > 0. \tag{10.10}$$

4. A distribution is *sub-exponential*, if  $\lim_{x \rightarrow \infty} \frac{\bar{F}_X(x)}{\exp(-\alpha x)} = \infty$ , implying that it has a heavier tail (goes to zero more slowly) than an exponential tail. All heavy tailed distributions are also sub-exponential.

Another form of heavy tailed distribution is that of the *Pareto form*, such that for some  $\theta > 0$ ,  $A > 0$ ,  $\lim_{x \rightarrow \infty} \frac{\bar{F}_X(x)}{x^{\theta+1}} = A$ . They are heavy tailed with *power-law* property  $\propto \frac{1}{x^{\theta+1}}$ .

**Table 10.3** Comparison of hazard functions and tail properties

	p.d.f. $f_X(x)$	Hazard $h_X(x)$	$\Pr\{X_s > x\}, x > 0$
Exponential	$\alpha e^{-\alpha x}$	Constant $\alpha$	$\frac{F_X(s+x)}{F_X(s)} = e^{-\alpha x}$ (exponential)
Gamma	$\frac{\alpha(\alpha x)^{\kappa-1}}{\Gamma(\kappa)} e^{-\alpha x}$	Converge $h(x) \rightarrow \alpha$	$\lim_{s \rightarrow \infty} \frac{F_X(s+x)}{F_X(s)} = e^{-\alpha x}$ (exponential)
Weibull (if $\beta < 1$ )	$\beta \alpha^\beta x^{\beta-1} e^{-(x\alpha)^\beta}$	$h(x) \downarrow 0$	$\lim_{s \rightarrow \infty} e^{\alpha^\theta (s^\theta - (s+x)^\theta)} = 1$ (heavy, not power-law)
Log-logistic	$\frac{\alpha\theta(\alpha x)^{\theta-1}}{(1+(\alpha x)^\theta)^2}$	$h(x) \downarrow 0$ After $x > x_0$	$\lim_{s \rightarrow \infty} \frac{1+(\alpha x)^\theta}{1+(\alpha(x+y))^\theta} = 1$ (heavy, not power-law)
Log-normal	$\frac{\theta}{x\sqrt{2\pi}} e^{-\frac{\theta^2(\log \alpha x)^2}{2}}$	$h(x) \downarrow 0$ After $x > x_0$	$\lim_{s \rightarrow \infty} \frac{F_X(s+x)}{F_X(s)} = 1$ (heavy, not power-law)
Pareto	$\frac{\kappa\alpha}{(1+\alpha x)^{\kappa+1}}$	$h(x) = \frac{\alpha\kappa}{1+\alpha x} \downarrow 0$	$\lim_{s \rightarrow \infty} \frac{(s\alpha+1)^\kappa}{(s\alpha+x\alpha+1)^\kappa} = 1$ (heavy and power-law)

### 10.2.4 Mixture of Distributions

In a heterogenous population an individual  $i$  is associated with a random variable  $X_i$  following a distribution with p.m.f. or p.d.f.  $f(x|\theta_i)$  specified up to a parameter  $\theta_i$ . If the heterogeneity can be observed through a vector of covariates  $\underline{z}$ , say, such as gender, birth date, height, etc., a common practice in statistics is to model  $\theta_i$  as a function of  $\underline{z}$  via a generalized linear model  $\eta(\theta_i) = \beta_1 z_1 + \beta_2 z_2 + \dots + \beta_q z_q$ , where  $\eta(\cdot)$  is a link function such that  $-\infty < \eta(\theta_i) < \infty$ .

If the heterogeneity is not observable, one assumes that  $\theta_i$  varies among individuals as independently and identically distributed (i.i.d.) random variables with expectation  $E_\theta[\cdot]$  such that at the population level, one may model  $X$  arising from a distribution given by

$$f_X(x) = E_\theta [f(x|\theta)] = \int_{\theta \in \Theta} f(x|\theta) dU(\theta),$$

where  $U(\theta)$  is a c.d.f. of the mixing distribution.

*Example 1.* Each individual is associated with an infectious period with a constant removal rate  $\lambda_i$ , and  $\lambda_i$  itself varies across individuals. Then at the individual level, this leads to an exponentially distributed infectious period with p.d.f.  $f(x|\lambda_i) = \lambda_i e^{-\lambda_i x}$ . If  $\lambda_i$  has a gamma distribution with p.d.f.  $u(\lambda) = \frac{\lambda^{\kappa-1}}{\alpha^\kappa \Gamma(\kappa)} e^{-\lambda/\alpha}$ , then the resulting distribution is the Pareto distribution with p.d.f.  $f_X(x) = \frac{\kappa\alpha}{(1+\alpha x)^{\kappa+1}}$ , survivor function  $\bar{F}_X(x) = \frac{1}{(1+\alpha x)^\kappa}$  and hazard function  $h_X(x) = \frac{\alpha\kappa}{1+x\alpha}$ .

There is often unobservable heterogeneity with respect to the infectious period, where *removal* can be due to deaths, recovery, or public health intervention such as isolation. By this example, even at the individual level it is justified to use an exponentially distributed infectious period with a removal rate  $\lambda_i$ , observed data from a population often arise as if the infectious period follows a distribution with a power-law heavy tail.

#### 10.2.4.1 Mixed Poisson Distributions

Mixed Poisson distributions play a central role in the chapter. It is constructed by  $f(x|\lambda) = \frac{\lambda^x}{x!} e^{-\lambda}$  and an arbitrary mixing distribution  $U(\lambda)$ . It is a discrete distribution with p.m.f. and p.g.f.

$$f_X(x) = \Pr\{X = x\} = \int_0^\infty \frac{\lambda^x}{x!} e^{-\lambda} dU(\lambda)$$

$$G_X(s) = \int_0^\infty e^{\lambda(s-1)} dU(\lambda) = E_\lambda \left[ e^{\lambda(s-1)} \right].$$

*Example 2.* In 1920, Greenwood and Yule [6] derived the negative binomial distribution as a mixed Poisson distribution. The mixing distribution is a gamma distribution with p.d.f.  $u(\lambda) = \frac{1}{\phi\mu\Gamma(\frac{1}{\phi})} \left(\frac{\lambda}{\phi\mu}\right)^{\frac{1}{\phi}-1} e^{-\frac{\lambda}{\phi\mu}}$  with  $E[\lambda] = \mu$  and  $\text{var}[\lambda] = \phi\mu^2$ . The p.m.f. of the mixed Poisson distribution is

$$f_X(x) = \Pr\{X = x\} = \frac{\Gamma\left(x + \frac{1}{\phi}\right)}{\Gamma(1+x)\Gamma\left(\frac{1}{\phi}\right)} \frac{(\phi\mu)^x}{(1+\phi\mu)^{x+\frac{1}{\phi}}} \quad (10.11)$$

and p.g.f.  $G_X(s) = \frac{1}{[1+\phi\mu(1-s)]^{\frac{1}{\phi}}}$ . The mean and variance is  $E[X] = \mu$  and  $\text{var}[X] = \phi\mu^2 + \mu$ . The special case when  $\phi = 1$  gives the exponential distribution for  $u(\lambda)$  and geometric distribution for  $\Pr\{X = x\}$ . The special case when  $\phi \rightarrow 0$  degenerates  $u(\lambda)$  to a fixed point and results in the Poisson distribution. Note that the p.d.f. of gamma distributions displayed in

Fig. 10.3 shows the remarkable resemblance of the p.m.f. to the negative binomial distributions in Fig. 10.2.

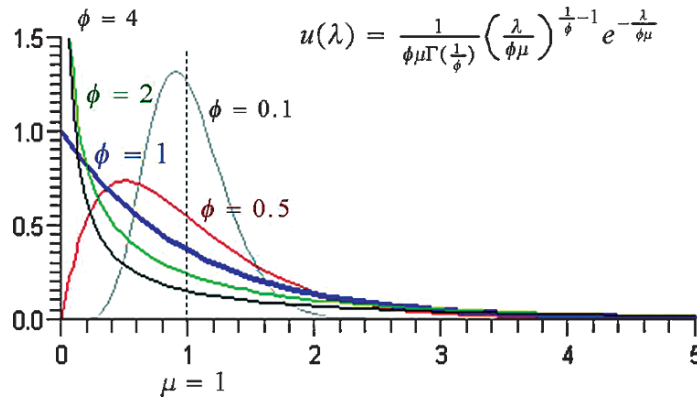


Fig. 10.3 P.d.f. for gamma distributions with  $\mu = 1$  and different  $\phi$  values

### 10.2.5 Stochastic Processes

A *stochastic process*  $\{X(t), t \in T\}$  is a collection of random variables. For each  $t$  in the index set  $T$ ,  $X(t)$  is a random variable. If  $t$  is referred to as time, then  $X(t)$  is the state of the process at time  $t$ . A realization of  $\{X(t), t \in T\}$  is called a *sample path*. This chapter is restricted to discrete, non-negative sample paths, that is, for given  $t$ ,  $X(t)$  is a non-negative discrete random variable taking values  $x = 0, 1, 2, \dots$ . The index  $t$  can be either discrete, or continuous. The distribution of  $X(t)$  for given  $t$  often depends on the past history of the process  $\mathcal{H}_t = \{X(u), 0 < u \leq t^-\}$ . The conditional probability  $\Pr\{X(t) = x | \mathcal{H}_t\}$  is meaningful.

If the conditional distribution of the future state at time  $t + s$ , given the present state at time  $s$  and all past states, depends only on the present state and is independent from the past, that is, for all continuous time  $s, t > 0$  and non-negative integers  $i, j$

$$\Pr\{X(t + s) = j | X(s) = i, \mathcal{H}_s\} = \Pr\{X(t + s) = j | X(s) = i\}, \quad (10.12)$$

we call it a *Markov process*. If, in addition,  $\Pr\{X(t + s) = j | X(s) = i\} = \Pr\{X(t) = j | X(0) = i\}$  is independent of  $s$ , then the stochastic process  $\{X(t)\}$  is a continuous time stationary Markov chain.

**10.2.5.1 Continuous Time Markov Chain SIR Model**

An SIR model can be expressed as a bivariate continuous time-homogeneous Markov chain  $\{S(t), I(t)\}$  as described in Allen [2]. At any given time  $t$ , both  $S(t)$  and  $I(t)$  take integer values. Transitions can only occur from  $\{S(t) = s, I(t) = i\}$  to  $\{S(t + \Delta t) = s - 1, I(t + \Delta t) = i + 1\}$  corresponding to a new infection, or from  $\{S(t) = s, I(t) = i\}$  to  $\{S(t + \Delta t) = s, I(t + \Delta t) = i - 1\}$  corresponding to a removal.

Let  $R(t)$  be the number of removed individuals at time  $t$ ;  $M(t) = I(t) + R(t)$  be the total number of infected individuals by time  $t$ ; and  $S(t) + I(t) + R(t) = n$ , assuming a closed population.  $\{R(t)\}$  and  $\{M(t)\}$  are also stochastic processes. Let  $H_t$  be the history of the epidemic process up to time  $t$ . Under the time stationary Markov chain assumption, the model in Allen [2] can be re-written as

$$\begin{cases} \Pr\{dM(t) = 1, dR(t) = 0|H_t\} \approx \beta \frac{S(t)}{n} I(t) dt, \\ \Pr\{dM(t) = 0, dR(t) = 1|H_t\} \approx \frac{1}{\mu} I(t) dt, \\ \Pr\{dM(t) = 0, dR(t) = 0|H_t\} \approx 1 - \beta \frac{S(t)}{n} I(t) dt - \frac{1}{\mu} I(t) dt. \end{cases} \tag{10.13}$$

Assuming the outbreak is originated from a single initial infective, the stochastic means follow the following renewal-type equations:  $E[M(t)] = 1 + \beta \int_0^t e^{-\frac{1}{\mu}x} E[M(t-x)] dx$ ,  $E[R(t)] = 1 - e^{-\frac{1}{\mu}t} + \beta \int_0^t e^{-\frac{1}{\mu}x} E[R(t-x)] dx$ . Therefore,

$$E[I(t)] = e^{-\frac{1}{\mu}t} + \beta \int_0^t e^{-\frac{1}{\mu}x} E[I(t-x)] dx \tag{10.14}$$

where  $I(t) = M(t) - R(t)$ . The first term  $e^{-\frac{1}{\mu}t}$  in (10.14) is the probability that the initial infective is still infectious at time  $t$  according to an exponentially distributed infectious period. With respect to the integration for the second term, during the interval  $(0, t]$  the initial infective makes many infectious contacts with a constant rate  $\beta$ , so that the expected number of infectious contacts at an infinitesimal interval containing  $x \in (0, t]$  is  $\beta e^{-\frac{1}{\mu}x}$ . The expected number of individuals who are still infectious at time  $t$  evolved from such contacts at  $x \in (0, t]$  is  $E[I(t-x)]$ . It can be shown that [7]

$$\frac{d}{dt} E[I(t)] = \left\{ \frac{\beta E[S(t)]}{n} - \frac{1}{\mu} \right\} E[I(t)] + \frac{\beta}{n} cov\{S(t), I(t)\} \tag{10.15}$$

where  $E[S(t)]$ ,  $E[I(t)]$  and  $cov\{S(t), I(t)\}$  are expected values for the random variables  $S(t)$  and  $I(t)$  as well as their covariance at fixed time  $t$ .

## Comparison with the Deterministic SIR Model

The deterministic counterpart of (10.13) is

$$\begin{cases} \frac{d}{dt}S(t) = -\beta\frac{S(t)}{n}I(t), \\ \frac{d}{dt}I(t) = \left\{\beta\frac{S(t)}{n} - \frac{1}{\mu}\right\}I(t). \end{cases} \quad (10.16)$$

The solution of the deterministic equations is not simply the mean of the stochastic process since the covariance term in (10.15) is ignored. Nevertheless, for a broad class of processes, the deterministic solution is a good approximation to the stochastic mean of a major outbreak when  $n$  is large.

Fig. 5.1 of Bailey [8],  $n=10$

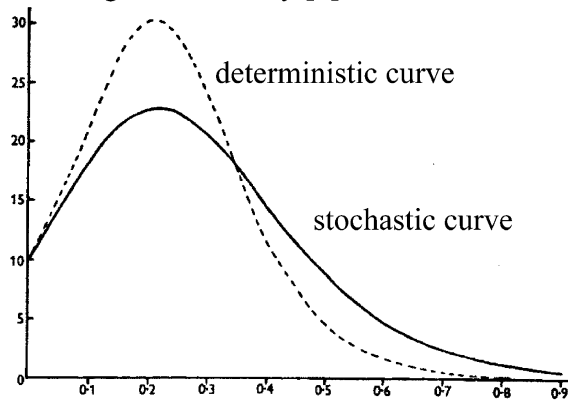
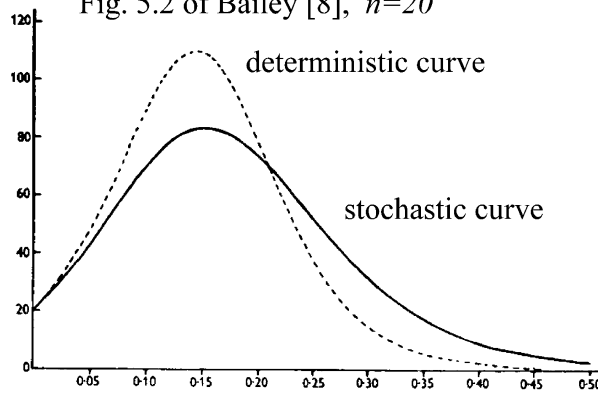


Fig. 5.2 of Bailey [8],  $n=20$



**Fig. 10.4**  $E[I(t)]$  by stochastic SIR model compared with its deterministic counterpart, from Bailey [8]

Bailey [8] gives a thorough discussion of the properties of deterministic and stochastic versions of the SIR model, along with comparisons of  $E[I(t)]$  (stochastic model) versus  $I(t)$  (deterministic model) for  $n = 10$  and  $n = 20$ . These are reproduced as Fig. 10.4.

### 10.2.5.2 Counting Processes

A *counting process*  $\{K(t), t \in [0, \infty)\}$  is a stochastic process with the meaning:

$$K(t) = \text{cumulative number of events by time } t.$$

$K(t)$  is a non-negative integer random variable for fixed time  $t$ , non-decreasing ( $K(s) \leq K(t)$ , if  $s < t$ ) and  $K(t) - K(s)$  equals the number of events in the interval  $(s, t]$ . For example,  $\{R(t)\}$  and  $\{M(t)\}$  in (10.13) are counting processes. The derivative  $\beta(x) = \frac{d}{dx}E[K(x)]$  is the *instantaneous increment* of the counting process  $\{K(x)\}$ . A counting process is said to have *independent increment*, if the numbers of events in disjoint intervals are independent. A counting process is said to have *stationary increment*, if the distribution of numbers of events that occur in any time interval depends only on the length of the time interval. For a stationary increment process,  $\beta(x) = \text{constant } \beta$ .

#### The Stationary Poisson Process

The stationary Poisson process is a counting process satisfying both the *independent increment* and the *stationary increment* properties. In addition, it satisfies  $K(0) = 0$ . It is also a stationary Markov chain with  $\Pr\{K(t + \Delta t) = k + 1 | K(t) = k, \mathcal{H}_t\} = \Pr\{K(\Delta t) = 1 | K(0) = 0\}$  such that  $\Pr\{K(\Delta t) = 1 | K(0) = 0\} = \lambda \Delta t + o(\Delta t)$ ,  $\Pr\{K(\Delta t) \geq 2 | K(0) = 0\} = o(\Delta t)$ , where  $\lambda$  is called the intensity of the process. It has the property

$$\Pr\{K(t + s) - K(s) = k\} = \Pr\{K(t) = k\} = \frac{(\lambda t)^k}{k!} e^{-\lambda t}$$

so that the number of events in an interval of length  $t$  is Poisson distributed with mean and variance  $E[K(t)] = \text{var}[K(t)] = \lambda t$ .

An important consequence of the *independent increment* and the *stationary increment* properties is that, if we denote  $X_1$  the time to the first event, and for  $k \geq 1$ ,  $X_k$  the time between the  $(k - 1)$ th and the  $k$ th events, then  $X_k : k = 1, 2, \dots$  are i.i.d. exponentially distributed random variables with mean  $\frac{1}{\lambda}$ .  $(X_1, X_2, \dots, X_k)$  are called *inter-arrival times* between events.

Let  $Y_1 = X_1, Y_2 = X_1 + X_2, \dots, Y_k = X_1 + X_2 + \dots + X_k$  denote the times that events occur, it can be further shown that, conditioning on  $K(t) = k$ , the  $k$  *arrival times* of events  $(Y_1, Y_2, \dots, Y_k)$  have the same distribution as the



order statistics corresponding to  $k$  independent uniformly distributed random variables on the interval  $(0, t)$ .

### Mixed Poisson Process

Analogue to the mixed Poisson distributions, if individual  $i$  is associated with a Poisson process with intensity  $\lambda_i$  which varies across individuals and if factors resulting in the heterogeneity cannot be observed or at present understood, one may consider a random variable  $\xi > 0$  with  $E[\xi] = \lambda$  and  $var[\xi] = \sigma > 0$ . This model is expressed by a conditional process  $\{K(t)|\xi\}$  and a marginal process  $\{K(t)\}$ .

At the individual level, the cumulative number of infectious contacts is the conditional process  $\{K(t)|\xi\}$  and is assumed to follow a Poisson process with intensity rate  $\xi$ . The mean and variance are

$$E[K(t)|\xi] = var[K(t)|\xi] = \xi t. \quad (10.17)$$

The process as seen at the cohort level is the marginal process  $\{K(t)\}$  and is a mixed Poisson process, of which, for given time  $t$ , the probability  $\Pr\{K(t) = k\}$  is

$$\Pr\{K(t) = k\} = \int_0^\infty \frac{(\xi t)^k}{k!} e^{-\xi t} dU(\xi). \quad (10.18)$$

For given  $t$ , one can write the p.g.f. for  $K(t)$  as

$$G_K(s, t) = \int_0^\infty e^{\xi t(s-1)} dU(\xi) = E_\xi[(e^{t(s-1)})^\xi]. \quad (10.19)$$

**Proposition 1.** *The mixed Poisson process  $\{K(t)\}$  is not a Poisson process. It preserves the stationary increment of the Poisson process, but loses the independent increment property.*

To show it is not a Poisson process, it is only necessary to notice that

$$\begin{aligned} E[K(t)] &= E\{E[K(t)|\xi]\} = \lambda x & (10.20) \\ var[K(t)] &= E\{var[K(t)|\xi]\} + var\{E[K(t)|\xi]\} \\ &= \lambda x + \sigma(\lambda x)^2 > E[K(t)]. \end{aligned}$$

To prove that  $\{K(t)\}$  does not have independent increment, one only needs to show that  $\Pr\{K(s) = k, K(s+t) - K(s) = l\} \neq \Pr\{K(s) = k\} \Pr\{K(s+t) - K(s) = l\}$ .

Unlike the Poisson process where  $E[X_1] = \frac{1}{\lambda}$ , in the mixed Poisson process,  $E[X_1] > \frac{1}{\lambda}$  as explained by Jensen's inequality,

$$E[X_1] = E\{E[X_1|\xi]\} = E\left[\frac{1}{\xi}\right] > \frac{1}{E[\xi]} = \frac{1}{\lambda}.$$

### 10.2.5.3 Branching Processes

Consider a population consisting of individuals or particles able to produce offspring of the same kind. Each individual  $i$  is associated with a generation time  $T_G$  and by the end of  $T_G$ , it produces a random number  $N_i$  of new offsprings. We use  $g = 0, 1, 2, \dots$  as the discrete time unit to represent generations. Let  $X_0$  be the number of individuals initially present at the zeroth generation. All offsprings of the zeroth generation constitute the first generation and their number is denoted by  $X_1$ . Let  $X_g$  denote the size of the  $g$ th generation. Given  $X_{g-1}$ , if the distribution of  $X_g$  only depends on  $X_{g-1}$ , then  $\{X_g\}$  is a discrete time Markov chain. This process  $\{X_g\}$  is called a branching process. Suppose that  $X_0 = 1$ , we can calculate

$$X_g = \sum_{i=0}^{X_{g-1}} N_i.$$

In most branching processes, it is assumed that  $N_i$  is i.i.d. according to a random variable  $N$  which does not vary over generations. We say a branching process becomes extinct at generation  $g$ , if  $X_{g-1} > 0$  but  $X_g = 0$ . In such case, we denote  $Z = \sum_g X_g$  as the final size upon extinction.

Branching processes are often used in infectious disease epidemiology to approximate the initial stage of an outbreak, where the depletion of the number of susceptible individuals is negligible. A discrete time branching process that is well studied in the literature is the Galton–Watson process.

*Galton–Watson process.* Each infected individual is associated with a fixed length of generation time  $T_G$ . At its end, this individual produces a random number of  $N$  secondary infections.

There are various types of continuous time branching processes.

*Bellman–Harris processes.* Infected individuals have independently and arbitrarily distributed generation time  $T_G$ . Each individual produces a random number of  $N$  secondary infections only at the end of the generation time.  $T_G$  and  $N$  are independent.

*Crump–Mode–Jagers (CMJ) processes.* Infected individuals have independently and arbitrarily distributed generation time  $T_G$ . Throughout the generation time, each individual produces secondary infections according to a counting process  $\{K(x)\}$ . Different individuals follow the same counting process. It is assumed that the generation time  $T_G$  and  $\{K(x)\}$  are independent. By the end of the generation time, an infected individual produces a random number of  $N$  secondary infections.

The CMJ processes have been used to approximate the early phase of the SIR models [9,10]), where the generation time  $T_G$  has the meaning of the infectious period.

In an SEIR model, let us denote  $T_E$  as the *latent period* during which an infected individual is unable to transmit the disease and  $T_I$  as the *infectious period* during which an infected individual is able to transmit the disease, and let  $T_G = T_E + T_I$ . If the infectious period degenerates to  $\mu = E[T_I] \rightarrow 0$ , such that by the end of the latent period, the infected individual instantly produces  $N$  new infections and is removed, then  $T_G = T_E$  and the branching process approximations are Bellman–Harris processes, including special cases (1) the Markov branching process assuming  $T_E$  is exponentially distributed; (2) the Galton–Watson process assuming  $T_E$  is non-random. If there is no latent period,  $T_G = T_I$ , the branching process approximations are CMJ processes. Therefore, we get:

*Combined Bellman–Harris–CMJ processes.*  $T_E$  and  $T_I$  are independent.  $T_E$  is random with an arbitrary but specified distribution. Only after  $T_E$  amount of time has elapsed, an infected individual can produce secondary infections according to a CMJ process.

In these branching processes, there is an embedded Galton–Watson branching process to track the generations. The basic reproduction number corresponds to the mean value of this embedded Galton–Watson branching process with  $R_0 = E[N]$ . A schematic illustration of these branching processes is given in Fig. 10.5.

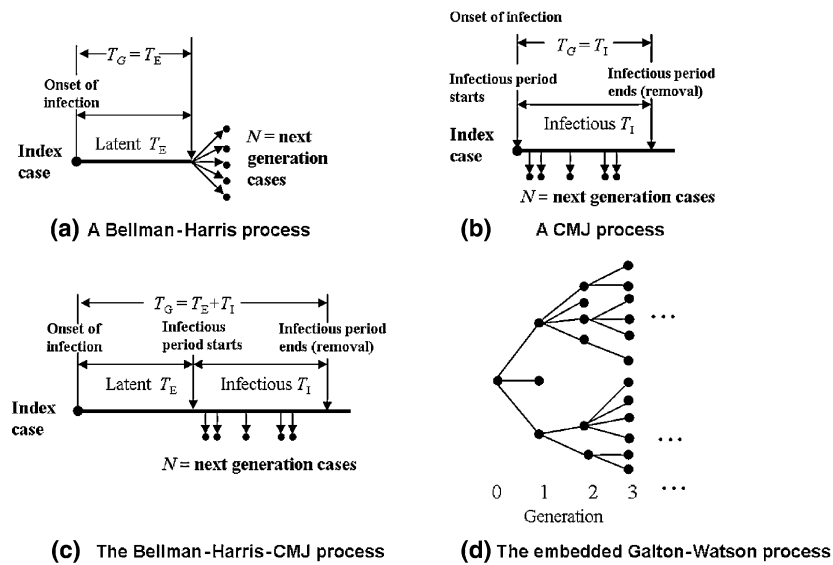


Fig. 10.5 Illustrations of branching processes in the context of SEIR models

### 10.2.6 Random Graph and Random Graph Process

As introduced in Brauer [3], a *graph*  $\mathcal{G}$  consists of a set of vertices  $V = \{v_1, \dots, v_n\}$  and a set of pairs of distinct vertices called edges. The *degree* of a vertex  $v_i$  is the number of vertices adjacent to it which is the number of edges attached to vertex  $v_i$ . A subgraph  $\mathcal{G}'$  is a graph whose vertices and edges form subsets of the vertices and edges of a given graph  $\mathcal{G}$ . A *component* is a connected subgraph. A graph may consist of a number of disjoint components. The size of a graph is  $n =$  the total number of vertices.

#### 10.2.6.1 Random Graph

A *random graph* is obtained by starting with a set of  $n$  vertices and adding edges between them at random. The degrees in a random graph are random associated with the *degree distribution*. In addition, a random graph has several measures on its geometry, such as measures on its *connectivity*, *diameter*, sizes of its components, *clustering coefficient*, etc. All these measures are outcomes of random events. Different random graph models produce different probability distributions on graphs.

#### 10.2.6.2 Random Graph Processes

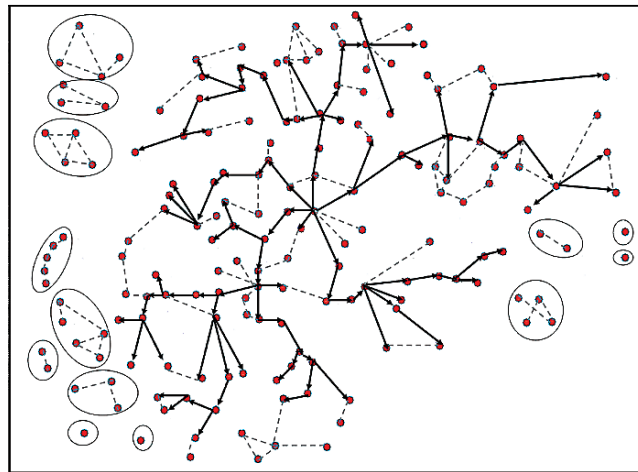
If new edges are added to vertices according to some stochastic processes over time, then it becomes a random graph process. It has not only a time dimension, but also a spatial dimension. At any snapshot at time  $t$ , one observes a realization of a random graph  $\mathcal{G}_t$ . This is analogous to a random variable  $X$  versus a stochastic process  $\{X(t)\}$ . One may aggregate, or superimpose, these random graphs per unit of time over a fixed period of time. The result is still a random graph. This gives an analogy to the counting process.

Similar to such concepts as independent increment, stationary increment, Markov, etc. that determine the temporal growth of the counting processes (e.g. the distribution of inter-arrival times and arrival times of events in a Poisson process), one may develop concepts to capture the spatial-temporal growth of random graph processes.

#### 10.2.6.3 Infectious Disease Transmission as a Subgraph in a Random Graph Process

Individuals are represented by vertices. Contacts are represented by edges. (Social) contacts can be regarded as a random graph process by itself. Contacts made over a fixed period of time is a random graph.

An infectious contact is a contact at which a transmission of infection takes place, and hence all infectious contacts during the same period make a subgraph. The geometry of this subgraph is different from the graph that represents social contacts. This subgraph grows along a *tree*, because if three individuals  $\{a, b, c\}$  are friends forming a triangle relationship, and if individual  $a$  infects both individuals  $\{b, c\}$ , then  $b$  and  $c$  can not infect each other. The social contact random graph may contain triangles and loops, as illustrated by broken lines in Fig. 10.6. The subgraph of infectious contacts can not. This tree – like subgraph, illustrated in Fig. 10.6 by edges, may resemble a realization of an embedded Galton–Watson branching process. However, its growth is limited to the social contact network of susceptible individuals. Only when the number of susceptible individuals is very large can the initial growth of the subgraph be approximated by such a branching process.



**Fig. 10.6** A random graph with several connected components, and a subgraph of infectious contacts

### 10.3 Formulating the Infectious Contact Process

The infectious contacts arise from a combination of two aspects:

1. *The environment.* The social contact network of individuals in a population as a random graph process, determined by the temporal and spatial network properties, such as whether the network is directed, the

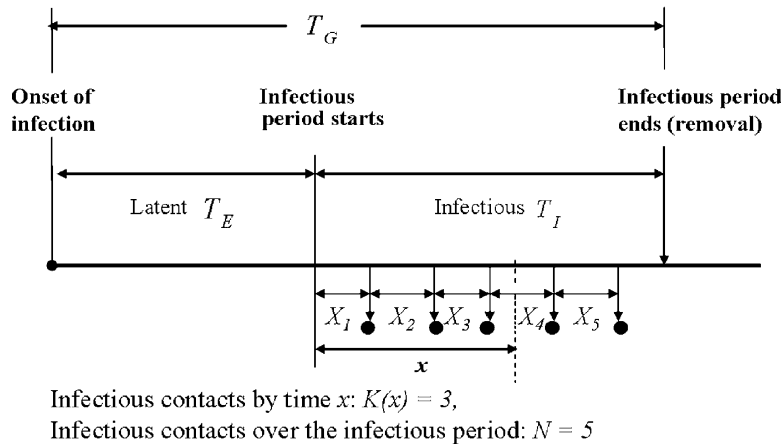
neighbourhood structure of the network, clustering, its growth over time (e.g. stationary increment), etc.

2. *The hosts.* (1) Whether all susceptible individuals are of the same type with equal susceptibility and (2) whether all infectious individuals have equal ability to infect others, so that the probability of transmission per contact, does not vary by contact to contact. If either (1) or (2) is not true, there exists heterogeneity among hosts and this is the intrinsic heterogeneity.

Let  $x$  denote the time measured along a typical infectious individual, starting from the beginning of the infectious period at  $x = 0$ . Following Bartlett [9], and Mode and Sleeman [10], we use a counting process over the time period  $\{K(x), x \in [0, \infty)\}$  where

$$K(x) = \text{cumulative number of infectious contacts by time } x.$$

This process is illustrated in Fig. 10.7, which is (c) in Fig. 10.5.



**Fig. 10.7** Event history and the point process for a typical infected individual by time  $x$  since the beginning of the infectious period

When an individual is still in the latent period, we write  $x < 0$ . Given  $x \geq 0$ ,  $K(x)$  is non-negative integer random variable with p.g.f.  $G_K(s, x) = E[s^{K(x)}] = \sum_{k=0}^{\infty} s^k \Pr\{K(x) = k\}$  and mean value  $E[K(x)]$ . We use the notation  $F_I(x) = \Pr\{T_I < x\}$  for the c.d.f. of the infectious period  $T_I$ . The mean infectious period is denoted by  $\mu = E[T_I]$ . Transmission occurs only when an infected individual is still infectious. The counting process  $\{K(x)\}$  stops when the infectious period  $T_I$  expires (removal). It is assumed that

$\{K(x)\}$  and  $T_I$  are independent.  $T_I$  serves as a random stopping time of the process  $\{K(x)\}$ .

### 10.3.1 The Expressions for $R_0$ and the Distribution of $N$ such that $R_0 = E[N]$

Let time  $\tau$  denote that time since infection of a typical infectious individual. A generic expression for  $R_0$  is given by the equation [5]

$$R_0 = \int_0^\infty \beta(\tau)A(\tau)d\tau \quad (10.21)$$

where  $A(\tau)$  is the probability that at time  $\tau$  since infection the individual is infectious. In other words,  $A(\tau) = \Pr\{T_E \leq \tau \cap T_E + T_I > \tau\}$ .  $\beta(\tau)$  is associated with the property of a counting process that generates new infectious individuals during the infectious period. The product  $\beta(\tau)A(\tau)$  is the expected infectivity at time  $\tau$  after infection.

If  $T_E$  and  $T_I$  are independent and if at time  $\tau$  since infection, an individual is infectious, then  $\tau \geq T_E$  and  $T_I > \tau - T_E$ . Therefore,

$$A(\tau) = \int_0^\tau \bar{F}_I(\tau - x)f_E(x)dx = \bar{F}_{E+I}(\tau) - \bar{F}_E(\tau), \quad (10.22)$$

which can be easily proven since  $\bar{F}_{E+I}(\tau) = \int_\tau^\infty \int_0^y f_I(y-x)f_E(x)dx dy$  and  $\bar{F}_E(\tau) = \int_\tau^\infty f_E(x)dx$ .  $f_E(x)$  and  $f_I(x)$  are the p.d.f.'s of  $T_E$  and  $T_I$ , respectively. Therefore,

$$\begin{aligned} \int_0^\infty A(\tau)d\tau &= \int_0^\infty \bar{F}_{E+I}(\tau)d\tau - \int_0^\infty \bar{F}_E(\tau)d\tau \\ &= E[T_E + T_I] - E[T_E] = E[T_I] = \int_0^\infty \bar{F}_I(\tau)dx = \mu. \end{aligned}$$

We first show that the formulation of  $R_0$  does not depend on any assumption on the latent period, during which transmission does not occur. For an individual with observed latent period  $T_E = t_E$ ,  $\beta(\tau) = 0$ , if  $\tau \leq t_E$ ;  $\beta(\tau) = \beta(x)$ , if  $\tau > T_E$ ,  $T_I > \tau - T_E$ , where  $x = \tau - t_E$ . The equation (10.21) becomes  $R_0 = \int_{t_E}^\infty \beta(\tau)A(\tau)d\tau = \int_0^\infty \beta(x)A(x + t_E)dx$ . One can also show that (exercise),  $A(x + t_E) = \bar{F}_I(x)$ . Therefore

$$R_0 = \int_0^\infty \beta(x)\bar{F}_I(x)dx. \quad (10.23)$$

Furthermore, if the counting process  $\{K(x)\}$  has stationary increment:  $\beta(x) \equiv \beta$ , then

$$R_0 = \beta\mu. \quad (10.24)$$

$\beta > 0$  is a parameter that captures the transmission rate in the agent–host–environment interface. It can be further sub-modelled to reflect the agent–host–environment interface. A frequently seen expression is  $\beta = \lambda p$  so that  $R_0 = \lambda p\mu$ .  $p$  is the probability of transmission per contact between an infectious host and a susceptible host.  $\lambda$  is the average number of contacts among hosts per unit of time in the environment. The control measure for  $\beta$  may be further categorized into interventions designed to alter the social-contact network and designed to alter the transmission probability.

One may also model  $\beta = ab$  where  $a$  measures the infectivity of an infectious individual who comes in contact with a susceptible individual, for whom, the susceptibility is measured by  $b$ . For example, to model the way individuals respond to vaccination, an individual may respond to vaccination with a change in their susceptibility to infection and if ever infected, their infectivity may change from what it is without vaccination. For reference, one may consult Becker and Starczak [11] which leads to references to many more publications in this area.

Formation of  $R_0$  by a multiplicative relationship is useful for statistical analyses and is thus of much public health interest. It leads to a log-linear model to explore the controlled reproduction number  $R_c$ :

$$\log R_c = \log R_0 + \text{covariates} \quad (10.25)$$

where covariates are associated with intervention measures, such as social distancing, vaccination, treatment of infected individuals with anti-viral drugs, or altering the duration of infectiousness such as rapid isolation of identified infectious individuals. If the probability distribution for  $N$  such that  $R_0 = E[N]$  is known, the (10.25) leads to the use of generalized linear regression analyses for exploring the effectiveness of these intervention measures aided by statistical packages.

An immediate generalization of (10.24) is when the infectious period can be divided into stages  $T_I^{(1)} \rightarrow T_I^{(2)} \rightarrow \dots \rightarrow T_I^{(l)}$ , where the duration  $T_I^{(j)}$  is associated with distribution  $F_j(x)$  with mean  $\mu_j$ . Let  $\beta_j(x) = \frac{d}{dx}E[K_j(x)]$ . It can be shown that  $R_0 = \sum_{j=1}^l \int_0^\infty \beta_j(x)\bar{F}_j(x)dx$  [10, p. 205]. In this case, the infectious contact process may not have stationary increment over the entire infectious period but has piecewise stationary increment within each stage so that  $\beta_j(x) = \beta_j$ . (10.24) becomes

$$R_0 = \beta_1\mu_1 + \beta_2\mu_2 + \dots + \beta_l\mu_l. \quad (10.26)$$

In order to derive the distribution for  $N$ , denote

$$N(x) = \begin{cases} K(x), & 0 < x < T_I \\ K(T_I), & x \geq T_I. \end{cases}$$



For fixed  $x$ ,  $N(x)$  is also a random variable with p.g.f.

$$G_N(s, x) = \sum_{j=0}^{\infty} s^j \Pr\{N(x) = j\}.$$

It has been shown that [10, pp. 177–178] the following two recursive formulae hold:

$$E[N(x)] = [1 - F_I(x)] E[K(x)] + \int_0^x E[K(u)] dF_I(u), \quad (10.27a)$$

$$G_N(s, x) = [1 - F_I(x)] G_K(s, x) + \int_0^x G_K(s, u) dF_I(u). \quad (10.27b)$$

$N = N(\infty)$  is the cumulative number of infectious contacts generated by an infectious individual throughout its entire infectious period. Let  $G_N(s) = \sum_{x=0}^{\infty} s^x \Pr\{N = x\}$  be the p.g.f. for  $N$ .  $G_N(s)$  uniquely defines the distribution  $\Pr\{N = x\}$  following the relationship (10.4).  $G_N(s)$  can be derived from (10.27b):

$$G_N(s) = \lim_{x \rightarrow \infty} G_N(s, x) = \int_0^{\infty} G_K(s, x) dF_I(x). \quad (10.28)$$

The mean and variance of  $N$  can be evaluated by (10.5), specifically,  $R_0 = G'_N(1)$ . It can be also shown that (10.23) can be obtained through integration by parts of (10.27a) so that  $E[N(x)] = \int_0^x \beta(u) \bar{F}_I(x) du$ .

The equation (10.28) implies that the probability distribution of  $N$  does not depend on the distribution of the latent period  $T_E$ , but depends on:

1. The infectious contact process  $\{K(x)\}$ , with p.d.f.  $G_K(s, x)$  incorporating properties of the contact process and the probability of transmission per contact
2. The infectious period distribution  $F_I(x) = \Pr\{T_I \leq x\}$

However, differently specified infectious contact processes defined by  $G_K(s, x)$  and infectious period distributions  $F_I(x)$  may result in the same probability distribution for  $N$  and the same  $R_0$ . We shall see later in this chapter that for some public health applications, such as determining the risk of whether a large outbreak may occur, or the distribution of the final size  $\eta$  (in  $\frac{E[Z]}{n} \rightarrow \eta$ ) should a large outbreak occur, knowing  $R_0$  will be sufficient. For some applications, one requires the knowledge of the distribution for  $N$ . Once the distribution for  $N$  is determined, one can use theories for the embedded Galton–Watson branching process to calculate quantities such as the probability of a small outbreak  $\pi$ , the final size of the small outbreak  $\Pr\{Z = z\}$  and the probability of time to extinction  $\Pr\{T_g = g\}$ . Yet there are also applications where the detailed distribution for  $N$  is not sufficient. One also needs to know the underlying stochastic mechanisms such as the property of the counting process  $\{K(x), x \in [0, \infty)\}$ , the distribution of the latent period  $T_E$  and the distribution of the infectious period  $T_I$ .

### 10.3.2 Competing Risks, Independence and Homogeneity in the Transmission of Infectious Diseases

*Competing risk* comes from survival analysis on a non-negative random variable  $X > 0$  associated with a “lifetime”. In a continuous framework,  $X$  is associated with a hazard function  $h(x)$  for “failure”. In the competing risk model, when failure occurs, it may be one of  $m$  distinct causes or types, denoted by  $J \in \{1, 2, \dots, m\}$ . The overall hazard function is the sum of type-specific hazard functions  $h(x) = \sum_{j=1}^m h_j(x)$  where

$$h_j(x) = \lim_{\Delta \rightarrow 0} \frac{\Pr\{x < X \leq x + \Delta; J = j | X > x\}}{\Delta}.$$

*Example 3.* In Fig. 10.7, if we define  $Y_k = X_1 + \dots + X_k$ ,  $Y_k > 0$  is a random variable. Let  $T = \min(Y_k, W)$ .  $T > 0$  is a random variable representing either the infectious individual is removed or the individual produces its  $k$ th infectious contact. The probability distribution for  $T$  arises from a competing risk framework.

*Example 4.* In a contact network, let us consider a vertex  $v$  is a susceptible individual attached to  $m$  edges, representing  $m$  neighbouring vertices with on-going social contacts with vertex  $v$ . All the  $m$  neighbours are infectious. Let  $T$  be the time until vertex  $v$  become infected. The type-specific hazard function  $h_j(t)$  represents the instantaneous risk of infection being transmitted by the  $j$ th neighbouring vertex.

The word *independence* in the study of infectious diseases has several different aspects.

1. The counting process  $\{K(x)\}$  and the infectious period  $T_I$  are independent. This also implies that in the competing risk framework in Example 3,  $Y_k$  and  $T_I$  are independent for all  $k$ .
2. Viewing the transmission as random graphs, if one randomly chooses a vertex  $v$  to be the initial infective, this vertex makes *independent* infectious contacts (i.e. adding edges) with other susceptible vertices throughout its infectious period.
3. If one randomly chooses a vertex  $v$  to be a susceptible individual, transmission of infection to this individual by any of its neighbouring infectious individuals is independent from potential transmission from other neighbouring infectious individuals.

If both 2 and 3 hold true, then we say that infectious contacts between different pairs are mutually independent.

The word *homogeneity* also consists of three aspects.

1. *The population is homogeneously mixed.* An individual makes contacts with other individuals with the same probability. As the population size  $\rightarrow \infty$ , the contact process itself is a stationary Poisson process with constant intensity  $\lambda$ .
2. *The hosts are homogeneous.* All individuals are of the same type the probability of transmission per contact between each pair of an infectious individual and a susceptible individual is a constant  $p$ .
3. The infectious period from all infected individuals are equal to some constant  $\mu$  with  $F_I(x)$  given by (10.29)

$$F_I(x) = \begin{cases} 0, & x \leq \mu \\ 1, & x > \mu \end{cases} \quad (10.29)$$

such that  $E[T_I] = \mu$  and  $var[T_I] = 0$ .

Violations to one or a combination of the above assumptions result in heterogeneous transmission.

## 10.4 Some Models Under Stationary Increment Infectious Contact Process $\{K(x)\}$

If  $\{K(x)\}$  satisfies *stationary increment*  $E[K(x)] = \beta x$  so that  $\beta(x) = \frac{d}{dx}E[K(x)] = \beta$  (constant), (10.23) has a simpler expression  $R_0 = \beta\mu$  where  $\mu = E[T_I] = \int_0^\infty \bar{F}_I(x)dx$  is the mean infectious period.

### 10.4.1 Classification of some Epidemics Where $N$ Arises from the Mixed Poisson Processes

Since the distribution of  $N$  does not depend on the distribution of the latent period, we restrict discussion to the case where the latent period is absent. In the expression  $G_N(s) = \int_0^\infty G_K(s, x)dF_I(x)$ , differently specified infectious contact process  $\{K(x)\}$  defined by  $G_K(s, x)$  and infectious period distribution  $F_I(x)$  may result in the same probability distribution for  $N$  at the macro level, with very different characteristics at the micro level. Some models are classified below as mixed Poisson processes.

#### 10.4.1.1 The Poisson Epidemic

The assumptions are: (1) the infectious contact process is a Poisson process with  $G(s, x) = e^{\beta x(s-1)}$ ; (2) contacts between different pairs are mutually

independent; (3) the infectious period from all infected individuals are equal to some constant  $\mu$  with  $F_I(x)$  given by (10.29). Under this model,

$$G_N(s) = e^{\beta\mu(s-1)} = e^{R_0(s-1)}. \quad (10.30)$$

Hence  $N$  is also Poisson distributed.

#### 10.4.1.2 The Randomized Epidemic

This terminology is used in von Bahr and Martin-Löf [12]. The model assumes that the infectious periods from all infected individuals are equal to some constant  $\mu$  with  $F_I(x)$  given by (10.29).  $\beta$  is further sub-modelled as  $\beta = \lambda p$  where  $p$  is a random probability with itself following some distribution  $F_p$  so that  $\beta = \lambda E[p]$ . In this case, it can be shown (later) that  $G_K(s, x) = \int_p e^{\lambda p x (s-1)} dF_p = E_p [e^{\lambda p x (s-1)}]$ . Under this model,  $G_N(s) = E_p [e^{\lambda p \mu (s-1)}]$ .

Without losing generality, we extend the above by assuming that factors resulting in heterogeneous mixing and/or heterogeneous transmission are not at present understood and the product  $\xi = \lambda p$  is a random variable following some distribution  $U(\xi)$  with  $E[\xi] = \beta$ . Therefore  $G_K(s, x) = E_\xi [e^{\xi x (s-1)}]$  and

$$G_N(s) = E_\xi [e^{\xi \mu (s-1)}]. \quad (10.31)$$

Provided that the mixing distribution  $U(\xi)$  is specified,  $G_N(s)$  uniquely defines the distribution of  $N$  as a mixed Poisson distribution.

#### 10.4.1.3 The Generalized Epidemic

This terminology is used in Lefèvre and Utev [13]. The assumptions are: (1) the infectious contact process is a Poisson process with  $G(s, x) = e^{\beta x (s-1)}$ ; (2) contacts between different pairs are mutually independent; (3) the infectious periods from all infected individuals are i.i.d. following an arbitrary distribution  $F_I(x)$ . Using (10.28),

$$G_N(s) = \int_0^\infty e^{\beta x (s-1)} dF_I(x) = E_{T_I} [e^{\beta T_I (s-1)}]. \quad (10.32)$$

One notices the duality between (10.31) and (10.32). As far as the distribution for  $N$  is concerned, the generalized epidemic and the randomized epidemic models can be unified as one mixed Poisson model with

$$G_N(s) = \int_0^\infty e^{\rho (s-1)} dU(\rho) = E_\rho [e^{\rho (s-1)}] \quad (10.33)$$

with a mixing distribution  $U(\rho)$ . In (10.32),  $\rho$  is re-scaled as  $\rho = \beta T_I$  where  $\beta$  is a constant and  $T_I$  is random such that  $E[\rho] = \beta \mu$ . In (10.31),  $\rho$  is

re-scaled as  $\rho = \xi\mu$  where  $\mu$  is constant, but  $\xi$  is random. It implies that, if one starts with a simple Poisson distribution with p.g.f.  $e^{\rho(s-1)}$  and chooses a mixing distribution  $U(\rho)$ , the resulting distribution obtained by (10.33) can be interpreted as arising either from a generalized epidemic with an appropriately chosen infectious period distribution, or from a randomized epidemic with an appropriately chosen distribution for  $\xi$ .

#### The General, or the Kermack–McKendrick, Epidemic

This is a special case of the generalized epidemic, by assuming  $F_I(x) = 1 - e^{-\frac{x}{\mu}}$  in (10.32). The p.d.f. is  $F_I(x) = \frac{1}{\mu}e^{-\frac{x}{\mu}}$  with  $E[T_I] = \mu$ . Under this model, (10.32) becomes

$$G_N(s) = \frac{1}{\mu} \int_0^\infty e^{\beta x(s-1)} e^{-\frac{x}{\mu}} dx = \frac{1}{1 + \beta\mu(1-s)}.$$

This p.g.f. gives the geometric distribution for  $N$  with  $R_0 = \beta\mu$ . This corresponds to the underlying assumption for both the deterministic SIR model and its stochastic counterpart, the bivariate Markov chain SIR model. Bailey [8] gave it the name *the general epidemic*. A better name for this may be the Kermack–McKendrick epidemic to reflect its early origins [14].

#### 10.4.1.4 The Randomized and Generalized Epidemics

The infectious contact process  $\{K(x)\}$  is a mixed Poisson process under the same assumptions as that in the randomized epidemic model, with  $G_K(s, x) = E_\xi[e^{\xi x(s-1)}]$ . The infectious periods from all infected individuals are i.i.d. following an arbitrary distribution  $F_I(x)$ , as that assumed in the generalized epidemic model, then

$$G_N(s) = \int_0^\infty E_\xi[e^{\xi x(s-1)}] dF_I(x) = E_{T_I} \left[ E_\xi[e^{\xi T_I(s-1)}] \right]. \quad (10.34)$$

With respect to (10.34), let  $\rho = \xi T_I$ . Conditioning on  $T_I = x$ ,  $\xi$  is random and hence the conditional distribution for  $\rho$ ,  $U_1(\rho|x)$ , depends on parameter  $x$ . The integrand  $E_\xi[e^{\xi x(s-1)}]$  can be regarded as a mixed Poisson distribution with p.g.f.  $\int_\rho e^{\rho(s-1)} dU_1(\rho|x)$ . Provided no dependencies between the parameters of the distributions considered, one can re-write (10.34) as

$$\int_\rho e^{\rho(s-1)} \left( \int_x dU_1(\rho|x) dF_I(x) \right) = \int_\rho e^{\rho(s-1)} dU(\rho)$$

so that it can be also unified as a mixed Poisson distribution with the mixing distribution  $U(\rho)$  as a random mixture of two mixing distributions  $U_1(\rho|x)$  and  $F_I(x)$ .

The unification among (10.32), (10.31) and (10.34) is helpful to reduce redundancy of proof for some theories. This unification can be only applied to address certain aspects of an outbreak, such as the assessment of the risk of a large outbreak and the final size, of which, the knowledge of the distribution of  $N$ , uniquely defined by the p.g.f.  $G_N(s)$ , is sufficient.

### 10.4.2 Tail Properties for $N$

Karlis and Xekalaki [15] pointed out that the shape of the p.m.f. of a mixed Poisson distribution exhibits a resemblance to that of the p.d.f. of the mixing distribution  $u(\lambda)$ . Lynch [16] proved that mixing carries the form of the mixing distribution over to the resulting mixed distribution in general. Tail properties of some commonly used probability models for continuous non-negative random variables have been summarized in Table 10.3. We now compare the shape of the distributions for  $N$  generated by p.g.f.  $\int_{\rho} e^{\rho(s-1)} dU(\rho)$  with that of their mixing distributions  $U(\rho)$ .

#### 10.4.2.1 $N$ Distributed According to Geometric and Negative-Binomial Distributions

Figures 10.3 and 10.2 illustrate that the shape of the geometric distribution resembles that of the exponential distribution and the shape of the negative binomial distribution resembles that of the gamma distribution. We may re-parametrize the negative-binomial distribution (10.11) as  $\Pr\{N = x\} = \frac{\Gamma(x+\frac{1}{\phi})}{\Gamma(x+1)\Gamma(\frac{1}{\phi})} \zeta^{\frac{1}{\phi}} (1-\zeta)^x$  by letting  $\zeta = \frac{1}{1+\phi\mu}$ . The geometric distribution is a special case  $\zeta(1-\zeta)^x$ .

1. The geometric distribution has exponential tail because for any  $x$ ,  $\bar{F}_N(x) = \sum_{l=x}^{\infty} \zeta(1-\zeta)^l = (1-\zeta)^x = e^{-\frac{x}{\tau}}$  where  $\frac{1}{\tau} = -\log(1-\zeta)$ . Hence  $\frac{\bar{F}_N(s+x)}{\bar{F}_N(s)} = e^{-\frac{x}{\tau}}$ .
2. The negative binomial distribution has exponential tail when  $\phi > 1$ . In fact, from page 210 of Johnson, Kotz and Kemp [17]

$$\Pr\{N \geq x\} = \sum_{l=x}^{\infty} \frac{\Gamma(l+\frac{1}{\phi})}{\Gamma(l+1)\Gamma(\frac{1}{\phi})} \zeta^{\frac{1}{\phi}} (1-\zeta)^l = f_N(x) {}_2F_1[1, x+\frac{1}{\phi}; x+1; 1-\zeta]$$

where  $f_N(x) = \Pr\{N = x\}$  and  ${}_2F_1[a, b; c; x]$  is the Gaussian hypergeometric function. If  $c > b > 0$ ,  ${}_2F_1[a, b; c; x] = \frac{\Gamma(c)}{\Gamma(b)\Gamma(c-b)} \int_0^1 \frac{v^{b-1}(1-v)^{c-b-1}}{(1-vx)^a} dv$ .

When  $\phi > 1$ ,

$$\begin{aligned} \frac{\overline{F}_N(s+x)}{\overline{F}_N(s)} &= \frac{f_N(s+x)}{f_N(s)} \frac{{}_2F_1[1, s+x+\frac{1}{\phi}; s+x+1; 1-\varsigma]}{{}_2F_1[1, x+\frac{1}{\phi}; x+1; 1-\varsigma]} \\ &= \frac{\int_0^1 \frac{v^{x+s+\frac{1}{\phi}-1}(1-v)^{-\frac{1}{\phi}}}{1-v(1-\varsigma)} dv}{\int_0^1 \frac{v^{x+\frac{1}{\phi}-1}(1-v)^{-\frac{1}{\phi}}}{1-v(1-\varsigma)} dv} (1-\varsigma)^x \rightarrow e^{-\frac{x}{\tau}}, \text{ as } s \rightarrow \infty. \end{aligned}$$

### 10.4.2.2 A Distribution Commonly Used in Social Networks Modelling for Infectious Diseases

A distribution with supports  $1, 2, \dots$  given by

$$\Pr\{N = x\} = Cx^{-\theta}e^{-\frac{x}{\tau}}, \quad x = 1, 2, 3, \dots \tag{10.35}$$

where  $C = Li_\theta^{-1}\left(e^{-\frac{1}{\tau}}\right)$  is the normalizing factor and  $Li_\theta(z) = \sum_{n=1}^\infty \frac{z^n}{n^\theta}$ , was mentioned in Brauer [3]. It has been used in modelling the spread of infectious diseases on scale-free networks by Newman [18]; Meyers, Pourbohloul et al. [19] and many others.

- If  $\theta \rightarrow 0$ , (10.35) returns to the (zero-truncated) geometric distribution  $\frac{x^{-\theta}e^{-\frac{x}{\tau}}}{Li_\theta\left(e^{-\frac{1}{\tau}}\right)} \rightarrow (1 - e^{-\frac{1}{\tau}})e^{-\frac{x-1}{\tau}}$ ,  $x = 1, 2, 3, \dots$ .
- If  $\tau \rightarrow \infty$ , (10.35) has the limiting distribution as the Zipf distribution  $\frac{x^{-\theta}e^{-\frac{x}{\tau}}}{Li_\theta\left(e^{-\frac{1}{\tau}}\right)} \rightarrow \frac{1}{\zeta(\theta)}x^{-\theta}$  where  $\zeta(\theta) = \sum_{n=1}^\infty \frac{1}{n^\theta}$ .

When  $\tau < \infty$ , the tail of this distribution is exponential. As  $s \rightarrow \infty$ ,

$$\frac{\Pr\{N \geq s+x\}}{\Pr\{N \geq s\}} = \frac{\sum_{j=s+x}^\infty j^{-\theta}e^{-\frac{j}{\tau}}}{\sum_{j=s}^\infty j^{-\theta}e^{-\frac{j}{\tau}}} = e^{-\frac{x}{\tau}} \frac{\sum_{j=s}^\infty (j+x)^{-\theta}e^{-\frac{j}{\tau}}}{\sum_{j=s}^\infty j^{-\theta}e^{-\frac{j}{\tau}}} \rightarrow e^{-\frac{x}{\tau}}.$$

There are many possible stochastic mechanisms for which a distribution like (10.35) may arise. One of them is a generalized epidemic model arising from mixed Poisson distributions p.g.f.  $\int_0^\infty e^{\beta x(s-1)} dF_I(x)$ , where the infectious period  $W$  arises from a competing process. For some individuals, the infectious period arises from an exponential distribution with constant hazard  $h_e(x) = \gamma$  as the removal rate. For other individuals, the infectious period follows a generally very short but highly skewed distribution, which may be fitted well with a Pareto form, with the hazard function expressed by  $h_p(x) = \frac{\alpha\theta}{1+\alpha x}$ . This scenario may arise if identified infectious individuals are aggressively isolated during an outbreak. The survivor function of the infectious period has a shape of that of a Pareto distribution with exponential cut-off:

$$\bar{F}_I(x) = \exp\left(-\int_0^x \left(\gamma + \frac{\alpha\theta}{1+\alpha t}\right) dt\right) = \frac{\alpha^\theta}{(1+\alpha x)^\theta} e^{-\gamma x}, \quad \alpha, \gamma, \theta > 0.$$

It has an exponential tail:

$$\frac{\bar{F}_I(s+x)}{\bar{F}_I(x)} = \frac{(1+\alpha s)^\theta}{(1+\alpha s+\alpha x)^\theta} e^{-\gamma x} \rightarrow e^{-\gamma x}, \quad \text{as } s \rightarrow \infty.$$

Although the exact distribution for  $N$ ,

$$\Pr\{N = j\} = \frac{\alpha^\theta}{j!} \int_0^\infty \frac{(\beta x)^j (\theta\alpha + \gamma(1+\alpha x))}{(1+\alpha x)^{\theta+1}} e^{-(\beta+\gamma)x} dx$$

may not be easy to calculate, we may use the results in Karlis and Xekalaki [15] to argue that it carries the shape of the mixing distribution  $\bar{F}_I(x)$  which is a continuous analogue of (10.35).

### 10.4.2.3 Discrete Power-Law Distributions as Mixed Distributions

The term “scale-free” [20] refers to networks with degrees following a power-law distribution with  $\Pr\{N = x\} \propto \frac{1}{x^{\theta+1}}$ . Scale-free models have gained much attention in infectious disease literature. Liljeros et al. [21] used the power-law distribution to model the web of sexual contacts with implication of studying sexually transmitted infections. A discrete power-law distribution is the Zipf distribution  $\frac{1}{\zeta(\theta+1)} x^{-(\theta+1)}$ , a discrete analogue to the continuous Pareto distribution. In a general sense, any distribution such that  $\lim_{x \rightarrow \infty} \frac{\bar{F}(x)}{x^{\theta+1}} = A$ , for some  $\theta > 0, A > 0$  is a power-law distribution. Romillard and Theodorescu [22] showed that certain Poisson mixtures are power-law.

A class of power-law distributions have the form with p.m.f.

$$\Pr\{N = x\} = \begin{cases} \theta \frac{\Gamma(x+\alpha)\Gamma(\alpha+\theta)}{\Gamma(\alpha)\Gamma(x+\alpha+\theta+1)}, & \theta > 0, \alpha > 0 \\ \theta \frac{\Gamma(x+1)\Gamma(\theta+1)}{\Gamma(x+\theta+2)}, & \text{special case } \alpha = 1 \end{cases} \quad (10.36)$$

which is the Waring distribution given by (6.149) and the special case Yule distribution corresponding to (6.139) when  $\alpha = 1$  of Johnson, Kotz and Kemp [17]. The mean and variance may not exist. The first moment exists:  $E[N] < \infty$  only if  $\theta > 1$ . Using the Barnes expansion [17, p. 6],

$$\frac{\Gamma(x+\alpha)}{\Gamma(x+\alpha+\theta+1)} \approx \frac{1}{x^{\theta+1}} \left(1 - \frac{(\theta+1)(\theta+2\alpha)}{2x} + \dots\right)$$



it shows that when  $x$  is sufficiently large, the Waring and the Yule distribution follow the power-law property:  $\propto \frac{1}{x^{\theta+1}}$  where the parameter  $\alpha$  plays little role.

The Waring (Yule) distribution can be generated as a mixture of the negative binomial distribution of the general form

$$\frac{\Gamma(x + \frac{1}{\phi})}{\Gamma(x + 1)\Gamma(\frac{1}{\phi})} \zeta^{\frac{1}{\phi}} (1 - \zeta)^x, \quad 0 < \zeta < 1. \quad (10.37)$$

If one takes a one-parameter Beta distribution  $u(\zeta) = \theta \zeta^{\theta-1}$  as the mixing distribution onto a negative binomial, then

$$\begin{aligned} \Pr\{N = x\} &= \frac{\Gamma(x + \frac{1}{\phi})}{\Gamma(x + 1)\Gamma(\frac{1}{\phi})} \int_0^1 \zeta^{\frac{1}{\phi}} (1 - \zeta)^x \theta \zeta^{\theta-1} d\zeta \\ &= \theta \frac{\Gamma(x + \alpha)\Gamma(\alpha + \theta)}{\Gamma(\alpha)\Gamma(x + \alpha + \theta + 1)}, \quad \theta > 0, \quad \alpha = \frac{1}{\phi} > 0. \end{aligned} \quad (10.38)$$

which returns to the Waring distribution. The Waring distribution can be justified as arising from a mixed Poisson [23, 24].

It can be also formulated as arising from a infectious contact process that itself arises from a mixed negative binomial (10.37) with Pareto distribution as its mixing distribution. Then one can use the results in Lynch [16] to justify why (10.38) carries the Pareto shape. In fact, if we write  $\zeta = \frac{1}{1+\phi\rho}$ , then  $d\zeta = -\frac{\phi}{(1+\phi\rho)^2} d\rho$ , and  $u(\zeta) = \theta \zeta^{\theta-1} = \theta \left(\frac{1}{1+\phi\rho}\right)^{\theta-1}$ . Hence (10.38) becomes

$$\frac{\Gamma(x + \frac{1}{\phi})}{\Gamma(x + 1)\Gamma(\frac{1}{\phi})} \int_0^\infty \left(\frac{1}{1 + \phi\rho}\right)^{\frac{1}{\phi}} \left(1 - \frac{1}{1 + \phi\rho}\right)^k \frac{\theta\phi}{(1 + \phi\rho)^{\theta+1}} d\rho$$

where  $u_1(\rho) = \frac{\theta\phi}{(1+\phi\rho)^{\theta+1}}$  is the Pareto mixing distribution.

## 10.5 The Invasion and Growth During the Initial Phase of an Outbreak

$S(t)$  is the random number of susceptible individuals at time  $t$  with expected value  $E[S(t)]$ .  $S_0$  is a fixed number of initial susceptible individuals at  $t = 0$ .  $n$  is the total number of individuals in the population. The *initial phase* of an outbreak is the period of time when depletion of susceptible individuals can be ignored, which is  $\left\{t : \frac{E[S(t)]}{n} \approx 1\right\}$ . During this phase, there are two approximations to describe the disease spread:

1. The branching process approximation: A typical infectious individual is associated with a generation time  $T_G = T_E + T_I$  and by its end, it produces a random number of  $N$  new infections. The mean number of these new infections is  $R_0$ . If  $R_0 \leq 1$ , with certainty (i.e. with probability one), this branching process will become extinct, resulting in a handful of total infections. The extinction is intrinsic.
2. The exponential growth approximation: If  $R_0 > 1$ , the expected number of infectious individuals at time  $t$  follows the Malthus' Law  $E[I(t)] \propto e^{rt}$  [25,26], characterized by a parameter  $r$ . The growth is intrinsic and  $r$  is known as the *intrinsic growth rate*, also known as the Malthusian parameter.

There is an Euler–Lotka equation [5]

$$\int_0^\infty e^{-r\tau} \beta(\tau) A(\tau) d\tau = 1, \tag{10.39}$$

where  $\beta(\tau)$  and  $A(\tau)$  are defined the same way as in (10.21).

### 10.5.1 Invasion and the Epidemic Threshold

Kendall [27] considered a continuous random variable  $Y = \frac{Z}{n}$  defined on  $(0, 1]$ , where  $Z = n - S_\infty$  is the final size of an outbreak. The shape of this distribution may have one of the two shapes: the J-shape and the U-shape. The term J-shape refers to a distribution that is monotonically decreasing so that it has a mode at zero. The distribution is said to have U-shape if it is bimodal. As shown in Fig. 10.8, the U-shaped distribution can be thought of as a weighted average between a J-shaped distribution with weight  $0 < \pi < 1$  and a uni-modal distribution of a bell-shape with weight  $1 - \pi$ .

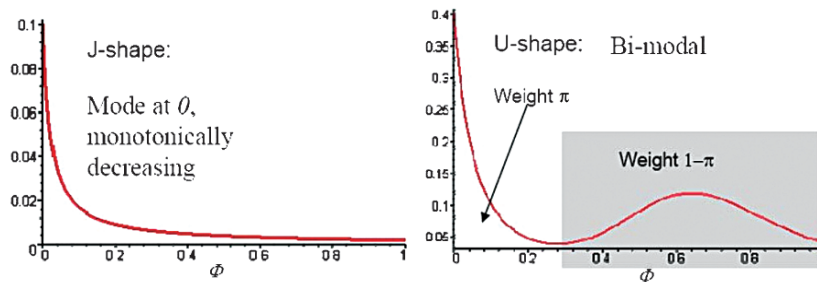


Fig. 10.8 J-shaped and U-shaped distributions for  $Y$

Näsell [28] describes the threshold as a value at which the distribution of  $Y$  makes a transition from J-shape to U-shape. In a population with finite size  $n$ , the transition occurs in the vicinity of 1 at the value  $1 + \frac{K}{n^{\frac{1}{3}}}$ , where  $K$  is a constant independent of  $n$ , but depends on the number of initially infected individuals  $I_0$ .

When  $n \rightarrow \infty$ , a *sufficient condition* for a J-shaped distribution of  $Y$  is  $R_0 < 1$ , under which,  $\pi = 1$  (see Fig.10.8). When  $R_0 > 1$ , either an outbreak dies out with a handful of cases with probability  $\pi < 1$ , or starts an exponential growth into a large outbreak with probability  $1 - \pi$ . Metz [29] showed that the outbreak can be either small or large with no middle road in between.

A small outbreak corresponds to a J-shaped distribution. The opposite is not true. When  $n$  is finite and  $R_0$  lies within the vicinity of 1 of the order of  $O(n^{-\frac{1}{3}})$ , then with probability  $\pi = 1$ ,  $Y = \frac{Z}{n}$  will have a J-shaped distribution with  $\frac{E[Z]}{n} \rightarrow 0$  meanwhile  $E[Z] \rightarrow \infty$ . In this case, the outbreak size is neither small, nor large. Martin-Löf [30] shows that  $Y^* = \frac{Z}{n^{\frac{2}{3}}}$  has a limit distribution as  $n \rightarrow \infty$ . It may have different shapes, from J-shape to a bimodal U-shape, to uni-modal with mode not at zero, or with a shape that is rather flat. This makes the final size unpredictable.

### 10.5.2 The Risk of a Large Outbreak and Quantities Associated with a Small Outbreak

#### 10.5.2.1 The Risk of a Large Outbreak $1 - \pi$

When  $n \rightarrow \infty$ , a necessary condition for a non-zero probability  $1 - \pi > 0$  is that  $R_0$  exists and  $R_0 > 1$ . It is possible that for some distributions for  $N$ ,  $R_0 = E[N]$  does not exist. Public health control measures against an outbreak are often centred around the reduction of  $R_0$  to some controlled reproductive number  $R_c$  by a reduction factor  $c$  so that

$$R_c = (1 - c) R_0 < R_0. \quad (10.40)$$

Ideally, one wants  $R_c < 1$  so  $1 - \pi = 0$ . If this is not achievable, it is important to investigate what other aspects of the distribution for  $N$  such as  $var[N]$  as well as aspects of the underlying stochastic mechanisms that manifest the p.g.f.  $G_N(s)$  contribute to the reduction of the risk of a large outbreak  $1 - \pi$ .

Using standard results from the (embedded) Galton–Watson branching process, for any  $R_0 > 0$  (if it exists), there is always a probability  $\pi$  so that the branching process will become extinct and produce a small outbreak.  $\pi$  is the smallest root of the Fixed-Point Equation

$$s = G_N(s). \quad (10.41)$$

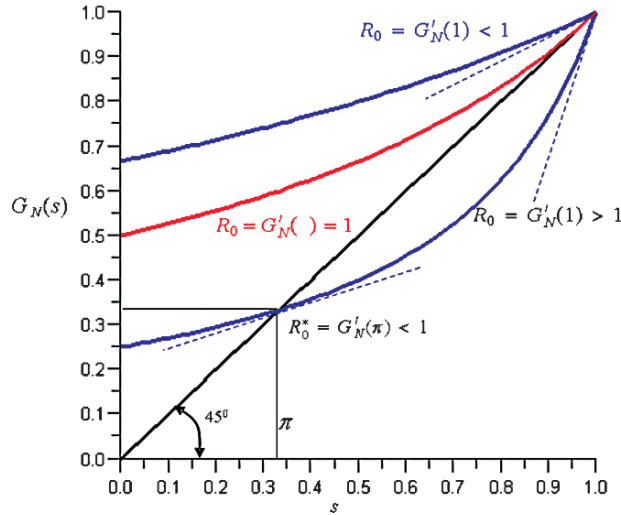


Fig. 10.9 The smallest root of the Fixed-Point equation  $s = G_N(s)$

From the properties of  $G_N(s)$  given in (10.3) and the fact that  $R_0 = G'_N(1)$ , the smallest root of (10.41) is illustrated in Fig. 10.9.

When  $R_0 = G'_N(1) \leq 1$ , the smallest root is  $\pi = 1$ . In this case, a large outbreak will not occur. When  $R_0 = G'_N(1) > 1$ , there is an unique solution  $\pi$  in the open interval  $(0, 1)$  and the risk of a large outbreak is  $1 - \pi$ . If the outcome happens to be a small outbreak, the observed branching process will be indistinguishable from that as if arising from a different “reproduction number”  $R_0^* = G'_N(\pi) < 1$  with its p.g.f. obtained by taking the graph Fig. 10.9 over  $[0, \pi]$  and re-scaling to make the domain and range  $[0, 1]$ .

Application to Some Specific Distributions of  $N$

*Poisson* In the Poisson epidemic,  $G_N(s) = e^{R_0(s-1)}$ .  $\pi$  is the smallest root of the Fixed-Point Equation (10.41). If  $R_0 > 1$ , the risk of a large outbreak is calculated by

$$\pi = e^{-R_0(1-\pi)} \tag{10.42}$$

If the outcome happens to be a small outbreak, the observed branching process will be indistinguishable from that as if arising from a different “reproduction number”

$$R_0^* = G'_N(\pi) = R_0 e^{R_0(\pi-1)} = \pi R_0 < 1.$$

*Geometric* If the p.g.f. for  $N$  is  $G_N(s) = \frac{1}{1+R_0(1-s)}$ , then  $N$  has the geometric distribution. One of the stochastic mechanisms for producing the

geometric distribution is the Kermack–McKendrick epidemic, with all the underlying assumptions governing the deterministic or stochastic bivariate Markov chain SIR models. Another stochastic mechanism for producing the geometric distribution is the randomized distribution with the infectious contact process arising from a mixed Poisson process with exponential mixing distribution. There are other stochastic mechanisms that also produce  $N$  with geometric distribution. However, for studying the initial behaviour using the embedded Galton–Watson branching process, it is only the p.g.f.  $G_N(s)$  that matters. If  $R_0 > 1$ , the risk of a large outbreak is calculated by  $\pi = \frac{1}{1+R_0(1-\pi)}$  with exact solution  $\pi = \frac{1}{R_0}$ . The risk of a large outbreak is  $1 - \frac{1}{R_0}$ . It can be also shown that  $R_0^* = G'_N(\pi) = \frac{1}{R_0}$ .

*Negative binomial* If the p.g.f. for  $N$  has the form  $G_N(s) = \frac{1}{[1+R_0\phi(1-s)]^{\frac{1}{\phi}}}$  for some  $\phi > 0$ , then  $N$  has the negative binomial distribution. It may arise as a generalized epidemic with gamma distributed infectious period, or as a randomized epidemic with the infectious contact process arising from a mixed Poisson process with gamma mixing distribution. There are also other stochastic mechanisms that can produce  $N$  with the negative binomial distribution. In addition,  $\frac{1}{[1+R_0\phi(1-s)]^{\frac{1}{\phi}}} \rightarrow e^{R_0(s-1)}$ , as  $\phi \rightarrow 0$ . If  $R_0 > 1$ , the risk of a large outbreak is calculated by

$$\pi = \frac{1}{[1 + R_0\phi(1 - \pi)]^{\frac{1}{\phi}}}. \tag{10.43}$$

For later use, we write down the derivatives

$$G'_N(s) = \frac{R_0}{(1+\phi R_0(1-s))^{\frac{1}{\phi}+1}}, \quad G''_N(s) = \frac{(1+\phi)R_0^2}{(1+\phi R_0(1-s))^{\frac{1}{\phi}+2}}. \tag{10.44}$$

**Proposition 2.** *Within the negative binomial family of distributions,  $\text{var}[N] = R_0 + \phi R_0^2$ ,  $G_N(s)$  is ordered by the parameter  $\phi$ . That is, for each fixed  $s \in (0, 1)$ ,  $\phi_1 < \phi_2$  implies  $\frac{1}{[1+R_0\phi_1(1-s)]^{\frac{1}{\phi_1}}} < \frac{1}{[1+R_0\phi_2(1-s)]^{\frac{1}{\phi_2}}}$ .*

**Corollary 1.** *If  $R_0 > 1$  and  $\pi \in (0, 1)$  is the Fixed-Point as the smallest root of (10.43), then  $\pi$  is an increasing function of  $\phi$ . The larger the value of  $\phi$ , the larger the probability that an initial outbreak will die out without evolving into a large outbreak and the smaller the risk.*

An alternative way to show that  $\pi$  is an increasing function of  $\phi$  is to use implicit differentiation for (10.43) to directly show that  $\frac{d\pi}{d\phi} > 0$ . In fact

$$\frac{d\pi}{d\phi} = \frac{1}{1 - \frac{R_0}{(\phi R_0(1-\pi)+1)^{\frac{1}{\phi}+1}}} \frac{(1+R_0\phi(1-\pi)) \log(1+R_0\phi(1-\pi)) - R_0\phi(1-\pi)}{\phi^2(\phi R_0(1-\pi)+1)^{\frac{1}{\phi}+1}}.$$

From (10.44),  $\frac{R_0}{(1+\phi R_0(1-\pi))^{\frac{1}{\phi}+1}} = G'_N(\pi) < 1$ . One only needs to show

$$(1 + R_0\phi(1 - \pi)) \log(1 + R_0\phi(1 - \pi)) - R_0\phi(1 - \pi) > 0$$

which is true because  $\log(1 + x) > \frac{x}{1+x}$  for any  $x > 0$ .

**Corollary 2.** *If  $R_0 > 1$ , the Poisson epidemic, as  $\phi \rightarrow 0$ , gives the smallest probability  $\pi$  and hence the highest risk of a large outbreak, compared with any other model within the negative binomial family of distributions with the same  $R_0$ .*

This statement can be extended beyond the negative binomial family. For all randomized and generalized epidemics that can be formulated as mixed Poisson distributions, the Poisson epidemic always produces the smallest probability  $\pi$ .

**Proposition 3.** *Let  $\pi_0$  be the smallest root of  $s = e^{R_0(s-1)}$  corresponding to the Poisson epidemic. Let  $\pi_\rho$  be the smallest root of  $s = \int e^{\rho(s-1)} dU(\rho)$  corresponding to an epidemic arising from some stochastic mechanisms such that  $G_N(s) = E_\rho [e^{\rho(s-1)}]$  can be interpreted as the p.g.f. of a mixed Poisson distribution. If the latter epidemic has finite mean  $R_0$  which equals that of the Poisson epidemic, then  $\pi_0 < \pi_\rho$ .*

Since from any distribution with p.g.f. given by  $G_N(s)$ ,  $\Pr\{N = 0\} = G_N(0)$  which is the probability that, after introducing the initially infected individuals into a susceptible population, transmission never occurs. This leads to the next Corollary, which is a well-known result that was originally proven by Feller [31] in 1943.

**Corollary 3.**  *$e^{R_0(s-1)} < E_\rho [e^{\rho(s-1)}]$  implies  $e^{-R_0} < G_N(0) = E_\rho [e^{-\rho}]$ . Therefore, the probability of  $N = 0$  is always higher under a mixed Poisson distribution than under a simple Poisson distribution with the same mean.*

It implies that variances imposed by infectious period, heterogeneous contact environment, heterogeneous transmission among individuals or combinations of them, all reduce the risk of an large outbreak.

### 10.5.2.2 Boom or Bust: Generations to Extinction in Small Outbreaks

Using the branching process approximation in the early stage of the epidemic and from the theory of branching process (Chap. 8 of [32]),  $\Pr\{T_g \leq g\}$  is uniquely determined by the p.g.f.  $G_N(s)$  and is calculated by

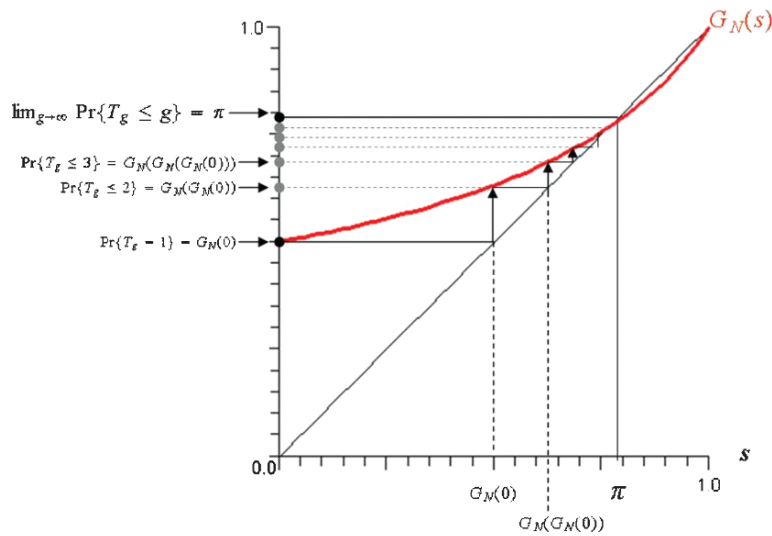
$$\Pr\{T_g \leq g\} = G_N^g(0) \stackrel{\text{def.}}{=} \underbrace{G_N(G_N(\cdots G_N(0) \cdots))}_{g \text{ times}} \underbrace{\cdots}_{g \text{ times}}. \tag{10.45}$$

If there is no secondary transmission, the initial infective individuals make the first generation, hence  $\Pr\{T_g = 1\} = \Pr\{N = 0\} = G_N(0)$ .  $\Pr\{T_g \leq g\}$

is a non-decreasing function of  $g$ . Starting from  $\Pr\{T_g = 1\} = G_N(0)$ , with the limit

$$\lim_{g \rightarrow \infty} \Pr\{T_g \leq g\} = \pi \begin{cases} = 1, & \text{if } R_0 < 1, \\ < 1, & \text{if } R_0 > 1. \end{cases}$$

For any  $R_0 > 0$ , the probability of a small outbreak that becomes extinct in a few generations is  $\pi$ , the smallest root of  $s = G_N(s)$ ,  $s \in (0, 1]$ . The recursive procedure and convergence of (10.45) are illustrated in Fig. 10.10.



**Fig. 10.10** Graphic presentation of  $\Pr\{T_g \leq g\} = G_N^g(0) \rightarrow \pi$ , as  $g \rightarrow \infty$

$\frac{1}{\pi} (1 - \Pr\{T_g \leq g\}) = \frac{\pi - G_N^g(0)}{\pi}$  is the conditional probability that, given the outbreak being small, it has become extinct after  $g$  generations. It can be shown that for a suitable positive constant  $A$ ,

$$\pi - G_N^g(0) = \pi - \Pr\{T_g \leq g\} \sim A [G'_N(\pi)]^g$$

and  $0 < G'_N(\pi) < 1$ . It implies that if extinction is going to occur, the smaller the value of  $G'_N(\pi)$ , the more likely it will happen quickly with very few generations.

When  $N$  Follows the Negative Binomial Distribution

When  $N$  arises from the negative-binomial distribution, (10.45) becomes

$$\begin{aligned} \Pr\{T_g = 1\} &= \Pr\{N = 0\} = (1 + \phi R_0)^{-\frac{1}{\phi}} \\ \Pr\{T_g \leq 2\} &= \left(1 + \phi R_0 - \phi R_0 (1 + \phi R_0)^{-\frac{1}{\phi}}\right)^{-\frac{1}{\phi}} \\ &\vdots \\ \Pr\{T_g \leq g\} &= \frac{1}{[1 + \phi R_0 (1 - \Pr\{T_g \leq g - 1\})]^{\frac{1}{\phi}}}, \end{aligned}$$

with the limit  $\lim_{g \rightarrow \infty} \Pr\{T_g \leq g\} = \pi$ .

It can be shown that,  $T_g$  is ranked by stochastic order in the sense of the survivor function  $\bar{F}_{T_g}(g) = \Pr\{T_g \geq g\} = 1 - \Pr\{T_g \leq g - 1\}$ , according to the parameter  $\phi$ . The larger the  $\phi$ , the shorter the distribution  $\Pr\{T_g \geq g\}$ . For  $N$  with negative-binomial distribution with mean value  $R_0$ , not only large variance  $var[N] = \phi R_0^2 + R_0$  lowers the risk of large outbreaks  $1 - \pi$ , but also that if extinction is going to occur, it is likely to happen quickly with very few generations. An extreme case is when  $\phi \rightarrow \infty$ . It can be shown that  $\lim_{\phi \rightarrow \infty} (1 + \phi R_0)^{-\frac{1}{\phi}} = 1$  and hence  $\lim_{\phi \rightarrow \infty} (1 + \phi R_0 - \phi R_0 \Pr\{T_g \leq g - 1\})^{-\frac{1}{\phi}} = 1$ , thus

$$\lim_{\phi \rightarrow \infty} \Pr\{T_g \leq g\} = 1, \text{ any } g \geq 2.$$

Special Cases as  $\phi \rightarrow 0$  and  $\phi = 1$

The special cases are summarized in Table 10.4.

**Table 10.4** The distributions for generation time to extinction

	Poisson distribution $\phi \rightarrow 0$	Geometric distribution $\phi = 1$
$G_N(s) =$	$\exp(-R_0(1 - s))$	$\frac{1}{1 + R_0(1 - s)}$
$\Pr\{T_g = 1\} =$	$e^{-R_0}$	$\Pr\{T_g \leq g\} = \frac{R_0^g - 1}{R_0^{g+1} - 1}$
$\Pr\{T_g \leq 2\} =$	$e^{R_0(e^{-R_0} - 1)}$	
$\Pr\{T_g \leq 3\} =$	$e^{R_0(e^{R_0(e^{-R_0} - 1)} - 1)}$	
$\vdots$	$\vdots$	

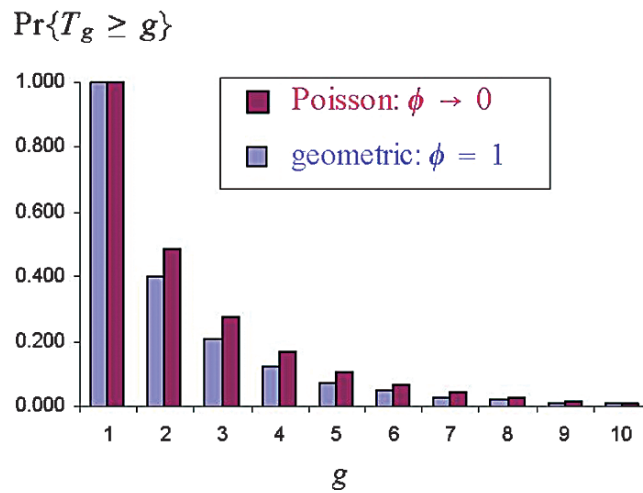
At  $\phi = 1$ ,

$$\Pr\{T_g \leq g\} = \frac{R_0^g - 1}{R_0^{g+1} - 1} \rightarrow \begin{cases} 1, & R_0 < 1 \\ \frac{1}{R_0}, & R_0 > 1 \end{cases} \text{ as } g \rightarrow \infty.$$

To demonstrate that  $T_g$  is stochastically longer when  $\phi \rightarrow 0$  compared to when  $\phi = 1$ , Fig.10.11 illustrates the survivor function  $\Pr\{T_g \geq g\}$



at  $R_0 = 0.667$ . Under the same  $R_0$ , the probability of lasting more than 5 generations before extinction if  $N$  is Poisson distributed, is approximately 1.4 times of that if  $N$  has a geometric distribution.



**Fig. 10.11** Under the same  $R_0$ , Poisson distributed  $N$  provides a stochastically longer generation time to extinction  $T_g$  than that based on a geometric distribution for  $N$

### 10.5.2.3 Distribution of the Final Size of Small Outbreaks

For the integer-valued random variable  $Z$  corresponding to the final size of a small minor outbreak, the probability

$$\sum_{z=1}^{\infty} \Pr\{Z = z\} = \pi \begin{cases} = 1, & \text{if } R_0 \leq 1 \\ < 1, & \text{if } R_0 > 1 \end{cases}$$

where  $\pi$  is the probability of a minor outbreak as a solution of (10.41). Let  $G_Z(s) = \sum_{z=1}^{\infty} s^z \Pr\{Z = z\}$ . It was shown [10, p. 193] that  $G_Z(s) = s \cdot G_N(G_Z(s))$ . In general,  $G_Z(s)$  is not a p.g.f. since  $G_Z(1) = \pi \leq 1$ . Taking derivatives with respect to  $s$ ,

$$G'_Z(s) = G'_N(G_Z(s)) + sG''_N(G_Z(s))G'_Z(s), \tag{10.46a}$$

$$G''_Z(s) = 2G'_N(G_Z(s))G'_Z(s) + sG''_N(G_Z(s))(G'_Z(s))^2 + sG'_N(G_Z(s))G''_Z(s). \tag{10.46b}$$

Mean and Variances for  $Z$  When  $R_0 < 1$

In this case,  $\pi = 1$  and  $G_N(1) = G_Z(1) = 1$ . Since  $G'_N(1) = R_0 < 1$ , letting  $s = 1$  in (10.46a), one gets  $G'_Z(1) = 1 + R_0 G'_Z(1)$ . Hence

$$E[Z] = G'_Z(1) = \frac{1}{1 - R_0}. \quad (10.47)$$

Therefore,  $E[Z] = \frac{1}{1 - R_0}$  is valid for any distribution of  $N$ . Similarly, letting  $s = 1$  in (10.46b) and using  $\text{var}[Z] = G''_Z(1) + G'_Z(1) - (G'_Z(1))^2$ , one gets

$$\text{var}[Z] = \frac{G''_N(1) + R_0(1 - R_0)}{(1 - R_0)^3} = \frac{\text{var}[N]}{(1 - R_0)^3}. \quad (10.48)$$

$\text{var}[Z]$  increases with the variance of  $N$ .

Mean and Variances for  $Z$  When  $R_0 > 1$

In this case, there exists  $\pi \in (0, 1)$  such that  $\pi = G_N(\pi)$ . With probability  $\pi$ , the observed branching process will be indistinguishable from that as if arising from a different “reproduction number”  $R_0^* = G'_N(\pi) < 1$ . (10.47) and (10.48) can be extended as the following conditional expectation and conditional variance:

$$E[Z|\text{small outbreak}] = \frac{1}{1 - R_0^*} \quad (10.49a)$$

$$\text{var}[Z|\text{small outbreak}] = \frac{\pi G''_N(\pi) + R_0^*[1 - R_0^*]}{(1 - R_0^*)^3} \quad (10.49b)$$

where (10.49a) and (10.49b) are extensions of (10.47) and (10.48) in the sense that they are valid for both  $R_0 > 1$  and  $R_0 < 1$ . For the latter,  $\pi = 1$  and  $G'_N(\pi) = R_0$ .

The Distribution of  $Z$

We treat  $G_Z(s) = \sum_{z=1}^{\infty} s^z \Pr\{Z = z\}$  as if a p.g.f. for both  $R_0 > 1$  and  $R_0 < 1$ , such that  $\Pr\{Z = z\} = \frac{1}{z!} G_Z^{(z)}(0)$  and  $G_Z^{(z)}(0) = \frac{d^z}{ds^z} G_Z(s)|_{s=0}$ . If  $R_0 > 1$ ,

$$\Pr\{Z = z|\text{small outbreak}\} = \frac{1}{\pi} \Pr\{Z = z\}$$

is the conditional distribution of the final size starting from one initial infective, conditioning on the outcome being a small outbreak.

For any given p.g.f.  $G_N(\cdot)$ , a closed analytic form of  $G_Z(s)$  may not always exist if one wants to solve  $G_Z(s) = sG_N(G_Z(s))$ . However,  $G_Z^{(z)}(0)$  can be sometimes solved recursively starting from  $\Pr\{Z = 1\} = G'_Z(0)$ . We use the convention that

$$\Pr\{Z = 1\} = G'_Z(0) = G_N(0) = \Pr\{N = 0\}$$

because the event  $\{Z = 1\}$  implies that there is no secondary transmission in the population. There is also a convention that  $G_Z(0) = \Pr\{Z = 0\} = 0$  as there must be at least one infective individuals to start an outbreak. The recursive procedure can be demonstrated for  $\Pr\{Z = 2\}$  and  $\Pr\{Z = 3\}$ . From (10.46b),  $G''_Z(0) = 2G'_N(G_Z(0))G'_Z(0) = 2G'_N(0)G_N(0)$ , which gives

$$\Pr\{Z = 2\} = \frac{1}{2}G''_Z(0) = \Pr\{N = 1\} \Pr\{N = 0\}.$$

It is the probability that the index case gives transmission to one individual with probability  $\Pr\{N = 1\}$  and the second individual does not transmit with probability  $\Pr\{N = 0\}$ . With a bit more calculus,  $G_Z^{(3)}(0) = 3G''_N(0)[G_N(0)]^2 + 6[G'_N(0)]^2 G_N(0)$  so that  $\Pr\{Z = 3\} = \frac{1}{6}G_Z^{(3)}(0)$  can be expressed as

$$\begin{aligned} \Pr\{Z = 3\} &= \frac{1}{2}G''_N(0)[G_N(0)]^2 + [G'_N(0)]^2 G_N(0) \\ &= \Pr\{N = 2\} (\Pr\{N = 0\})^2 + (\Pr\{N = 1\})^2 \Pr\{N = 0\}. \end{aligned}$$

It implies that either the index case produces two secondary cases with probability  $\Pr\{N = 2\}$  and neither of the secondary cases produces further transmission with probability  $(\Pr\{N = 0\})^2$ ; or the index case produces one transmission and the secondary case produce one transmission with joint probability  $(\Pr\{N = 1\})^2$  and the third case does not transmit with probability  $\Pr\{N = 0\}$ .

### The Case of Negative-Binomial Distribution for $N$

When  $G_N(s)$  has a relatively simple form, one can use  $G_N(s)$  and the recursive procedure to generate the entire distribution  $\frac{1}{\pi} \Pr\{Z = z\}$ . Let  $G_N(s) = \frac{1}{[1 + R_0\phi(1-s)]^{\frac{1}{\phi}}}$ .  $G_Z(s) = sG_N(G_Z(s))$  can be written as:

$$G_Z(s) = \frac{s}{[1 + R_0\phi(1 - G_Z(s))]^{\frac{1}{\phi}}}. \quad (10.50)$$

For  $z = 1$ ,  $\Pr\{Z = 1\} = G'_Z(0) = \frac{1}{[1+R_0\phi]^{\frac{1}{\phi}}}$ . We can calculate recursively for  $z \geq 2$ ,  $G_Z^{(z)}(0) = \prod_{j=0}^{z-2} (j\phi + z) \left(\frac{1}{\phi R_0 + 1}\right)^{\frac{z}{\phi}} \left(\frac{R_0}{\phi R_0 + 1}\right)^{z-1}$  and hence  $\Pr\{Z = z|\text{small outbreak}\}$  is

$$\frac{1}{\pi} \Pr\{Z = z\} = \frac{1}{\pi z!} \prod_{j=0}^{z-2} (j\phi + z) \left(\frac{1}{\phi R_0 + 1}\right)^{\frac{z}{\phi}} \left(\frac{R_0}{\phi R_0 + 1}\right)^{z-1}, \quad (10.51)$$

where  $\pi$  needs to be numerically calculated from the equation  $\pi = \frac{1}{[1+R_0\phi(1-\pi)]^{\frac{1}{\phi}}}$  if  $R_0 > 1$ . When  $R_0 < 1$ , the mean and variance with respect to (10.51) is

$$E[Z] = \frac{1}{1 - R_0}, \quad \text{var}[Z] = \frac{(1 + \phi)R_0^2 + R_0(1 - R_0)}{(1 - R_0)^3}. \quad (10.52)$$

*Example 5.* When  $\phi \rightarrow 0$  and  $R_0 < 1$ , (10.51) is

$$\Pr\{Z = z\} = \frac{(R_0 z)^{z-1}}{z!} e^{-R_0 z}. \quad (10.53)$$

This distribution was first discovered by Borel (1942) and called the Borel-Tanner distribution. It is discussed in Durrett [33] as Corollary 2.6.2. Its variance is  $\text{var}[Z] = \frac{R_0}{(1-R_0)^3}$ .

*Example 6.* When  $\phi = 1$  and  $R_0 < 1$ , (10.51) is

$$\Pr\{Z = z\} = \frac{1}{z!} \prod_{j=0}^{z-2} (j + z) \left(\frac{1}{1 + R_0}\right)^z \left(\frac{R_0}{1 + R_0}\right)^{z-1}. \quad (10.54)$$

This distribution can be found as (6.619) in Mode and Sleeman [10]. Its variance is  $\text{var}[Z] = \frac{R_0(R_0+1)}{(1-R_0)^3}$ .

When  $R_0 > 1$ , to calculate the condition mean  $E[Z|\text{small outbreak}]$  and the conditional variance  $\text{var}[Z|\text{small outbreak}]$ , one uses (10.49a) and (10.49b) for the calculation and substitutes  $R_0^* = G'_N(\pi) = \frac{R_0}{(1+\phi R_0(1-\pi))^{\frac{1}{\phi}+1}}$  and  $G''_N(\pi) = \frac{(1+\phi)R_0^2}{(1+\phi R_0(1-\pi))^{\frac{1}{\phi}+2}}$ . In the geometric distribution where  $\phi = 1$  and  $\pi = \frac{1}{R_0}$ , one gets simple expressions for  $R_0 > 1$  [10, p. 196]

$$E[Z|\text{small outbreak}] = \frac{R_0}{R_0 - 1}, \quad \text{var}[Z|\text{small outbreak}] = \frac{R_0(R_0 + 1)}{(R_0 - 1)^3}.$$

### 10.5.3 Behaviour of a Large Outbreak in its Initial Phase: The Intrinsic Growth

For the assessment of the risk of a large outbreak  $1 - \pi$  and quantities associated with a small outbreak, it is sufficient to know the distribution for  $N$ , without the necessity of knowing the distributions for the latent and infectious periods. On the other hand, should a large outbreak occur, the intrinsic growth rate  $r$ , also known as the Malthusian parameter, for  $E[I(t)] \propto e^{rt}$ , depends crucially on the latent and infectious periods distributions. In other words, even detailed information of the distribution for  $N$  is not sufficient. One needs to know the stochastic mechanisms that manifest the distribution for  $N$ .

Yan [34] re-writes the equation (10.39) under the following conditions:

1. The infectious contact process  $\{K(x)\}$  has stationary increment  $\beta(x) \equiv \beta$  over the infectious period
2.  $T_E$  and  $T_I$  are independent
3. The Laplace transforms for the latent period and the infectious period:  $\mathcal{L}_E(r) = \int_0^\infty e^{-rx} f_E(x) dx$  and  $\mathcal{L}_I^*(r) = \int_0^\infty e^{-rx} \bar{F}_I(x) dx$  exist, then

$$\beta \mathcal{L}_E(r) \mathcal{L}_I^*(r) = 1, \quad (10.55)$$

implying that, the property of the infectious contact process  $\{K(x)\}$  as summarized by the parameter  $\beta$ , the distribution of the latent period as summarized by  $\mathcal{L}_E(r)$  and the distribution of the infectious period as summarized by  $\mathcal{L}_I^*(r)$ , separately shape the shape of  $E[I(t)]$  during the initial phase of an outbreak and a general relationship between the intrinsic growth rate  $r$  and the basic reproduction number  $R_0$ .

In fact,  $\int_0^\infty e^{-r\tau} \beta(\tau) A(\tau) d\tau = 1$  becomes

$$\beta \int_0^\infty e^{-r\tau} [\bar{F}_{E+I}(\tau) - \bar{F}_E(\tau)] d\tau = \beta [\mathcal{L}_{E+I}^*(r) - \mathcal{L}_E^*(r)] = 1,$$

where  $\mathcal{L}_{E+I}^*(r) = \int_0^\infty e^{-r\tau} \bar{F}_{E+I}(\tau) d\tau$  and  $\mathcal{L}_E^*(r) = \int_0^\infty e^{-r\tau} \bar{F}_E(\tau) d\tau$ . Since  $T_E$  and  $T_I$  are independent, the Laplace transform of the generation time  $T_E + T_I$  is  $\mathcal{L}_{E+I}(r) = \mathcal{L}_E(r) \mathcal{L}_I(r)$ . By writing  $\mathcal{L}_{E+I}^*(r) = \frac{1 - \mathcal{L}_E(r) \mathcal{L}_I(r)}{r}$  and  $\mathcal{L}_E^*(r) = \frac{1 - \mathcal{L}_E(r)}{r}$ , one immediately gets  $\beta \mathcal{L}_E(r) \mathcal{L}_I^*(r) = 1$  in (10.55). Since  $R_0 = \beta\mu$ , one further gets

$$R_0 = \frac{\mu}{\mathcal{L}_E(r) \mathcal{L}_I^*(r)} = \begin{cases} \frac{1}{\mathcal{L}_E(r)}, & \text{if } E[T_I] \rightarrow 0, \\ \frac{\mu}{\mathcal{L}_I^*(r)}, & \text{if } E[T_E] = 0. \end{cases} \quad (10.56)$$

The necessary condition for  $r > 0$  is  $R_0 > 1$ . Together with  $R_0 = \beta\mu$ , one gets  $\mu > \beta^{-1}$ . In this case, the relationship (10.55) can be illustrated in

Fig. 10.12, where  $\mathcal{L}_E(r)\mathcal{L}_I^*(r) = \int_0^\infty e^{-r\tau} A(\tau) d\tau$  is a decreasing function of  $r$ , satisfying  $\lim_{r \rightarrow 0} \mathcal{L}_E(r)\mathcal{L}_I^*(r) = \mu > \frac{1}{\beta}$  and  $\lim_{r \rightarrow \infty} \mathcal{L}_E(r)\mathcal{L}_I^*(r) = 0$ .

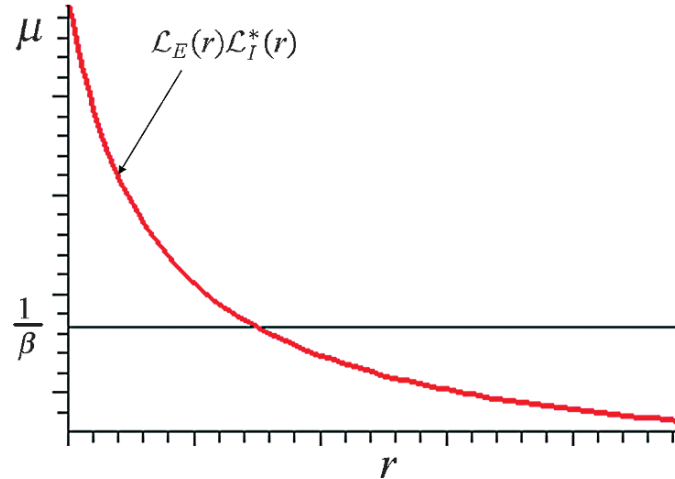


Fig. 10.12 Expression (10.55) as illustrated

Recalling the discussions on stochastic ordering and the relationship in (10.8), one can immediately see that when  $\beta$  is fixed, stochastic ordering of the latent and infectious periods determines the intrinsic growth rate  $r$ . Therefore we have the following two propositions.

**Proposition 4.** *When  $\beta$  and the infectious period distribution  $F_I(x)$  are given, the longer the latent period  $T_E$ , the smaller the intrinsic growth  $r$ . In this statement, the word longer refers to conditions so that  $T_E$  is larger in Laplace transform order.*

Figure 10.12 shows that, when  $\mathcal{L}_E(r)$  is smaller, the root for  $r$  in the equation  $\mathcal{L}_E(r)\mathcal{L}_I^*(r) = \beta^{-1}$  is smaller. By consequence, the existence of a latent period produces a smaller initial growth rate than that produced by a model in the absence of a latent period. Since the distribution of  $T_E$  does not affect the basic reproduction number  $R_0$ , we also have:

**Corollary 4.** *For fixed infectious period distribution  $F_I(x)$  and empirically observed  $r$ , if one takes a distribution for the latent period which is shorter in Laplace order than it really is, one underestimates  $R_0$ .*

**Proposition 5.** *When  $\beta$  and the latent period distribution  $F_E(x)$  are given, among the distributions for the infectious period with equal mean value  $\mu = E[T_I]$ , the longer the infectious period  $T_I$ , the larger is the intrinsic growth rate  $r$ . In this statement, the word longer refers to conditions so that  $T_I$  is larger in Laplace transform order.*

Figure 10.12 shows that, when  $\mathcal{L}_I^*(r) = \frac{1-\mathcal{L}_I(r)}{r}$  is larger, the root for  $r$  in the equation  $\mathcal{L}_E(r)\mathcal{L}_I^*(r) = \beta^{-1}$  is larger. In addition, the comparison is restricted to infectious periods with equal mean value  $\mu = E[T_I]$  because  $R_0 = \beta\mu$  so that comparisons can be made under the same basic reproduction number.

**Corollary 5.** *Given empirically observed  $r$  and mean infectious period  $\mu$ , if one takes a distribution for the infectious period which is larger in Laplace transform order than what it should be, one underestimates  $R_0$ .*

**10.5.3.1 The Expressions (10.55) and (10.56) When the Distributions of  $T_E$  and  $T_I$  Arise from Some Specific Parametric Families**

The gamma distribution with p.d.f. given in (10.7), re-parametrized by  $\alpha = \frac{\kappa}{\mu}$  gives  $f_X(x) = \frac{\alpha(\alpha x)^{\kappa-1}}{\Gamma(\kappa)}e^{-\alpha x} = \frac{\frac{\kappa}{\mu}(\frac{\kappa}{\mu}x)^{\kappa-1}}{\Gamma(\kappa)}e^{-\frac{\kappa}{\mu}x}$  such that  $E[X] = \mu$  and  $var[X] = \frac{\mu^2}{\kappa}$ . The Laplace transform exists and has a simple expression  $\mathcal{L}_X(r) = (1 + \frac{r\mu}{\kappa})^{-\kappa}$  and hence  $\mathcal{L}_X^*(r) = \frac{1-(1+\frac{r\mu}{\kappa})^{-\kappa}}{r}$ .

If two random variables  $T_E$  and  $T_I$  are both gamma distributed, we reserve  $\mu = E[T_I]$  for the mean infectious period. We introduce  $\nu = E[T_E]$  for the mean latent period. Thus,

$$\mathcal{L}_E(r) = \left(1 + \frac{r\nu}{\kappa_1}\right)^{-\kappa_1}, \quad \mathcal{L}_I^*(r) = \frac{1 - \left(1 + \frac{r\mu}{\kappa_2}\right)^{-\kappa_2}}{r}$$

where  $\kappa_1$  and  $\kappa_2$  are the shape parameters for the latent and infectious periods when both are gamma distributed. In this case, The expressions (10.55) and (10.56) become

$$\frac{\beta}{r} \left(1 + \frac{r\nu}{\kappa_1}\right)^{-\kappa_1} \left(1 - \left(1 + \frac{r\mu}{\kappa_2}\right)^{-\kappa_2}\right) = 1 \tag{10.57a}$$

$$R_0 = \frac{r\mu \left(1 + \frac{r\nu}{\kappa_1}\right)^{\kappa_1}}{1 - \left(1 + \frac{r\mu}{\kappa_2}\right)^{-\kappa_2}}. \tag{10.57b}$$

The expression (10.57b) was originally given by Anderson and Watson [35] and recently re-visited by Wearing et al. [36] It has many special cases as summarized by Table 10.5.

In particular, Cases C1, C4, C5, C7 and C11 are highlighted below

**Table 10.5** Special cases with gamma distributed latent and infectious periods

Cases	$\nu$	$\mu$	$\kappa_1$	$\kappa_2$	$\mathbf{R}_0$
C1	$\nu$	$\rightarrow 0$	$\rightarrow \infty$	$\kappa_2$	$e^{r\nu} = e^{rT_G}$
C2	$\nu$	$\rightarrow 0$	$= 1$	$\kappa_2$	$1 + r\nu = 1 + rE[T_G]$
C3	$\nu$	$\rightarrow 0$	$\kappa_1$	$\kappa_2$	$\left(1 + \frac{r\nu}{\kappa_1}\right)^{\kappa_1}$
C4	0	$\mu$	$\kappa_1$	$\rightarrow \infty$	$\frac{r\mu}{1-e^{-r\mu}} = \frac{rT_G}{1-e^{-rT_G}}$
C5	0	$\mu$	$\kappa_1$	$= 1$	$1 + r\mu = 1 + rE[T_G]$
C6	0	$\mu$	$\kappa_1$	$\kappa_2$	$\frac{r\mu}{1-\left(1+\frac{r\mu}{\kappa_2}\right)^{-\kappa_2}}$
C7	$\nu$	$\mu$	$\rightarrow \infty$	$\rightarrow \infty$	$e^{r\nu} \frac{r\mu}{(1-e^{-r\mu})}$
C8	$\nu$	$\mu$	$= 1$	$\rightarrow \infty$	$(1+r\nu) \frac{r\mu}{1-e^{-r\mu}}$
C9	$\nu$	$\mu$	$\kappa_1$	$\rightarrow \infty$	$\left(1 + \frac{r\nu}{\kappa_1}\right)^{\kappa_1} \frac{r\mu}{1-e^{-r\mu}}$
C10	$\nu$	$\mu$	$\rightarrow \infty$	$= 1$	$e^{r\nu} (1+r\mu)$
C11	$\nu$	$\mu$	$= 1$	$= 1$	$(1+r\nu)(1+r\mu)$
C12	$\nu$	$\mu$	$\kappa_1$	$= 1$	$\left(1 + \frac{r\nu}{\kappa_1}\right)^{\kappa_1} (1+r\mu)$
C13	$\nu$	$\mu$	$\rightarrow \infty$	$\kappa_2$	$e^{r\nu} \frac{r\mu}{1-\left(1+\frac{r\mu}{\kappa_2}\right)^{-\kappa_2}}$
C14	$\nu$	$\mu$	$= 1$	$\kappa_2$	$(1+r\nu) \frac{r\mu}{1-\left(1+\frac{r\mu}{\kappa_2}\right)^{-\kappa_2}}$
General	$\nu$	$\mu$	$\kappa_1$	$\kappa_2$	$\left(1 + \frac{r\nu}{\kappa_1}\right)^{\kappa_1} \frac{r\mu}{1-\left(1+\frac{r\mu}{\kappa_2}\right)^{-\kappa_2}}$

$$R_0 = e^{rE[T_G]} \quad (10.58a)$$

$$R_0 = \frac{r\mu}{1-e^{-r\mu}} \quad (10.58b)$$

$$R_0 = 1 + r\mu \quad (10.58c)$$

$$R_0 = e^{r\nu} \frac{r\mu}{1-e^{-r\mu}} \quad (10.58d)$$

$$\begin{aligned} R_0 &= (1+r\nu)(1+r\mu) \\ &= 1 + rE[T_G] + f(1-f)(rE[T_G])^2, \end{aligned} \quad (10.58e)$$

where  $f = \frac{E[T_E]}{E[T_G]} = \frac{\nu}{\nu+\mu}$ . Of these expressions, (10.58a) is the most intuitive and appears in ecology textbooks (e.g. [37]), assuming that the variation in the generation time  $T_G$  is negligible and only if  $T_G = T_E$  so that transmission only occurs at an instantaneous moment at the end of the latent period. In the absence of a latent period, a non-random infectious period gives (10.58b) which can be found in Anderson and May [38]. The most commonly encountered relationship is (10.58c) which can be derived from the deterministic or stochastic SIR models assuming an exponentially distributed infectious period without a latent period, as in Chap. 2 of this book. If one assumes that both  $T_E = \nu$  and  $T_I = \mu$  are not random, one gets (10.58d). In recent years, (10.58e) is frequently seen in the literature, such as Lipsitch et al. [39] in the application to the SARS epidemic in Singapore; Chowell et al. [40] for



influenza, etc. The underlying assumption in (10.58e) is that both the latent and infectious periods are exponentially distributed.

For gamma distributed latent period, the Laplace transform is  $\mathcal{L}_E(r) = \left(1 + \frac{r\nu}{\kappa_1}\right)^{-\kappa_1}$ . Both  $\nu$  and  $\kappa_1$  rank  $T_E$  according to Laplace transform order. For fixed  $\kappa_1$

$$\frac{d}{d\nu} \mathcal{L}_E(r) = -\frac{r}{\left(\frac{1}{\kappa_1}(\kappa_1 + r\nu)\right)^{\kappa_1+1}} < 0,$$

implying that the longer the mean latent period, the larger the latent period in Laplace transform order. On the other hand, for the same mean latent period  $\nu$ ,

$$\frac{d}{d\kappa_1} \mathcal{L}_E(r) = -\frac{\kappa_1^{\kappa_1}}{(\kappa_1 + r\nu)^{\kappa_1+1}} \left[ (\kappa_1 + r\nu) \log \frac{\kappa_1 + r\nu}{\kappa_1} - r\nu \right] < 0,$$

implying that the larger the value of the shape parameter  $\kappa_1$  (hence the smaller the variance  $var[T_E] = \frac{\nu^2}{\kappa_1}$ ), the smaller the value of  $\mathcal{L}_E(r)$  and hence the longer the latent period in Laplace transform order. In both cases, if  $\beta$  and  $\mathcal{L}_I^*(r)$  are fixed, a longer latent period in Laplace transform order implies a smaller value of  $r$ .

Two benchmarks are  $\kappa_1 = 1$  and  $\kappa_1 \rightarrow \infty$ . Among a subset of the gamma distribution with  $\kappa_1 \geq 1$ , for the same  $R_0$ , the exponentially distributed latent period gives the largest  $r$ . When the latent period distribution degenerates to a fixed point with  $T_E = \nu$ , one gets the smallest  $r$ . Conversely, if  $r$  is empirically observed, then the exponentially distributed latent period yields the smallest  $R_0$  whereas the fixed latent period yields the largest  $R_0$ .

To examine the effects of the infectious period distribution on  $r$  with a given latent period distribution  $F_E(x)$ , since  $R_0 = \beta\mu$ , we only consider distributions for the infectious period with equal mean value  $\mu = E[T_I]$ . Under this condition, the longer the infectious period  $T_I$  in Laplace transform order, the larger is the intrinsic growth rate  $r$ . For gamma distributed infectious period,  $\mathcal{L}_I^*(r) = \frac{1 - \left(1 + \frac{r\mu}{\kappa_2}\right)^{-\kappa_2}}{r}$  and

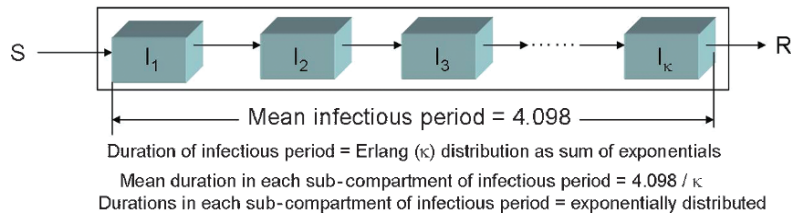
$$\frac{d}{d\kappa_2} \mathcal{L}_I^*(r) = \frac{\kappa_2^{\kappa_2}}{r(\kappa_2 + r\mu)^{\kappa_2+1}} \left[ (\kappa_2 + r\mu) \log \frac{\kappa_2 + r\mu}{\kappa_2} - r\mu \right] > 0.$$

In this case, since we keep the mean  $\mu = E[T_I]$  fixed and  $var[T_I] = \frac{\mu}{\kappa_2}$ , a longer infectious period  $T_I$  in Laplace transform order implies that the variance is smaller. In other words, under the same  $R_0$  and fixed latent period distribution, a gamma distributed infection period with smaller variance produces larger initial growth rate. Among a subset of the gamma distribution with  $\kappa_2 \geq 1$ , for the same  $R_0$ , the exponentially distributed infectious period ( $\kappa_2 = 1$ ) gives the smallest  $r$  and the fixed infectious period ( $\kappa_2 \rightarrow \infty$ ) gives the largest  $r$ . Conversely, if  $r$  is empirically observed and if the mean

infectious period  $\mu$  is given (along with the given latent period distribution), the larger the value  $\kappa_2$  (hence the smaller the variance), the smaller the  $R_0$ . This can be also seen by taking the derivative of (10.57b) with respect to  $\kappa_2$ :

$$\frac{d}{d\kappa_2} R_0 = -\frac{r\mu\kappa_2^{\kappa_2} (\kappa_1 + r\nu)^{\kappa_1} \left[ (\kappa_2 + r\mu) \log \frac{1}{\kappa_2} (\kappa_2 + r\mu) - r\mu \right]}{\kappa_1^{\kappa_1} (\kappa_2 + r\mu)^{1-\kappa_2} (\kappa_2^{\kappa_2} - (\kappa_2 + r\mu)^{\kappa_2})^2} < 0.$$

*Example 7.* Let us consider an SIR model without the latent period. Let us assume that the infectious contacts arise from a Poisson process and that the infectious period has mean  $\mu = 4.098$ . In this example, let  $R_0 = \beta\mu = 1.386$ . The infectious period  $T_I$  has the distribution  $f_I(x) = \frac{\kappa^\kappa x^{\kappa-1}}{\mu^\kappa \Gamma(\kappa)} e^{-\frac{\kappa x}{\mu}}$ ,  $\mu > 0, \kappa = 1, 2, 3, \dots$ , a special case of the gamma distribution (the Erlang distribution) with integer-valued  $\kappa$ . It can be viewed as the distribution of the sum of  $\kappa$  i.i.d. exponential random variables with mean  $\frac{\mu}{\kappa}$ . A “linear chain trick” is to consider a compartment model as given by Fig. 10.13 and to use deterministic ordinary differential equations to numerically calculate  $I(t) \approx E[I(t)]$ . Figure 10.14 shows results with  $\kappa = 1, 2, 3, 4$ . When  $\kappa = 1$ ,



**Fig. 10.13** Illustration of the linear chain trick

the model reduces to the SIR model with exponentially distributed infectious period with  $r = \frac{R_0-1}{\mu} = \frac{0.386}{4.098} = 0.094192$ . The larger the  $\kappa$ , the steeper the initial increase one expects. If  $\kappa = 4$ ,  $r$  can be solved via the equation:  $\frac{1.386}{4.098r} \left( 1 - \left( 1 + \frac{4.098r}{4} \right)^{-4} \right) = 1$  for the non-negative real value. The solution is  $r = 0.14122$ .

One can replace the gamma distribution for the latent or the infectious period by other distributions, provided that their Laplace transforms exist. For example, one may consider an inverse-Gaussian distribution for a non-negative random variable  $X$  with p.d.f.

$$f_X(x) = \sqrt{\frac{\kappa\mu}{2\pi x^3}} \exp \left\{ -\frac{\kappa(x - \mu)^2}{2\mu x} \right\}, \quad \mu, \kappa > 0. \tag{10.59}$$

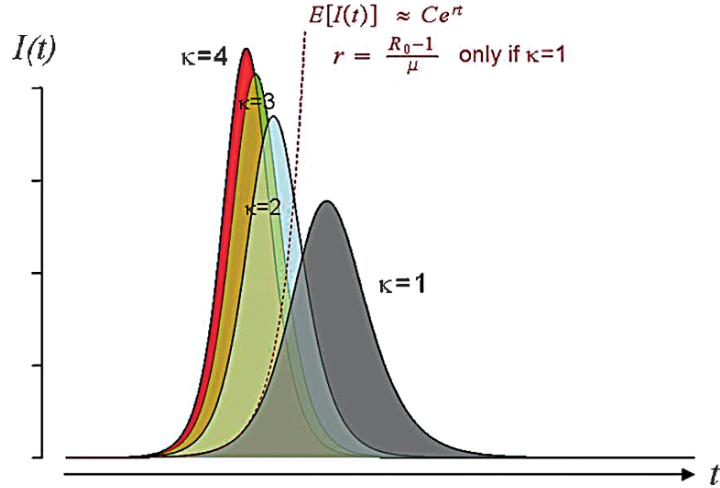


Fig. 10.14 Same  $R_0$  : the larger the  $\kappa$ , the larger the growth rate  $r$

It has been parametrized such that  $E[X] = \mu$  and  $var[X] = \frac{\mu^2}{\kappa}$ , like for the gamma distribution. The Laplace transform is  $\mathcal{L}_X(r) = \exp \left\{ \kappa \left( 1 - \sqrt{\frac{2r\mu + \kappa}{\kappa}} \right) \right\}$ .

If two random variables  $T_E$  and  $T_I$  are both inverse-Gaussian distributed, as before, we reserve  $\mu = E[T_I]$  for the mean infectious period and use  $\nu = E[T_E]$  for the mean latent period. Then  $\mathcal{L}_E(r) = \exp \left\{ \kappa_1 \left( 1 - \sqrt{\frac{2r\nu + \kappa_1}{\kappa_1}} \right) \right\}$  and  $\mathcal{L}_I^*(r) = \frac{1 - \exp \left\{ \kappa_2 \left( 1 - \sqrt{\frac{2r\mu + \kappa_2}{\kappa_2}} \right) \right\}}{r}$ . The expressions (10.55) and (10.56) become

$$\frac{\beta}{r} \exp \left\{ \kappa_1 \left( 1 - \sqrt{\frac{2r\nu + \kappa_1}{\kappa_1}} \right) \right\} \left( 1 - \exp \left\{ \kappa_2 \left( 1 - \sqrt{\frac{2r\mu + \kappa_2}{\kappa_2}} \right) \right\} \right) = 1,$$

$$R_0 = \frac{1}{\exp \left\{ \kappa_1 \left( 1 - \sqrt{\frac{2r\nu + \kappa_1}{\kappa_1}} \right) \right\}} \times \frac{r\mu}{1 - \exp \left\{ \kappa_2 \left( 1 - \sqrt{\frac{2r\mu + \kappa_2}{\kappa_2}} \right) \right\}}.$$

Similar to Table 10.5, one can make a table of all the special cases; see Table 10.6.

One does not need to assume that the latent and infectious periods arise from the same distribution family. For example, one may take an inverse-Gaussian distributed latent period to combine with a gamma distributed infectious period and derive

$$R_0 = \frac{1}{\exp \left\{ \kappa_1 \left( 1 - \sqrt{\frac{2r\nu + \kappa_1}{\kappa_1}} \right) \right\}} \times \frac{r\mu}{1 - \left( 1 + \frac{r\mu}{\kappa_2} \right)^{-\kappa_2}}$$

**Table 10.6** Cases with inv.-Gaussian distributed latent and infectious periods

	$\nu$	$\mu$	$\kappa_1$	$\kappa_2$	$\mathbf{R}_0$	Remarks
C1	$\nu$	$\rightarrow 0$	$\rightarrow \infty$	$\kappa_2$	$e^{r\nu} = e^{rT_G}$	C1 in Table 10.5
C2	$\nu$	$\rightarrow 0$	$= 1$	$\kappa_2$	$\frac{1}{\exp(1-\sqrt{1+2r\nu})}$	
C3	$\nu$	$\rightarrow 0$	$\kappa_1$	$\kappa_2$	$\frac{1}{\exp\left\{\kappa_1\left(1-\sqrt{\frac{2r\nu+\kappa_1}{\kappa_1}}\right)\right\}}$	
C4	$0$	$\mu$	$\kappa_1$	$\rightarrow \infty$	$\frac{r\mu}{1-e^{-r\mu}}$	C4 in Table 10.5
C5	$0$	$\mu$	$\kappa_1$	$= 1$	$\frac{r\mu}{1-\exp\left\{\left(1-\sqrt{2r\mu+1}\right)\right\}}$	
C6	$0$	$\mu$	$\kappa_1$	$\kappa_2$	$\frac{r\mu}{1-\exp\left\{\kappa_2\left(1-\sqrt{\frac{2r\mu+\kappa_2}{\kappa_2}}\right)\right\}}$	
C7	$\nu$	$\mu$	$\rightarrow \infty$	$\rightarrow \infty$	$e^{r\nu} \frac{r\mu}{1-e^{-r\mu}}$	C7 in Table 10.5
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	Other cases

or a gamma distributed latent period to combine with an inverse-Gaussian distributed infectious period and derive

$$R_0 = \left(1 + \frac{r\nu}{\kappa_1}\right)^{\kappa_1} \frac{r\mu}{1 - \exp\left\{\kappa_2\left(1 - \sqrt{\frac{2r\mu+\kappa_2}{\kappa_2}}\right)\right\}}.$$

### 10.5.4 Summary for the Initial Phase of an Outbreak

#### 10.5.4.1 Invasion and Everything about a Small Outbreak

The latent period does not play any role. Knowledge of the distribution for  $N$  is sufficient. One uses the p.g.f.  $G_N(s)$  to calculate the probability  $1-\pi$  for the risk of a large outbreak. If the outbreak is small,  $G_N(s)$  further determines the distribution of the generation time to extinction  $\Pr\{T_g \leq g\}$  and final size at extinction  $\Pr\{Z = z\}$ .

If the distribution of  $N$  can be derived from observed data, then details with respect to underlying stochastic mechanisms that give rise to  $G_N(s)$ , such as the property of the infectious contact process  $\{K(x)\}$  and infectious period distribution  $F_I(x)$ , are irrelevant.

On the other hand, with knowledge of the property of the infectious contact process  $\{K(x)\}$  and the infectious period distribution  $F_I(x)$ , one can use the CMJ branching process to derive the p.g.f.  $G_N(s)$  for  $N$ .

#### 10.5.4.2 When the Outbreak is Large

The initial phase of a large outbreak is characterized by the approximation  $E[I(t)] \propto e^{rt}$ . Under the condition that  $\{K(x)\}$  has stationary increment

property,  $r$  is determined by (10.55). It shows that  $\beta$ , the distribution of the latent period and the distribution of the infectious period separately shape the shape of  $E[I(t)]$  during the initial phase. However, the distribution for  $N$  is irrelevant.

## 10.6 Beyond the Initial Phase: The Final Size of Large Outbreaks

For a large outbreak, the expected final outbreak size number scales linearly with the size of the susceptible population. In other words,  $E[Z] \rightarrow \infty$  but  $\frac{E[Z]}{n} \rightarrow \eta$  where  $\eta$  is a positive quantity,  $0 < \eta < 1$ . Therefore, one considers the continuous random variable  $Y = \frac{Z}{n}$ , distributed over the range  $(0, 1)$ , as the final size.

**Theorem 1.** *When  $R_0 > 1$ , conditioning on the outcome being a large outbreak and assuming that  $\lim_{n \rightarrow \infty} \frac{I_0}{n} \rightarrow \varepsilon$ , let  $\eta$  be the root of the equation*

$$1 - \eta = \exp(-R_0(\eta + \varepsilon)). \quad (10.60)$$

*Then  $\frac{S_\infty - n\eta}{\sqrt{n}}$  has Gaussian limit distribution  $N(0, \sigma^2)$  and the asymptotic variance is given by*

$$\sigma^2 = \frac{\eta(1-\eta)}{(1-R_0\eta)^2} + \frac{\eta^2(\text{var}[N] - R_0)(1-\eta+\varepsilon)}{(1-R_0\eta)^2}. \quad (10.61)$$

This central limit theorem has been developed from different mathematical approaches by von Bahr and Martin-Löf [12], Ludwig [41], Scalia-Tomba [42], Martin-Löf [43] and Lefèvre and Picard [44]. The final size proportion  $Y = \frac{Z}{n}$  converges in distribution to a point mass at  $\eta$ , the root of (10.60). The fluctuations around the limit are Gaussian of order  $\frac{1}{\sqrt{n}}$ , which become large if the variance  $\text{var}[N]$  is large. Contrary to the study of the intrinsic growth rate  $r$  at the initial phase, the final size is more robust with respect to the stochastic mechanisms at the micro level. Even the distribution of  $N$  does not play a significant role, except for its first two moments:  $R_0 = E[N]$  and  $\text{var}[N]$ .

In von Bahr and Martin-Löf [12], Theorem 1 was first proven under a Reed-Frost epidemic model [45]. For such a model, it is assumed that an individual  $i$  is infected at time  $t$ . A given individual  $j$  is contacted by  $i$  and if  $j$  is susceptible then  $j$  becomes infected at time  $t + 1$ . Meanwhile,  $i$  becomes removed (by immunity or death) and plays no further part in the epidemic process. All contacts are assumed to be independent of each other. At each increment of time from  $t$  to  $t + 1$ , an individual produces a random number of infectious contacts among the available susceptible individuals following a binomial distribution. When  $n$  is large, the binomial distribution

is approximated by a Poisson distribution. von Bahr and Martin-Löf [12] then extended their proof to the randomized epidemic model where each infectious individual  $i$  has its own transmission probability per contact  $p_i$ ; the  $p_i$  are i.i.d. random variables with a given distribution.

Earlier in this chapter we made the statement that as far as the distribution for  $N$  is concerned, the generalized epidemic and the randomized epidemic models can be unified as one mixed Poisson model with  $G_N(s) = \int_0^\infty e^{\rho(s-1)} dU(\rho) = E_\rho [e^{\rho(s-1)}]$ . This corresponds to Ludwig [41], where it was noted that as far as the distribution of  $Y = \frac{Z}{n}$  is concerned, the generalized epidemic model with an arbitrary but specified infectious period distribution can be reformulated as a special case of the randomized epidemic model.

### 10.6.1 Generality of the Mean Final Size

Subject to the approximation  $\frac{S_0}{n} \approx 1$  and if one re-writes  $x = 1 - \frac{S_\infty}{S_0}$ ,  $\varepsilon = \frac{I_0}{S_0}$ , the asymptotic mean of a large outbreak (10.60) is in close agreement with that given by Kermack and Mckendrick [14], of which, given  $(R_0, S_0, I_0)$ , one solves for  $S_\infty$  in the equation

$$S_0 - S_\infty + I_0 + \frac{S_0}{R_0} \log \left( \frac{S_\infty}{S_0} \right) = 0. \quad (10.62)$$

From a deterministic perspective, Ma and Earn [46] used integro-differential equations to show that the final size calculated by (10.62) is invariant, including the existence of a latent period, arbitrarily distributed infectious period, any number of distinct infectious stages and/or a stage during which infectious individuals are isolated, as well as the existence of super-spreading events.

From a probabilistic perspective, let us consider a typical susceptible individual  $\nu_s$ . We define a type-specific hazard function

$$h_j^{(s)}(t - t_j) \begin{cases} > 0, & \text{if } t > t_j \\ = 0, & \text{otherwise,} \end{cases}$$

where  $t_j$  is the time of infection of the individual  $j$ , representing the instantaneous risk of infection being transmitted by the  $j$ th infectious individual. As illustrated by Example 4, the hazard of a susceptible individual  $\nu_s$  to become infected at time  $t$ , denoted by  $h^{(s)}(t)$ , can be thought as a competing risk problem. Under the independence assumption,  $h^{(s)}(t) = \sum_j h_j^{(s)}(t - t_j)$ . Then the probability that a susceptible individual  $\nu_s$  ever gets infected over the course of the epidemic is  $\eta_s = 1 - \exp \left\{ - \sum_j \int_0^\infty h_j^{(s)}(t - t_j) dt \right\}$ . Hence,

$\eta_s$  depends on the set of infectious contact processes that correspond to the hazard  $h_j^{(s)}$  only through the cumulative hazard  $\int_0^\infty h_j^{(s)}(t)dt$ .

Then we add two homogeneity assumptions:

1. *Homogeneous mixing.* As population size  $\rightarrow \infty$ , the contact process itself is a stationary Poisson process with constant intensity  $\lambda$ ;
2. *Homogeneous hosts.* All individuals are of the same type the probability of transmission per contact between each pair of an infectious individual and a susceptible individual is a constant  $p$ .

Under these assumptions, the type-specific hazard is  $h_j^{(s)}(t) = \beta^* = \lambda p$ . The overall hazard of a susceptible individual  $\nu_s$  to become infected at time  $t$  becomes  $h^{(s)}(t) = h(t)$  which does not depend on  $\nu_s$  (from assumption 2) and  $h(t) = \beta^* E[I(t)]$ .  $E[I(t)]$  is the expected number of infectious individuals at time  $t$ . The probability that a susceptible individual ever get infected over the course of the epidemic is

$$\eta = 1 - \exp \left\{ - \int_0^\infty h(t)dt \right\} = 1 - \exp \left\{ -\beta^* \int_0^\infty E[I(t)]dt \right\}. \quad (10.63)$$

Note that  $\int_0^\infty E[I(t)]dt$  is the expected total infectious time per person.  $\mu = E[T_I]$  is the average time spent infectious per infection. Thus,  $\int_0^\infty E[I(t)]dt = \eta S_0 E[T_I] = \eta S_0 \mu$

$$\Rightarrow \eta = 1 - \exp \{ -(\beta^* S_0 \mu) \eta \} = 1 - \exp \{ -R_0 \eta \}$$

which is (10.60) and  $R_0 = \beta^* S_0 \mu = \beta \mu$ . Ludwig [41] used this analogy in a discrete time setting, and provided a rigorous proof that the final size distribution does not depend on the duration of latency in the individuals, or on the time course of infectivity, but only on the “time-integrated infectivity” in discrete time. The “time-integrated infectivity” is analogous to  $\int_0^\infty h_j^{(s)}(t)dt$ , for closed populations with homogeneous mixing.

## 10.6.2 Some Cautionary Remarks

### 10.6.2.1 The Risk of Large Outbreak = Final Size?

In the literature, one sometimes encounter such a statement that “the risk of large outbreak = the final size of the large outbreak”. In general, this statement is not true. On one hand, the final size equations (10.60) and (10.62) are functions of  $R_0 = E[N]$ , but do not depend on the exact distribution of  $N$ . On the other hand, the risk of a large outbreak  $1 - \pi$  is determined by the equation (10.41) which is crucially dependent on  $G_N(s)$ , the probability generating function of  $N$ .

To give a counterexample, if  $N$  follows a geometric distribution, with  $R_0 > 1$ , the risk of a large outbreak is calculated with  $\pi = \frac{1}{1+R_0(1-\pi)}$  with exact solution  $\pi = \frac{1}{R_0}$ . The risk of a large outbreak is  $1 - \frac{1}{R_0}$ . On the other hand, in a Kermack–McKendrick SIR model,  $N$  follows a geometric distribution, but the final size equations are (10.60) and (10.62).

The statement holds if the outbreak can be described by a Poisson epidemic. In this case, the probability of a large outbreak is  $1 - \pi = e^{-R_0\pi}$  as derived from (10.42) and it is identical to the final size equation (10.60) as  $\varepsilon \rightarrow 0$ . Recall that a Poisson epidemic arises in the following manner.

1. As  $n \rightarrow \infty$ , the social contact network grows in such a way that at any time  $t$ , the realization can be regarded as a Bernoulli random graph [47] with Poisson degree distribution with mean  $\lambda t$ . If  $D$  is the duration of an outbreak, the random graph as observed at  $D$  is a large Bernoulli random graph approximated by a Poisson degree distribution with mean  $R_0^* = \lambda D$ .
2. The infectious contact subgraph also grows according to a Poisson degree distribution with mean  $\lambda pt = \beta t$ . Every infective has a fixed infectious period  $\mu$ . By the end of the outbreak, the observed infectious contacts makes a subgraph which is a large Bernoulli random graph with i.i.d. Poisson degree distributions with mean  $R_0 = \beta\mu$ .

Using Theorem 2.3.2. of Durrett [33] (which can be proven using random walk theory), if  $R_0^* > 1$ , with probability one, there is only one giant component with size  $\sim \eta^* n$  where  $\eta^*$  is root  $x$  of the equation  $1 - x = \exp(-R_0^* x)$  in  $(0, 1)$ . All other components are *small* in the sense that there is a constant  $\omega$  such that the largest of the remaining components can not have more than  $\omega \log n$  vertices. The infectious contact subgraph is proportional to the social contact graph with  $R_0 \propto R_0^*$  by a factor  $\frac{\beta\mu}{D}$ .

There is a difference in concept between a random graph and a realization of a random graph. The random graph belongs to a probability space. A realization of a large outbreak takes place only within the giant component of the social contact graph. Since the relative sizes of all other component in the social contact graph  $\rightarrow 0$  as  $n \rightarrow \infty$ , the size of a realized large outbreak  $\eta$  is thus proportional to  $\eta^*$  by the same factor  $\frac{\beta\mu}{D}$ . Therefore we get the final size equation  $1 - \eta = \exp(-R_0\eta)$ .

There are two independence properties involved.

1. A transmission from an infectious vertex  $v_i$  to a susceptible vertex  $v_j$  is independent from infections to other susceptible vertices derived from  $v_i$ .
2. All infectious vertices transmit the diseases independently.

A heuristic argument is that, if one randomly chooses vertex  $v_i$  to be the initial infective, the probability that it will lead to a large outbreak is the same probability that it belongs to the giant component. And hence, “the risk of a large outbreak = its final size”.



However, if there is a random period of time  $T_I^{(i)}$  to each vertex so that  $v_i$ , where  $T_I^{(i)}$ 's are i.i.d. with distribution  $F_I(x)$ , the evolution of the infectious contact subgraph will be very different from the evolution of the subgraph where every vertex has a fixed infectious period, even though the social contact network is the same Bernoulli random graph. If one chooses a vertex  $v_i$  to be the initial infective, then each of the other susceptible vertices in the graph has a probability  $\int_0^\infty (1 - e^{-\lambda px}) F_I(x)$  to be ever infected by  $v_i$ . It can be shown that the probability of  $v_i$  infects  $v_j$  is dependent on other infections of other susceptible vertices with  $v_i$  as their direct origin of transmission. By the end of the outbreak the degree of the infectious contact subgraph has the mean value  $R_0 = \lambda p E[T_I]$ . The degree distribution has p.g.f.  $G_N(s) = \int_0^\infty e^{\beta x(s-1)} dF_I(x)$ .  $N$  is associated with a larger variance, with many infectious vertices having few edges due to a shorter infectious period and some infectious vertices having a large number of vertices due to a longer infectious period. Because of the loss of independency and the large variance, the equality between the risk of a large outbreak and the final size of the large outbreak is lost in generalized epidemic models.

#### 10.6.2.2 Situations Where (10.63) may be Violated

Under the independence assumption that transmission of infection to individual  $\nu_s$  by individual  $j$  is independent from potential transmissions from other infectious individuals, then the hazard function for individual  $\nu_s$  to be infected at time  $t$  is  $h^{(s)}(t) = \sum_j h_j^{(s)}(t - t_j)$ . There are occasions that this *independent competing risk* can be violated. Such an occasion can arise in a highly clustered social contact network where a number of infectious individuals are correlated within a social cluster. Another occasion is that susceptible individuals are removed by quarantine if they have been identified as exposed to known infectives. In these circumstances, final size equations (10.60) and (10.62) may be incorrect.

### 10.7 When the Infectious Contact Process may not Have Stationary Increment

If the infectious contact process  $\{K(x)\}$  has  $\beta(x) = \frac{d}{dx} E[K(x)]$  as a function of  $x$ , (10.21) and (10.39) do not have simple forms. Most of the results discussed in previous sections will no longer apply.

### 10.7.1 The Linear Pure Birth Processes and the Yule Process

Let us consider a process without the stationary increment property, with  $\beta(x) = \frac{d}{dx}E[K(x)] = \beta e^{\beta\phi x}$  as a function of  $x$ . It can be constructed in the following manner. Consider a linear pure birth process, defined by the conditional probability with the Markov property so that  $\Pr\{K(x+h) - K(x) = 1 | \mathcal{H}^x\}$ ,  $k = 0, 1, 2, \dots$  is equal to

$$\Pr\{K(x+h) = k+1 | K(x) = k\} = (\beta_1 k + \beta_2)h + o(h). \quad (10.64)$$

Conditioning on  $K(x) = k$ , the instantaneous rate of producing the next infectious contact during  $[t, t+h)$  can be considered as an independent competing risk hazard: either from a global environment, with constant rate  $\beta_2$ , or from a clustered environment with non-constant rate  $\beta_1 k$  and  $\beta_1 \neq \beta_2$ . The hazard of producing an infectious contact at time  $x$  is

$$\lim_{h \rightarrow 0} \frac{\Pr\{K(x+h) = k+1 | K(x) = k\}}{h} = \beta_1 k + \beta_2 = \beta(k\phi + 1).$$

When  $\phi = \frac{\beta_1}{\beta_2} \rightarrow 0$ , the linear pure birth process reduces to a Poisson process with  $\beta = \beta_2$

$$\Pr\{K(x+h) = k+1 | K(x) = k\} = \beta h + o(h), \quad k = 0, 1, 2, \dots \quad (10.65)$$

When  $\phi = 1$ , the linear pure birth process is the Yule process with

$$\Pr\{K(x+h) = k+1 | K(x) = k\} = \beta(k+1)h + o(h), \quad k = 0, 1, 2, \dots \quad (10.66)$$

According to (10.66), given that an infectious individual has produced  $k$  infectious contacts by time  $x$ , the hazard for producing the  $(k+1)^{st}$  contact is an increasing function of  $k$ . Starting at  $x = 0$ , corresponding to the beginning of the infectious period for an infectious individual, the waiting time to producing the first infectious contact is exponentially distributed with mean  $E[X_1] = \frac{1}{\beta_1}$ ; conditioning on the first infectious contact, the waiting time to the second infectious contact is exponentially distributed with mean  $E[X_2] = \frac{1}{2\beta_1}; \dots$ ; and conditioning on an infectious individual who has produced  $k$  infectious contacts, the waiting time to producing the  $(k+1)^{st}$  infectious contact is exponentially distributed with mean  $E[X_{k+1}] = \frac{1}{(k+1)\beta_1}$ . On the surface, it looks as if the more infectious contacts it produces, the more likely it produces more infectious contacts.

### 10.7.1.1 A Justification of Whether the Linear Pure Birth Processes may be a Sensible Model

This infectious contact process may arise from the following hypothesis. A typical infectious individual resides in a highly clustered environment (household, hospital ward, etc.) but meanwhile has contacts with susceptible individuals from outside this environment. The contact network structures in the clustered environment is different from that in the “global” environment. During its infectious period, this individual may infect:

1. Susceptibles from the highly clustered environment such as household members (if such environment is a household) or nurses and other patients (if such environment is a clustered hospital ward), such that this network manifest data as if arising from a preferential attachment model
2. Susceptibles from a “global” environment that can be approximated by a large Bernoulli random graph

For outbreaks that mainly spread within and among a highly clustered environment, infected individuals directly and indirectly attributed to the index case during the time  $x \leq T_I$  (infectious period) are often recorded as exposed and counted as the next generation of the index case. This artificially changes the order of events and creates artificial “generations” of infectives. However, real-life epidemiologic data may arise in this “artificial” order. Let us modify the definition of  $\{K(x)\}$  so that  $K(x)$  is not only the cumulative number of infectious contacts produced directly by an infectious individual, but also includes those infected cases attributed to itself in later generations, counted up to time  $x$  when the original index case is still infectious. By time  $x$ , if an infected individual is still infectious, then

$$\begin{aligned} \lim_{h \rightarrow 0} \frac{\Pr\{K(x+h) - K(x) = 1 | K(x) = 0\}}{h} &= \beta_1 \\ \lim_{h \rightarrow 0} \frac{\Pr\{K(x+h) - K(x) = 1 | K(x) = 1\}}{h} &= 2\beta_1 \\ &\vdots \end{aligned} \quad (10.67)$$

where (10.67) implies that given the index case has produced one infectious case, and at time  $x$  both cases are infectious, the instantaneous rate of a new infectious contact attributed to the index case is due to the contribution of the index case itself and of the other infectious individual.  $\{K(x)\}$  is a Yule process which could be manifested by real epidemiologic data, if the index case resides in a highly clustered and connected environment and simultaneously gives exposure (not necessarily transmission) to a large number of people. It is the environment that manifests a large number of infected individuals (i.e. *super-spreading events*) and data “directly link” them to the first case in the environment.

### 10.7.2 *Parallels to the Preferential Attachment Model in Random Graph Theory*

In random graph theory, there is a concept of “preferential attachment” [20] of the random graphs over the space of vertices. The linear pure birth process is an analogue to such a concept over time. There is an ongoing debate whether preferential attachment actually happen in growing networks. Liljeros et al. [21] are convinced of preferential attachment as a mechanism for sexual networks, as “people become more attractive the more partners they get.” However, Jones and Handcock [48] are skeptical and argue that networks with infinitely large variances but dramatically different structures can manifest the same marginal degree distribution, whereas these different network structures produce different epidemic behaviour. This debate has a longer history. In 1919, Greenwood and Woods [49] put forward three hypotheses into the occurrence of accidents:

1. *Pure chance*, which gives rise to the Poisson process (10.65)
2. *True contagion*, i.e. initially all individuals have the same probability of incurring an accident, but this probability is modified by each accident sustained to give rise to the linear pure birth process
3. *Apparent contagion (proness)*, i.e. individuals have constant but unequal probabilities of having an accident and the resulting process being a mixed Poisson process (10.18)

Xekalaki [50] gives a comprehensive survey of the history of these hypotheses and related models. The arguments on occurrence of accidents can be equally applied to disease transmission: whether observed data can distinguish if the underlying stochastic mechanism is arising from a linear pure birth process or a mixed Poisson process with large variance. The two very different stochastic mechanisms produce quantitatively very different epidemic behaviour.

### 10.7.3 *Distributions for $N$ when $\{K(x)\}$ Arises as a Linear Pure Birth Process*

Let us start with an infectious contact process  $\{K(x)\}$  with a marginal distribution having the negative binomial form

$$\Pr\{K(x) = k\} = \frac{\Gamma(k + \frac{1}{\phi})}{\Gamma(k + 1)\Gamma(\frac{1}{\phi})} \zeta^{\frac{1}{\phi}} (1 - \zeta)^k \quad (10.68)$$

which a parameter  $0 < \zeta < 1$ .

If  $\{K(x)\}$  arises as a linear pure birth process given by (10.64), from page 274 of Bhattacharya and Waymire [51], the marginal distribution for  $K(x)$  is

$$\Pr\{K(x) = k\} = \frac{\Gamma(k + \frac{1}{\phi})}{\Gamma(k+1)\Gamma(\frac{1}{\phi})} (e^{-\beta\phi x})^{\frac{1}{\phi}} (1 - e^{-\beta\phi x})^k. \quad (10.69)$$

In this case,  $\varsigma = e^{-\beta\phi x}$ .

For comparison, a mixed Poisson process in (10.33) has marginal distribution

$$\Pr\{K(x) = k\} = \frac{\Gamma(k + \frac{1}{\phi})}{\Gamma(k+1)\Gamma(\frac{1}{\phi})} \left(\frac{1}{1 + \beta\phi x}\right)^{\frac{1}{\phi}} \left(\frac{\beta\phi x}{1 + \beta\phi x}\right)^k \quad (10.70)$$

where  $K(x)$  has p.g.f.  $G_K(s, x) = \int_0^\infty e^{\xi x(s-1)} dU(\xi)$  and  $\xi$  follows a gamma distribution. In this case,  $\varsigma = \frac{1}{1 + \beta\phi x}$ .

The link functions  $\varsigma = \frac{1}{1 + \beta\phi x}$  and  $\varsigma = e^{-\beta\phi x}$  are two hypotheses for whether  $\{K(x)\}$  has stationary increment or not. However, they are often not identifiable through data.

### 10.7.3.1 Degenerate Distribution of the Infectious Period

$$T_I = \mu$$

An infectious contact process  $\{K(x)\}$  with marginal distribution (10.68) can be further stopped by a randomly distributed infectious period to generate distributions for  $N$ . If all infectious individuals have constant infectious period  $\mu$ , then  $N$  also has a negative binomial distribution:

$$\Pr\{N = j\} = \frac{\Gamma(j + \frac{1}{\phi})}{\Gamma(j+1)\Gamma(\frac{1}{\phi})} \varsigma^{\frac{1}{\phi}} (1 - \varsigma)^j.$$

If data are available to suggest a distribution for  $N$  which is negative binomial, there may be two further assumptions, either  $\varsigma = \frac{1}{1 + \beta\phi\mu}$  or  $\varsigma = e^{-\beta\phi\mu}$ , associated with two completely different stochastic mechanisms for how  $\{K(x)\}$  arises. In addition, we have also seen a third way to get the negative distribution for  $N$ . It corresponds to  $G(s, x) = e^{-\beta x(1-s)}$  with gamma distributed infectious period and  $E[T_I] = \mu$ . Therefore, there are three stochastic mechanisms that give rise to the identical distribution for  $N$ . Observed data can not identify these underlying models.

**10.7.3.2 Exponential Distribution of the Infectious Period with  $E[T_I] = \mu$**

If  $T_I$  follows an exponential distribution with p.d.f.  $F_I(x) = \frac{1}{\mu}e^{-\frac{x}{\mu}}$  and if the infectious contacts follow a linear pure birth process with  $\Pr\{K(x) = k\}$  given by (10.69), the resulting distribution for  $N$  is

$$\int_0^\infty \frac{\Gamma(j + \frac{1}{\phi})}{\Gamma(j + 1)\Gamma(\frac{1}{\phi})} (e^{-\beta\phi x})^{\frac{1}{\phi}} (1 - e^{-\beta\phi x})^j \left(\frac{1}{\mu}e^{-\frac{x}{\mu}}\right) dx. \tag{10.71}$$

Since  $\varsigma = e^{-\beta\phi x}$ , (10.71) becomes

$$\begin{aligned} \Pr\{N = j\} &= \frac{\Gamma(j + \frac{1}{\phi})}{\Gamma(j + 1)\Gamma(\frac{1}{\phi})} \int_0^1 \varsigma^{\frac{1}{\phi}} (1 - \varsigma)^j (\theta\varsigma^{\theta-1}) d\varsigma \\ &= \theta \frac{\Gamma(j + \alpha)\Gamma(\alpha + \theta)}{\Gamma(\alpha)\Gamma(j + \alpha + \theta + 1)}, \theta > 0, \alpha = \frac{1}{\phi} > 0. \end{aligned} \tag{10.72}$$

where  $\theta = \frac{1}{\beta\phi\mu} > 0$ . It can be regarded as a mixing distribution in  $\frac{\Gamma(k + \frac{1}{\phi})}{\Gamma(k + 1)\Gamma(\frac{1}{\phi})} \int \varsigma^{\frac{1}{\phi}} (1 - \varsigma)^k u(\varsigma) d\varsigma$  with  $u(\varsigma) = \frac{1}{\beta\phi\mu} \varsigma^{\frac{1}{\beta\phi\mu} - 1} = \theta\varsigma^{\theta-1}$ ,  $0 < \varsigma < 1$ . We have seen it before as (10.36), with the power-law property:  $\propto \frac{1}{j^{\theta+1}}$ .

Notice that the same Waring distribution can also arise if  $\{K(x)\}$  has marginal distribution given by (10.70) combined with a Pareto infections period distribution. Therefore, there are multiple stochastic mechanisms that generate the distribution for  $N$  with power-law tail behaviour.

**10.7.3.3 A General Observation for Models with Non-stationary Increment Process  $\{K(x)\}$  with Random Mixing**

If  $\{K(x)\}$  arises from a non-stationary increment process described by the linear pure birth process (10.64), the marginal distribution for  $K(x)$  is given by a negative-binomial form (10.68) with the link  $\varsigma = e^{-\phi\beta x}$ . Any further assumption on randomness in  $\phi\beta x$ , such as a random infectious period, will result in a mixed negative-binomial distribution with some mixing distribution  $U(\varsigma)$ . It has been shown by Karlis and Xekalaki [52] that  $\Pr\{N = j\} \propto j^{-\theta} \sum_{l=0}^j \binom{j}{l} (-1)^{j-l} E(\varsigma^{j-\theta})$  which is a finite series of non-integral moments of the mixing distribution  $E(\varsigma^{j-\theta})$ , with a predominant power-law factor. It is heavy-tailed and power-law, if

$$\lim_{j \rightarrow \infty} \frac{\sum_{l=0}^{j+1} \binom{j+1}{l} (-1)^{j-l+1} E(\varsigma^{j-\theta+1})}{\sum_{l=0}^j \binom{j}{l} (-1)^{j-l} E(\varsigma^{j-\theta})} = 1.$$

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