Some Models and Tests for Carryover Effects and Trends in Recurrent Event Processes

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Recurrent events experienced by individual units or systems occur in many fields. The main target of this thesis is to develop formal tests for certain features of recurrent event processes, and to discuss their properties. In particular, carryover effects and time trends are considered. The former is related to clustering of events together in time, and the latter refers to a tendency for the rate of event occurrence to change over time in some systematic way. Score tests are developed for models incorporating carryover effects or time trends. The tests considered are easily interpreted and based on simple models but have good robustness properties against a range of carryover and trend alternatives. Asymptotic properties of test statistics are discussed when the number of processes approaches infinity as well as when one process is under observation for a long time. In applications involving multiple systems or individuals, heterogeneity is often apparent, and there is a need for tests developed for such cases. Allowance for heterogeneity is, therefore, considered. Methods are applied to data sets from industry and medicine. The results are supported by simulation studies.

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To Yıldız

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Chapter 1

Models and Methodology

The aim of this chapter is to introduce the research topics, concepts and notation for this thesis. A general discussion of some problems involving recurrent events is given in Section 1.1 with real life examples. We also discuss types of data. In Section 1.2 terminology and notation for recurrent event processes are briefly introduced, and some useful results are presented. We next introduce some families of models for recurrent event settings in Section 1.3. This section includes Poisson processes and renewal processes as well as more general models. We discuss multiplicative models and hypothesis testing in Section 1.4. Simulation procedures for recurrent event processes are explained in Section 1.5. In the last section, we give the outline of thesis.

1.1 Introduction

In many fields of study, processes or individuals may have a chance of experiencing events more than once over time or space in a probabilistic way. The processes that involve such recurrent events are called *recurrent event processes*, and the data generated are called *recurrent event data*.

Recurrent event processes have been extensively studied in areas such as medicine, public health, reliability, engineering, economics, insurance, and sociology. For example; in medical area, Byar (1980) and Gail et al. (1980) examine the occurrence of tumors over time, Aalen and Husebye (1991) discuss recurrent small bowel cycles; in software engineering, Dalal and McIntosh (1994) give data in debugging a large software system; in reliability, Lawless and Nadeau (1995) consider data on automobile warranty claims. Many models for recurrent events have been proposed and studied; see, for example, Cox and Isham (1980) and Daley and Vere-Jones (2003) for a wide variety of models, and Cook and Lawless (2007) for statistical methods of analysis.

In the thesis, we deal with tests for certain features of recurrent event processes. In particular, a *time trend* is often of interest in recurrent event studies. The presence of this feature amounts to a change in the rate of event occurrence in a systematic way over time. Another important feature is clustering of events. *Carryover effects* are a special type of this feature in which there is an effect for a limited time after each event occurrence. In the thesis, tests are developed to assess the presence or absence of time trends and carryover effects.

1.1.1 Examples

The following examples illustrate some problems involving recurrent event data that will be studied in the thesis.

Unscheduled maintenance events for a submarine engine

Lee (1980) presents cumulative operating hours until the occurrence of significant maintenance events ("failures") for the main propulsion diesel engine of the submarine U.S.S. Grampus No. 4. The original data set, given in Table A.1 of appendix, includes event times of 58 unscheduled corrective maintenance actions as well as 7 scheduled engine overhauls. The time axis represents the operating times (in hours of operation) of the submarine engine. The observation time ends with an observed event at time $t = 22,575$. An important issue here is to reveal whether the reliability is improving or deteriorating over time. That is, we want to check if there is a time trend in event times of unscheduled maintenance actions. Lee (1980) considered the unscheduled corrective maintenance events, and showed that there is a tendency for the rate of events to first decrease and then increase. He therefore concluded that there is a need for a more comprehensive model than a simple trend model for this data set. Another process feature that is of interest here is clustering of events in time. Statistical tests for the absence or presence of trend and clustering effects would be useful here.

Hydraulic systems of LHD machines

Load-haul-dump (LHD) machines are used to pick up ore or waste rock from mining points and for dumping it into trucks or ore passes. Kumar and Klefsjo (1992) discuss data on the time (in operating hours) between successive failures of hydraulic systems of the diesel-operated LHD machines used in Kiruna mine, Sweden. The operation and maintenance cards of LHD machines were used to collect the data for two years. Although the original data were given for a fleet of LHD machines, Kumar and Klefsjo (1992) classify the machines into 3 groups (old, medium old and new), and present data only for

2 machines from each group. The data are tabulated in Table A.2 of appendix, where LHD 1 and LHD 3 are old, LHD 9 and LHD 11 are medium old, and LHD 17 and LHD 20 are new machines. Since the end of observation times are not clearly denoted, we consider that the last failure times of each machine are the end of observation times. The main objectives of study are here to analyze any time trend in the rate of occurrence of failures and to assess the presence or absence of clustering of failures.

Asthma prevention trial

Duchateau et al. (2003) give data from an asthma prevention trial in infants. At the start of the study the subjects who were 6 months of age had not yet experienced any asthma attacks but were chosen from a population with a high risk of asthma. The follow-up period for each subject was approximately 18 months, and started after a random allocation of each subject into a placebo control group or an active drug treatment group. The main aim of this study was to assess the effect of the drug on the occurrence of asthma attacks. Furthermore, the evolution of the asthma recurrent event rate over time and how the appearance of an event influences the event rate were also of interest. Since an asthma attack can be longer than one day, and a patient is not considered at-risk over that time, the timescale of the study should be arranged accordingly. Duchateau et al. (2003) present the data for the subjects who had at least one asthma attack over the at-risk period, and discuss three different timescales; the calendar time, the gap time and the total time. A part of the data is given in Table A.3 in Appendix A.3.

1.1.2 Types of Data

Data on recurrent events are generally presented as event occurrence times or gap times between successive events with fixed or time-varying covariates. There are also applications in which the subjects are observed intermittently with only the number of events occurred between inspections available (see Cook and Lawless, 2007, Section 7.1).

Data are obtained through *prospective* or *retrospective* studies. In a prospective study the observed event history data are conditionally independent of whether a person or unit is chosen for the study, given covariates and event history prior to selection. In retrospective studies this may not be true, and it may be necessary to account for this. The time scale is usually calendar time but in some settings, especially in reliability, usage measures such as operating time are also used. For example, in the study of unscheduled maintenance events for a submarine, the time t represents the operating times of the submarine engine but, in the asthma prevention trial, t stands for real or calendar time. The choice of the origin of a time scale is also important, especially, in settings where more than one process is of interest.

A subject is observed longitudinally over an observation window $[\tau_{0i}, \tau_i]$ that may vary for each subject, and data on event times are collected. An event process is often assumed to start at time $t = 0$, and observation of a subject starts at time $\tau_{i0} \geq 0$. In each example given in Section 1.1.1, $\tau_{i0} = 0$ for all subjects. However, *left-truncated* data or delayed entries of subjects to a study are also possible. Observation of a subject is typically *right-censored* at time τ_i. An important issue about the τ_i as well as the τ_{i0} is whether they are prespecified or random. This issue is important in likelihood constructions, and discussed in Section 1.4.1.

1.2 Terminology and Notation

In this section, we introduce the notation and basic definitions used in the later developments. We will use standard notation for event processes, as follows.

A *stochastic process* $\{X(t); t \in \mathcal{T}\}$ is a collection of random variables indexed by a set $\mathcal{T}$ which is called the *index set*. In this study, $\mathcal{T} = \mathcal{R}^+ = [0, \infty)$, and t is continuous time. Let us start with a single recurrent event process in continuous time where the starting time of the process is 0. Let $T_0 < T_1 < T_2 < \cdots$ denote the event times, where T_j is the time of the jth event and $T_0 = 0$. Then, $W_j = T_j - T_{j-1}$ $(j = 1, 2, \ldots)$ is called the *waiting time* or *gap time* between the $(j-1)$st and jth events.

A *counting process* $\{N(t); t \geq 0\}$ is a stochastic process in which $N(t)$ represents the number of events occurring in the interval $[0, t]$. Let $I(A)$ be the *indicator random variable* of event A; that is, $I(A)$ equals 1 if A occurs and 0 otherwise. Then, $N(t) = \sum_{k=1}^{\infty} I(T_k \leq t)$. The random variable $N(t)$ is a nondecreasing and integer valued function of time with jumps of size one only. Let $N(s, t)$ denote the number of events occurring in the interval $(s, t]$. Then, $N(s, t) = N(t) - N(s)$. The mean and rate functions of a counting process are defined as $\mu(t) = E\{N(t)\}$ and $\rho(t) = \mu'(t)$, respectively.

We next define the intensity function. Let $\Delta N(t) = N(t + \Delta t^-) - N(t^-)$ denote the number of events occuring in the interval $[t, t + \Delta t)$, and $\mathcal{H}(t) = \{N(s); 0 \leq s < t\}$ denote the history of a process at time t. The *intensity function* $\lambda(t|\mathcal{H}(t))$ for a counting process specifies the instantaneous probability of an event occurring at time t, conditional on the process history $\mathcal{H}(t)$. The intensity function is defined as

$$\lambda(t|\mathcal{H}(t)) = \lim_{\Delta t \downarrow 0} \frac{\Pr\{\Delta N(t) = 1|\mathcal{H}(t)\}}{\Delta t}, \qquad t \geq 0. \tag{1.1}$$

The intensity function completely specifies a recurrent event process for which two or more events cannot occur simultaneously. It can be easily generalized by including *fixed* or *time-varying* covariates in the history of a process so that covariates which are believed having effects on the event occurrences can be included in a model via the intensity function. We use the notation x to represent a fixed covariate and $x(t)$ to represent a time-varying covariate. A covariate is categorized as *external* when its value is determined independently of the occurrence of events, and otherwise it is categorized as *internal*. Note that all fixed covariates are categorized as external. Let $\boldsymbol{x}(t) = (x_1(t), \ldots, x_p(t))'$ denote a p-dimensional *vector of covariates*, and $x^{(t)} = \{\boldsymbol{x}(s); 0 \leq s \leq t\}$ denote the *history of covariates* up to and including time t. We assume for notational convenience that the *complete covariate path* denoted by $x^{(\infty)}$ is known at the start of the process. In other words, we assume that $x^{(\infty)}$ is included in $\mathcal{H}(0)$. It is assumed, however, that the intensity function depends only on the covariate path until time t. We also let $\boldsymbol{z}(t) = (z_1(t), \ldots, z_p(t))'$ denote a p-dimensional vector of observable functions whose components could contain both external covariates and functions of t or the event history $\mathcal{H}(t)$; this is used in specifying models for $\lambda(t|\mathcal{H}(t))$.

Let W be a continuous, nonnegative random variable, e.g. a response time. The *cumulative distribution function* of W is then defined as $F(w) = \Pr\{W \leq w\}$, and the *probability density function* of W is given by $f(w) = dF(w)/dw$. The *survivor function* of W is defined as $S(w) = 1 - F(w)$. Another important function is the *hazard function* of a response time W that is defined as

$$h(w) = \lim_{\Delta w \downarrow 0} \frac{Pr\{w \leq W < w + \Delta w | W \geq w\}}{\Delta w}, \qquad w \geq 0. \tag{1.2}$$

Note that $h(w) = f(w)/S(w)$, $w > 0$. The properties of these functions can be found in, for example, Lawless (2003, p. 9).

It is useful to denote when an individual or process is under observation and at risk of an event. This can be done with the *at-risk indicator* $Y(t)$. For example, let a subject be observed over the interval $[\tau_0, \tau]$. If the subject is under risk of having an event all over the observation window, then $Y(t) = I(\tau_0 \leq t \leq \tau)$. Note that τ_0 is referred to as a *starting time* for the observed process and τ is called a *right censoring time* or *end-of-followup time* for the observed process. It should be pointed out that it can be useful in studies where the subjects are intermittently observed or cease to be at risk temporarily. For example, in the asthma prevention trial example, the subjects are assumed to be risk-free while they have an attack. That is, $Y(t) = 0$ whenever a subject has an asthma attack.

We next give a number of useful results based on the intensity function. The following lemma follows from (1.1) and the fact that two events cannot occur at the same time, and can be used to prove Theorem 1.2.1 below.

Lemma 1.2.1. *Under the assumption that two or more events cannot occur simultaneously, the event process* $\{N(t); t \geq 0\}$ *with the intensity function* (1.1) *has the following* *jump probabilities in a small interval* $[t, t+\Delta t)$*;*

$$\Pr\{\Delta N(t) = n|\mathcal{H}(t)\} = \begin{cases} 1 - \lambda(t|\mathcal{H}(t))\Delta t + o(\Delta t), & \textit{if } n = 0; \\ \lambda(t|\mathcal{H}(t))\Delta t + o(\Delta t), & \textit{if } n = 1; \\ o(\Delta t), & \textit{otherwise,} \end{cases}$$

where $n = 0, 1, \ldots,$ *and* $o(t)$ *represents a function* $h(t)$ *with* $h(t)/t \to 0$ *as* $t \to 0$.

We are now in a position to state the theorem that is pivotal in writing down the likelihood functions used for statistical inference procedures in recurrent event settings. For a more comprehensive discussion about likelihood construction, see Andersen et al. (1993, Section 2.7) and Cook and Lawless (2007, Section 2.1).

Theorem 1.2.1. *Let* $\{N(t); t \geq 0\}$ *be a counting process of a specified type of event observed over the prespecified interval* $[\tau_0, \tau]$ *for an individual or a single system with the intensity function* (1.1)*. Then*

$$\prod_{j=1}^{n} \lambda\left(t_j|\mathcal{H}\left(t_j\right)\right) \;\; \exp\left\{-\int_{\tau_0}^{\tau} \lambda\left(u|\mathcal{H}\left(u\right)\right)\, du\right\} \tag{1.3}$$

is the probability density function of the event "exactly n *events occur at times* $t_1 < t_2 < \cdots < t_n$ *over the observation interval* $[\tau_0, \tau]$*", conditional on* $\mathcal{H}(\tau_0)$*.*

The likelihood function (1.3) is also valid in more general cases in which τ may depend on prior event history (Cook and Lawless, 2007, Section 2.6). The following theorem and corollary are useful in statistical analysis of gap times and simulation of recurrent events. Their proofs can be found in Cook and Lawless (2007, p. 30).

Theorem 1.2.2. *Let* $\{N(t); t \geq 0\}$ *be a counting process with an absolutely continuous intensity function* $\lambda(t|\mathcal{H}(t))$*. Then, conditional on* $\mathcal{H}(s^+) = \{N(u); 0 \leq u \leq s\}$*, the probability of the event "*$\{N(t); t \geq 0\}$ *has no jump over the interval* $(s, t]$*" is*

$$\exp\left\{-\int_{s}^{t} \lambda(u|\mathcal{H}(u))\, du\right\}. \tag{1.4}$$

Corollary 1.2.1. *Let* $W_j = T_j - T_{j-1}$ *be the waiting time between the* $(j-1)$*st and* j*th events, where* $T_0 = 0$ *and* $j = 1,2,\ldots$ *Then*

$$\Pr\{W_j > w|T_{j-1} = t_{j-1}, \mathcal{H}(t_{j-1})\} = \exp\left\{-\int_{t_{j-1}}^{t_{j-1}+w} \lambda(u|\mathcal{H}(u))\, du\right\}. \tag{1.5}$$

Other technical details regarding counting processes in the context of this study are given by Fleming and Harrington (1991) and Andersen et al. (1993). Chief among them is the concept of a martingale which is briefly discussed in Section 1.4.2.

1.3 Some Families of Models

This section provides an overview of the most commonly used models for recurrent event data; Poisson processes and renewal processes, and other models. Event counts over specified time intervals are often useful in describing recurrent events. The *Poisson process* is a basic mathematical model for the analysis of event counts, and it is introduced in Section 1.3.1. Models based on gap times are another important class of models that are useful in analyzing recurrent events. In particular, these models are often used in settings where interest is in prediction of the next event or when there exist interventions after occurrence of an event. The *renewal process* is a mathematical model that is widely used to model gap times; it is introduced in Section 1.3.2. Some other recurrent event models are briefly discussed in Section 1.3.3.

1.3.1 Poisson Processes

There are various mathematically equivalent ways to characterize a Poisson process. For example, the Poisson process with rate function $\rho(t)$ is a counting process with the following postulates; (i) $\Pr\{N(0)=0\}=1$; (ii) the process $\{N(t); t \geq 0\}$ has the independent increment property; that is, for any $0 \leq a < b \leq c < d$, the random variables $N(a,b)$ and $N(c,d)$ are independent; and (iii) for any $0 \leq s < t$, the increment $N(s,t)$ is a Poisson random variable with mean $\mu(s,t) = \mu(t) - \mu(s)$ where $\mu(t) = \int_0^t \rho(u)\, du$. That is, for $n = 0,\ 1,\ 2,\ \ldots,$

$$Pr\{N(s,t)=n\} = \frac{\mu^n(s,t)}{n!} \exp\{-\mu(s,t)\}. \tag{1.6}$$

Because of the independent increment property, Poisson processes are Markovian. Another characterization of a Poisson process is given, for example, by Cook and Lawless (2007, p. 31) via the intensity function as follows. The counting process $\{N(t); t \geq 0\}$ is said to be a *Poisson process* if the intensity function is of the form

$$\lambda\left(t|\mathcal{H}(t)\right) = \rho(t), \qquad t \geq 0, \tag{1.7}$$

where $\rho(t)$ is a positive valued function on $[0, \infty)$. It is easily seen from the definition that $\rho(t)$ is the rate function for the process. Moreover, if $\rho(t)$ is constant, say ρ, then the process is called a *homogeneous Poisson process* (HPP). Otherwise, it is called a *nonhomogeneous Poisson process* (NHPP). Note that (1.7) implies that the intensity function in a Poisson process is independent of the history of the process.

In a reliability context, if after a repair a system is in exactly the same condition as it was just before the failure then the repair is called *minimal repair* (Rigdon and Basu, 2000, p. 30). In this case, an NHPP can be used to model a repairable system. Thus, a NHPP is sometimes called a minimal repair model. There is a vast literature on Poisson processes and their properties. For example, Snyder and Miller (1991) and Grandell (1997) give many details and examples about Poisson processes. Here, we state only the following two useful properties. The former is useful in simulation of an HPP, and the latter is useful in simulation of an NHPP and other processes. The proof of the first one can be found in Rigdon and Basu (2000, pp. 45–49). For the second one, see Cook and Lawless (2007, p. 33).

Proposition 1.3.1. *The waiting times are independent and identically distributed exponential variables with mean ρ^{-1} if and only if the associated process is a HPP with intensity ρ.*

Proposition 1.3.2. *Suppose that $\{N(t); t \geq 0\}$ is an NHPP with mean function $\mu(t) = \int_0^t \rho(u)\, du$ and $\{N^*(s); s \geq 0\}$ is an HPP with rate function $\rho^*(s) = 1$. If $s = \mu(t)$, then $N^*(s) = N(\mu^{-1}(s))$ for all $s > 0$.*

As noted in Section 1.2, external covariates can be included in a Poisson process model via the intensity function. Let $x^{(t)} = \{\boldsymbol{x}(u); 0 \leq u \leq t\}$ be an external covariate history and $\boldsymbol{z}(t)$ be a vector that could contain both external covariates and functions of t or the event history $\mathcal{H}(t)$. Then, consider intensities of the form

$$\lambda(t|\mathcal{H}(t)) = \rho_0(t)\, g(\boldsymbol{z}(t); \boldsymbol{\beta}), \qquad t \geq 0, \tag{1.8}$$

where $\mathcal{H}(t) = \{N(s); 0 \leq s < t;\ x^{(\infty)}\}$ is the process history including the complete covariate path at time 0, $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)'$ is a p-dimensional vector of regression parameters, and $\rho_0(t)$ and $g(\boldsymbol{z}(t); \boldsymbol{\beta})$ are positive-valued functions. In (1.8), $\rho_0(t)$ is called *baseline intensity* or *baseline rate function*. The model (1.8) is called the *multiplicative model* or *log linear model*. It is called *parametric* if $\rho_0(t)$ is specified up to a finite parameter, and *semiparametric* if $\rho_0(t)$ is not specified parametrically. Many semiparametric models for recurrent event data are summarized by Cai and Schaubel (2004). Although there are other choices in the literature, the function $g(\boldsymbol{z}(t); \boldsymbol{\beta})$ is usually chosen as $\exp\{\boldsymbol{z}'(t)\boldsymbol{\beta}\}$ so that it is guaranteed that $g(\boldsymbol{z}(t); \boldsymbol{\beta})$ is positive-valued. It should be pointed out that models containing values in $\boldsymbol{z}(t)$ such as the backward recurrence time are not Poisson processes because they include internal covariate components. These models are called *modulated Poisson processes* (Cook and Lawless, 2007, p. 35).

Other types of models are often useful, for example, *additive models* in which the intensity function is of the form

$$\lambda(t|\mathcal{H}(t)) = \rho_0(t) + g(\boldsymbol{z}(t); \boldsymbol{\beta}), \qquad t \geq 0, \tag{1.9}$$

and *time transform models* in which the intensity function is given by

$$\lambda\left(t|\mathcal{H}(t)\right) = \rho_0\left(\int_0^t \exp\left(\boldsymbol{z}'\left(u\right)\boldsymbol{\beta}\right)\, du\right) \exp\left(\boldsymbol{z}'(t)\boldsymbol{\beta}\right), \qquad t \geq 0. \tag{1.10}$$

The Poisson models are adequate in many applications. Conditioning on the covariates provides more flexibility in modeling event processes. However, in some settings involving multiple systems or individuals, heterogeneity is often apparent (e.g. Lawless, 1987; Cook and Lawless, 2007, Section 3.5). Because of heterogeneity across individual processes, the plausibility of a Poisson process may be in doubt in certain settings. This is indicated when the variance of $N_i(t)$ is significantly larger than the expectation of $N_i(t)$, conditional on any fixed covariates being considered. Note that in a Poisson process the expectation and variance of the counts $N_i(t)$ should be equal. This problem may be addressed by introducing unobservable *random effects* into the model. Suppose that m individuals are under observation. Let u_i be an i.i.d. random effect having a distribution function $G(u)$ with finite mean. Then, given u_i and a fixed covariate vector $\boldsymbol{z}_i$, the intensity function

$$\lambda_i\left(t|\boldsymbol{z}_i, u_i\right) = \rho_i\left(t|\boldsymbol{z}_i, u_i\right) = u_i \rho_0(t) \exp\left(\boldsymbol{z}_i' \boldsymbol{\beta}\right), \qquad t \geq 0, \tag{1.11}$$

defines the Poisson process $\{N_i(t); t \geq 0\}$; $i = 1, \ldots, m$. We may assume without loss of generality that $E(u_i) = 1$ and $Var(u_i) = \phi$. In this case, for any distribution function for u_i, the unconditional mean and variance of $N_i(s,t)$ are, respectively, given by $E\{N_i(s,t)\} = \mu_i(s,t)$ and $Var\{N_i(s,t)\} = \mu_i(s,t) + \phi\mu_i^2(s,t)$ where $\mu_i(s,t) = \int_s^t \rho(v|\boldsymbol{z}_i)\, dv$. Furthermore, the unconditional covariance function is given by $Cov\{N_i(s_1,t_1), N_i(s_2,t_2)\} = \phi\mu_i(s_1,t_1)\mu_i(s_2,t_2)$ for nonoverlapping intervals $(s_1,t_1]$ and $(s_2,t_2]$. Note that $Var\{N_i(s,t)\} = E\{N_i(s,t)\}$ and $Cov\{N_i(s_1,t_1), N_i(s_2,t_2)\} = 0$ when $\phi = 0$.

The gamma distribution with mean 1 and variance ϕ is the most commonly used distribution for u_i. That is, u_i has the probability density function of the form

$$g(u;\phi) = \frac{u^{\phi^{-1}-1} \exp(-u/\phi)}{\phi^{\phi^{-1}} \Gamma(\phi^{-1})}, \qquad u > 0. \tag{1.12}$$

In this case, given $\boldsymbol{z}_i$ and u_i, $N_i(s,t)$ has a Poisson distribution with mean function $u_i\mu_i(s,t)$. However, conditional only on $\boldsymbol{z}_i$, the distribution of $N_i(s,t)$ is not Poisson anymore but is negative binomial with probability distribution function given by

$$\Pr\{N_i(s,t) = n|\boldsymbol{z}_i\} = \frac{\Gamma(n+\phi^{-1})}{n!\,\Gamma(\phi^{-1})} \frac{\{\phi\mu_i(s,t)\}^n}{\{1+\phi\mu_i(s,t)\}^{n+\phi^{-1}}}, \qquad n = 0, 1, 2, \ldots. \tag{1.13}$$

As ϕ approaches 0, (1.13) converges to a Poisson distribution (Cook and Lawless, 2007, p. 36), and the process becomes a Poisson process. When $\phi > 0$ the process is called a *negative binomial process*, and the intensity function can be shown to be (Cook and Lawless, 2007, Section 2.2.3)

$$\lambda_i(t|\mathcal{H}_i(t)) = \frac{\left(1+\phi N_i(t^-)\right)\rho_i(t)}{1+\phi\mu_i(t)}, \qquad t \geq 0, \tag{1.14}$$

so the process is Markovian.

1.3.2 Renewal Processes

Let T_j denote the event time for the jth event and $W_j = T_j - T_{j-1}$ the waiting (gap) time between the $(j-1)$st and the jth events. A *renewal process* is one in which the waiting times $W_1, W_2, \ldots$ are independent and identically distributed. This definition implies that the intensity function of a renewal process is given by

$$\lambda(t|\mathcal{H}(t)) = h(B(t)), \qquad t \geq 0, \tag{1.15}$$

where $B(t)$ is the time since the last event strictly before time t; that is, $B(t) = t - T_{N(t^-)}$, and is referred to as the *backward recurrence time*. The function $h(w)$ in (1.15) is the hazard function for the distribution of a gap time W_j. In a reliability context, the renewal processes are called *perfect repair* models in which after a repair the system becomes *like new*.

In a general renewal process, $\Pr\{N(s,t) = n\}$ is complicated, and so is $\mu(s,t) = E\{N(s,t)\}$. An exception is the case where the W_j are exponentially distributed because in this case the renewal process is an HPP. Although in general the distribution of $N(s,t)$ is not mathematically tractable, the distribution of $N(t) = N(0,t)$ can be obtained using the fact that the events "$N(t) \geq n$" and "$T_n \leq t$" are equivalent. Therefore,

$$\Pr\{N(t) \geq n\} = \Pr\{T_n \leq t\} = \Pr\left\{\sum_{i=1}^{n} W_i \leq t\right\}, \tag{1.16}$$

where the W_i are i.i.d. Now, it is easy to show that

$$\mu(t) = E\{N(t)\} = \sum_{n=1}^{\infty} \Pr\{T_n \leq t\}. \tag{1.17}$$

Similar to Poisson process models, fixed covariates or external time-varying covariates can be introduced into renewal process models. Survival regression models are useful when fixed covariates are present. As noted by Cook and Lawless (2007, p. 40), two important families of such models are the *proportional hazards model* and *accelerated failure time model* that are specified with the conditional hazard functions of the form $h(w|\boldsymbol{z}) = h_0(w)\exp(\boldsymbol{z}'\boldsymbol{\beta})$ and $h(w|\boldsymbol{z}) = h_0[w\exp(\boldsymbol{z}'\boldsymbol{\beta})]\exp(\boldsymbol{z}'\boldsymbol{\beta})$, respectively. When $\boldsymbol{z}(t)$ contains both external covariates and functions of t or $\mathcal{H}(t)$, the models are called *modulated renewal processes* (Cox, 1972). In particular, multiplicative models in which the intensity function of the form $\lambda(t|\mathcal{H}(t)) = h_0(B(t))\exp(\boldsymbol{z}'(t)\boldsymbol{\beta})$ are very useful. Modulated renewal processes are explained by Cook and Lawless (2007, Section 4.2.4). Random effects can also be incorporated into renewal processes by certain approaches; see, e.g., Cook and Lawless (2007, Section 4.2.2).

1.3.3 Other Models

Although in many cases Poisson and renewal processes and their extensions are convenient to model recurrent event processes, if they are needed, more general models are available as well. Cook and Lawless (2007, Section 2.4 and Chapter 5) and books on point processes (e.g. Cox and Isham, 1980; Daley and Vere-Jones, 2003) give examples. Discrete time models are also proposed in the literature. More details about discrete time models are given by Cook and Lawless (2007, Section 2.5).

In reliability literature, other than the minimal and perfect repair models, *imperfect repair* models are also proposed. Brown and Proschan (1983) suggest an imperfect repair model in which a perfect repair is given with probability p and a minimal repair is given with probability $1-p$ at event (or failure) times. Kijima (1989) extends this model by introducing the concept of the *virtual age* or *effective age* of the system, which is defined as the present condition of a system at a calendar time t (system's age). The literature and more details (including mathematical definitions) about these models, with parametric and nonparametric statistical inference procedures, is reviewed by Lindqvist (2006). Baker (2001) considers some general models to study the dependence of failure rate on system (medical equipment) age and time since repair. In a review paper, Pena (2006) gives examples of models where the dependence on history is allowed for. Also, Aalen et al. (2008) investigate some additive models with covariates including number of previous events in the process.

1.4 Multiplicative Models and Hypothesis Testing

In this section, we focus on score test procedures for multiplicative models with intensity function of the form

$$\lambda(t|\mathcal{H}(t);\boldsymbol{\alpha},\boldsymbol{\beta}) = \lambda_0(t;\boldsymbol{\alpha})g(\boldsymbol{z}(t);\boldsymbol{\beta}), \qquad t \geq 0, \tag{1.18}$$

where $\boldsymbol{\alpha} = (\alpha_1,\ldots,\alpha_r)'$ is an $r \times 1$ vector of unknown parameters, $\boldsymbol{\beta} = (\beta_1,\ldots,\beta_p)'$ is a $p\times 1$ vector of unknown regression parameters, $\boldsymbol{z}(t) = (z_1(t),\ldots,z_p(t))'$ is a $p\times 1$ vector, λ_0 is a baseline intensity function and g is a positive valued function. Note that $\boldsymbol{z}(t)$ could contain both external covariates and functions of t or the event history $\mathcal{H}(t)$. Models of the form (1.18) are widely used in modeling recurrent event data in many settings, and are by far the most common framework to specify the covariate effects (Cook and Lawless, 2007, p. 60). The adequacy of any model should be checked in applications, and we will consider this by embedding models in larger families; this is often called *model expansion*. We will assume that the expanded model family is adequate. However, this can be checked by model diagnostics (see, e.g., Cook and Lawless, 2007, Section 5.2.3). Therefore, the interest is often to test a composite null hypothesis $H_0 : \lambda(\cdot) \in \mathcal{G} =$

$\{\lambda(\cdot;\boldsymbol{\theta});\boldsymbol{\theta}=(\boldsymbol{\alpha}',\boldsymbol{\beta}')'\in\Omega\}$, where Ω is a subset of a q-dimensional Euclidean space and $q=r+p$, and the alternative hypothesis is $H_1:\lambda(\cdot)\notin\mathcal{G}$. Score tests, introduced by Rao (1947), can be used for testing H_0. They are convenient in ways discussed below, and we consider them here.

1.4.1 Likelihood for Multiplicative Models

To develop a score test, we need to write down the likelihood function for the data observed over the observation window $[\tau_0,\tau]$. For convenience, $\tau_0=0$ in this study unless otherwise stated. When τ_0 and τ are fixed, from (1.3) the likelihood function for the event "n events occur at exact times $t_1<\cdots<t_n$, $t_i\in[\tau_0,\tau]$, $i=1,\ldots,n$", given $\mathcal{H}(\tau_0)$, is

$$L(\boldsymbol{\theta})=\prod_{j=1}^{n}\lambda\left(t_j|\mathcal{H}\left(t_j\right)\right)\ \exp\left\{-\int_{\tau_0}^{\tau}\lambda\left(u|\mathcal{H}\left(u\right)\right)\,du\right\}, \tag{1.19}$$

where $\boldsymbol{\theta}$ is a parameter vector specifying $\lambda(t|\mathcal{H}(t))$. However, this likelihood is valid in more general cases as well. Here, we only underline a couple of points, referring to Andersen et al. (1993, Chapter 2) and Cook and Lawless (2007, Section 2.6).

When starting and end-of-followup times of an observation window are random but they are determined independently of the event process, a more general case in which (1.19) is the p.d.f. "n events occur at exact times $t_1<\cdots<t_n$, $t_i\in[\tau_0,\tau]$, $i=1,\ldots,n$", conditional not only on $\mathcal{H}(\tau_0)$ but also on τ_0 and τ, is obtained. This censoring mechanism is called *completely independent* censoring. When the starting and ending times are not independent of an event process but are stopping times with respect to the process, then (1.19) is still valid providing that the event intensity is defined as

$$\lambda(t|\mathcal{H}(t))=\lim_{\Delta t\downarrow 0}\frac{\Pr\left\{\Delta N(t)=1|\mathcal{H}(t),\tau_0\leq t\leq\tau\right\}}{\Delta t},\qquad t\geq\tau_0, \tag{1.20}$$

(Cook and Lawless, 2007). The concept of a *stopping time* with respect to a process is formally defined by, for example, Andersen et al. (1993, Section 2.2), yet it intuitively means that the decision to specify the random times τ_0 and τ should be determined by the information provided by an event history up to and including times τ_0 and τ, respectively, but not after those times. In this case, (1.19) is not a likelihood function anymore but a *partial likelihood function*, which was introduced by Cox (1975), and can be still used for statistical inference purposes; see Fleming and Harrington (1991) and Andersen et al. (1993) for details.

Sometimes it is more convenient to write down the likelihood function by using the at-risk indicator defined in Section 1.2. Following the notation given by Cook and Lawless (2007, Section 2.6), the observed part of the process, called the *observable process*, can be written as $\bar{N}(t) = \int_{\tau_0}^{t} Y(u)\, dN(u)$ where $Y(t) = I\{\text{process is observed at time } t\}$. Then, the intensity function of the observable process is

$$\bar{\lambda}(t|\bar{\mathcal{H}}(t)) = \lim_{\Delta t \downarrow 0} \frac{\Pr\{\Delta \bar{N}(t) = 1|\bar{\mathcal{H}}(t)\}}{\Delta t}, \qquad t \geq \tau_0, \tag{1.21}$$

where $\bar{\mathcal{H}}(t) = \{\bar{N}(s), Y(s); \tau_0 \leq s < t\}$ is the history of the observable process. In order to facilitate further development, we need a *conditionally independent censoring* mechanism; that is, $\Delta N(t)$ and $Y(t)$ are conditionally independent given $\mathcal{H}(t)$, so that $\bar{\lambda}(t|\bar{\mathcal{H}}(t)) = Y(t)\lambda(t|\mathcal{H}(t))$ (Cook and Lawless, 2007). As a consequence of this, the likelihood (1.19) can be written as

$$L(\boldsymbol{\theta}) = \prod_{j=1}^{n} \lambda\left(t_j|\mathcal{H}\left(t_j\right)\right) \; \exp\left\{-\int_0^\infty Y(u)\lambda\left(u|\mathcal{H}\left(u\right)\right)\, du\right\}. \tag{1.22}$$

This allows us to deal with more general cases in which, for example, τ_0 and τ are stopping times or the observation is intermittent or a process may have a period of not being at-risk of having an event during the observation period.

So far, the discussion has been concentrated on univariate counting processes. However, a setup for multivariate counting processes is required when there is more than one process. For example, we need multivariate counting processes when we examine large sample properties of goodness-of-fit test statistics. Here, we consider only independent processes when we observe multiple independent units or individuals.

Suppose that m independent processes are under observation over the observation windows $[\tau_{i0}, \tau_i]$, where τ_{i0} and τ_i are, respectively, the starting and end-of-followup times for process i, and process i experiences events at times $t_{i1} < \cdots < t_{in_i}$, $i = 1, 2, \ldots, m$. Then, under the conditionally independent censoring mechanism the likelihood function of the m independent processes is

$$L(\boldsymbol{\theta}) = \prod_{i=1}^{m}\prod_{j=1}^{n_i} \lambda_i\left(t_{ij}|\mathcal{H}_i(t_{ij})\right) \exp\left\{-\int_{\tau_0}^{\tau} Y_i(u)\lambda_i\left(u|\mathcal{H}_i(u)\right)\, du\right\}, \tag{1.23}$$

where $Y_i(t) = I\{\tau_{i0} \leq t \leq \tau_i\}$ is the at-risk indicator of process i, $\mathcal{H}_i(t)$ is the history of process i, $\tau_0 = \min(\tau_{10}, \ldots, \tau_{m0})$, $\tau = \max(\tau_1, \ldots, \tau_m)$ and

$$\lambda_i(t|\mathcal{H}_i(t)) = \lim_{\Delta t \downarrow 0} \frac{\Pr\{\Delta N_i(t) = 1|\mathcal{H}_i(t)\}}{\Delta t}, \qquad t \geq \tau_{i0}, \tag{1.24}$$

is the intensity function for process i. Each intensity (1.24) is specified in terms of parameter vector $\boldsymbol{\theta}$. Fixed or time-varying covariates of process i can be incorporated into $\mathcal{H}_i(t)$ as explained in Section 1.2.

1.4.2 Martingale Framework

In this section, a martingale is informally defined and the use of martingales in a rigorous development of asymptotics is discussed. For an extensive treatment, see Fleming and Harrington (1991) and Andersen et al. (1993).

Suppose that m subjects are under observation. Let $\{N_i(t); t \geq 0\}$ be a counting process for subject i with an absolutely continuous intensity function $\lambda_i(t|\mathcal{H}_i(t))$, $t \in [0, \tau_i]$, and $\{\bar{N}_i(t); t \geq 0\}$ be the associated observable process with an intensity function $\bar{\lambda}_i(t|\bar{\mathcal{H}}_i(t)) = Y_i(t)\lambda_i(t|\mathcal{H}_i(t))$. A formal definiton of a martingale can be found in, for example, Andersen et al. (1993, Section 2.3.1). It arises in this study of the form

$$M_i(t) = \bar{N}_i(t) - \int_0^t Y_i(u)\lambda_i(u|\mathcal{H}_i(u))\, du, \tag{1.25}$$

which is called a *counting proceses martingale*. A *martingale increment* over a small interval $[t, t + dt)$ is defined as $dM_i(t) = d\bar{N}_i(t) - Y_i(t)\lambda_i(t|\mathcal{H}_i(t))\, dt$. A *predictable variation process* of $M_i(t)$ (cf. Andersen et al., 1993, Section 2.3.2), which is denoted by $\langle M_i \rangle(t) = \int_0^t \bar{\lambda}_i(s|\mathcal{H}(s))\, ds$, is another important stochastic process because of the relation $d\langle M_i \rangle(t) = Var(dM_i(t)|\mathcal{H}_i(t))$. Many important properties of martingales and predictable variation processes are given by Fleming and Harrington (1991) and Andersen et al. (1993).

In certain recurrent event settings, counting process martingales can be used in rigorous development of asymptotic properties of test statistics, which can be expressed in terms of martingales. They provide a mathematical basis to develop central limit theorems. It should be noted that there are several central limit theorems for martingales, but Rebolledo's central limit theorem given in Andersen et al. (1993, p. 83) is suitable for this thesis. The idea is that normalized martingales that arise from a sequence of counting processes converge weakly to a Gaussian martingale in the limit providing that (i) the predictable variation processes of these counting process martingales should converge in probability to a deterministic function as a normalizing constant increases, and (ii) the jump sizes of these counting process martingales should approach 0 as the normalizing constant increases.

Let H_i be a predictable process. That is, $H_i(t)$ is a measurable random variable with respect to the history $\mathcal{H}_i(t)$. The above discussion also applies when we have functions of the structure

$$\sum_{i=1}^{m} \int_0^t H_i(u) dM_i(u), \qquad t \in [0, \tau], \tag{1.26}$$

which is a sum of *stochastic integrals* (cf. Andersen et al., 1993, Section 2.3.3). In other words, under certain conditions, a normalized version of (1.26) converges weakly to a Gaussian process with mean zero and a variance function, say $\Sigma(t)$, $t \in [0, \tau]$. In

Section 1.4.3, we will see an example of how martingales occur in maximum likelihood estimation.

1.4.3 Likelihood Inference and Score Tests

In this section, we first introduce general concepts of score procedures, and then, score test procedures for recurrent event processes in the context of Section 1.4.2. A more detailed introduction of asymptotic theory is given by Serfling (1980). The use of martingale framework in asymptotic theory for the estimators and test statistics considered here is given by Fleming and Harrington (1991) and Andersen et al. (1993).

Suppose that $\boldsymbol{D} = (D_1, \ldots, D_m)'$ is an m-dimensional vector of i.i.d. random variables, $\boldsymbol{d} = (d_1, \ldots, d_m)'$ is an m-dimensional vector of observations, and $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_q)'$ is a q-dimensional vector of parameters, where $\boldsymbol{\theta} \in \Omega$ and $\Omega \subset \mathbb{R}^q$. Let $L(\boldsymbol{\theta})$ be the *likelihood function* of $\boldsymbol{\theta}$ that depends on data $\boldsymbol{D}$, and $\ell(\boldsymbol{\theta})$ be the *log likelihood function*; that is, $\ell(\boldsymbol{\theta}) = \log L(\boldsymbol{\theta})$. If it exists, the value of $\boldsymbol{\theta}$ that maximizes $L(\boldsymbol{\theta})$, or equivalently $\ell(\boldsymbol{\theta})$, is called the *maximum likelihood estimate* of $\boldsymbol{\theta}$, and denoted by $\hat{\boldsymbol{\theta}} = (\hat{\theta}_1, \ldots, \hat{\theta}_q)'$. For convenience, we generally maximize the log likelihood function, instead of the likelihood function, with respect to $\boldsymbol{\theta}$.

Let $\boldsymbol{U}(\boldsymbol{\theta}) = (U_1(\boldsymbol{\theta}), \ldots, U_q(\boldsymbol{\theta}))'$ be a $q \times 1$ *score vector* with entries, $U_j(\boldsymbol{\theta}) = \partial \ell(\boldsymbol{\theta})/\partial \theta_j$, $j = 1, \ldots, q$, called *score functions*. Then, $\hat{\boldsymbol{\theta}}$ is usually given by the solution of $\boldsymbol{U}(\boldsymbol{\theta}) = \boldsymbol{0}$, where $\boldsymbol{0}$ is a $q \times 1$ vector of zeros, and the $U_j(\boldsymbol{\theta}) = 0$ are called *maximum likelihood equations*. The *observed information matrix* $\boldsymbol{I}(\boldsymbol{\theta}) = [(I_{jk}(\boldsymbol{\theta}))]$ is a $q \times q$ matrix where $I_{jk}(\boldsymbol{\theta}) = -\partial^2 \ell(\boldsymbol{\theta})/\partial\theta_j \partial\theta_k = -\partial U_k(\boldsymbol{\theta})/\partial\theta_j$; j, $k = 1, \ldots, q$, and the *expected information matrix* or *Fisher information matrix* $\boldsymbol{J}(\boldsymbol{\theta}) = [(J_{jk}(\boldsymbol{\theta}))]$ is a $q \times q$ matrix with components $J_{jk}(\boldsymbol{\theta}) = E\{-\partial^2 \ell(\boldsymbol{\theta})/\partial\theta_j\partial\theta_k\} = E\{-\partial U_k(\boldsymbol{\theta})/\partial\theta_j\}$; j, $k = 1, \ldots, q$, where the model is assumed correct, with $\boldsymbol{\theta}$ the true parameter value. For regular models $E\{\boldsymbol{U}(\boldsymbol{\theta})\} = \boldsymbol{0}$ and the covariance matrix of $\boldsymbol{U}(\boldsymbol{\theta})$ is the expected information matrix; that is, $\boldsymbol{J}(\boldsymbol{\theta}) = Cov\{\boldsymbol{U}(\boldsymbol{\theta})\} = E\{\boldsymbol{U}(\boldsymbol{\theta})\boldsymbol{U}'(\boldsymbol{\theta})\}$. We assume models are regular and that matrix inverses in the following development exist. A test statistic having the form

$$\boldsymbol{U}'(\boldsymbol{\theta}_0)\boldsymbol{J}(\boldsymbol{\theta}_0)^{-1}\boldsymbol{U}(\boldsymbol{\theta}_0) \tag{1.27}$$

for testing the null hypothesis $H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0$ is referred to as a *score statistic*, and a test based on (1.27) is called a *score test*. Under regularity conditions and a correctly specified model the asymptotic distribution of (1.27) is a chi-squared distribution with q degrees of freedom under H_0.

If the interest is not in all parameters of $\boldsymbol{\theta} = (\boldsymbol{\alpha}', \boldsymbol{\beta}')'$ but in a part of it, say $\boldsymbol{\beta}$, then $\boldsymbol{\alpha}$ is an r-dimensional vector of nuisance parameters and $\boldsymbol{\beta}$ is a p-dimensional vector of parameters of interest. Accordingly, $\boldsymbol{U}(\boldsymbol{\theta})$ is partitioned into two components $\boldsymbol{U}_\alpha(\boldsymbol{\theta})$ and

$\boldsymbol{U}_\beta(\boldsymbol{\theta})$. Then, the partitioned expected information matrix $\boldsymbol{J}(\boldsymbol{\theta})$ is of the form

$$\boldsymbol{J}(\boldsymbol{\theta}) = \begin{pmatrix} \boldsymbol{J}_{\alpha\alpha}(\boldsymbol{\theta}) & \boldsymbol{J}_{\alpha\beta}(\boldsymbol{\theta}) \\ \boldsymbol{J}_{\beta\alpha}(\boldsymbol{\theta}) & \boldsymbol{J}_{\beta\beta}(\boldsymbol{\theta}) \end{pmatrix}, \tag{1.28}$$

where $\boldsymbol{J}_{\alpha\alpha}(\boldsymbol{\theta})$ is $r \times r$, $\boldsymbol{J}_{\alpha\beta}(\boldsymbol{\theta})$ is $r \times p$, and so on. The observed information matrix $\boldsymbol{I}(\boldsymbol{\theta})$ is also partitioned in a similar manner. The inverse matrix of (1.28) is denoted by

$$\boldsymbol{J}^{-1}(\boldsymbol{\theta}) = \begin{pmatrix} \boldsymbol{J}^{\alpha\alpha}(\boldsymbol{\theta}) & \boldsymbol{J}^{\alpha\beta}(\boldsymbol{\theta}) \\ \boldsymbol{J}^{\beta\alpha}(\boldsymbol{\theta}) & \boldsymbol{J}^{\beta\beta}(\boldsymbol{\theta}) \end{pmatrix}. \tag{1.29}$$

Let $\boldsymbol{\beta}_0$ be a fixed value of $\boldsymbol{\beta}$. Then, $L(\boldsymbol{\alpha}, \boldsymbol{\beta}_0)$, or equivalently $\ell(\boldsymbol{\alpha}, \boldsymbol{\beta}_0)$, is maximized for a value of $\boldsymbol{\alpha}$ that is denoted by $\tilde{\boldsymbol{\alpha}}(\boldsymbol{\beta}_0)$. The function $L(\tilde{\boldsymbol{\alpha}}(\boldsymbol{\beta}), \boldsymbol{\beta})$ is called the *profile likelihood function* for $\boldsymbol{\beta}$, and the corresponding *profile log likelihood function* for $\boldsymbol{\beta}$ is given by $\ell(\tilde{\boldsymbol{\alpha}}(\boldsymbol{\beta}), \boldsymbol{\beta}) = \log L(\tilde{\boldsymbol{\alpha}}(\boldsymbol{\beta}), \boldsymbol{\beta})$. Then, the score statistic

$$\boldsymbol{U}'_\beta(\tilde{\boldsymbol{\theta}}_0)\, \boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)\, \boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0) \tag{1.30}$$

can be used to test the null hypothesis $H_0 : \boldsymbol{\beta} = \boldsymbol{\beta}_0$, where $\tilde{\boldsymbol{\theta}}_0 = (\tilde{\boldsymbol{\alpha}}(\boldsymbol{\beta}_0), \boldsymbol{\beta}_0)$. A test for hypothesis $H_0 : \boldsymbol{\beta} = \boldsymbol{\beta}_0$ based on (1.30) is called a *partial score test*. Under $H_0 : \boldsymbol{\beta} = \boldsymbol{\beta}_0$, a correctly specified model and some regularity conditions, the asymptotic distribution of (1.30) is a chi-squared with p degrees of freedom, and the same asymptotic result holds when a consistent estimator of $\boldsymbol{J}^{\beta\beta}(\boldsymbol{\theta}_0)$ is used in place of $\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)$ (Boos, 1992). Henceforth, we will use $\tilde{\boldsymbol{\alpha}}$ to denote $\tilde{\boldsymbol{\alpha}}(\boldsymbol{0})$.

Score tests in a family of multiplicative recurrent event models (1.18) can be developed in this way. Suppose that m individuals are under observation. Let $\{N_i(t); t \geq 0\}$ be a counting process for subject i with the intensity function (1.18), in which the function g is specified with $\exp\{\boldsymbol{z}'_i(t)\boldsymbol{\beta}\}$; that is,

$$\lambda_i(t|\mathcal{H}_i(t); \boldsymbol{\theta}) = \lambda_0(t; \boldsymbol{\alpha}) \exp\{\boldsymbol{z}'_i(t)\boldsymbol{\beta}\}, \qquad t \geq 0, \tag{1.31}$$

where $\boldsymbol{z}_i(t) = (z_{i1}(t), \ldots, z_{ip}(t))'$ is a p-dimensional vector that may contain external covariates as well as previous event information. Suppose the interest is in estimation or testing of $\boldsymbol{\beta}$, and thus $\boldsymbol{\alpha}$ is a vector of unknown nuisance parameters. Let $\{\bar{N}_i(t); t \geq 0\}$ be the associated observable process for subject i with the intensity function $\bar{\lambda}_i(t|\bar{\mathcal{H}}_i(t)) = Y_i(t)\lambda_i(t|\mathcal{H}_i(t); \boldsymbol{\theta})$, where $Y_i(t)$ is the at-risk process of the ith subject. In this context, the (partial) likelihood function $L(\boldsymbol{\theta})$ is given by (1.23). Therefore, the log likelihood function is given by $\ell(\boldsymbol{\theta}) = \sum_{i=1}^m \ell_i(\boldsymbol{\theta})$, where

$$\ell_i(\boldsymbol{\theta}) = \sum_{j=1}^{n_i} \log \lambda_i(t_{ij}|\mathcal{H}_i(t_{ij}); \boldsymbol{\theta}) - \int_0^\infty Y_i(u)\lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta})\, du. \tag{1.32}$$

Using a Riemann-Stieltjes integral (cf. Cook and Lawless, 2007, p. 29), we can rewrite the log likelihood (1.32) as follows;

$$\ell_i(\boldsymbol{\theta}) = \int_0^\infty Y_i(u) \log \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta})\, dN_i(u) - \int_0^\infty Y_i(u)\lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta})\, du, \tag{1.33}$$

where $dN_i(t) = N_i(t) - N_i(t^-)$. Assuming mild conditions so that the order of differentiation and integration are interchangeable, the score vector is $\boldsymbol{U}(\boldsymbol{\theta}) = (\boldsymbol{U}_\alpha(\boldsymbol{\theta})', \boldsymbol{U}_\beta(\boldsymbol{\theta})')'$, where $\boldsymbol{U}_\alpha(\boldsymbol{\theta}) = (U_{\alpha_1}(\boldsymbol{\theta}), \ldots, U_{\alpha_r}(\boldsymbol{\theta}))'$ is an r-dimensional vector with components $U_{\alpha_l}(\boldsymbol{\theta}) = \partial\ell(\boldsymbol{\theta})/\partial\alpha_l$, $l = 1, \ldots, r$, and $\boldsymbol{U}_\beta(\boldsymbol{\theta}) = (U_{\beta_1}(\boldsymbol{\theta}), \ldots, U_{\beta_p}(\boldsymbol{\theta}))'$ is a p-dimensional vector with components $U_{\beta_k}(\boldsymbol{\theta}) = \partial\ell(\boldsymbol{\theta})/\partial\beta_k$, $k = 1, \ldots, p$, composed of the terms

$$U_{\alpha_l}(\boldsymbol{\theta}) = \sum_{i=1}^m \int_0^\infty Y_i(u) \left(\frac{\partial}{\partial\alpha_l} \log\lambda_0(u; \boldsymbol{\alpha}) \right) \{dN_i(u) - \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta})\, du\}, \tag{1.34}$$

and

$$U_{\beta_k}(\boldsymbol{\theta}) = \sum_{i=1}^m \int_0^\infty Y_i(u) z_{ik}(u) \{dN_i(u) - \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta})\, du\}. \tag{1.35}$$

The observed information matrix $\boldsymbol{I}(\boldsymbol{\theta})$ can be partitioned as follows;

$$\boldsymbol{I}(\boldsymbol{\theta}) = \begin{pmatrix} \boldsymbol{I}_{\alpha\alpha}(\boldsymbol{\theta}) & \boldsymbol{I}_{\alpha\beta}(\boldsymbol{\theta}) \\ \boldsymbol{I}_{\beta\alpha}(\boldsymbol{\theta}) & \boldsymbol{I}_{\beta\beta}(\boldsymbol{\theta}) \end{pmatrix}, \tag{1.36}$$

where, under the interchangeability of the order of the differentiation and integration, the components of $\boldsymbol{I}(\boldsymbol{\theta})$ are given below:
$\boldsymbol{I}_{\alpha\alpha}(\boldsymbol{\theta}) = [(I_{\alpha_l\alpha_k}(\boldsymbol{\theta}))]$ is an $r \times r$ matrix with components $I_{\alpha_l\alpha_k}(\boldsymbol{\theta}) = -(\partial^2/\partial\alpha_l\partial\alpha_k)\ell(\boldsymbol{\theta})$, l, $k = 1, \ldots, r$, so that

$$\begin{aligned} I_{\alpha_l\alpha_k}(\boldsymbol{\theta}) = &-\sum_{i=1}^m \int_0^\infty Y_i(u) \left(\frac{\partial^2}{\partial\alpha_l\partial\alpha_k} \log\lambda_0(u; \boldsymbol{\alpha}) \right) \{dN_i(u) - \lambda_i\left(u|\mathcal{H}_i(u); \boldsymbol{\theta}\right) du\} \\ &+ \sum_{i=1}^m \int_0^\infty Y_i(u) \left(\frac{\partial}{\partial\alpha_l} \log\lambda_0(u; \boldsymbol{\alpha}) \right) \left(\frac{\partial}{\partial\alpha_k} \log\lambda_0(u; \boldsymbol{\alpha}) \right) \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta})\, du, \end{aligned} \tag{1.37}$$

$\boldsymbol{I}_{\alpha\beta}(\boldsymbol{\theta}) = (\boldsymbol{I}_{\beta\alpha}(\boldsymbol{\theta}))' = [(I_{\alpha_l\beta_k}(\boldsymbol{\theta}))]$ is an $r \times p$ matrix where $I_{\alpha_l\beta_k}(\boldsymbol{\theta}) = -(\partial^2/\partial\alpha_l\partial\beta_k)\ell(\boldsymbol{\theta})$, $l = 1, \ldots, r$, $k = 1, \ldots, p$, is given by

$$I_{\alpha_l\beta_k}(\boldsymbol{\theta}) = \sum_{i=1}^m \int_0^\tau Y_i(u) z_{ik}(u) \left(\frac{\partial}{\partial\alpha_l} \log\lambda_0(u; \boldsymbol{\alpha}) \right) \lambda_i\left(u|\mathcal{H}_i(u); \boldsymbol{\theta}\right) du, \tag{1.38}$$

and $\boldsymbol{I}_{\beta\beta}(\boldsymbol{\theta}) = [(I_{\beta_l\beta_k}(\boldsymbol{\theta}))]$ is a $p \times p$ matrix with components $I_{\beta_l\beta_k}(\boldsymbol{\theta}) = -(\partial^2/\partial\beta_l\partial\beta_k)\ell(\boldsymbol{\theta})$, l, $k = 1, \ldots, p$, that is;

$$I_{\beta_l\beta_k}(\boldsymbol{\theta}) = \sum_{i=1}^m \int_0^\tau Y_i(u) z_{il}(u) z_{ik}(u) \lambda_i\left(u|\mathcal{H}_i(u); \boldsymbol{\theta}\right) du. \tag{1.39}$$

Note that if we take the expectation of (1.37), the first term in the right hand side of (1.37) becomes 0 because $E\left\{dN_i(u) - \lambda_i\left(u|\mathcal{H}_i(u)\right) du|\mathcal{H}_i(u)\right\} = 0$.

Let $\lambda(t|\mathcal{H}(t))$ be an unknown intensity function of a counting process $\{N(t); t > 0\}$, and consider the model $\lambda_0(t|\mathcal{H}(t); \boldsymbol{\alpha})$ whose functional form is known up to a finite parameter vector $\boldsymbol{\alpha}$, and that belongs to a class such that $\mathcal{D} = \{\lambda(\cdot;\boldsymbol{\alpha});\, \boldsymbol{\alpha} \in \mathbb{R}^r\}$. Suppose we want to test the hypothesis $H_0 : \lambda(t|\mathcal{H}(t)) \in \mathcal{D}$. This can be done with a widely used approach called model expansion (see, e.g., Lawless, 2003, pp. 469–471). A general method of expanding a null model was suggested by Neyman (1937). The score tests from his method are generally referred to as *Neyman's smooth tests*, and is not suitable for applications involving censored data. Pena (1998) extended his method in this respect. For example, consider embedding the base model $\lambda_0(t|\mathcal{H}(t);\boldsymbol{\alpha})$ into an expanded model of the form (1.18) with $g(\boldsymbol{z}(t);\boldsymbol{\beta}) = \exp\{\boldsymbol{z}'(t)\boldsymbol{\beta}\}$ which belongs to a larger class $\mathcal{G} = \{\lambda(\cdot;\boldsymbol{\theta});\, \boldsymbol{\theta} = (\boldsymbol{\alpha}', \boldsymbol{\beta}')' \in \mathbb{R}^q\}$. Then $\boldsymbol{\beta} = \mathbf{0}$ corresponds to the base model, which would be tested by testing $H_0 : \boldsymbol{\beta} = \mathbf{0}$.

More generally, we can test the null hypothesis $H_0 : \boldsymbol{\beta} = \boldsymbol{\beta}_0$ against the alternative hypothesis $H_1 : \boldsymbol{\beta} \neq \boldsymbol{\beta}_0$. A partial score test can be used for testing H_0. For example, following the previous development in this section, let $\boldsymbol{\theta}_0 = (\boldsymbol{\alpha}_0', \boldsymbol{\beta}_0')'$ be a q-dimensional vector in which $\boldsymbol{\alpha}_0$ is the true value of $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}_0 = \mathbf{0}$ is the value of $\boldsymbol{\beta}$ under the null hypothesis so in this case $\boldsymbol{\theta}_0 = (\boldsymbol{\alpha}_0', \mathbf{0}')'$. Then, let $\tilde{\boldsymbol{\alpha}}$ denote the value of $\boldsymbol{\alpha}_0$ that maximizes $\ell(\boldsymbol{\theta}_0)$. The score statistic (1.30) for testing $H_0 : \boldsymbol{\beta} = \mathbf{0}$ is in the form

$$\boldsymbol{U}_\beta'(\tilde{\boldsymbol{\theta}}_0)\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0), \tag{1.40}$$

where $\tilde{\boldsymbol{\theta}}_0 = (\tilde{\boldsymbol{\alpha}}', \mathbf{0}')'$, $\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0) = (U_{\beta_1}(\tilde{\boldsymbol{\theta}}_0), \ldots, U_{\beta_p}(\tilde{\boldsymbol{\theta}}_0))'$ is a p-dimensional score vector with components, $k = 1, \ldots, p$,

$$U_{\beta_k}(\tilde{\boldsymbol{\theta}}_0) = \sum_{i=1}^{m} \int_0^\infty Y_i(u) z_{ik}(u) \left\{ dN_i(u) - \lambda_i(u|\mathcal{H}_i(u);\tilde{\boldsymbol{\theta}}_0)\, du \right\}, \tag{1.41}$$

and $\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)$ is a $p \times p$ matrix given by

$$\left[\boldsymbol{J}_{\beta\beta}(\tilde{\boldsymbol{\theta}}_0) - \boldsymbol{J}_{\beta\alpha}(\tilde{\boldsymbol{\theta}}_0)\boldsymbol{J}_{\alpha\alpha}^{-1}(\tilde{\boldsymbol{\theta}}_0)\boldsymbol{J}_{\alpha\beta}(\tilde{\boldsymbol{\theta}}_0)\right]^{-1}. \tag{1.42}$$

Note that replacing $\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)$ in (1.40) with $\boldsymbol{I}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)$ does not change the asymptotic results. We will use this method frequently in the following chapters.

Let's also consider a setting in which only one process is observed over time period $[0, \tau]$, so $m = 1$ above. The score statistic for testing the null hypothesis $H_0 : \boldsymbol{\beta} = \mathbf{0}$ is still in the form of (1.40) where components $\boldsymbol{U}(\tilde{\boldsymbol{\theta}}_0)$ and $\boldsymbol{I}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)$ are considered when $m = 1$. Asymptotic properties of the score test can be considered in this case as τ approaches infinity, or in some cases, as certain components of $\boldsymbol{\alpha}$ increase in size.

In Section 1.4.2, we mentioned that there is a link between martingales and maximum likelihood estimation in recurrent event settings. Note that the score functions (1.34) and (1.35) can be rewritten as follows; for any finite interval $[0, t]$,

$$U_{\alpha_l}(t;\boldsymbol{\theta}) = \sum_{i=1}^{m} \int_0^t H_{\alpha_l}(u)\, dM_i(u;\boldsymbol{\theta}), \qquad l = 1, \ldots r, \tag{1.43}$$

and

$$U_{\beta_k}(t;\boldsymbol{\theta}) = \sum_{i=1}^{m} \int_0^t H_{\beta_k}(u)\, dM_i(u;\boldsymbol{\theta}), \qquad k = 1, \ldots, p, \tag{1.44}$$

where $H_{\alpha_l}(t) = Y_i(t)(\partial/\partial\alpha_l)\log\lambda_0(t;\boldsymbol{\alpha})$, $H_{\beta_k}(t) = Y_i(t)z_{ik}(t)$ and $dM_i(t;\boldsymbol{\theta}) = dN_i(t) - \lambda_i(t|\mathcal{H}_i(t);\boldsymbol{\theta})\, dt$. Assuming that H_{α_l} and H_{β_k} are predictable processes, and that $\lambda_i(u|\mathcal{H}_i(u);\boldsymbol{\theta})$ is absolutely continuous, then the score functions (1.43) and (1.44) are of the form (1.26), that is, a martingale structure. Therefore, it is possible, under certain conditions, to show that appropriately normalized score functions (1.43) and (1.44) converge weakly to a normal distribution with mean zero and a specific variance. This key result will lead to derivation of the asymptotic properties of partial score statistics (1.40) in certain settings.

1.4.4 Robust Methods Based on Marginal Characteristics of Event Processes

Methods involving full specification of the processes via the intensity functions are very useful, in particular, when an extensive understanding of a recurrent event process is needed. In some cases, however, it is possible to develop methods using marginal characteristics of processes such as the rate and mean functions. One use of these methods is to give robust tests with respect to certain model features. For example, in Chapters 4 and 5 we will introduce robust tests for time trends based on rate and mean functions.

Suppose that m independent processes are under observation. Let $\boldsymbol{\theta} = (\boldsymbol{\alpha}', \boldsymbol{\beta}')'$ and $\boldsymbol{x}_i(t)$ be a vector of time-dependent external covariates for subject i ($i = 1, \ldots, m$). Following the notation of the previous section, we consider the mean function $\mu_i(t) = E\{N_i(t)\}$ and the parametric rate function $\rho_i(t)\, dt = d\mu_i(t)$, where

$$\rho_i(t;\boldsymbol{\theta}) = \rho_0(t;\boldsymbol{\alpha}) \exp(\boldsymbol{x}_i(t)'\boldsymbol{\beta}). \tag{1.45}$$

From score vectors (1.34) and (1.35), with intensity function (1.45) of the Poisson form score estimating equations are obtained as

$$\begin{aligned} \mathbf{0} = \boldsymbol{U}_\alpha(\boldsymbol{\theta}) &= \sum_{i=1}^{m} \boldsymbol{U}_{\alpha i}(\boldsymbol{\theta}) \\ &= \sum_{i=1}^{m} \int_0^\infty Y_i(s) \frac{\partial \log \rho_0(s;\boldsymbol{\alpha})}{\partial \boldsymbol{\alpha}} \left[dN_i(s) - \rho_i(s;\boldsymbol{\theta})\, ds \right], \end{aligned} \tag{1.46}$$

and

$$
\begin{aligned}
\mathbf{0} = \boldsymbol{U}_\beta(\boldsymbol{\theta}) &= \sum_{i=1}^{m} \boldsymbol{U}_{\beta i}(\boldsymbol{\theta}) \\
&= \sum_{i=1}^{m} \int_0^\infty Y_i(s)\boldsymbol{x}_i(s)\left[dN_i(s) - \rho_i(s;\boldsymbol{\theta})\,ds\right]. \qquad (1.47)
\end{aligned}
$$

When observation processes $\{Y_i(t); t > 0\}$ and event processes $\{N_i(t); t > 0\}$ are independent, expectations of (1.46) and (1.47) are zero. This result holds as long as $E\{dN_i(t)\} = \rho_i(t;\boldsymbol{\theta})\,dt$, where $dN_i(t)$ represents the number of events in an arbitrary short interval $(t - dt, t]$. Under some regularity conditions (White, 1982) and applying results on empirical processes (Lin et al., 2000), as $m \to \infty$,

$$
\frac{1}{\sqrt{m}}\boldsymbol{U}(\boldsymbol{\theta}) = \frac{1}{\sqrt{m}}(\boldsymbol{U}_\alpha(\boldsymbol{\theta})', \boldsymbol{U}_\beta(\boldsymbol{\theta})')' \xrightarrow{\mathcal{D}} MVN(\mathbf{0}, \boldsymbol{B}(\boldsymbol{\theta})),
$$

where MVN stands for the multivariate normal distribution, $\mathbf{0}$ is a vector of zeros, $\boldsymbol{B}(\boldsymbol{\theta}) = \lim_{m\to\infty} E\{\boldsymbol{B}_m(\boldsymbol{\theta})\}$ and $\boldsymbol{B}_m(\boldsymbol{\theta}) = \frac{1}{m}\sum_{i=1}^{m} \boldsymbol{U}_i(\boldsymbol{\theta})\boldsymbol{U}_i(\boldsymbol{\theta})'$. A consistent estimator of $\boldsymbol{B}(\boldsymbol{\theta})$ is $\boldsymbol{B}_m(\hat{\boldsymbol{\theta}})$ where $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\alpha}}', \hat{\boldsymbol{\beta}}')'$ is the Poisson process maximum likelihood estimator of $\boldsymbol{\theta}$ obtained by solving (1.46) and (1.47). Under the above conditions, an asymptotic variance estimate of $\boldsymbol{U}(\hat{\boldsymbol{\theta}})$ is, therefore, given by $\sum_{i=1}^{m} \boldsymbol{U}_i(\hat{\boldsymbol{\theta}})\boldsymbol{U}_i(\hat{\boldsymbol{\theta}})'$, which is valid under a Poisson process as well as under departures from the Poisson process.

Consider testing the null hypothesis $H_0 : \boldsymbol{\beta} = \mathbf{0}$. From the above argument, assuming $Y_i(t)$ and $N_i(t)$ are independent and specification of the rate function is correct, a robust asymptotic variance estimate of $\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0)$ is given by $\sum_{i=1}^{m} \boldsymbol{U}_{\beta i}(\tilde{\boldsymbol{\theta}}_0)\boldsymbol{U}_{\beta i}(\tilde{\boldsymbol{\theta}}_0)'$, where $\tilde{\boldsymbol{\theta}}_0 = (\tilde{\boldsymbol{\alpha}}', \mathbf{0}')'$, and $\tilde{\boldsymbol{\alpha}}$ is the maximum likelihood estimator of $\boldsymbol{\alpha}$ obtained by solving (1.46) when $\boldsymbol{\beta} = \mathbf{0}$.

1.5 Simulation Procedures for Event Processes

In this section, we introduce how a recurrent event process with a given intensity function can be simulated, and discuss how this could be used in order to either (i) study the null distribution of a test statistic, (ii) study the distribution of a test statistic under an alternative model (for looking at power), or (iii) obtain a p-value based on a given data set. First, simulation algorithms for a recurrent event process are explained, and then these situations are discussed. In the following discussion we assumed that a process is observed over an observation window $[0, \tau]$ uninterruptedly; that is, $Y(t) = I(0 \le t \le \tau)$, and τ is prespecified.

1.5.1 Simulation of an Event Process with a Given Intensity Function

Let $\{N(t); t \geq 0\}$ be a counting process with an associated intensity function $\lambda(t|\mathcal{H}(t))$. A computer simulation algorithm to generate event times of an intensity based model can be given by using the result of Corollary 1.2.1. In particular, if we let

$$E_j = \int_{t_{j-1}}^{t_{j-1}+W_j} \lambda(t|\mathcal{H}(t))\, dt \qquad j = 1, 2, \ldots, \tag{1.48}$$

where the W_j are the gap times generated by the process $\{N(t); t \geq 0\}$ with intensity $\lambda(t|\mathcal{H}(t))$, then it is easy to show that, given t_{j-1} and $\mathcal{H}(t_{j-1})$, each random variable E_j has an exponential distribution with mean 1. This follows from the fact that $\Pr\{W_j > w|T_{j-1} = t_{j-1}, \mathcal{H}(t_{j-1})\} = \exp\left\{-\int_{t_{j-1}}^{t_{j-1}+w} \lambda(t|\mathcal{H}(t))\, dt\right\}$, $j = 1, 2, \ldots$, and so $U_j = \exp(-E_j)$ has a standard uniform distribution. In the algorithm, we need to solve the equation $E_j = \int_{t_{j-1}}^{t_{j-1}+W_j} \lambda(t|\mathcal{H}(t))\, dt$ for each W_j. This can be done numerically (see, e.g., Lawless and Thiagarajah, 1996). To generate failure times for a general intensity based model by a computer simulation, the algorithm used in this thesis is then given as follows:

1. Set $j = 1$ and $t_0 = 0$.
2. Generate U_j from a standard uniform distribution.
3. Use the transformation $E_j = -\log(U_j)$.
4. Calculate the jth event time T_j by solving $E_j = \int_{t_{j-1}}^{T_j} \lambda(t|\mathcal{H}(t))\, dt$ for T_j, where $T_j = t_{j-1} + W_j$.
5. If $T_j \leq \tau$, advance j by 1 and let $t_{j-1} = T_{j-1}$. Then, return to the second step. Otherwise, stop the loop and the recurrent event times observed over $[0, \tau]$ are given by $t_1, \ldots, t_n$, where $n = j - 1$.

It should be noted that the history $\mathcal{H}(t)$ may include external covariates. There are other proposed simulation algorithms in order to generate arrival times or, equivalently, failure times for an intensity based model in the literature; for more details, see Daley and Vere-Jones (2003) and Cook and Lawless (2007, Problem 2.2).

When generating the event times from a HPP with the rate function ρ, steps 2–4 of the above algorithm give $W_j = -\rho^{-1}\log(U_j)$, $j = 1, 2, \ldots$. Event times for a NHPP with the rate function $\rho(t)$ and mean function $\mu(t)$ can be generated by using Proposition 1.3.2. In this case, steps 2–4 give the event times of a HPP with rate 1 as $\mu(T_j) = \mu(t_{j-1}) - \log(U_j)$, $j = 1, 2, \ldots$. Then, the inverse transformation $T_j = \mu^{-1}(\mu(t_{j-1}) - \log(U_j))$ gives the j'th event time for the NHPP.

1.5.2 The Use of Simulation Procedures

By generating data using simulation, it is possible to study the distribution of a test statistic under both null and alternative hypotheses, and obtain a p-value for a given data set.

Suppose that the expanded model is in the form of a multiplicative model; that is $\lambda(t|\mathcal{H}(t);\boldsymbol{\theta}) = \lambda_0(t;\boldsymbol{\alpha})\exp\{\boldsymbol{z}'(t)\boldsymbol{\beta}\}$. Then, we can simulate B realizations of the data under the null hypothesis. For each realization, the estimate $\tilde{\boldsymbol{\theta}}_0 = (\tilde{\boldsymbol{\alpha}}', \mathbf{0}')'$, the partial score vector $\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0)$, the matrix $\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)$ and the partial score statistic $\boldsymbol{U}'_\beta(\tilde{\boldsymbol{\theta}}_0)\,\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)\,\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0)$ are obtained, and kept in a B-dimensional vector. Then, we use these vectors in order to study the null distribution of a score test statistic.

If the interest is in the power of a score test, a simulation study can be conducted as follows. The power function of the test of hypothesis

$$H_0 : \boldsymbol{\beta} = \mathbf{0},\ \boldsymbol{\alpha} \in \mathbb{R}^r \qquad \text{vs.} \qquad H_1 : \boldsymbol{\beta} \neq \mathbf{0},\ \boldsymbol{\alpha} \in \mathbb{R}^r \tag{1.49}$$

is defined by $P(\boldsymbol{\beta}_1) = \Pr\{\text{reject}\, H_0;\ \boldsymbol{\beta} = \boldsymbol{\beta}_1\}$. Therefore, in order to look at the power function, data sets should be generated from the expanded model for different values of $\boldsymbol{\beta}_1$. We then simulate B realizations of the data set at some value $\boldsymbol{\beta}_1 \neq \mathbf{0}$. For each realization, the estimate $\tilde{\boldsymbol{\theta}}_0 = (\tilde{\boldsymbol{\alpha}}', \mathbf{0}')'$, the partial score vector $\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0)$, the matrix $\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)$ and the partial score statistic $\boldsymbol{U}'_\beta(\tilde{\boldsymbol{\theta}}_0)\,\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)\,\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0)$ are obtained, and kept in a B-dimensional vector. Then, we use these vectors in order to look at the power function $P(\boldsymbol{\beta}_1)$ of the test (1.49) for a given nominal test size.

Under the null hypothesis of (1.49), a partial score statistic (1.30) has an approximate chi-square distribution with p degrees of freedom in some situations. Then, a p-value for a data set is given by $\Pr\{\chi^2_p \geq \boldsymbol{U}'_\beta(\tilde{\boldsymbol{\theta}}_0)\,\boldsymbol{J}^{\beta\beta}(\tilde{\boldsymbol{\theta}}_0)\,\boldsymbol{U}_\beta(\tilde{\boldsymbol{\theta}}_0)\}$, where $\tilde{\boldsymbol{\theta}}_0 = (\tilde{\boldsymbol{\alpha}}', \mathbf{0}')'$. However, we can also obtain a p-value by simulation. To do this we generate data sets D_j under H_0, then calculate the partial score statistic Z_j. Repeat this step B times, and then the p-value is estimated by

$$\frac{\sum_{j=1}^{B} I(Z_j > Z_{\text{obs}})}{B}, \tag{1.50}$$

where Z_{obs} is the test statistic based on the given data set. The adequacy of χ^2 approximations for test statistics will be examined in the following chapters. In settings where they are inaccurate, we recommend using simulation to determine p-values.

1.6 Outline of Thesis

The main target of this thesis is to develop formal tests for certain features of recurrent event processes, and to discuss their properties. In particular, a carryover effect and a time trend are of interest. The former may cause clustering of events together in time, and the latter refers to a tendency for the rate of event occurrence to change over time in some systematic way. In this chapter, we introduced notation and families of models that are widely used in recurrent event settings as well as mathematical concepts and simulation methods that are useful in the subsequent chapters. The remainder of the thesis is organized as follows.

In Chapter 2, we discuss testing for carryover effects in identical recurrent event processes. We first consider testing for carryover effects in homogeneous Poissson processes. A model expansion technique is considered for test procedures. This amounts to including internal covariates in models. Asymptotic properties of test statistics are discussed when the number of processes approaches infinity as well as when the observation period or a model parameter increases for a single process. Tests are investigated by simulations. We present an example from industry to illustrate the methods. We then consider testing for carryover effects in nonhomogeneous Poisson processes. Large sample properties of tests are discussed, and an example is given.

In Chapter 3, we introduce models and tests that are useful in testing for carryover effects when heterogeneity is present between processes. In particular, although individual processes may be adequately described by a modulated Poisson process, the process rate functions may vary across individuals. Such variation is typically due to unmeasured differences in the individuals or the environment in which the processes operate. If carryover effects tests developed for homogeneous processes are used when substantial heterogeneity is present, false indications of an effect can occur, producing an inflated Type 1 error rate. Therefore, we focus on testing for carryover effects under fixed and random effects models. A simulation study is conducted to investigate the properties of test statistics. We also present an example from medicine to illustrate the tests.

We discuss testing for trend in identical recurrent event processes as well as definitions of trend in Chapter 4. We focus on the case where several processes are under observation, and consider tests based on Poisson and renewal processes. Robust trend tests based on rate functions are also discussed. The main aim of Chapter 4 is to introduce the robust tests, and to compare them with other prominent tests. These topics are considered under two different censoring schemes with both the presence and absence of covariates. An extensive simulation study is given to investigate large sample approximations and power properties of tests. In Chapter 5, we discuss tests for trends in nonidentical recurrent event processes. We extend the tests given in Chapter 4, and follow a parallel approach to investigate their properties with simulation. We illustrate the tests with an example.

We summarize the results of the previous chapters, and give practical recommendations in Chapter 6. Also, future research topics are discussed.

Chapter 2

Testing for Carryover Effects in Identical Processes

In the previous chapter, we mentioned the concept of carryover effects in recurrent event processes. We discuss this feature here and in the following chapter. In this chapter, we consider testing for carryover effects in a single process or in m identical processes. The outline of this chapter is as follows. We first discuss carryover effects and the purpose of this chapter. We next introduce the models and estimation methods for carrover effects testing. In Section 2.3, tests of no carryover effect for homogeneous processes are introduced. We discuss the large sample properties of test statistics in different settings. In Section 2.4, we present results of simulation studies. In Section 2.5, we give an example to illustrate the methods explained in previous sections. In the last section, we discuss testing for carryover effects in nonhomogeneous Poisson process settings.

2.1 Introduction

In certain settings the event intensity may be temporarily increased (or in some cases, decreased) after an event occurs; we refer to this as a *carryover effect*. This phenomenon has been widely discussed for hardware or software systems where the repairs undertaken to deal with a failure may not resolve the problem or may even create new problems (see e.g. Baker, 2001; Pena, 2006). A number of general models have been proposed for repairable systems (see Lindqvist, 2006; Stocker and Pena, 2007), which provide considerable flexibility in specifying the effects of past events on the intensity function. However, such models are complex and tie the examination and interpretation of event patterns to assumptions that may be hard to check. Our purpose here is to consider some simple models and tests for carryover effects. The tests are easily interpreted, robust and less subject to the criticism that they are carried out after elaborate model fitting.

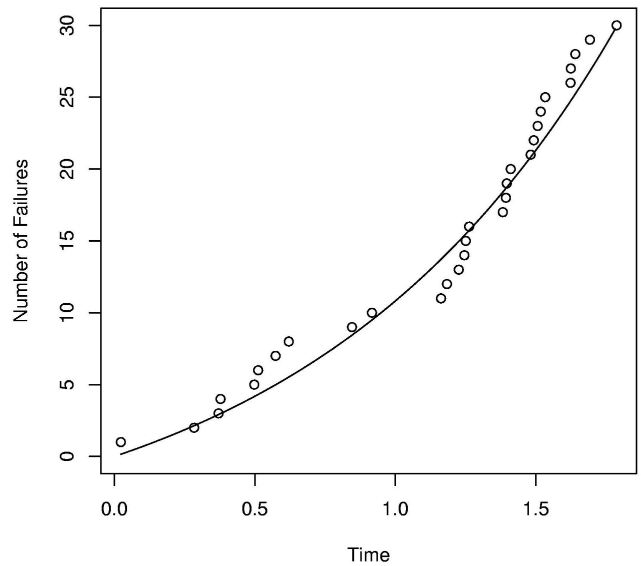

Figure 2.1: Cumulative air-conditioning failures. Time unit is thousands of hours of operation.

Our approach is based on an expansion of ideas in Lawless and Thiagarajah (1996) and Cook and Lawless (2007, Section 5.2). To motivate and illustrate the approach in a simple setting, we show in Figure 2.1 a plot of cumulative failures versus total hours of operation for the air-conditioning system in an airplane (Cook and Lawless, 2007, pp. 167–170). The data suggest the rate of failures is increasing with time. In addition, we observe a pattern of clustering of failures that may indicate a carryover effect, and analysis by Cook and Lawless (2007, pp. 167–169) suggests the presence of such an effect.

In this chapter, we develop simple tests of carryover effects, and study their properties. Our approach can deal with single or multiple systems, and cases where the event intensity is either temporarily increased or decreased following an event. We remark that, although there is some similarity, the carryover effect concept is different than the concept of temporal clustering in a series of events (e.g. see Xie et al., 2009). In the latter case the emphasis is on detecting and identifying clusters and models in which some underlying process generates clusters of varying size are typically used (e.g. Cox and Isham, 1980).

2.2 Models and Estimation

2.2.1 Models for Carryover Effects

We assume that an individual process is observed over time $[0, \tau]$, and let $N(t)$ denote the number of events in $[0, t]$. The event generating counting process $\{N(t); t \geq 0\}$ is assumed to have an associated intensity function $\lambda(t|\mathcal{H}(t))$, which is defined in Section 1.2. The times of events in $[0, \tau]$ are denoted $T_1 < \cdots < T_n$, and $B(t) = t - T_{N(t^-)}$ is the *backward recurrence time*; that is, the time since the most recent event prior to t. In some settings, we may need to introduce the at-risk indicator $Y(t)$ into the model. This is discussed in Section 1.4.1. Therefore, the following discussion can be easily generalized to more complex observation schemes such as random censoring as well as intermittent observation.

Poisson models often turn out to be adequate in practical settings, if allowance is made for heterogeneity across systems. In some settings, however, there is a tendency for the intensity of events to increase for a limited time period after each event. We consider such effects here through modulated Poisson process models in which the intensity function takes the form

$$\lambda(t|\mathcal{H}(t)) = \rho_0(t)\, \exp\left(\boldsymbol{z}'(t)\boldsymbol{\beta}\right), \qquad t \geq 0, \tag{2.1}$$

where $\boldsymbol{z}(t)$ is a $q \times 1$ vector of time-varying covariates that is allowed to contain functions of the event history $\mathcal{H}(t)$ as well as external covariates. More specifically, we consider models for which $\boldsymbol{z}(t)$ includes terms that are zero except for a limited time period following the occurrence of an event. Such terms specify what we call carryover effects.

A simple but very useful model is one where $\boldsymbol{z}(t)$ in (2.1) includes one term, and takes the form

$$z(t) = I\left(N(t^-) > 0\right) I\left(B(t) \leq \Delta\right), \tag{2.2}$$

where $\Delta > 0$ is a specified value. In that case the intensity function following an event temporarily changes from $\rho_0(t)$ to $\rho_0(t)\, e^{\beta}$. Tests of the null hypothesis $H_0 : \beta = 0$, developed below, provide simple and intuitive tests of no carryover effect.

Tests for carryover effects based on (2.1)–(2.2) are attractive, as we show here. However, other models with carryover effects can also be specified. For example, a model (2.1) with $z(t) = I(N(t^-) > 0) \exp(-\gamma B(t))$ or a linear self-exciting process (Cox and Isham, 1980, Section 3.3) with $\lambda(t|\mathcal{H}(t)) = \rho_0(t) + \beta \sum_{j=1}^{N(t^-)} e^{-\gamma(t-t_j)}$ also produce transient effects following events, while allowing possible time trends as in (2.1). However, they are more difficult to handle than (2.1)–(2.2), and do not impose a time limit on the duration of an effect.

Models where the times between events have mixture forms can be used for introducing carryover effects in renewal processes. For example, a discrete mixture model for gap times

W_j is given by $f(w) = \pi f_1(w) + (1-\pi) f_2(w)$, where f is the p.d.f. of the W_j, f_1 and f_2 are two different p.d.f.'s for the gap times, and $0 < \pi < 1$. A carryover effect would correspond to one component (say f_1) being "early" and f_2 being "late". The model (2.1)–(2.2) is a "delayed" modulated renewal model in which W_1 has a different distribution than W_j ($j \geq 2$), in the case when $\rho_0(t) = \rho_0$ is constant. Other models in which the times between successive events have mixture models with substantial mass near zero could be specified (e.g. see Lindqvist, 2006; Pena, 2006) but they are more difficult to handle than (2.1)–(2.2). The tests we consider are easily interpreted and robust in the sense that they retain good power to reject the hypothesis of no carryover effect even when model (2.1) is misspecified. Simulation results in Section 2.4 demonstrate this.

The discussion given above is for a single process. When multiple processes are identical, the generalization of model (2.1) with (2.2) is then given by $\lambda_i(t|\mathcal{H}_i(t)) = \rho_0(t)\exp(\beta z_i(t))$, where $z_i(t) = I\left(N_i(t^-) > 0\right) I\left(B_i(t) \leq \Delta\right)$ and $B_i(t) = t - T_{N_i(t^-)}$ is the backward reccurence time for subject i at time t.

The tests here require specification of a value for Δ. We discuss this, and study robustness of the test to misspecification of Δ, or of the model (2.1), in the following sections.

2.2.2 Estimation and Testing for No Carryover Effect

Consider model (2.1) with $\rho_0(t)$ specified parametrically as $\rho_0(t;\boldsymbol{\alpha})$, with $\boldsymbol{\alpha}$ a $p \times 1$ vector of parameters, and $\boldsymbol{z}(t)$ given by (2.2) with a specified value of Δ. Suppose m independent systems have identical intensity functions (2.1) and that system i is observed over the interval $[0, \tau_i]$ and has n_i events, at times t_{ij} ($j = 1, \ldots, n_i$). We also define $t_{i0} = 0, t_{i,n_i+1} = \tau_i$ and $w_{ij} = t_{ij} - t_{i,j-1}$ ($j = 1, \ldots, n_i + 1$); for $j = 2, \ldots, n_i$ the w_{ij} are the times between successive events for system i. For notational convenience we define

$$R(\boldsymbol{\alpha}, \beta) = \sum_{i=1}^{m} \int_0^{\tau_i} \rho_0(t;\boldsymbol{\alpha}) \exp\left(\beta z_i(t)\right)\, dt. \tag{2.3}$$

The log likelihood function for $\boldsymbol{\alpha}$ and β, based on the observed event histories for systems $i = 1, \ldots, m$, is (cf. Section 1.4.3)

$$\ell(\boldsymbol{\alpha}, \beta) = \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} \left[\beta z_i(t_{ij}) - \log \rho_0(t_{ij};\boldsymbol{\alpha})\right] \right\} - R(\boldsymbol{\alpha}, \beta). \tag{2.4}$$

Estimates $\hat{\boldsymbol{\alpha}}, \hat{\beta}$ are obtained by maximizing $\ell(\boldsymbol{\alpha}, \beta)$ and if $\beta = 0$, an estimate $\tilde{\boldsymbol{\alpha}}$ is obtained by maximizing $\ell(\boldsymbol{\alpha}, 0)$. This is easily done with optimization software that does not require coding of expressions for derivatives of $\ell(\boldsymbol{\alpha}, \beta)$. In this thesis we make extensive use of the R function nlm. We note for use later that $R(\boldsymbol{\alpha}, \beta)$ in (2.4) may be rewritten from (2.2) and (2.3) as

$$R(\boldsymbol{\alpha}, \beta) = \sum_{i=1}^{m} \left\{ \left(e^{\beta} - 1\right) \sum_{j=1}^{n_i} \int_{t_{ij}}^{\min(t_{i,j+1},\, t_{ij}+\Delta)} \rho_0(t; \boldsymbol{\alpha})\, dt + \int_0^{\tau_i} \rho_0(t; \boldsymbol{\alpha})\, dt \right\}. \tag{2.5}$$

A test of no carryover effect within the family of models (2.1) can be obtained by testing the null hypothesis $H_0 : \beta = 0$. This can be tested using the likelihood ratio statistic $\Lambda = 2\ell(\hat{\boldsymbol{\alpha}}, \hat{\beta}) - 2\ell(\tilde{\boldsymbol{\alpha}}, 0)$, where $\tilde{\boldsymbol{\alpha}}$ maximizes $\ell(\boldsymbol{\alpha}, 0)$. An alternative test that requires us to find only $\tilde{\boldsymbol{\alpha}}$, and not $\hat{\boldsymbol{\alpha}}, \hat{\beta}$, is based on the score statistic $U_\beta(\tilde{\boldsymbol{\alpha}}, 0)$, where $U_\beta(\boldsymbol{\alpha}, \beta) = \partial\ell(\boldsymbol{\alpha}, \beta)/\partial\beta$ (cf. Section 1.4.3). This gives

$$U_\beta(\tilde{\boldsymbol{\alpha}}, 0) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} z_i(t_{ij}) - R^{(\beta)}(\tilde{\boldsymbol{\alpha}}, 0), \tag{2.6}$$

where

$$R^{(\beta)}(\boldsymbol{\alpha}, \beta) = \partial R(\boldsymbol{\alpha}, \beta)/\partial\beta = \sum_{i=1}^{m} \left\{ e^{\beta} \sum_{j=1}^{n_i} \int_{t_{ij}}^{\min(t_{i,j+1},\, t_{ij}+\Delta)} \rho_0(t; \boldsymbol{\alpha})\, dt \right\}. \tag{2.7}$$

Inspection of (2.6) shows it to be of the form "Observed - Expected", where "Observed" is the total number of events that follow the previous event by a time of Δ or smaller, and "Expected" is an estimate of the expected number of such occurrences under the null hypothesis. A variance estimate for $U_\beta(\tilde{\boldsymbol{\alpha}}, 0)$ under H_0 is given by asymptotic theory for counting processes in the case where $m \to \infty$ (Andersen et al, 1993, Chapter 6; Pena, 1998). This takes the standard form (see (1.40) and (1.42))

$$\widehat{Var}\left\{U_\beta(\tilde{\boldsymbol{\alpha}}, 0)\right\} = I_{\beta\beta}(\tilde{\boldsymbol{\alpha}}, 0) - \boldsymbol{I}_{\beta\alpha}(\tilde{\boldsymbol{\alpha}}, 0)\boldsymbol{I}_{\alpha\alpha}^{-1}(\tilde{\boldsymbol{\alpha}}, 0)\boldsymbol{I}_{\alpha\beta}(\tilde{\boldsymbol{\alpha}}, 0), \tag{2.8}$$

where the components of (2.8) are given by (cf. Section 1.4.3)

$$\begin{aligned}
I_{\beta\beta}(\tilde{\boldsymbol{\alpha}}, 0) &= R^{(\beta)}(\tilde{\boldsymbol{\alpha}}, 0) && (2.9)\\
\boldsymbol{I}_{\alpha\alpha}(\tilde{\boldsymbol{\alpha}}, 0) &= -\sum_{i=1}^{m}\sum_{j=1}^{n_i} \frac{\partial^2 \log \rho_0(t_{ij}; \tilde{\boldsymbol{\alpha}})}{\partial\tilde{\boldsymbol{\alpha}}\partial\tilde{\boldsymbol{\alpha}}'} + \sum_{i=1}^{m} \int_0^{\tau_i} \frac{\partial^2 \rho_0(t; \tilde{\boldsymbol{\alpha}})}{\partial\tilde{\boldsymbol{\alpha}}\partial\tilde{\boldsymbol{\alpha}}'}\, dt && (2.10)\\
\boldsymbol{I}_{\alpha\beta}(\tilde{\boldsymbol{\alpha}}, 0) &= \boldsymbol{I}'_{\beta\alpha}(\tilde{\boldsymbol{\alpha}}, 0) = \left(\frac{\partial^2 R(\boldsymbol{\alpha}, \beta)}{\partial\boldsymbol{\alpha}\partial\beta}\right)\Bigg|_{(\tilde{\boldsymbol{\alpha}}, 0)} \\
&= \sum_{i=1}^{m}\sum_{j=1}^{n_i} \int_{t_{ij}}^{\min(t_{i,j+1},\, t_{ij}+\Delta)} \frac{\partial\rho_0(t; \tilde{\boldsymbol{\alpha}})}{\partial\tilde{\boldsymbol{\alpha}}}\, dt. && (2.11)
\end{aligned}$$

The standardized partial score statistic for testing H_0 is then

$$S = U_\beta(\tilde{\boldsymbol{\alpha}}, 0)/\widehat{Var}\left\{U_\beta(\tilde{\boldsymbol{\alpha}}, 0)\right\}^{1/2}. \tag{2.12}$$

The $p \times p$ matrix (2.10) is the negative Hessian matrix from the model with $\beta = 0$ and so is obtained by fitting the null model. The scalar (2.9) and $p \times 1$ vector (2.11) are readily computed from the fitted null model. For illustration, consider the often-used power law model $\rho_0(t; \boldsymbol{\alpha}) = \alpha_1 \alpha_2 t^{\alpha_2 - 1}$. Then $U_\beta(\tilde{\boldsymbol{\alpha}}, 0)$ is given by (2.6) with

$$R^{(\beta)}(\tilde{\boldsymbol{\alpha}}, 0) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} \tilde{\alpha}_1 \left\{ \left[\min\left(t_{i,j+1}, t_{ij} + \Delta\right)\right]^{\tilde{\alpha}_2} - t_{ij}^{\tilde{\alpha}_2} \right\} \tag{2.13}$$

and (2.8) contains the elements

$$I_{\beta\beta}(\tilde{\boldsymbol{\alpha}}, 0) = R^{(\beta)}\left(\tilde{\boldsymbol{\alpha}}, 0\right) \tag{2.14}$$

$$\boldsymbol{I}_{\alpha\beta}(\tilde{\boldsymbol{\alpha}}, 0) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} \int_{t_{ij}}^{\min(t_{i,j+1},\, t_{ij}+\Delta)} \begin{pmatrix} \alpha_2 t^{\alpha_2 - 1} \\ \alpha_1 t^{\alpha_2 - 1} \left(1 + \alpha_2 \log t\right) \end{pmatrix} dt \tag{2.15}$$

and $\boldsymbol{I}_{\alpha\alpha}(\tilde{\boldsymbol{\alpha}}, 0)$, which is the 2×2 Hessian matrix from the fitted null model $\rho_0(t; \boldsymbol{\alpha}) = \alpha_1 \alpha_2 t^{\alpha_2 - 1}$. Good optimization software can give this without requiring analytical derivatives for $\ell(\boldsymbol{\alpha}, 0)$, by using numerical differentiation. The only elements requiring additional computation are (2.14) and (2.15); the former is trivial but the latter requires numerical integration.

Asymptotic distributions for the test statistics Λ and S as $m \to \infty$ take, under mild assumptions on $\rho_0(t; \boldsymbol{\alpha})$ and β, the usual $\chi^2_{(1)}$ and $N(0, 1)$ forms (Andersen et al., 1993, Chapter 6; Pena, 1998). We will discuss these assumptions and aymptotics in the next section for the case where $\rho_0(t; \alpha) = \alpha$. Simulation studies in Section 2.4 consider the adequacy of these as approximations for finite sample settings. In cases where m is small but event occurrence rates or the τ_i are sufficiently large, the same approximations may be used. In some settings the asymptotic approximations are inaccurate and we then recommend obtaining p-values by simulation. This can be done by simulating B (=1000, say) data sets under the null model with $\boldsymbol{\alpha} = \tilde{\boldsymbol{\alpha}}$, obtaining estimates and test statistic Λ or S for each, and then taking the proportion of the B samples for which the statistic exceeds the observed value in the original sample as the (estimated) p-value. We described a method for simulating Poisson processes in Section 1.5. The special case where the null model is an HPP is of special interest in many settings, including ones involving a single system observed over a long period of time. We consider this in the next section.

2.3 Tests of No Carryover Effect for Homogeneous Poisson Processes

In this section, we discuss tests for no carryover effect in identical processes and their asymptotic properties. We consider the HPP as the null hypothesis of no carryover effect throughout this section. When the null model is an HPP with rate function α for subject i ($i = 1, \ldots, m$), both the likelihood ratio and partial score statistics take a simple form. Let $z_i(t)$ be as given in (2.2). For convenience, we then define

$$O(\Delta) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} z_i(t_{ij}), \qquad E(\Delta) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} \min\left(W_{i,j+1}, \Delta\right), \tag{2.16}$$

and let $n = \sum_{i=1}^{m} n_i,\ \tau = \sum_{i=1}^{m} \tau_i$. The log likelihood (2.4) is then

$$\ell(\alpha, \beta) = \beta O(\Delta) + n \log \alpha - \alpha \left\{ (e^{\beta} - 1) E(\Delta) + \tau \right\} \tag{2.17}$$

and solving $\partial \ell / \partial \alpha = 0,\ \partial \ell / \partial \beta = 0$, we find

$$e^{\hat{\beta}} = \frac{O(\Delta)\left[\tau - E(\Delta)\right]}{E(\Delta)\left[n - O(\Delta)\right]}, \qquad \hat{\alpha} = \frac{n}{(\hat{\theta} - 1)E(\Delta) + \tau}. \tag{2.18}$$

The estimate $e^{\hat{\beta}}$ of the relative intensity for the carryover period of length Δ has the intuitive form $O(\Delta)/E(\Delta)$ divided by $[n - O(\Delta)]/[\tau - E(\Delta)]$, which estimates the event rate within and outside of a carryover period, respectively. In particular, note that $O(\Delta)$ and $n - O(\Delta)$ are the observed numbers of events inside and outside a carryover period.

The estimate $\tilde{\alpha}$ under the null hypothesis $H_0 : \beta = 0$ is $\tilde{\alpha} = n/\tau$, and the likelihood ratio statistic for testing H_0 reduces to

$$\Lambda = 2\hat{\beta} O(\Delta) - 2n \log \left\{ 1 + \left(e^{\hat{\beta}} - 1 \right) E(\Delta)/\tau \right\}. \tag{2.19}$$

The partial score statistic (2.6) also takes a simple form:

$$U_{\beta}(\tilde{\alpha}, 0) = O(\Delta) - \frac{n}{\tau} E(\Delta), \tag{2.20}$$

which is the observed number of events in a carryover period minus an estimate of the expected number, under H_0. The variance estimate (2.8) reduces here to

$$\widehat{Var}\left\{ U_{\beta}(\tilde{\alpha}, 0) \right\} = \frac{n E(\Delta) \left\{ \tau - E(\Delta) \right\}}{\tau^2}. \tag{2.21}$$

Significance levels (p-values) can often be computed by using asymptotic $\chi^2_{(1)}$ and $N(0,1)$ approximations for $\Lambda = 2\ell(\hat{\alpha}, \hat{\beta}) - 2\ell(\tilde{\alpha}, 0)$ and

$$S = U_{\beta}(\tilde{\alpha}, 0) / \widehat{Var}\left\{ U_{\beta}(\tilde{\alpha}, 0) \right\}^{1/2}, \tag{2.22}$$

respectively. Simulation results in Section 2.4 provide guidance as to when these approximations are reliable. When they are not, simulation may be used. We discuss large sample properties of (2.22) in the next two subsections; first, when $m \to \infty$, and then when $m = 1$.

2.3.1 Settings with Large m

In recurrent event settings, convergence of maximum likelihood estimators and asymptotic distributions of test statistics for a model of multiplicative type can be derived by methods similar to those of the classical case of i.i.d. random variables under sufficient conditions. The difference between the two cases is that, in the recurrent event setup, the score functions evaluated at a given parameter vector are in the form of stochastic integrals, and these integrals may not be well-defined. Technical details can be found in many textbooks on stochastic integration (e.g., Kuo, 2006). We are interested in versions of the law of large numbers and central limit theorem for counting processes. Fortunately, these are available from the theory of stochastic processes. Chief among them are Lenglart's inequality and martingale central limit theorem. These results are rigorously discussed by Andersen et al. (1993, Section II.5). Here, we discuss the asymptotics for a general multiplicative model with intensity function

$$\lambda(t|\mathcal{H}(t);\boldsymbol{\theta}) = \lambda_0(t;\boldsymbol{\alpha}) \exp\left\{\boldsymbol{z}'(t)\boldsymbol{\beta}\right\}, \qquad t \geq 0, \tag{2.23}$$

where $\boldsymbol{\theta} = (\boldsymbol{\alpha}', \boldsymbol{\beta}')'$. The interest is to test null hypothesis $H_0 : \boldsymbol{\beta} = \mathbf{0}$. In the following discussion, we first discuss sufficient conditions for some important asymptotic properties of score test statistics to hold. We focus on score test statistics when the null model is a homogeneous Poisson process and the expanded model is modulated Poisson process including a term for a carryover effect. In Section 2.6 we discuss the results when the null model is a nonhomogenenous Poisson process.

The large sample properties of the maximum likelihood estimator $\hat{\boldsymbol{\theta}}$ under the multiplicative intensity assumption are carefully derived by Andersen et al. (1993, Chapter 6), and sufficient conditions for these asymptotic results to hold are given as well. These conditions have to be checked for each specific model under study. Checking such conditions is usually tedious and often tricky (see, for example, Ogata (1978) and van Pul (1990, 1992) for earlier examples). The asymptotic properties of partial score functions in the context of this chapter are studied by Pena (1998). He basically uses the approach of Andersen et al. (1993), and applies it to a family of models. The models with intensity of the form (2.23) are a special case of the models considered by Pena (1998). A set of sufficient conditions similar to that given by Andersen et al. (1993) is given by Pena (1998) in order for these asymptotic results to hold. When $\boldsymbol{z}(t)$ does not depend on any parameter, as here, then these two sets of conditions become the same. In the following, we check that these conditions are satisfied for the models under study.

Andersen et al. (1993, p. 420–421) state five conditions (Condition A–E) to derive the large sample properties of the maximum likelihood estimators. Condition A and Condition E are regularity conditions concerning the continuity, boundedness and convergence of log likelihood derivatives, similar to those found in the classical case. Condition A allows us to use a Taylor series expansion and it holds for the models with intensity (2.23), with $\boldsymbol{z}(t)$ as in (2.2). Condition E should be checked in order to show that the remainder term in a Taylor expansion is negligible. The crucial conditions, which we discuss now, are Conditions B–D.

Condition B is given to ensure that predictable variation processes and thus the variances of score functions converge in probability to deterministic functions. That is, for the model with intensity (2.23), the sum

$$a_m^{-2} \sum_{i=1}^{m} \int_0^{\infty} \left\{ \frac{\partial}{\partial \theta_k} \log \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta}_0) \right\} \left\{ \frac{\partial}{\partial \theta_l} \log \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta}_0) \right\} \times Y_i(u) \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta}_0)\, du, \tag{2.24}$$

should converge, as $m \to \infty$, in probability to a deterministic function $\sigma_{kl}(\boldsymbol{\theta}_0)$, ($k$, $l = 1$, …, q), for some sequence $(a_m)_{m=1}^{\infty}$ of positive constants increasing to infinity. Typically, $a_m = \sqrt{m}$ can be used.

Condition C is required to show that jumps of martingales or stochastic integrals with respect to these martingales approach zero as the normalizing constant a_m approaches infinity. That is, for all $\varepsilon > 0$ and $k = 1$, …, q, the sum

$$a_m^{-2} \sum_{i=1}^{m} \int_0^{\infty} \left\{ \frac{\partial}{\partial \theta_k} \log \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta}_0) \right\}^2 I \left\{ \left| \frac{\partial}{\partial \theta_k} \log \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta}_0) \right| > a_m \varepsilon \right\} \times Y_i(u) \lambda_i(u|\mathcal{H}_i(u); \boldsymbol{\theta}_0)\, du, \tag{2.25}$$

should converge in probability to 0 as $m \to \infty$. Condition D is that the matrix constituted by the $\sigma_{kl}(\boldsymbol{\theta}_0)$ defined in Condition B should be positive definite.

For the case of model (2.1) and (2.2) with $m \to \infty$, we can take $a_m^2 = m$. The conditions B–D then can be shown to hold, provided that $\frac{1}{m} \sum_{i=1}^{m} Y_i(t) \xrightarrow{p} y(t) > 0$ for some interval $0 \le t \le \tau$. The conditions that need to be satisfied are considered here for the null hypothesis model

$$\lambda_i(t|\mathcal{H}_i(t); \alpha) = \alpha, \qquad t \ge 0, \qquad i = 1, \ldots, m, \tag{2.26}$$

where $\alpha \in \mathbb{R}^+$. The intensity function of the observed counting process $\{\bar{N}_i(t); t \ge 0\}$, $i = 1$, …, m, is then

$$\bar{\lambda}_i(t|\bar{\mathcal{H}}_i(t); \alpha) = Y_i(t)\, \alpha, \qquad t \ge 0, \tag{2.27}$$

where $Y_i(t)$ is the at-risk indicator. The data for m independent individual processes are $\{(\bar{N}_i(t), Y_i(t)); i = 1, \ldots, m\}$, and inference for α can be based on the likelihood function (cf. Section 1.4.1) $\alpha^{n.} \exp\left\{-\alpha \sum_{i=1}^{m} \int_0^{\infty} Y_i(u)\, du\right\}$, where $n. = \sum_{i=1}^{m} n_i$.

In order to check the sufficient conditions of Andersen et al. (1993), we make the following rather weak assumption. Suppose that for a specified $\tau > 0$,

$$\frac{1}{m} \sum_{i=1}^{m} \int_0^t Y_i(u)\, du \xrightarrow{p} r(t), \qquad t \in [0, \tau], \tag{2.28}$$

as $m \to \infty$, where $r(t)$ is a positive constant for any $t \in [0, \tau]$. By the convergence (2.28), we assume that the exposure is stabilized on average as m increases. Under this assumption, we can show that the conditions given by Andersen et al. (1993) hold for the model (2.26).

Condition A is a Cramer-type condition, and it is easy to see that it holds for (2.26). In order to show that Condition B is fulfilled, we show that for $\alpha_0 > 0$,

$$\frac{1}{m}\sum_{i=1}^{m}\int_0^{\tau}\left[\frac{\partial(\log\alpha_0)}{\partial\alpha_0}\right]^2 Y_i(u)\alpha_0\,du \xrightarrow{p} \sigma^2(\alpha_0), \tag{2.29}$$

as $m \to \infty$, where $\tau = \max(\tau_i) = \max\{t; Y_i(t) > 0\}$ and $\sigma^2(\alpha_0) > 0$. Since the left hand side of (2.29) is

$$\frac{1}{\alpha_0}\frac{1}{m}\sum_{i=1}^{m}\int_0^{\tau} Y_i(u)\,du, \tag{2.30}$$

the convergence (2.29) directly follows from (2.28) with $\sigma^2(\alpha_0) = r(\tau)/\alpha_0$.

Condition C of Andersen et al. (1993) for the model (2.26) is that, for all $\varepsilon > 0$,

$$\frac{1}{m}\sum_{i=1}^{m}\int_0^{\tau}\frac{1}{\alpha_0} I\left\{\frac{(1/\alpha_0)}{\sqrt{m}} > \varepsilon\right\} Y_i(u)\,du \xrightarrow{p} 0 \tag{2.31}$$

as $m \to \infty$. Note that, the left hand side of (2.31) is $(r(\tau)/\alpha_0)I(\frac{1}{\sqrt{m}} > \alpha_0\varepsilon)$ which converges to 0 as $m \to \infty$. Condition D is about positiveness of $\sigma^2(\alpha_0)$, and is fulfilled since both $r(\tau)$ and α_0 are positive constants.

Condition E is stated to regulate the remainder term of a Taylor series expansion in the proof of the theorem given by Andersen et al. (1993, p. 422). We need to show that, first, for any m, supremum norms of the third derivative of (2.26) and the log of (2.26) with respect to α are bounded by some predictable processes that are independent of α for any m and $t \in [0, \tau]$.

Suppose that $\alpha \geq M$ for some $M > 0$. Since $(\partial^3/\partial\alpha^3)(\alpha) = 0$, $(\partial^3/\partial\alpha^3)(\log\alpha) = 2/\alpha^3$ and $\alpha > 0$, the required supremum norms are bounded by a positive constant, say c, which does not depend on α for any m. Furthermore, from (2.28), $\frac{1}{m}\sum_{i=1}^{m}\int_0^{\tau} cY_i(u)\,du \xrightarrow{p} c\,r(\tau)$ and $\frac{1}{m}\sum_{i=1}^{m}\int_0^{\tau} c\,Y_i(u)\alpha_0\,du \xrightarrow{p} c\,\alpha_0\,r(\tau)$, as $m \to \infty$. Therefore, the first part of Condition E holds for the model (2.26). Next, by a similar argument, $\frac{1}{m}\sum_{i=1}^{m}\int_0^{\tau}\{(\partial^2/\partial\alpha^2)(\log\alpha_0)\}^2\,Y_i(u)\alpha_0\,du$ converges to $r(\tau)/\alpha^3$ in probability as m increases. The last part of Condition E holds since, for all $\varepsilon > 0$,

$$\frac{1}{m}\sum_{i=1}^{m}\int_0^{\tau} c\,I\left\{m^{-1/2}\sqrt{c} > \varepsilon\right\}\,Y_i(u)\alpha_0\,du \xrightarrow{p} 0$$

as $m \to \infty$. This completes the requirements for the model (2.26) to have the usual large sample properties for $\hat{\alpha}$ and also for likelihood ratio and score statistics. Thus,

$\hat{\alpha} = (\sum_{i=1}^m N_i(\tau_i))/(\sum_{i=1}^m \int_0^\infty Y_i(u)\, du)$ is a consistent estimator of α_0, and

$$\sqrt{m}(\hat{\alpha} - \alpha_0) \xrightarrow{\mathcal{D}} Z \sim N(0, \sigma^2) \tag{2.32}$$

as $m \to \infty$, where $\sigma^2 = \alpha_0/r(\tau)$ can be consistently estimated by $\hat{\alpha}/r(\tau)$ (Andersen et al., 1993). Furthermore, the score statistic $U(\alpha) = \sum_{i=1}^m U_i(\alpha)$,where

$$U_i(\alpha) = \frac{N_i(\tau_i)}{\alpha} - \int_0^\infty Y_i(u)\, du,$$

satisfies

$$\frac{1}{\sqrt{m}} U(\alpha_0) \xrightarrow{\mathcal{D}} Z \sim N(0, \sigma^2(\alpha_0)) \tag{2.33}$$

as $m \to \infty$, where $\sigma^2(\alpha_0) = r(\tau)/\alpha_0$ can be consistently estimated by $r(\tau)/\hat{\alpha}$. A score test then can be developed from (2.33) for testing $H_0 : \alpha = \alpha_0$.

We now consider models with a carryover effect, where the intensity is

$$\lambda_i(t|\mathcal{H}_i(t); \alpha, \beta) = \alpha \exp\{\beta z_i(t)\}, \qquad t \in [0, \tau_i], \qquad i = 1, \ldots, m, \tag{2.34}$$

where $\alpha > 0$ and $z_i(t) = I(N_i(t^-) > 0) I(B_i(t) \leq \Delta)$ is a function of the recurrent event history at time t. For simplicity, we assume that the observation processes are completely independent of the event occurrence processes. The log likelihood function (cf. Section 1.4.3) is then given by

$$\ell(\alpha, \beta) = n.\log\alpha + \beta \sum_{i=1}^m \sum_{j=1}^{n_i} z_i(t_{ij}) - \sum_{i=1}^m \int_0^\infty Y_i(u) \alpha e^{\beta z_i(u)}\, du, \tag{2.35}$$

where $n. = \sum_{i=1}^m n_i$, $Y_i(t)$ is the at-risk process, and $z_i(t)$ is a function of the event history at time $t \in [0, \tau_i]$; $i = 1, \ldots, m$. The score functions are then given by

$$U_\alpha(\alpha, \beta) = \frac{n.}{\alpha} - \sum_{i=1}^m \int_0^\infty Y_i(u) e^{\beta z_i(u)}\, du \tag{2.36}$$

and

$$U_\beta(\alpha, \beta) = \sum_{i=1}^m \sum_{j=1}^{n_i} z_i(t_{ij}) - \sum_{i=1}^m \int_0^\infty Y_i(u) z_i(u) \alpha e^{\beta z_i(u)}\, du. \tag{2.37}$$

Furthermore, the observed information matrix $\boldsymbol{I}(\alpha, \beta)$ consists of the following components:

$$I_{\alpha\alpha}(\alpha, \beta) = \frac{n.}{\alpha^2}, \tag{2.38}$$

$$I_{\alpha\beta}(\alpha, \beta) = I_{\beta\alpha}(\alpha, \beta) = \sum_{i=1}^m \int_0^\infty Y_i(u) z_i(u) e^{\beta z_i(u)}\, du, \tag{2.39}$$

and

$$I_{\beta\beta}(\alpha, \beta) = \sum_{i=1}^{m} \int_0^{\infty} Y_i(u) z_i^2(u) \alpha e^{\beta z_i(u)}\, du. \tag{2.40}$$

The partial score statistic for testing $H_0 : \beta = 0$ is given by $U_\beta^2(\tilde{\alpha}(0), 0) J^{\beta\beta}(\tilde{\alpha}(0), 0)$. The partial score function $U_\beta(\tilde{\alpha}(0), 0)$ is obtained by plugging $(\alpha, \beta) = (\tilde{\alpha}(0), 0)$ into the score function (2.37), where $\tilde{\alpha}(0) = n./\tau.$ and $\tau. = \sum_{i=1}^m \tau_i$. When $\beta = 0$, this case becomes that in the previous section. However, now we need to deal with the convergence in probability of

$$\frac{1}{m} \sum_{i=1}^{m} \int_0^{\infty} Y_i(u) z_i(u)\, du, \tag{2.41}$$

as $m \to \infty$, where $z_i(t)$, $i = 1, \ldots, m$, is given by

$$z_i(t) = I(N_i(t^-) > 0)\, I(t - T_{N_i(t^-)} \leq \Delta), \qquad t \in [0, \tau_i]. \tag{2.42}$$

Let the event $A_i(t)$ be "the ith individual experiences at least 1 event in $[\max(t - \Delta, 0), t]$". Note that the function (2.42) for the ith individual is then

$$z_i(t) = I\{A_i(t)\}, \qquad t \in [0, \tau_i]. \tag{2.43}$$

Under the null hypothesis $H_0 : \beta = 0$, we can easily check the sufficient conditions A–E given by Andersen et al. (1993, p. 420–421) for the model (2.34). Suppose that the true value of α is α_0, and that the convergence (2.28) holds. Condition A (Cramer-type condition) can easily be shown that it holds for the model (2.34). In order to check Condition B, we need to show that

$$\frac{1}{m} \sum_{i=1}^{m} \int_0^{\tau} \frac{1}{\alpha_0} Y_i(u)\, du \xrightarrow{p} \sigma_{\alpha\alpha}, \tag{2.44}$$

$$\frac{1}{m} \sum_{i=1}^{m} \int_0^{\tau} Y_i(u) z_i(u)\, du \xrightarrow{p} \sigma_{\alpha\beta}, \tag{2.45}$$

and

$$\frac{1}{m} \sum_{i=1}^{m} \int_0^{\tau} \alpha_0 Y_i(u) z_i(u)\, du \xrightarrow{p} \sigma_{\beta\beta}, \tag{2.46}$$

as $m \to \infty$, where $\sigma_{\alpha\alpha}$, $\sigma_{\alpha\beta}$ and $\sigma_{\beta\beta}$ are defined on $\mathbb{R}^+$ and $\tau > 0$ is pre-specified. The convergence (2.44) immediately follows from the assumption (2.28), which gives that $\sigma_{\alpha\alpha} = r(\tau)/\alpha_0$. To show (2.45) and (2.46), we need to deal with the convergence of (2.41) as $m \to \infty$. Note that, from (2.43), $E\{z_i(t)\} = \Pr\{A_i(t)\}$. Therefore, under $H_0 : \beta = 0$ and $\alpha = \alpha_0$,

$$\Pr\{A_i(t)\} = I\{t < \Delta\}(1 - e^{-\alpha_0 t}) + I\{t \geq \Delta\}(1 - e^{-\alpha_0 \Delta}). \tag{2.47}$$

The probability (2.47) and the assumption that the at-risk processes Y_i and the event processes N_i are completely independent lead to result that the expectation of the left-hand side of (2.45) is

$$\int_0^\Delta E\{Y_i(u)\}(1 - e^{-\alpha_0 u})\, du + \int_\Delta^\tau E\{Y_i(u)\}(1 - e^{-\alpha_0 \Delta})\, du, \tag{2.48}$$

where we assume $\{Y_i(t); t \geq 0\}$ has an expected value for $0 \leq t < \infty$. Thus, as $m \to \infty$, by a weak law of large numbers the left hand side of (2.45) converges in probability to (2.48), which is $\sigma_{\alpha\beta}$ in (2.45). Similarly, $\sigma_{\beta\beta}$ in (2.46) is $\alpha_0 \sigma_{\alpha\beta}$, where $\sigma_{\alpha\beta}$ is given by (2.48).

Condition C for the model (2.34) is just the condition in (2.31), and directly follows from the assumption (2.28). We next need to show that, for all $\varepsilon > 0$,

$$\alpha_0 \frac{1}{m} \sum_{i=1}^m \int_0^\tau z_i(u)\, I\left\{\frac{1}{\sqrt{m}} z_i(u) > \varepsilon\right\} Y_i(u)\, du \xrightarrow{p} 0, \tag{2.49}$$

as $m \to \infty$. Since $z_i(t) = 0$ or 1 only, it is easy to see that the convergence (2.49) is satisfied as $m \to \infty$.

Condition D is fulfilled if the matrix $\mathbf{\Sigma} = [(\sigma_{jl})]$ $(j,\ l = \alpha,\ \beta)$ with the components given by the right-hand side of (2.44), (2.45) and (2.46) is positive definite. Note that $\sigma_{\alpha\alpha}$ is positive because $r(\tau) > 0$ and $\alpha_0 > 0$. Furthermore, we need to show that the determinant of $\mathbf{\Sigma}$ which is $\sigma_{\alpha\beta}(r(\tau) - \sigma_{\alpha\beta})$ is positive. Since $\sigma_{\alpha\beta}$ given by (2.48) is positive, Condition D is satisfied when $r(\tau) > \sigma_{\alpha\beta}$. This follows directly from (2.48).

Condition E can be shown to hold in a similar way to that of the illustration of the previous subsection. This completes the requirements for the convergence of $(\hat{\alpha}, \hat{\beta})$ to normality under $H_0 : \beta = 0, \alpha \in \mathbb{R}^+$, and also that

$$\frac{1}{\sqrt{m}} U_\beta(\tilde{\alpha}, 0)/\sigma(\alpha_0) \xrightarrow{\mathcal{D}} Z \sim N(0, 1), \tag{2.50}$$

as $m \to \infty$, where $\tilde{\alpha}(0) = (\sum_{i=1}^m N_i(\tau_i))/(\sum_{i=1}^m \int_0^\infty Y_i(u)\, du)$ and $\sigma^2(\alpha_0) = \sigma_{\beta\beta} - (\sigma_{\alpha\beta}^2/\sigma_{\alpha\alpha})$ (see, Andersen et al. (1993) and Pena (1998)). Note that the left-hand side of (2.50) is not a statistic since it depends on the unknown parameter α_0. A partial score statistic for testing $H_0 : \beta = 0, \alpha \in \mathbb{R}^+$ is obtained by replacing $\sigma^2(\alpha_0)$ with any consistent estimator of it, and it also converges in distribution to $N(0, 1)$ as $m \to \infty$.

The conditions A–E can also be verified in a similar way when $\beta \neq 0$. A simple condition that suffices to satisfy A–E is to bound $|\beta| < B$ for some B. Then $|e^{\beta z_i(u)}| \in (e^{-B}, e^{B})$ and simple modifications of the arguments above show A–E hold.

2.3.2 Settings with $m = 1$

A case of special interest in some applicatons is that of a single process observed over a long period. The aforementioned asymptotic results can also be shown to apply under suitable conditions when $m = 1$ and $\tau \to \infty$ as well as when $m = 1$ and a parameter approaches infinity. The $\tau \to \infty$ case is more important and we consider it first.

Testing the null hypothesis of a Poisson process with known intensity is discussed by Dachian and Kutoyants (2006). They consider self-exciting type processes under contiguous alternatives, and construct locally asymptotically uniformly most powerful tests. They obtain the asymptotic distribution as $\tau \to \infty$. We here consider testing the null hypothesis of a homogeneous Poisson process with unknown rate function against the alternative of a model with carryover effect. We focus once again on the model

$$\lambda(t|\mathcal{H}(t);\alpha,\beta) = \alpha \exp\{\beta z(t)\}, \qquad t \geq 0, \tag{2.51}$$

where

$$z(t) = I\{N(t^-) > 0\} I\{t - T_{N(t^-)} \leq \Delta\}.$$

The proof below based on Cigsar and Lawless (2010) and was developed from an outline provided by the second author.

The likelihood function (cf. 1.4.1) for this model is given by

$$\prod_{j=1}^{n} \alpha e^{\beta z(t_j)} \exp\left\{-\int_0^\infty Y(u)\alpha e^{\beta z(u)}\, du\right\}, \tag{2.52}$$

where $0 < T_1 < \cdots < T_n < \tau$ denote the event times. In the following discussion $Y(t) = I(0 \leq t \leq \tau)$, and τ is prespecified. The partial score function obtained from the log of (2.52) is

$$U_\beta(\tilde{\alpha}, 0) = \sum_{j=1}^{n} z(t_j) - \tilde{\alpha} \int_0^\tau z(u)\, du, \tag{2.53}$$

where $\tilde{\alpha} = N(\tau)/\tau$. We want to show under the null model (i.e. the model is an HPP with rate α_0) that

$$U_\beta(\tilde{\alpha}, 0)/\widehat{Var}(U_\beta(\tilde{\alpha}, 0))^{1/2} \xrightarrow{\mathcal{D}} Z \sim N(0, 1) \tag{2.54}$$

when $m = 1$ and $\tau \to \infty$. We will use martingale convergence results. Let us rewrite (2.53) as

$$U_\beta(\tau; \tilde{\alpha}) = U_\beta(\tilde{\alpha}, 0) = \int_0^\tau z(t)\{dN(t) - \tilde{\alpha}\, dt\}, \tag{2.55}$$

and then

$$U_\beta(\tau; \alpha_0) = \int_0^\tau z(t)\{dN(t) - \alpha_0\, dt\}. \tag{2.56}$$

First we note that

$$\frac{1}{\sqrt{\tau}}U_\beta(\tau;\tilde{\alpha}) = \frac{1}{\sqrt{\tau}}U_\beta(\tau;\alpha_0) - \sqrt{\tau}(\tilde{\alpha}-\alpha_0)\,\frac{1}{\tau}\int_0^\tau z(t)\,dt. \tag{2.57}$$

We now show that the two parts of (2.57) are asymptotically bivariate normal. We first show that, as $\tau \to \infty$,

$$\frac{1}{\sqrt{\tau}}U_\beta(\tau;\alpha_0) \xrightarrow{\mathcal{D}} N(0,\sigma^2), \tag{2.58}$$

where $\sigma^2 = \alpha_0 Q = \alpha_0(1-e^{-\alpha_0\Delta})$. Since $\{M(t) = \int_0^t [dN(s)-\alpha_0\,ds]; t \geq 0\}$ is a martingale, the convergence in (2.58) holds under following conditions (Karr 1991, Theorem B.21):
(i) As $\tau \to \infty$,

$$\frac{1}{\tau}\int_0^\tau z(t)\,\alpha_0\,dt \xrightarrow{p} \sigma^2, \tag{2.59}$$

where $z(t)$ is a predictable process and $0 < \sigma^2 < \infty$.
(ii) For every $\varepsilon > 0$,

$$\lim_{\tau\to\infty}\frac{1}{\tau}E\left\{\int_0^\tau z(t)\,I\left(|z(t)| > \varepsilon\sqrt{\tau}\right)\,\alpha_0\,dt\right\} = 0. \tag{2.60}$$

Note that $z(t) = I(N(t^-) > 0)I(t - T_{N(t^-)} \leq \Delta)$ is measurable at time $t^- \in [0,\tau]$ with respect to $\mathcal{H}(t)$; that is, given the history, $z(t)$ is a known quantity just before t, and thus, it is predictable. From the previous section we know that if we let $A(t)$ be the event "at least one event in $[\max(t-\Delta,0),t]$", then $z(t) = I\{A(t)\}$ and

$$\begin{aligned} E\left\{\frac{1}{\tau}\int_0^\tau z(t)\,dt\right\} &= \frac{1}{\tau}\left[\int_0^\Delta \left(1-e^{-\alpha_0 t}\right)\,dt + \int_\Delta^\tau \left(1-e^{-\alpha_0\Delta}\right)\,dt\right] \\ &= \frac{1}{\tau}\left[\Delta + \left(\tau - \Delta - \alpha_0^{-1}\right)\left(1-e^{-\alpha_0\Delta}\right)\right]. \end{aligned} \tag{2.61}$$

Therefore,

$$\lim_{\tau\to\infty} E\left\{\frac{1}{\tau}\int_0^\tau z(t)\,dt\right\} = 1 - e^{-\alpha_0\Delta} = Q. \tag{2.62}$$

This shows that, by a weak law of large numbers, condition (i) holds with $\sigma^2 = \alpha_0\,Q$. Since $z(t) = 0$ or 1, for a sufficiently large τ and for every $\varepsilon > 0$, $I\left(|z(t)| > \varepsilon\sqrt{\tau}\right) = 0$ for all $0 \leq t \leq \tau$. Hence, as $\tau \to \infty$, condition (ii) holds. Therefore, by a central limit theorem (see, Karr, 1991, Theorem B.21), we obtain the convergence in (2.58) with $\sigma^2 = \alpha_0\,Q$.

In the next part we need to show that $\sqrt{\tau}(\tilde{\alpha}-\alpha_0) \xrightarrow{\mathcal{D}} Z \sim N(0,\alpha_0)$, as $\tau \to \infty$. Note that $\tilde{\alpha} = N(\tau)/\tau = \int_0^\tau dN(t)/\tau$ and so

$$\sqrt{\tau}(\tilde{\alpha}-\alpha_0) = \frac{1}{\sqrt{\tau}}\int_0^\tau \{dN(t) - \alpha_0\,dt\}\,. \tag{2.63}$$

It is easy to see that, with $z(t) = 1$ in (2.56), conditions (i) and (ii) hold for (2.63). Therefore, we showed that

$$\sqrt{\tau}(\tilde{\alpha} - \alpha_0) \xrightarrow{\mathcal{D}} Z \sim N(0, \alpha_0), \tag{2.64}$$

as $\tau \to \infty$.

Now let $dM(t) = dN(t) - \alpha_0\, dt$, and note that $E\{dM(t)\} = 0$ under H_0. Then, from Fleming and Harrington (1991, Sections 2.4–2.7),

$$\begin{aligned} Cov\left\{\frac{1}{\sqrt{\tau}} U_\beta(\tau;\alpha_0), \sqrt{\tau}(\tilde{\alpha} - \alpha_0)\right\} &= \frac{1}{\tau} Cov\left\{\int_0^\tau z(t)\, dM(t), \int_0^\tau dM(t)\right\} \\ &= \frac{1}{\tau} E\left\{\int_0^\tau z(t)\, d\left\langle M\right\rangle(t)\right\} \\ &= \frac{1}{\tau} E\left\{\int_0^\tau z(t)\alpha_0\, dt\right\} \\ &\to \alpha_0\, Q, \qquad \text{as } \tau \to \infty, \end{aligned} \tag{2.65}$$

where $\left\langle M\right\rangle(t)$ is defined in Section 1.4.2.

Therefore, from (2.58), (2.64) and (2.65), and the bivariate version of Theorem 13.3.9 in Daley and Vere-Jones (1988) we obtain

$$\begin{pmatrix} \frac{1}{\sqrt{\tau}} U_\beta(\tau;\alpha_0) \\ \sqrt{\tau}(\tilde{\alpha} - \alpha_0) \end{pmatrix} \xrightarrow{\mathcal{D}} N_2\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \alpha_0\, Q & \alpha_0\, Q \\ \alpha_0\, Q & \alpha_0 \end{pmatrix}\right], \tag{2.66}$$

as $\tau \to \infty$. (2.57) can be written as

$$\frac{1}{\sqrt{\tau}} U_\beta(\tau;\tilde{\alpha}) = \begin{pmatrix} 1 & -\frac{1}{\tau}\int_0^\tau z(t)\, dt \end{pmatrix} \begin{pmatrix} \frac{1}{\sqrt{\tau}} U_\beta(\tau;\alpha_0) \\ \sqrt{\tau}(\tilde{\alpha} - \alpha_0) \end{pmatrix}. \tag{2.67}$$

By using (2.66), $(1/\tau)\int_0^\tau z(t)\, dt \xrightarrow{p} Q$, as $\tau \to \infty$, and Slutsky's lemma, (2.67) is asymptotically normally distributed with mean 0 and variance

$$\begin{pmatrix} 1 & -Q \end{pmatrix} \begin{pmatrix} \alpha_0 Q & \alpha_0 Q \\ \alpha_0 Q & \alpha_0 \end{pmatrix} \begin{pmatrix} 1 \\ -Q \end{pmatrix} = \alpha_0 Q(1 - Q). \tag{2.68}$$

Hence, as $\tau \to \infty$,

$$\frac{\frac{1}{\sqrt{\tau}} U_\beta(\tau;\tilde{\alpha})}{\sqrt{\alpha_0 Q(1-Q)}} \xrightarrow{D} N(0,1) \tag{2.69}$$

and the term $\alpha_0 Q(1 - Q)$ in the denominator can be estimated by $\tilde{\alpha}\tilde{Q}(1 - \tilde{Q})$. The variance estimator (2.21) when $m = 1$ is asymptotically equivalent to this.

We could also consider asymptotic properties of the test statistic when a model parameter approaches infinity, in this case, α_0. A similar situation in which asymptotic properties of the maximum likelihood estimators are derived is considered by van Pul (1990,

1992) for a class of software reliability models. His study is also discussed by Andersen et al. (1993, p. 430). We can however equate the case where α_0 becomes arbitrarily large with that where $\tau \to \infty$ and the rate is fixed. If $\alpha_m = m\gamma$, say, is the Poisson process rate then we just consider the new time scale $t_{(m)} = m\tau$ with the rate γ unchanged. Thus, $E\{N(0, t_{(m)})\} = \gamma mt = \gamma t_{(m)}$ and $\tau_{(m)} = m\tau$ is the follow-up time. The results for $\tau \to \infty$ above thus can be applied here. It is important to note, however, that if we consider the alternative models (2.51) then, when t changes to $t_{(m)}$, Δ must change to $\Delta_{(m)} = \Delta/m$. This makes sense, because when $\alpha_m = m\gamma$ increases, $\Delta = \Delta_{(m)}$ must decrease or else the probability of an event within time Δ of the previous event approaches one. We can then consider the model of interest, $\lambda(t|\mathcal{H}(t)) = \alpha \exp\{\beta Z(t)\}$, $t \geq 0$, and discuss the asymptotics under the null hypothesis $H_0 : \beta = 0$ when $\alpha \to \infty$, and when $\beta \neq 0$, by referring to the preceding results for $\tau \to \infty$.

2.3.3 Power and Consistency of Tests

The tests of $H_0 : \beta = 0$ in the preceding two sections are based on a specific family of alternative hypotheses. However, it can be shown that the tests of the null Poisson processes are also consistent against some carryover alternatives that are not in the specific family represented by (2.1) and (2.2). That is, as $m \to \infty$ (or as $\tau \to \infty$ in the $m = 1$ case of Section 2.3), the probability H_0 is rejected approaches one under the alternative. We illustrate this property via simulation in the next section. This result is important, because in practice a carryover effect will never be of exactly the form of (2.1) and (2.2), with the assumed value of Δ.

In choosing a value of Δ, we should consider how long a carryover effect might last for the specific process under study. A technical requirement is that Δ be sufficiently small relative to the mean time α^{-1} between events under H_0, but this is sure to be met in reasonable applications of the carryover concept. Simulation studies below suggest that it is better to choose a value of Δ that is a little too small than one that is a little big relative to the true value of Δ. It would be possible to consider Δ as a parameter to be estimated, but our objective here is to provide simple, powerful tests for carryover effect that can be routinely applied before extensive model fitting and checking has been undertaken. Some examination of the data is needed to determine whether the null hypothesis should be an HPP or an NHPP, and we recommend first plotting the Nelson-Aalen estimate $\hat{\mu}(t)$ of the mean function $\mu(t) = \int_0^t \rho(s)ds$ (Cook and Lawless, 2007, p. 68). If $\hat{\mu}(t)$ is close to linear then we apply the tests of Section 2.3. If this is not the case then it is necessary to fit a NHPP with a parametric rate function $\rho_0(t; \alpha)$ (Cook and Lawless, 2007, Section 3.2), following which the tests of Section 2.2.2 can be applied.

2.4 Simulation Studies

In this section, we present the results of simulation studies conducted to assess when asymptotic normal approximations for score test statistics are satisfactory, to investigate the performances of test statistics and to evaluate their robustness with respect to different types of model misspecification. The results of the simulations show that the normal approximations are suitable for certain finite sample settings when $m = 1$ and $\tau \to \infty$ and when $m \to \infty$. The score test is powerful for testing carryover efects, and robust with respect to certain model misspecifications which are explained below. When there is significant heterogeneity across individual processes, results of the simulation studies, however, reveal that the tests considered in this chapter may give misleading conclusions.

We first consider testing for no carryover effect in a single process ($m = 1$). The model is then (2.51). The hypothesis of no carryover effect, i.e. $H_0 : \beta = 0$, is tested with the partial score statistic

$$S = U_\beta(\tilde{\alpha}, 0)/\widehat{Var}\{U_\beta(\tilde{\alpha}, 0)\}^{1/2}, \tag{2.70}$$

where the score function U_β and its estimated variance are given by (2.20) and (2.21). We first investigate the null distribution of S and assess the standard normal approximation for it as τ increases. Without loss of generality, we fixed α at 1, and generated $10,000$ realizations of the HPP for various τ and Δ values. In practice we would be interested in small values of Δ, and in the simulations we consider $\Delta = 0.0202$, 0.0513 and 0.1054. The W_j under a homogeneous Poisson process model with intensity α_0 are i.i.d. exponential random variables with mean $1/\alpha_0$ so $\Pr(W_j \le \Delta) = 1 - e^{-\alpha_0 \Delta} = c$ (say). With $\alpha_0 = 1$, the preceding values of Δ give $c = 0.02$, 0.05 and 0.10. Normal quantile-quantile (Q-Q) plots of the 10,000 values of S are shown for scenarios with $\Delta = 0.0202$ in Figure 2.2. The standard normal distribution is suitable when τ is 1000, but off in the tails when $\tau = 100$ or 500. Similar results are shown for $\Delta = 0.0513$ in Figure 2.3, where the approximation is seen to be quite accurate at $\tau = 500$ and 750. For $\Delta = 0.1054$ (see Figure 2.4), the approximations are better still at $\tau = 250$ and 500 but off in the tails for $\tau = 100$.

The results in Figures 2.2, 2.3 and 2.4 may seem discouraging in showing that the expected number of events $\alpha\tau$ under H_0 must be very large for the normal approximation to be accurate, but this is not too surprising. The expected number of events occurring within time Δ of the preceding event is approximately $\tau(1 - e^{-\Delta})$ under H_0 and for $\Delta = 0.0202$, $\tau = 100$, for example, this is only 2. A normal approximation for a discrete count variable with this small a mean is not especially accurate. In spite of the departures in the tails of the distribution, the approximation is, however, is useful for testing. Let Q_p be the pth quantile of the standard normal distribution. Table 2.1 presents empirical pth quantiles, $\hat{Q}_p$, of the 10,000 score statistics S as well as the estimates of $\Pr(S > Q_p) = 1 - p$. Table 2.1 presents empirical pth quantiles, $\hat{Q}_p$, of the 10,000 score statistics S as well as the estimates of $\Pr(S > Q_p) = 1 - p$, where $p = 0.950$, 0.975 and 0.990.

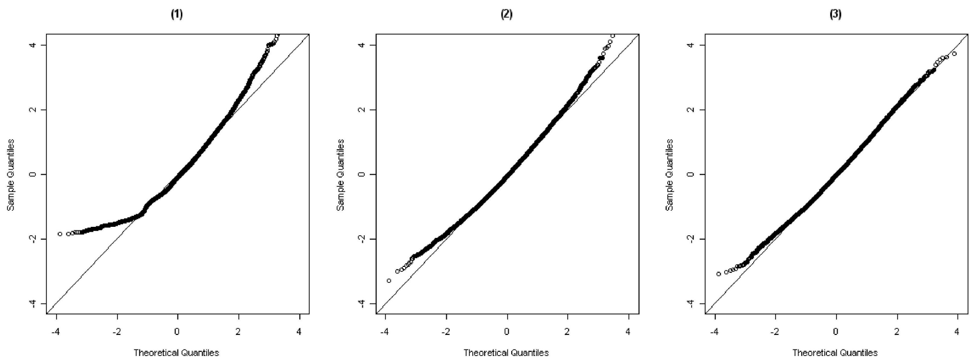

Figure 2.2: Normal Q-Q plots of 10,000 simulated values of S when $m = 1$, $\Delta = 0.0202$, and (1) $\tau = 100$, (2) $\tau = 500$ and (3) $\tau = 1,000$.

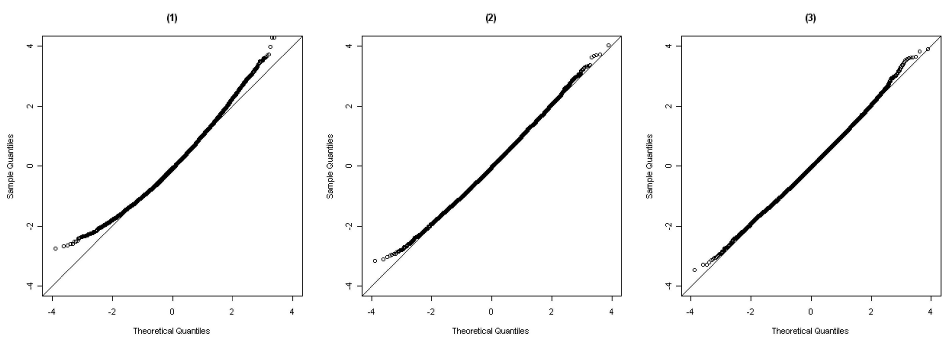

Figure 2.3: Normal Q-Q plots of 10,000 simulated values of S when $m = 1$, $\Delta = 0.0513$, and (1) $\tau = 100$, (2) $\tau = 500$ and (3) $\tau = 750$.

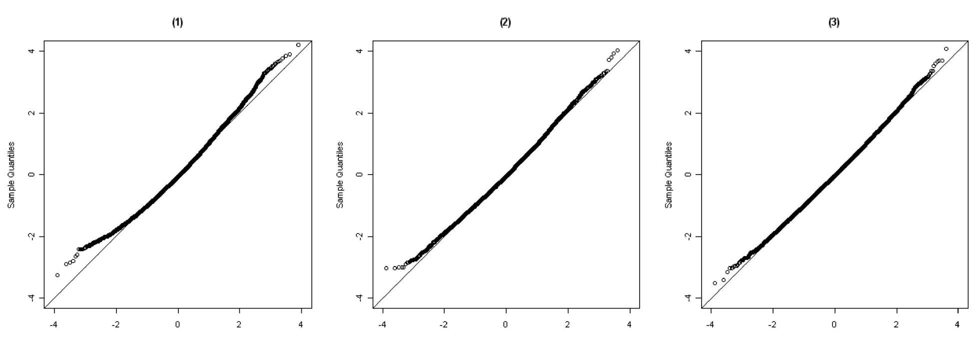

Figure 2.4: Normal Q-Q plots of 10,000 simulated values of S when $m = 1$, $\Delta = 0.1054$, and (1) $\tau = 50$, (2) $\tau = 250$ and (3) $\tau = 500$.

Δ	τ	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(S > 1.645)$	$\widehat{\Pr}(S > 1.960)$	$\widehat{\Pr}(S > 2.326)$
0.0202	100	1.773	2.224	2.786	0.0632	0.0371	0.0214
	200	1.744	2.173	2.626	0.0599	0.0353	0.0185
	500	1.706	2.106	2.560	0.0558	0.0330	0.0168
	1,000	1.669	2.019	2.401	0.0522	0.0278	0.0120
0.0513	100	1.729	2.128	2.608	0.0583	0.0338	0.0177
	200	1.695	2.075	2.493	0.0543	0.0298	0.0140
	500	1.670	2.041	2.506	0.0521	0.0301	0.0141
	1,000	1.664	2.027	2.386	0.0527	0.0293	0.0118
0.1054	100	1.716	2.039	2.445	0.0574	0.0297	0.0134
	200	1.709	2.038	2.433	0.0566	0.0302	0.0124
	500	1.694	2.073	2.423	0.0543	0.0311	0.0128
	1,000	1.636	1.948	2.331	0.0490	0.0242	0.0103

Table 2.1: $\hat{Q}_p$ is the empirical pth quantile of S computed from 10,000 samples when $m = 1$. $\widehat{\Pr}(S > Q_p)$ is the proportion of the values of S in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

The normal approximation overestimates right tail probabilities less than 0.05 by 0.01 or less for cases where $\Delta\tau > 2$. The normal approximation might be improved if one were to consider a transformation of $O(\Delta)$ and treat it as normal. We can also estimate p-values by simulation, however, and that is the approach we will use in cases where the approximation is inadequate.

We also considered the score statistic (2.70) when $m > 1$. We fixed τ at 10, and generated 10,000 realizations of m processes under the null homogeneous Poisson processes with rate one, for various m values, with $\Delta = 0.0202$, 0.0513 and 0.1054. Normal probability plots (Figures 2.5, 2.6 and 2.7) closely resemble those of the $m = 1$ case with the equivalent total expected number of events under H_0. For example, the plots for $m = 10$, 50 and 100 are close to those for $\tau = 100$, 500 and 1000 in Figures 2.2, 2.3 and 2.4. A table similar to Table 2.1 was also constructed. Table 2.2 shows $\hat{Q}_p$ and estimated $\Pr(S > Q_p)$ values when $p = 0.950$, 0.975 and 0.990. The results are very similar to those in Table 2.1. For example, with $\Delta = 0.0202$ and $(m, \tau) = (100, 10)$, the probabilities corresponding to the values 0.0522, 0.0278, 0.0120 for $\tau = 1000$ in Table 2.1, and are 0.0532, 0.0278, 0.0141. Also, as m increases, the standard normal distribution approximates the distribution of the test statistic S quite well.

The power of the statistic (2.70) against specific alternative hypotheses was also investigated by Monte Carlo studies. We used the 10,000 realizations of the null model for different (Δ, τ) combinations discussed above to estimate the 5% critical values, in order to estimate powers for a test with true size 0.05. We considered $\tau = 100$ and 200, and

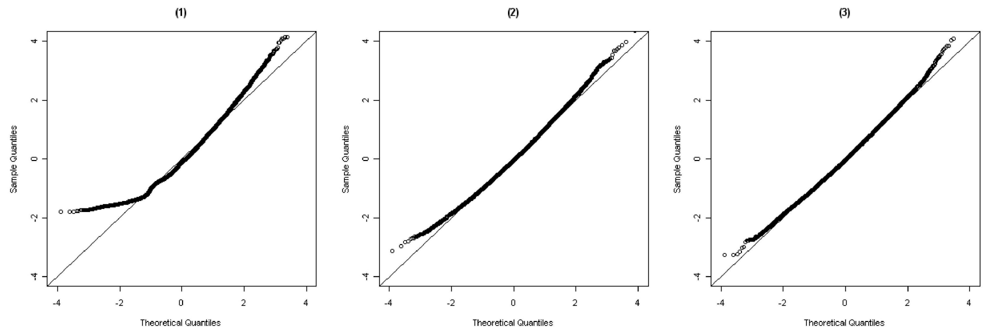

Figure 2.5: Normal Q-Q plots of 10,000 simulated values of the test statistic S when $\tau = 10$, $\Delta = 0.0202$, and (1) $m = 10$, (2) $m = 50$ and (3) $m = 100$.

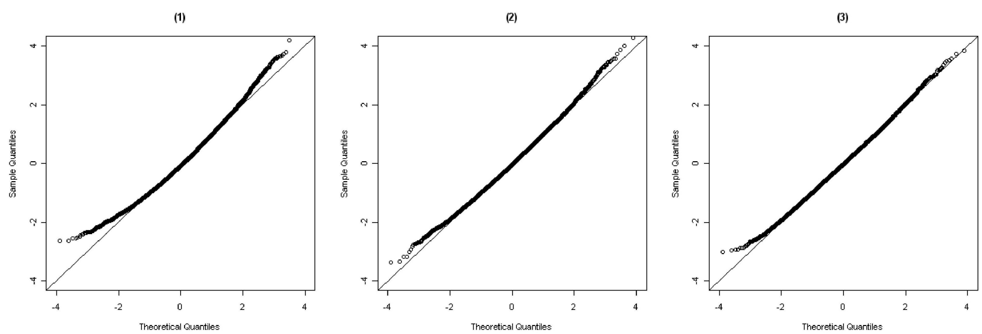

Figure 2.6: Normal Q-Q plots of 10,000 simulated values of the test statistic S when $\tau = 10$, $\Delta = 0.0513$, and (1) $m = 10$, (2) $m = 50$ and (3) $m = 75$.

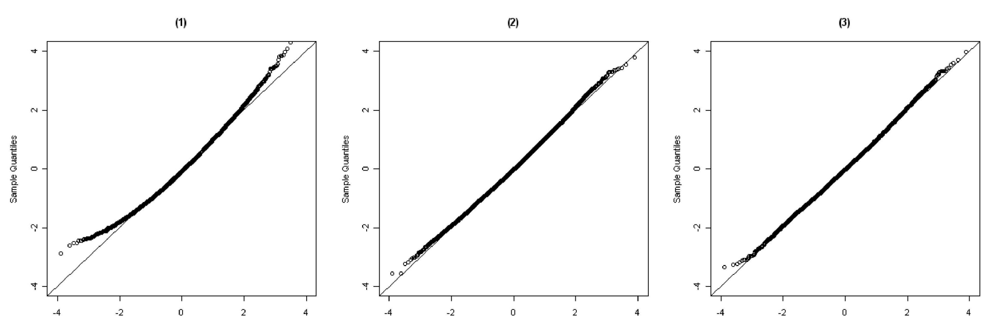

Figure 2.7: Normal Q-Q plots of 10,000 simulated values of the test statistic S when $\tau = 10$, $\Delta = 0.1054$, and (1) $m = 5$, (2) $m = 25$ and (3) $m = 50$.

Δ	m	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\hat{P}(S > 1.645)$	$\widehat{\Pr}(S > 1.960)$	$\widehat{\Pr}(S > 2.330)$
0.0202	10	1.824	2.241	2.807	0.0668	0.0405	0.0214
	20	1.752	2.141	2.551	0.0591	0.0348	0.0162
	50	1.741	2.083	2.551	0.0586	0.0333	0.0146
	100	1.671	2.016	2.422	0.0530	0.0286	0.0133
0.0513	10	1.706	2.132	2.599	0.0551	0.0337	0.0172
	20	1.689	2.053	2.538	0.0548	0.0298	0.0144
	50	1.691	2.031	2.441	0.0541	0.0295	0.0130
	100	1.670	1.993	2.347	0.0520	0.0265	0.0107
0.1054	10	1.694	2.028	2.465	0.0554	0.0288	0.0135
	20	1.686	2.036	2.434	0.0550	0.0295	0.0128
	50	1.664	1.986	2.412	0.0517	0.0274	0.0118
	100	1.615	1.965	2.375	0.0469	0.0254	0.0111

Table 2.2: $\hat{Q}_p$ is the empirical pth quantile of S computed from 10,000 samples when $m > 1$ and $\tau = 10$. $\widehat{\Pr}(S > Q_p)$ is the proportion of the values of S in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

generated 1,000 processes under scenarios based on two different types of models:

$$\text{Model A:} \quad \lambda(t|\mathcal{H}(t)) = \alpha \exp\{\beta I(N(t^-) > 0) I(B(t) \leq \Delta_0)\}, \tag{2.71}$$

$$\text{Model B:} \quad \lambda(t|\mathcal{H}(t)) = \alpha + \beta I(N(t^-) > 0) D(t), \tag{2.72}$$

where $\alpha = 1$. Model B is a piecewise model in which $D(t) = \{1.5I(B(t) \leq 0.5\Delta_0) + I(0.5\Delta_0 < B(t) \leq \Delta_0) + 0.5I(\Delta_0 < B(t) \leq 1.5\Delta_0)\}$, and is of additive rather than multiplicative form. The value of Δ_0 in (2.71) is not necessarily the same as the value Δ used in the test statistic; this allows us to assess the effect of an incorrect choice of Δ. Scenarios were considered with various combinations of $(\Delta, \Delta_0, \tau, e^\beta)$. The data were generated according to an algorithm for point processes given in Section 1.5 under the various models. Results for Model A are presented in Table 2.3; the entries are the proportion of samples in which S exceeds its 5% critical value. The power of the test is high for almost all scenarios with $e^\beta = 4$ and 6, which represent levels of increased risk that would be of interest in many applications. As expected, the power increases as τ and Δ increase. Regarding misspecification of Δ, some loss of power results from choosing too large a value of Δ (i.e. Δ_0 is less than Δ), but choosing a value that is a little too small has little effect. This should be kept in mind when selecting Δ in practice.

In a similar simulation study, we considered model misspecification by generating 1,000 processes under various scenarios from Model B. We used the statistic (2.70) once again for testing $H_0 : \beta = 0$. The power results are given in Table 2.4; values are slightly smaller than those of Table 2.3, but very good overall, which indicate that S is robust in the sense that it retains power to reject the hypothesis of no carryover effect when

Δ	Δ_0	$\tau = 100$			$\tau = 200$		
		$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$	$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$
0.0202	$\frac{2}{3}\Delta$	0.140	0.580	0.886	0.247	0.850	0.991
	Δ	0.273	0.836	0.986	0.468	0.977	1.000
	$\frac{4}{3}\Delta$	0.237	0.852	0.993	0.434	0.975	1.000
0.0513	$\frac{2}{3}\Delta$	0.285	0.912	0.999	0.474	0.996	1.000
	Δ	0.510	0.993	1.000	0.754	1.000	1.000
	$\frac{4}{3}\Delta$	0.456	0.993	1.000	0.746	1.000	1.000
0.1054	$\frac{2}{3}\Delta$	0.480	0.993	1.000	0.740	1.000	1.000
	Δ	0.788	1.000	1.000	0.993	1.000	1.000
	$\frac{4}{3}\Delta$	0.751	1.000	1.000	0.945	1.000	1.000

Table 2.3: Power of S: Model A, $m = 1$.

Δ	Δ_0	$\tau = 100$			$\tau = 200$		
		$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$	$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$
0.0202	$\frac{2}{3}\Delta$	0.154	0.607	0.893	0.262	0.858	0.998
	Δ	0.207	0.718	0.958	0.348	0.941	0.998
	$\frac{4}{3}\Delta$	0.217	0.771	0.971	0.379	0.960	0.999
0.0513	$\frac{2}{3}\Delta$	0.280	0.910	0.995	0.467	0.997	1.000
	Δ	0.377	0.980	1.000	0.614	1.000	1.000
	$\frac{4}{3}\Delta$	0.363	0.981	1.000	0.655	1.000	1.000
0.1054	$\frac{2}{3}\Delta$	0.487	0.996	1.000	0.721	1.000	1.000
	Δ	0.618	0.999	1.000	0.867	1.000	1.000
	$\frac{4}{3}\Delta$	0.637	1.000	1.000	0.865	1.000	1.000

Table 2.4: Power of S: Model B, $m = 1$.

Δ	Δ_0	$\tau = 10$			$\tau = 20$		
		$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$	$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$
	$\frac{2}{3}\Delta$	0.157	0.594	0.876	0.241	0.850	0.987
0.0202	Δ	0.252	0.857	0.990	0.411	0.973	1.000
	$\frac{4}{3}\Delta$	0.251	0.839	0.980	0.423	0.972	1.000
	$\frac{2}{3}\Delta$	0.282	0.917	0.998	0.476	0.995	1.000
0.0513	Δ	0.487	0.988	1.000	0.718	1.000	1.000
	$\frac{4}{3}\Delta$	0.452	0.993	1.000	0.745	1.000	1.000
	$\frac{2}{3}\Delta$	0.497	0.999	1.000	0.762	1.000	1.000
0.1054	Δ	0.752	1.000	1.000	0.963	1.000	1.000
	$\frac{4}{3}\Delta$	0.700	1.000	1.000	0.946	1.000	1.000

Table 2.5: Power of S: Model C, $m = 10$.

Δ	Δ_0	$\tau = 5$			$\tau = 10$		
		$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$	$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$
	$\frac{2}{3}\Delta$	0.153	0.596	0.868	0.257	0.842	0.985
0.0202	Δ	0.281	0.831	0.982	0.414	0.981	0.998
	$\frac{4}{3}\Delta$	0.249	0.825	0.984	0.431	0.983	1.000
	$\frac{2}{3}\Delta$	0.295	0.913	0.995	0.482	0.996	1.000
0.0513	Δ	0.485	0.993	1.000	0.749	1.000	1.000
	$\frac{4}{3}\Delta$	0.496	0.995	1.000	0.722	1.000	1.000
	$\frac{2}{3}\Delta$	0.464	0.997	1.000	0.716	1.000	1.000
0.1054	Δ	0.745	1.000	1.000	0.952	1.000	1.000
	$\frac{4}{3}\Delta$	0.690	1.000	1.000	0.935	1.000	1.000

Table 2.6: Power of S: Model C, $m = 20$.

the model (2.51) is misspecified. This is in line with the consistency result mentioned in Section 2.3.3.

We also considered power for scenarios with $m > 1$. The null model, like in the previous case, is a homogeneous Poisson process with the rate function $\rho_0(t) = \alpha = 1$. We consider the expanded model,

$$\text{Model C:} \quad \lambda_i(t|\mathcal{H}_i(t)) = \alpha \exp\{\beta I(N_i(t^-) > 0) I(B_i(t) \le \Delta_0)\}, \qquad i = 1, \ldots, m, \tag{2.73}$$

which is just Model A but with $m > 1$. The statistic S was once again used for testing the null hypothesis of no carryover effect. We consider the cases $m = 10$, 20 and $\tau = 5$, 10, 20 here. The empirical powers of the test are presented in Table 2.5 when $m = 10$ and in Table 2.6 when $m = 20$ for various (Δ, Δ_0, τ, e^β) combinations. The results in the two tables are similar, with power depending on β and the value of $m\tau$. The test is also robust with respect to the misspecification of Δ, with features similar to Table 2.3.

Δ	Δ_0	$\tau = 10$				$\tau = 20$			
		$e^{\beta}=1$	$e^{\beta}=2$	$e^{\beta}=4$	$e^{\beta}=6$	$e^{\beta}=1$	$e^{\beta}=2$	$e^{\beta}=4$	$e^{\beta}=6$
	$\frac{2}{3}\Delta$	0.043	0.178	0.596	0.889	0.045	0.258	0.869	0.993
0.0202	Δ	0.055	0.257	0.839	0.981	0.049	0.447	0.978	1.000
	$\frac{4}{3}\Delta$	0.053	0.269	0.854	0.987	0.051	0.389	0.981	1.000
	$\frac{2}{3}\Delta$	0.037	0.289	0.913	0.998	0.046	0.484	0.998	1.000
0.0513	Δ	0.052	0.466	0.991	1.000	0.046	0.750	1.000	1.000
	$\frac{4}{3}\Delta$	0.047	0.469	0.991	1.000	0.045	0.756	1.000	1.000
	$\frac{2}{3}\Delta$	0.034	0.481	0.993	1.000	0.062	0.768	1.000	1.000
0.1054	Δ	0.045	0.746	1.000	1.000	0.049	0.956	1.000	1.000
	$\frac{4}{3}\Delta$	0.053	0.719	0.999	1.000	0.060	0.956	1.000	1.000

Table 2.7: Power of S: Model D, $\phi = 0.002$, $m = 10$.

Δ	Δ_0	$\tau = 5$				$\tau = 10$			
		$e^{\beta}=1$	$e^{\beta}=2$	$e^{\beta}=4$	$e^{\beta}=6$	$e^{\beta}=1$	$e^{\beta}=2$	$e^{\beta}=4$	$e^{\beta}=6$
	$\frac{2}{3}\Delta$	0.049	0.153	0.612	0.890	0.055	0.158	0.863	0.989
0.0202	Δ	0.043	0.247	0.838	0.986	0.045	0.440	0.978	1.000
	$\frac{4}{3}\Delta$	0.048	0.252	0.840	0.988	0.046	0.429	0.974	1.000
	$\frac{2}{3}\Delta$	0.042	0.295	0.917	0.999	0.055	0.479	0.998	1.000
0.0513	Δ	0.045	0.514	0.996	1.000	0.049	0.758	1.000	1.000
	$\frac{4}{3}\Delta$	0.046	0.469	0.992	1.000	0.047	0.722	1.000	1.000
	$\frac{2}{3}\Delta$	0.062	0.484	0.995	1.000	0.055	0.770	1.000	1.000
0.1054	Δ	0.050	0.749	1.000	1.000	0.051	0.943	1.000	1.000
	$\frac{4}{3}\Delta$	0.047	0.718	1.000	1.000	0.053	0.954	1.000	1.000

Table 2.8: Power of S: Model D, $\phi = 0.002$, $m = 20$.

ϕ	$\tau = 10$	$\tau = 20$
0.002	0.055	0.049
0.3	0.077	0.095
0.6	0.125	0.191

Table 2.9: Empirical Type 1 error for S with $\Delta = 0.0202$ under heterogeneity of the processes $i = 1, \ldots, m$ ($m = 10$).

Finally, we consider the effect of heterogeneity that is not accounted for by the tests by generating data from the following model:

$$\text{Model D:} \quad \lambda_i(t|\mathcal{H}_i(t)) = \alpha_i \exp\{\beta I(N_i(t^-) > 0) I(B_i(t) \leq \Delta_0)\}, \tag{2.74}$$

where the α_i ($i = 1, \ldots, m$) are generated from a gamma distribution with mean 1 and variance ϕ in each simulation run. The degree of heterogeneity depends on the choice of ϕ. We first chose $\phi = 0.002$, representing minimal heterogeneity, and then $\phi = 0.3$ and 0.6. The power results are given in Table 2.7 and Table 2.8, where we used the critical values obtained earlier when data are generated from HPPs with rate $\alpha = 1$ ($i = 1, \ldots, m$) in 10,000 simulation runs. Comparing them to Table 2.5 and Table 2.6, respectively, the results are very similar. Note that since $\phi = 0.002$ is very small, and, thus, the heterogeneity between processes is small, the empirical type 1 errors given under $e^\beta = 1$ column in Tables 2.7 and 2.8 are close to nominal size 0.05. However, when the α_i are generated from a gamma distribution with the variance $\phi = 0.3$ and $\phi = 0.6$, the Type 1 errors are inflated. This can be seen in Table 2.9, where the empirical Type 1 errors are given under combinations of (τ, ϕ) when $m = 10$. This is caused by the fact that the test is more sensitive to the processes having different α_i's than to the processes having a carryover effect. These are based on 1,000 samples generated under Model D for each scenario; the entries in the table give the proportion of the samples in which the test statistic S exceeded the 5% critical values obtained when the α_i are equal 1. When there is a minimal degree of heterogeneity ($\phi = 0.002$) in the m processes the Type 1 error is close to 0.05, but as ϕ increases, there is substantial inflation. Similar results are found with other values of m and Δ, with the Type 1 error inflation increasing with m and Δ. The important message is that failure to recognize heterogeneity can lead to incorrect rejection of the hypothesis of no carryover effect. If there is any indication of heterogeneity, the tests of this chapter should therefore not be used, and instead one should use tests for the heterogeneity case in the following chapter.

2.5 Example: Submarine Engine Data

Here, we give an illustration of testing for carryover effects developed in the preceding sections for the $m = 1$ case.

In Section 1.1.1, we introduced the data set of unscheduled maintenance events for a submarine engine (Lee, 1980). Although the data set includes 7 scheduled engine overhauls, we are interested in event times of 58 unscheduled corrective maintenance actions. The last two failure times are suspicious outliers. Since our objective here is to illustrate the carryover effect test procedures, we omit the last two failure times without further investigation. A plot of the cumulative number of the first 56 failures versus cumulative operating time is given in Figure 2.8. The figure reveals an approximate

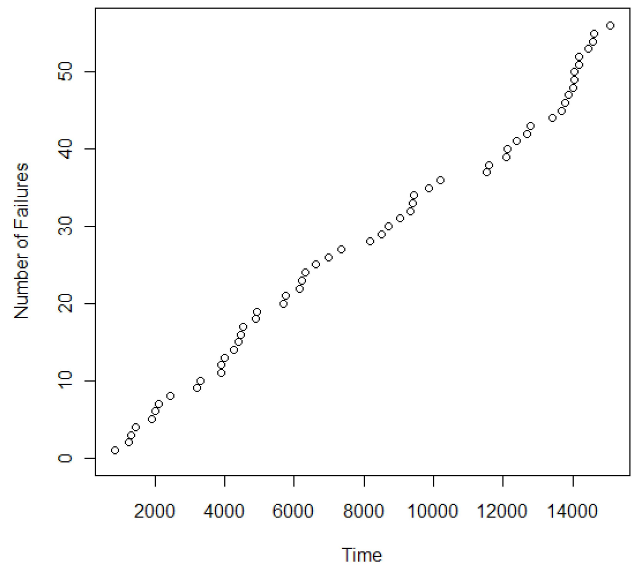

Figure 2.8: Cumulative operating hours (in hours of operation) until the occurrence of unscheduled significant maintenance events for the U.S.S. Grampus No. 4 main propulsion diesel engine.

straight line with a slight departure towards the end. This suggests there is little or no trend in the data. In addition, the Lewis-Robinson trend test introduced in Chapter 4 gives a p-value of 0.305. That is, there is no significant evidence of a trend in the data.

Figure 2.8 may suggest clustering of failures together in time. We, therefore, consider the expanded model $\lambda(t|\mathcal{H}(t)) = \alpha e^{\beta z(t)}$, where $z(t)$ is given in (2.2), and test the null hypothesis $\beta = 0$. The reduced model is then a HPP with rate function α. The estimates of the parameters and the maximized log likelihood values are given in Table 2.10 for the null and expanded models for various Δ values. The estimated values of $c = \Pr\{W_j \leq \Delta|\lambda(t) = \alpha\}$ are presented in Table 2.10 as well. For example, when $\Delta = 10$, $c = \Pr\{W_j \leq \Delta\} = 1 - e^{-\tilde{\alpha}\Delta} = 0.04$ under a HPP with rate function $\tilde{\alpha} = 0.004$.

The score test using the statistic (2.22) was performed. The results are given in Table 2.11 for different Δ values. To calculate the p-values, we used parametric bootstrap with 1,000 simulation runs. Two-sided p-values, i.e. $\Pr\{|S| > |S_{obs}||\tilde{\alpha}\}$ where S_{obs} is the observed S, based on bootstrap and $N(0,1)$ are presented. Note that p-values based on $N(0,1)$ (denoted as p^*-value in the table) are very similar to the simulation p-values. It is observed that there is no evidence against H_0 for each Δ. Hence, a carryover effect is not significant in the model. The likelihood ratio test $2\ell(\hat{\alpha}, \hat{\beta}) - 2\ell(\tilde{\alpha}, 0)$ for testing H_0 gives similar results, as can be seen from Table 2.10.

		Expanded Model			Reduced Model	
Δ	c	$\hat{\alpha}$	$\hat{\beta}$	$\ell(\hat{\alpha}, \hat{\beta})$	$\tilde{\alpha}$	$\ell(\tilde{\alpha}, 0)$
5	0.02	0.004	-0.003	-369.326	0.004	-369.326
10	0.04	0.004	0.430	-369.094	0.004	-369.326
15	0.06	0.004	0.328	-369.144	0.004	-369.326
50	0.18	0.004	-0.025	-369.324	0.004	-369.326
75	0.26	0.004	-0.027	-369.324	0.004	-369.326
100	0.33	0.004	0.170	-369.149	0.004	-369.326
125	0.39	0.003	0.293	-368.748	0.004	-369.326
150	0.45	0.003	0.304	-368.686	0.004	-369.326

Table 2.10: The results of the test statistic S which is given by (2.23) for various Δ values (in hours of operation). The expanded model is $\alpha e^{\beta z(t)}$ and the reduced model is α.

Δ	$O(\Delta)$	$\tilde{\alpha}E(\Delta)$	$U_\beta(\tilde{\alpha}, 0)$	$\widehat{Var}(U_\beta(\tilde{\alpha}, 0))$	S	p-value	p^*-value
5	1	1.003	-0.003	0.985	-0.003	0.995	0.998
10	3	1.988	1.012	1.917	0.731	0.467	0.465
15	4	2.939	1.061	2.785	0.636	0.537	0.525
50	9	9.190	-0.190	7.682	-0.068	0.946	0.946
75	13	13.270	-0.270	10.125	-0.085	0.935	0.932
100	19	16.930	2.070	11.812	0.602	0.541	0.547
125	24	20.092	3.908	12.883	1.089	0.303	0.276
150	27	22.809	4.191	13.519	1.140	0.251	0.254

Table 2.11: Results for S given by (2.23), for various Δ values (in hours of operation).

2.6 Tests for Nonhomogeneous Poisson Processes

In this section, we discuss testing the null hypothesis of a nonhomogeneous Poisson process model against the alternative of a model with a carryover effect. The models that we consider are of the multiplicative form with the intensity function

$$\lambda(t|\mathcal{H}(t); \boldsymbol{\alpha}, \beta) = \rho_0(t; \boldsymbol{\alpha}) \exp\{\beta z(t)\}, \qquad t > 0, \tag{2.75}$$

where the baseline rate function $\rho_0(t; \boldsymbol{\alpha})$ defines a NHPP, and $z(t)$ is a function of the recurrent event history at time t. A test for no carryover effect in NHPP is obtained by testing the null hypothesis $H_0 : \beta = 0$. This is the model considered in Section 2.2.2 (see (2.1)) but we use slightly different counting process notation here in order to discuss asymptotic results below. General results in Section 1.4.3 apply to tests for models (2.75). Our objective in this section is to discuss conditions for asymptotic normality of estimators and score statistics, along the lines of Section 2.3 for homogeneous processes, and to consider an illustration.

For discussion, we consider a specific model that belongs to (2.75), given by ($i = 1$, ..., m)

$$\lambda_i(t|\mathcal{H}_i(t)) = \exp\{\alpha + \beta t + \gamma z_i(t)\}, \qquad t > 0, \tag{2.76}$$

where $z_i(t) = I\{N_i(t^-) > 0\}I\{B_i(t) \le \Delta\}$ and $B_i(t)$ is the backward recurrence time for the ith process. The likelihood function for the data $\{(\bar{N}_i(s), Y_i(s)); 0 \le s \le t; i = 1, \dots, m\}$ is then given by (cf. Section 1.4.1)

$$L(\boldsymbol{\theta}) = \prod_{i=1}^{m} L_i(\boldsymbol{\theta}), \tag{2.77}$$

where $\boldsymbol{\theta} = (\alpha, \beta, \gamma)'$ and

$$L_i(\boldsymbol{\theta}) = \left[\prod_{j=1}^{n_i} \lambda_i(t_{ij}|\mathcal{H}_i(t_{ij}))\right] e^{-\int_0^\infty Y_i(t)\lambda_i(t|\mathcal{H}_i(t))\,dt}. \tag{2.78}$$

The log likelihood function $\ell(\boldsymbol{\theta}) = \log L(\boldsymbol{\theta})$ is then given by

$$\begin{aligned} \ell(\boldsymbol{\theta}) &= \sum_{i=1}^{m} \int_0^\infty Y_i(u) \left[\log \lambda_i(t|\mathcal{H}_i(t))\, dN_i(t) - \lambda_i(t|\mathcal{H}_i(t))\, du\right], \\ &= \alpha n. + \beta t. + \gamma z. - \sum_{i=1}^{m} \int_0^\infty Y_i(t) e^{\alpha+\beta t+\gamma z_i(t)}\, dt, \end{aligned} \tag{2.79}$$

where $n. = \sum_{i=1}^m n_i$, $t. = \sum_{i=1}^m \sum_{j=1}^{n_i} t_{ij}$ and $z. = \sum_{i=1}^m \sum_{j=1}^{n_i} z_i(t_{ij})$. When testing $H_0 : \gamma = 0$, the parameters α and β are nuisance parameters. The restricted maximum likelihood estimators $\tilde{\alpha}$ and $\tilde{\beta}$ can be found by maximizing $\ell(\alpha, \beta, 0)$. The score vector $\boldsymbol{U}(\boldsymbol{\theta}) = (\partial/\partial\boldsymbol{\theta})\ell(\boldsymbol{\theta})$ is given by

$$\begin{aligned}\boldsymbol{\theta} &= \big(U_\alpha(\boldsymbol{\theta}) \quad U_\beta(\boldsymbol{\theta}) \quad U_\gamma(\boldsymbol{\theta})\big)' \\ &= \sum_{i=1}^{m} \int_0^\infty Y_i(t)\boldsymbol{H}_i(t)[dN_i(t) - \lambda_i(t|\mathcal{H}_i(t))\,dt],\end{aligned} \tag{2.80}$$

where $\boldsymbol{H}_i(t) = (1, t, z_i(t))'$. Note that when $\gamma = 0$, the score vector (2.83) gives

$$\boldsymbol{U}(\alpha,\beta,0) = \begin{pmatrix} U_\alpha(\alpha,\beta,0) \\ U_\beta(\alpha,\beta,0) \\ U_\gamma(\alpha,\beta,0) \end{pmatrix} = \begin{pmatrix} n. - \sum_{i=1}^m \int_0^\infty Y_i(t)e^{\alpha+\beta t}\,dt \\ t. - \sum_{i=1}^m \int_0^\infty Y_i(t)te^{\alpha+\beta t}\,dt \\ z. - \sum_{i=1}^m \int_0^\infty Y_i(t)z_i(t)e^{\alpha+\beta t}\,dt \end{pmatrix} \tag{2.81}$$

The information matrix $\boldsymbol{I}(\boldsymbol{\theta}) = -(\partial^2/\partial\boldsymbol{\theta}\partial\boldsymbol{\theta}')\ell(\boldsymbol{\theta})$ is given by

$$\boldsymbol{I}(\boldsymbol{\theta}) = \begin{pmatrix} I_{\alpha\alpha}(\boldsymbol{\theta}) & I_{\alpha\beta}(\boldsymbol{\theta}) & I_{\alpha\gamma}(\boldsymbol{\theta}) \\ I_{\beta\alpha}(\boldsymbol{\theta}) & I_{\beta\beta}(\boldsymbol{\theta}) & I_{\beta\gamma}(\boldsymbol{\theta}) \\ I_{\gamma\alpha}(\boldsymbol{\theta}) & I_{\gamma\beta}(\boldsymbol{\theta}) & I_{\gamma\gamma}(\boldsymbol{\theta}) \end{pmatrix}, \tag{2.82}$$

where

$$\begin{aligned}
I_{\alpha\alpha}(\boldsymbol{\theta}) &= \sum_{i=1}^m \int_0^\infty Y_i(t)\, e^{\alpha+\beta t+\gamma z_i(t)}\,dt, \\
I_{\alpha\beta}(\boldsymbol{\theta}) &= \sum_{i=1}^m \int_0^\infty Y_i(t)\, t\, e^{\alpha+\beta t+\gamma z_i(t)}\,dt, \\
I_{\alpha\gamma}(\boldsymbol{\theta}) &= \sum_{i=1}^m \int_0^\infty Y_i(t)\, z_i(t)\, e^{\alpha+\beta t+\gamma z_i(t)}\,dt, \\
I_{\beta\beta}(\boldsymbol{\theta}) &= \sum_{i=1}^m \int_0^\infty Y_i(t)\, t^2\, e^{\alpha+\beta t+\gamma z_i(t)}\,dt, \\
I_{\beta\gamma}(\boldsymbol{\theta}) &= \sum_{i=1}^m \int_0^\infty Y_i(t)\, t\, z_i(t)\, e^{\alpha+\beta t+\gamma z_i(t)}\,dt,
\end{aligned}$$

and

$$I_{\gamma\gamma}(\boldsymbol{\theta}) = \sum_{i=1}^m \int_0^\infty Y_i(t)\, z_i^2(t)\, e^{\alpha+\beta t+\gamma z_i(t)}\,dt,$$

A score statistic for testing $H_0 : \gamma = 0$ is then given by

$$S = U_\gamma^2(\tilde{\alpha},\tilde{\beta},0)I^{\gamma\gamma}(\tilde{\alpha},\tilde{\beta},0), \tag{2.83}$$

where

$$I^{\gamma\gamma}(\boldsymbol{\theta}) = \left[I_{\alpha\alpha}(\boldsymbol{\theta}) - \big(I_{\gamma\alpha}(\boldsymbol{\theta}) \quad I_{\gamma\beta}(\boldsymbol{\theta})\big) \begin{pmatrix} I_{\alpha\alpha}(\boldsymbol{\theta}) & I_{\alpha\beta}(\boldsymbol{\theta}) \\ I_{\beta\alpha}(\boldsymbol{\theta}) & I_{\beta\beta}(\boldsymbol{\theta}) \end{pmatrix} \begin{pmatrix} I_{\alpha\gamma}(\boldsymbol{\theta}) \\ I_{\beta\gamma}(\boldsymbol{\theta}) \end{pmatrix}\right]^{-1}.$$

Alternatively, the likelihood ratio statistic

$$\Lambda = 2\ell(\hat{\boldsymbol{\theta}}) - 2\ell(\tilde{\boldsymbol{\theta}}), \tag{2.84}$$

where $\tilde{\boldsymbol{\theta}} = (\tilde{\alpha}, \tilde{\beta}, 0)'$, can be used for testing the hypothesis $H_0 : \gamma = 0$ of no carryover effect.

We next discuss the asymptotic properties of the test statistic S and Λ.

2.6.1 Settings with Large $\boldsymbol{m}$

The case of main interest for nonhomogeneous processes is when $m \to \infty$, and we consider the asymptotic properties of the partial score test statistic (2.83) for testing the null hypothesis $\gamma = 0$. We want to show, under the null hypothesis $\gamma = 0$, that

$$\frac{1}{\sqrt{m}} U_\gamma(\tilde{\boldsymbol{\theta}}) = \frac{1}{\sqrt{m}} \sum_{i=1}^{m} \int_0^\infty Y_i(u) z_i(u) \left[dN_i(u) - e^{\tilde{\alpha}+\tilde{\beta}u}\, du \right], \tag{2.85}$$

converges weakly to a mean zero Gaussian process with a covariance function that may be estimated by the observed or expected information matrix as in (2.83). We can show this by checking conditions A–E given by Andersen et al. (1993, pp. 420–421) as in Section 2.3.1. Once again we focus on the crucial conditions B, C and D. The at-risk processes $\{Y_i(t); t \geq 0\}$ are here assumed to be *completely independent* of the underlying event processes $\{N_i(t); t \geq 0\}$. Let τ be a prespecified (fixed) time such that $\tau \in [0, \infty)$. By replacing the upper limit of the integral in the partial score function (2.85) with t, $t \in [0, \tau]$, we obtain stochastic integrals.

Let us define the vector of the nuisance parameters $\boldsymbol{\eta} = (\alpha, \beta)'$ and vector of the restricted maximum likelihood estimators $\tilde{\boldsymbol{\eta}} = (\tilde{\alpha}, \tilde{\beta})'$, and suppose that $\boldsymbol{\eta}_0 = (\alpha_0, \beta_0)'$ is the vector of true parameter values. Condition A holds for the null model with intensity $\lambda_i(t) = \exp\{\alpha + \beta t\}$ because the partial derivatives of λ_i and $\log \lambda_i$ of the first, second, and third order with respect to $\boldsymbol{\eta}$ exist, and are continous. Moreover, it can be easily shown that $\ell(\tau; \alpha, \beta, 0)$ in (2.79) can be differentiated three times with respect to $\boldsymbol{\eta}$ by interchanging the order of differentiation and integration.

We now consider conditions B and D. Let

$$\boldsymbol{H}_i(t) = \begin{pmatrix} H_{i,(1,1)}(t) & H_{i,(1,2)}(t) & H_{i,(1,3)}(t) \\ H_{i,(2,1)}(t) & H_{i,(2,2)}(t) & H_{i,(2,3)}(t) \\ H_{i,(3,1)}(t) & H_{i,(3,2)}(t) & H_{i,(3,3)}(t) \end{pmatrix} = \begin{pmatrix} z_i(t) & z_i(t) & z_i(t)t \\ z_i(t) & 1 & t \\ z_i(t)t & t & t^2 \end{pmatrix}. \tag{2.86}$$

We need to show that, as m approaches infinity,

$$\frac{1}{m} \sum_{i=1}^{m} \int_0^\tau \boldsymbol{H}_i(u) Y_i(u) e^{\alpha_0+\beta_0 u}\, du \xrightarrow{p} \boldsymbol{\Sigma}(\tau; \boldsymbol{\eta}_0), \tag{2.87}$$

where

$$\boldsymbol{\Sigma}(t;\boldsymbol{\eta}_0) = \begin{pmatrix} \sigma_{\gamma\gamma}(t;\boldsymbol{\eta}_0) & \sigma_{\gamma\alpha}(t;\boldsymbol{\eta}_0) & \sigma_{\gamma\beta}(t;\boldsymbol{\eta}_0) \\ \sigma_{\alpha\gamma}(t;\boldsymbol{\eta}_0) & \sigma_{\alpha\alpha}(t;\boldsymbol{\eta}_0) & \sigma_{\alpha\beta}(t;\boldsymbol{\eta}_0) \\ \sigma_{\beta\gamma}(t;\boldsymbol{\eta}_0) & \sigma_{\beta\alpha}(t;\boldsymbol{\eta}_0) & \sigma_{\beta\beta}(t;\boldsymbol{\eta}_0) \end{pmatrix} \tag{2.88}$$

have finite components $[(\sigma_{ij}(t;\boldsymbol{\eta}_0))]$, $i,j = \alpha,\ \beta,\ \gamma$, for all $t \in [0,\tau]$, and $\boldsymbol{\Sigma}(\tau;\boldsymbol{\eta}_0)$ is positive definite. To show the convergence result (2.87), let the event $A_i(t)$ be "the ith individual experiences at least one event in $[\max(t-\Delta,0),t)]$" as in Section 2.3.1. Then, $z_i(t) = I\{A_i(t)\}$ and $E\{z_i(t)\} = \Pr\{A_i(t)\}$, and under H_0

$$\begin{aligned}\Pr\{A_i(t)\} =& I\{t<\Delta\}\left[1-\exp\left\{-\frac{\alpha_0}{\beta_0}\left(e^{\beta_0 t}-1\right)\right\}\right] \\ &+ I\{t\geq\Delta\}\left[1-\exp\left\{-\frac{\alpha_0}{\beta_0}\left(e^{\beta_0 t}[1-e^{-\beta_0\Delta}]\right)\right\}\right].\end{aligned} \tag{2.89}$$

Thus, assuming that the expectations of the at-risk processes Y_i exist, under the null hypothesis $\gamma = 0$, the convergence result (2.87) holds by a weak law of large numbers. Then, the components of $\boldsymbol{\Sigma}(t;\boldsymbol{\eta}_0)$ are given by

$$\begin{aligned}
\sigma_{\gamma\gamma}(t;\boldsymbol{\eta}_0) &= \int_0^t E\{Y_i(u)\}\Pr\{A_i(u)\}\, e^{\alpha_0+\beta_0 u}\,du, \\
\sigma_{\gamma\alpha}(t;\boldsymbol{\eta}_0) &= \sigma_{\alpha\gamma}(t;\boldsymbol{\eta}_0) = \int_0^t E\{Y_i(u)\}\Pr\{A_i(u)\}\, e^{\alpha_0+\beta_0 u}\,du, \\
\sigma_{\gamma\beta}(t;\boldsymbol{\eta}_0) &= \sigma_{\beta\gamma}(t;\boldsymbol{\eta}_0) = \int_0^t E\{Y_i(u)\}\Pr\{A_i(u)\}\, ue^{\alpha_0+\beta_0 u}\,du, \\
\sigma_{\alpha\alpha}(t;\boldsymbol{\eta}_0) &= \int_0^t E\{Y_i(u)\}\, e^{\alpha_0+\beta_0 u}\,du, \\
\sigma_{\alpha\beta}(t;\boldsymbol{\eta}_0) &= \sigma_{\beta\beta}(t;\boldsymbol{\eta}_0) = \int_0^t E\{Y_i(u)\}\, ue^{\alpha_0+\beta_0 u}\,du,
\end{aligned}$$

and

$$\sigma_{\beta\beta}(t;\boldsymbol{\eta}_0) = \int_0^t E\{Y_i(u)\}\, u^2 e^{\alpha_0+\beta_0 u}\,du.$$

The resulting matrix (2.88) can be shown to be positive definite. This completes conditions B and D.

We next consider Condition C which is a Lindeberg-type condition for proving the weak convergence of the stochastic integrals using the martingale central limit theorem (see Andersen et al. 1993, pp. 83–84). We need to check that; for any $\varepsilon > 0$,

$$\frac{1}{m}\sum_{i=1}^m \int_0^t \{H_{i,(j,l)}(u)\}^2 I\left\{\left|\frac{1}{\sqrt{m}}H_{i,(j,l)}(u)\right| > \varepsilon\right\} Y_i(u)e^{\alpha_0+\beta_0 u}\,du \xrightarrow{p} 0, \tag{2.90}$$

as $m \to \infty$, where $H_{i,(j,l)}(t)$ (j, $l = 1, 2, 3$) is defined in (2.86). Let us first consider $H_{i,(1,1)}(t) = H_{i,(1,2)}(t) = H_{i,(2,1)}(t) = z_i(t)$. Since $z_i(t) = 0$ or 1, for a sufficiently large m, $I\left\{z_i(u) > \varepsilon\sqrt{m}\right\} = 0$ for all $0 \leq u \leq \tau$. Thus,

$$\frac{1}{m}\sum_{i=1}^{m}\int_0^t z_i(u) I\left\{z_i(u) > \varepsilon\sqrt{m}\right\} Y_i(u) e^{\alpha_0+\beta_0 u}\, du \tag{2.91}$$

convergences to zero in probability. The convergence results for $H_{i,(1,3)}(t) = H_{i,(3,1)}(t) = t z_i(t)$ can be shown similarly. For $H_{i,(2,2)}(t) = 1$, we denote $E_i(t) = \int_0^t Y_i(u) e^{\alpha_0+\beta_0 u}\, du$, $t \in [0, \tau]$, and then assume that

$$\frac{1}{m}\sum_{i=1}^{m} E_i(t) \xrightarrow{p} e(t), \quad t \in [0, \tau], \tag{2.92}$$

as $m \to \infty$. This rather weak assumption implies that the average expected number of events should stabilize as m increases (see, Andersen et al. 1993, p. 428). Under this assumption, the convergence result for

$$\frac{1}{m}\sum_{i=1}^{m}\int_0^t I\left\{1 > \varepsilon\sqrt{m}\right\} Y_i(u) e^{\alpha_0+\beta_0 u}\, du \tag{2.93}$$

follows directly. Other convergence results can be shown in a similar manner.

Condition E holds when we restrict $0 \leq t \leq \tau$ for some τ and $|\alpha| < R$ and $|\beta| < M$ for some $R > 0$ and $M > 0$. Then, the conditions of Andersen et al. (1993, pp. 420–421) are satisfied for the model under $H_0 : \gamma = 0$. Then, from a theorem given by Andersen et al. (1993, p. 422), we conclude that $\tilde{\boldsymbol{\eta}}$ converges in probability to $\boldsymbol{\eta}_0$ as $m \to \infty$. Furthermore, Pena (1998) showed that, under contitions A–E and the null hypothesis $H_0 : \gamma = 0$,

$$\frac{1}{\sqrt{m}} U_\gamma(\tilde{\boldsymbol{\eta}}, 0) \xrightarrow{\mathcal{D}} Z \sim N\left(0, \sigma_\gamma^2(\tau)\right)$$

as $m \to \infty$, where

$$\sigma_\gamma^2(\tau) = \sigma_{\gamma\gamma}(\tau) - \left(\sigma_{\gamma\alpha}(\tau), \sigma_{\gamma\beta}(\tau)\right) \begin{pmatrix} \sigma_{\alpha\alpha}(\tau) & \sigma_{\alpha\beta}(\tau) \\ \sigma_{\beta\alpha}(\tau) & \sigma_{\beta\beta}(\tau) \end{pmatrix}^{-1} \begin{pmatrix} \sigma_{\alpha\gamma}(\tau) \\ \sigma_{\beta\gamma}(\tau) \end{pmatrix},$$

which can be estimated by any consistent estimator of $\sigma_\gamma^2(\tau)$. Therefore, significance levels (p-values) can be computed by using $N(0, 1)$ approximation for S in (2.83). Also, the limiting distribution of Λ in (2.84) is $\chi^2_{(1)}$ when $m \to \infty$.

2.6.2 Example: Hydraulic Systems of LHD Machines

Kumar and Klefsjo (1992) present failure times of hydraulic systems of 6 load-haul-dump (LHD) machines which are chosen from a fleet of LHD machines. The data set is given in

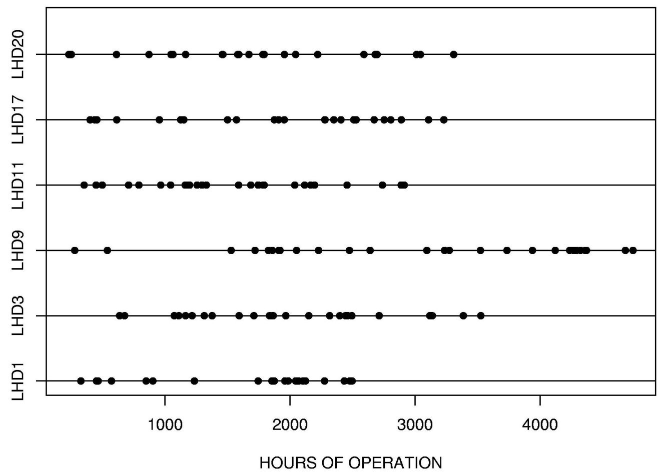

Figure 2.9: Time (on operating hours) dot plots for failures of hydraulic systems of LHD machines.

the appendix. The main aim of their analysis is to study the pattern in the reliability of the hydraulic systems. Furthermore, some maintenance policies are suggested to minimize the total cost of operation and maximize the availability of the hydraulic systems. We consider the LHD machines here individually (i.e. $m = 1$) to illustrate the carryover effects testing in nonhomogeneous Poisson processes.

End-of-followup times of machines are not given explicitly by Kumar and Klefsjo. Therefore, it is supposed in our study that the last failure time of the hydraulic system for each machine is the end-of-followup time of the machine under observation. It is, however, worth noting that the data are not failure truncated but time truncated. As discussed in Section 1.1.1, Kumar and Klefsjo categorize the machines as old (LHD 1 and LHD 3), medium old (LHD 9 and LHD 11) and new (LHD 17 and LHD 20). For the machines LHD 1, LHD 3, LHD 9, LHD 11, LHD 17 and LHD 20 the number of failures during the observation periods are 23, 25, 27, 28, 26 and 23, and the last failure times are 2496, 3526, 4743, 2913, 3230 and 3309, respectively.

The data set is displayed as an *event dot plot* for each LHD machine in Figure 2.9 to gain an insight into the frequency and patterns of the data. Since we consider the last failure times as end-of-followup times, LHD 1 and LHD 9 machines have the smallest and the longest observation periods, respectively. All machines experienced a similar number of failures at the end of their observation periods. The dot plot suggests clustering of events after each failure occurrence for some machines (e.g. LHD 11). Plots of the cumulative number of failures versus cumulative operating time for each machine are given in Figure 2.10. An approximate linearity in the plots of LHD 3, LHD 11 and LHD 20 in Figure 2.10 suggests that the HPP may be a suitable model, whereas plots

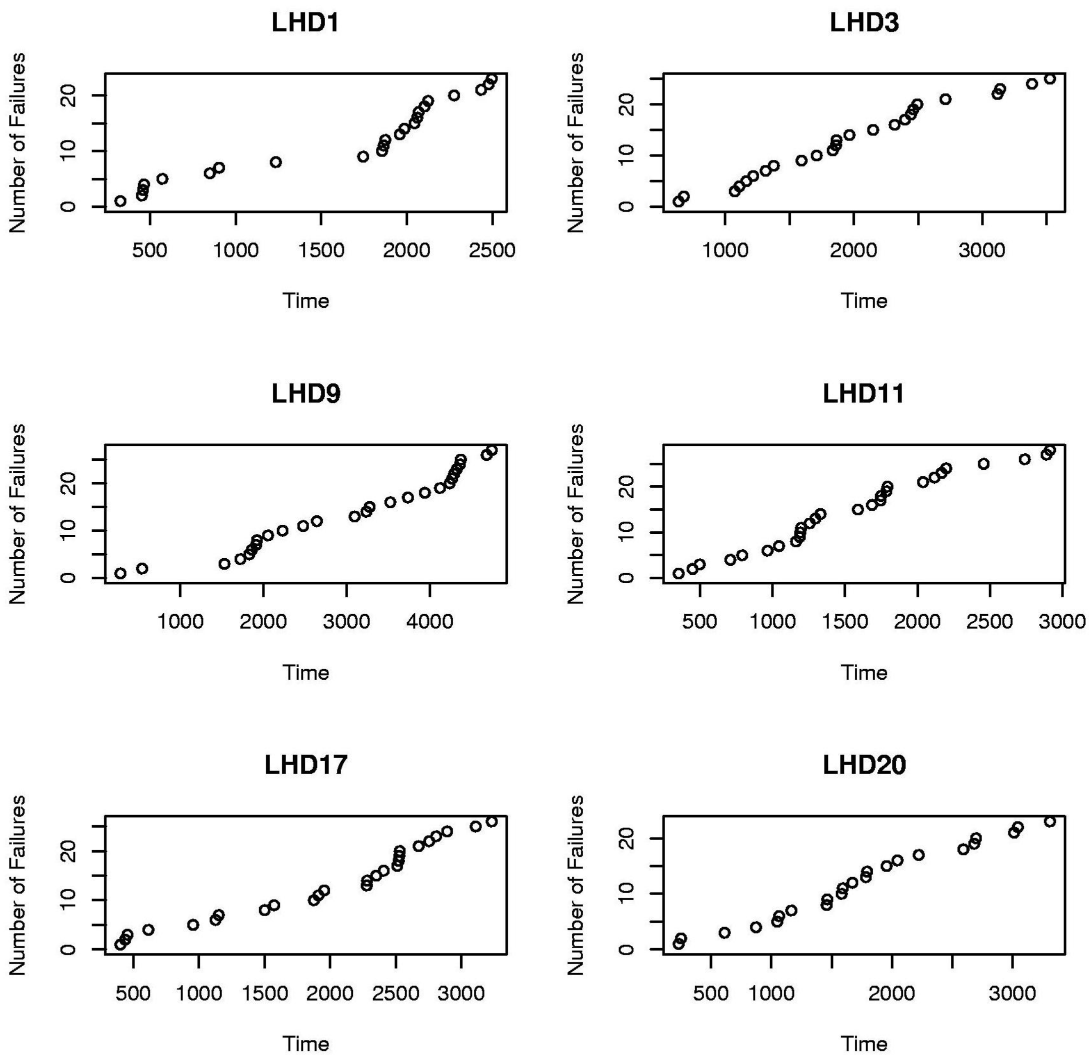

Figure 2.10: Cumulative failures of the hydraulic systems of LHD machines versus operating hours.

Machine	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\gamma}$
LHD 1	-5.738 (0.5473)	0.000640 (0.000342)	0.257 (0.4479)
LHD 3	-5.395 (0.4744)	0.000206 (0.000203)	0.120 (0.4034)
LHD 9	-6.050 (0.4929)	0.000383 (0.000152)	-0.385 (0.4055)
LHD 11	-5.112 (0.4861)	0.000121 (0.000233)	0.455 (0.4048)
LHD 17	-5.563 (0.4820)	0.000383 (0.000231)	0.107 (0.0657)
LHD 20	-5.068 (0.4632)	0.000103 (0.000216)	-0.167 (0.4209)

Table 2.12: Estimates of α, β and γ in Model A for each machine. The numbers in the parentheses are the standard errors of parameter estimates.

for other machines display an increasing rate of occurrence of failures. As this is based on the interpretation of plots, we shall consider these comments further with statistical tests.

Since Figure 2.9 and Figure 2.10 suggest clustering of failures for some machines, an analysis for a carryover effect for each LHD machine could be useful. Figure 2.10 suggests that trend is also present in the rate of failure of LHD 1, LHD 9 and LHD 17 machines as well. We, therefore, consider the following model:

$$\text{Model A:} \qquad \lambda(t|\mathcal{H}(t)) = \exp\left\{\alpha + \beta t + \gamma z(t)\right\}, \qquad t \geq 0,$$

where $z(t) = I(N(t^-) > 0)I(t - T_{N(t^-)} \leq 100)$, and we want to test the null hypothesis $H_0 : \gamma = 0$. The value $\Delta = 100$ is chosen for illustration. By maximizing the log likelihood (2.79), we obtain the maximum likelihood estimates and their standard errors which are displayed in Table 2.12. The reduced model is an NHPP including a term for a monotonic time trend. That is,

$$\text{Model B:} \qquad \lambda(t) = \exp\left\{\alpha + \beta t\right\}, \qquad t \geq 0.$$

The maximum likelihood estimates with standard errors for Model B are displayed in Table 2.13. The null hypotheses of no carryover effect ($\gamma = 0$) can be tested with likelihood ratio statistic Λ in (2.84), and the results are given in Table 2.14. We used χ^2 approximation to estimate p-values. From the p-values, the likelihood ratio tests for the absence of a carryover effect in nonhomogeneous Poisson process do not show evidence against the null hypothesis $H_0 : \gamma = 0$ for all LHD machines. Similar p-values and conclusions are obtained if we use Wald statistics $\hat{\gamma}/se(\hat{\gamma})$ from Table 2.14 to test that $\gamma = 0$. Finally, the partial score statistic (2.83) can also be used. This requires a bit of computation beyond the results of fitting models A and B, but it is also valid to use (2.83) with $I^{\gamma\gamma}(\hat{\alpha}, \hat{\beta}, \hat{\gamma})$ used in place of $I^{\gamma\gamma}(\tilde{\alpha}, \tilde{\beta}, 0)$.

Machine	$\hat{\alpha}$	$\hat{\beta}$
LHD 1	-5.679 (0.5375)	0.000697 (0.000311)
LHD 3	-5.349 (0.4426)	0.000213 (0.000199)
LHD 9	-6.124 (0.4914)	0.000354 (0.000150)
LHD 11	-4.836 (0.3966)	0.000127 (0.000226)
LHD 17	-5.539 (0.4709)	0.000401 (0.000219)
LHD 20	-5.138 (0.4351)	0.000099 (0.000219)

Table 2.13: Estimates of α and β in Model B for each machine. The numbers in the parentheses are the standard errors of parameter estimates.

Machine	$l(\hat{\boldsymbol{\theta}})$	$l(\tilde{\boldsymbol{\theta}})$	Λ	W
LHD 1	-127.94	-128.11	0.334 (0.5634)	0.330 (0.5660)
LHD 3	-148.10	-148.15	0.088 (0.7668)	0.088 (0.7669)
LHD 9	-163.12	-163.58	0.925 (0.3362)	0.902 (0.3422)
LHD 11	-157.23	-157.89	1.323 (0.2501)	1.262 (0.2612)
LHD 17	-149.60	-149.63	0.066 (0.7978)	0.065 (0.7982)
LHD 20	-137.10	-137.18	0.158 (0.6915)	0.157 (0.6924)

Table 2.14: The maximized log likelihoods for Model A and Model B, $\Lambda = 2l(\hat{\boldsymbol{\theta}}) - 2l(\tilde{\boldsymbol{\theta}})$ and $W = \hat{\gamma}^2/s^2(\hat{\gamma})$. The numbers in the parentheses are the p-values.

Chapter 3

Testing for Carryover Effects in Nonidentical Processes

In the preceding chapter, we discussed testing for carryover effects in identical processes. In this section, we deal with the nonidentical processes case by considering fixed and random effects models. We give the tests for carryover effects in nonhomogeneous Poisson processes in Section 3.2. In Section 3.3, we present the results of simulation studies. In Section 3.4, we illustrate the methods with an application from an asthma prevention trial in infants.

3.1 Introduction

In applications involving multiple systems or individuals, heterogeneity is often apparent (e.g. Lawless, 1987; Baker, 2001; Lindqvist, 2006; Cook and Lawless, 2007, Section 3.5), even after adjustment for known covariates. In particular, although individual processes may be adequately described by a modulated Poisson process, the process rate functions may vary across individuals. Such variation is typically due to unmeasured differences in the individuals or the environment in which the processes operate. If the tests developed for identical processes are used when substantial heterogeneity is present, false indications of an effect can occur, producing an inflated Type 1 error rate, as we showed in Section 2.4 (see Table 2.9).

A useful extension of modulated Poisson process models to include heterogeneity is where independent processes $i = 1, \ldots, m$ have rate functions

$$\rho_i(t|\mathcal{H}_i(t)) = \alpha_i \rho_0(t; \boldsymbol{\gamma}) \exp\left\{\boldsymbol{z}_i'(t)\boldsymbol{\beta}\right\}, \tag{3.1}$$

where $\alpha_1, \ldots, \alpha_m$ are positive parameters and $\boldsymbol{\gamma}$ is a $p \times 1$ vector of parameters. Models for which $\boldsymbol{\gamma}$ is also allowed to vary across individuals can be considered, but we will focus on (3.1). Such fixed effects models can be problematic when m is large; the number of parameters $m+p+1$ is large and estimates of the α_i are not consistent as $m \to \infty$. An alternative is to assume the α_i are independent and identically distributed random effects with some distribution function $G(\alpha; \boldsymbol{\phi})$, where $\boldsymbol{\phi}$ is a vector of parameters (Cook and Lawless, 2007, Section 3.5). Both these models are widely applied, and we consider related tests for carryover effects under these two models.

3.2 Tests of No Carryover Effect for Heterogeneous Processes

To develop tests for carryover effects, we consider the modulated Poisson process models with intensity function (3.1), where $\boldsymbol{z}_i(t)$ is a $q \times 1$ vector of external covariates as well as time-varying covariates including a term for carryover effects. As in Chapter 2, we focus on

$$z_i(t) = I\left\{N_i(t^-) > 0\right\} I\left\{B_i(t) \le \Delta\right\}, \tag{3.2}$$

where $B_i(t)$ is the backward recurrence time at time t for the processes i. A test for no carryover effect can be then developed by considering the hypothesis

$$H_0: \beta = 0, \boldsymbol{\gamma} \in \mathbb{R}^+ \qquad \text{vs.} \qquad H_1: \beta \neq 0, \boldsymbol{\gamma} \in \mathbb{R}^+. \tag{3.3}$$

We now discuss the fixed and random effects approaches. In the following sections, we assume as before that m independent processes are under observation, with process i observed continuously over an observation window $[0, \tau_i]$ $(i = 1, \ldots, m)$. However, the methods below are also valid under certain conditions for more general observation schemes.

3.2.1 Fixed Effects Model

In the fixed effects model case (the model (3.1) with (3.2), where the $\alpha_i > 0$ are unknown parameters), data on m independent processes give the likelihood function (cf. Section 1.4.1)

$$L(\boldsymbol{\alpha}, \boldsymbol{\gamma}, \beta) = \prod_{i=1}^{m} \left\{ \left[\prod_{i=1}^{n_i} \alpha_i \rho_0(t_{ij}; \boldsymbol{\gamma}) e^{\beta z_i(t_{ij})} \right] e^{-\int_0^{\tau_i} \alpha_i \rho_0(t; \boldsymbol{\gamma}) e^{\beta z_i(t)}\, dt} \right\}, \tag{3.4}$$

where $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m)'$. Then, the log likelihood function is

$$\ell(\boldsymbol{\alpha}, \boldsymbol{\gamma}, \beta) = \sum_{i=1}^{m} \left\{ n_i \log \alpha_i + \sum_{j=1}^{n_i} \left[\log \rho_0(t_{ij}; \boldsymbol{\gamma}) + \beta z_i(t_{ij}) \right] - \alpha_i R_i(\boldsymbol{\gamma}, \beta) \right\}, \tag{3.5}$$

where

$$R_i(\boldsymbol{\gamma}, \beta) = \int_0^{\tau_i} \rho_0(t; \boldsymbol{\gamma}) e^{\beta z_i(t)}\, dt \tag{3.6}$$
$$= \left(e^{\beta} - 1\right) \sum_{i=1}^{n_i} \int_{t_{ij}}^{\min(t_{i,j+1}, t_{ij}+\Delta)} \rho_0(t; \boldsymbol{\gamma})\, dt + \int_0^{\tau_i} \rho_0(t; \boldsymbol{\gamma})\, dt.$$

For given $\boldsymbol{\gamma}$ and β, the log likelihood function (3.5) is maximized by $\tilde{\alpha}_i(\boldsymbol{\gamma}, \beta) = n_i / R_i(\boldsymbol{\gamma}, \beta)$, and substitution of this into (3.5) gives the profile log likelihood as a constant plus

$$\ell_p(\boldsymbol{\gamma}, \beta) = \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} \left[\log \rho_0(t_{ij}; \boldsymbol{\gamma}) + \beta z_i(t_{ij})\right] - n_i \log R_i(\boldsymbol{\gamma}, \beta) \right\}. \tag{3.7}$$

A likelihood ratio test of $H_0 : \beta = 0$ requires estimates $\hat{\boldsymbol{\gamma}}, \hat{\beta}$ obtained by maximizing (3.7) and the estimate $\tilde{\boldsymbol{\gamma}}$ obtained by maximizing $\ell_p(\boldsymbol{\gamma}, 0)$. This is readily handled by general optimization software. A likelihood ratio statistic, $\Lambda = 2\ell(\hat{\boldsymbol{\gamma}}, \hat{\beta}) - 2\ell(\tilde{\boldsymbol{\gamma}}, 0)$, can be used to test H_0.

A score test can be based on $U_\beta(\tilde{\boldsymbol{\gamma}}, 0)$, where $U_\beta(\boldsymbol{\gamma}, \beta) = (\partial/\partial\beta)\ell_p(\boldsymbol{\gamma}, \beta)$, This takes a simple form for homogeneous Poisson processes. In this case $\rho_0(t; \boldsymbol{\gamma})$ in (3.1) is one, and the model is then $\lambda_i(t|\mathcal{H}_i(t)) = \alpha_i \exp\{\beta z_i(t)\}$. When $\beta = 0$, $\tilde{\boldsymbol{\alpha}} = (\tilde{\alpha}_1, \ldots, \tilde{\alpha}_m)' = (n_1/\tau_m, \ldots, n_m/\tau_m)'$. The profile log likelihood function (3.7) becomes a constant plus $\beta \sum_{i=1}^{m} \sum_{j=1}^{n_i} z_i(t_{ij}) - \sum_{i=1}^{m} n_i \log R_i(\mathbf{0}, \beta)$. This can be rewritten as

$$\ell_p(\beta) = \beta\, O(\Delta) - \sum_{i=1}^{m} n_i \log \left\{ \left(e^{\beta} - 1\right) E_i(\Delta) + \tau_i \right\}, \tag{3.8}$$

where $O(\Delta) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} z_i(t_{ij})$ and $E_i(\Delta) = \sum_{j=1}^{n_i} \min(W_{i,j+1}, \Delta)$. The standardized score statistic for testing $H_0 : \beta = 0$ is then

$$S_1 = \left(\frac{\partial \ell_p(\beta)/\partial\beta}{\left[-\partial^2 \ell_p(\beta)/\partial\beta^2\right]^{1/2}} \right)\Bigg|_{\beta=0} = \frac{U_\beta(\tilde{\boldsymbol{\alpha}}, 0)}{\left[\widehat{Var}(U_\beta(\tilde{\boldsymbol{\alpha}}, 0))\right]^{1/2}}, \tag{3.9}$$

where

$$U_\beta(\tilde{\boldsymbol{\alpha}}, 0) = O(\Delta) - \sum_{i=1}^{m} n_i E_i(\Delta)/\tau_i \tag{3.10}$$

and its variance estimate based on the standard asymptotics represented in (2.8) is

$$\widehat{Var}(U_\beta(\tilde{\boldsymbol{\alpha}}, 0)) = \sum_{i=1}^{m} n_i E_i(\Delta) \left\{\tau_i - E_i(\Delta)\right\} / \tau_i^2. \tag{3.11}$$

Note that the score function (3.10) is in the simple form of the sum of the observed number of events in a carryover period minus an estimate of the expected number for each process, under H_0. This can be compared to the statistic (2.20) of the previous chapter.

For the homogeneous Poisson process case, the unrestricted m.l.e of α_i is $\hat{\alpha}_i = n_i/[E_i(\Delta)(e^{\hat{\beta}} - 1) + \tau_i]$, $i = 1, \ldots, m$, and the m.l.e. of β is $\hat{\beta} = O(\Delta)/\sum_{i=1}^{m} \hat{\alpha}_i E_i(\Delta)$, so a likelihood ratio test is also straightforward. The likelihood ratio statistic for testing $H_0 : \beta = 0$ is

$$\begin{aligned} \Lambda_1 &= 2\ell(\hat{\boldsymbol{\alpha}}, \hat{\beta}) - 2\ell(\tilde{\boldsymbol{\alpha}}, 0), \\ &= 2\hat{\beta}\, O(\Delta) - 2\sum_{i=1}^{m} n_i \log\left[1 + \frac{E_i(\Delta)(e^{\hat{\beta}} - 1)}{\tau_i}\right], \end{aligned} \tag{3.12}$$

where $\hat{\boldsymbol{\alpha}} = (\hat{\alpha}_1, \ldots, \hat{\alpha}_m)'$.

A problem with S_1 and Λ_1 is that if $m \to \infty$ but the τ_i are fixed, the standard asymptotics do not hold and the limiting distributions are not standard normal and $\chi^2_{(1)}$, respectively. This is due to the fact that the α_i are not estimated consistently. When the $z_i(t)$ are external, this problem can be solved by considering a conditional test by looking at a conditional likelihood for β. This is based on the distribution of the event times $\{(N_i(\tau_i) = n_i, t_{i1}, \ldots, t_{in_i}); i = 1, \ldots, m\}$, given $N_i(\tau_i) = n_i$ and the covariate histories $\{z_i(t); 0 \leq t \leq \tau_i\}$, and is easily seen to be

$$L_c(\beta) = \prod_{i=1}^{m} \left\{ \frac{n_i! \prod_{j=1}^{n_i} e^{\beta z_i(t_{ij})}}{\left(\int_0^{\tau_i} e^{\beta z_i(u)}\, du\right)^{n_i}} \right\}.$$

The conditional score function is then

$$U_c(\beta) = \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} z_i(t_{ij}) - \frac{n_i \int_0^{\tau_i} z_i(u) e^{\beta z_i(u)}\, du}{\int_0^{\tau_i} e^{\beta z_i(u)}\, du} \right\},$$

which, when $\beta = 0$, gives

$$\begin{aligned} U_c(0) &= \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} z_i(t_{ij}) - \frac{n_i}{\tau_i} \int_0^{\tau_i} z_i(u)\, du \right\}, \\ &= O(\Delta) - \sum_{i=1}^{m} n_i E_i(\Delta)/\tau_i. \end{aligned}$$

Note that neither $L_c(\beta)$ nor $U_c(\beta)$ depend on the α_i, and thus a score test for $\beta = 0$ may be based on $U_c(0)$, which is the same as the unconditional score statistic $U_\beta(\tilde{\boldsymbol{\alpha}}, 0)$ given in (3.10). Unfortunately, when $z_i(t)$ is internal as in (3.2), we cannot get this because $\Pr\{N_i(t) = n_i\}$ is not a Poisson distribution anymore. However, normal and χ^2 approximations for S_1 and Λ_1, respectively, may be adequate in cases where m is not too large and the numbers of events per process are fairly large. In cases where m is large, an option would be to obtain $E\{U_{ci}(0)\}$ and its variance, where $U_{ci}(0)$ is the ith term in $U_c(0)$, and then to apply a central limit theorem as $m \to \infty$. However, p-values for the statistic S_1 can be obtained by simulation, and that is our proposed approach. The adequacy of the standard approximation for S_1 is investigated in the simulation study of Section 3.3.

3.2.2 Random Effects Model

In Section 1.3.1, random effects in Poisson processes are discussed briefly. Random effects models employ a distribution for the α_i in (3.1), which are assumed independent. To illustrate this approach we assume the α_i have a gamma distribution with mean 1 and variance ϕ, as is widely done. Let $G(\alpha_i;\phi)$ and $g(\alpha_i;\phi)$ denote the distribution and probability density functions of α_i, respectively. Suppose that, given α_i, $i = 1, \ldots, m$, the process $\{N_i(t); t \geq 0\}$ has the intensity

$$\lambda_i(t|\mathcal{H}_i, \alpha_i) = \lim_{\Delta t \downarrow 0} \frac{\Pr\{\Delta N_i(t) = 1|\mathcal{H}_i(t), \alpha_i\}}{\Delta t} = \alpha_i \rho_0(t;\boldsymbol{\gamma}) e^{\beta z_i(t)}. \tag{3.13}$$

The unconditional intensity of the process $\{N_i(t); t \geq 0\}$, $i = 1, \ldots, m$, is then given by

$$\lambda_i(t|\mathcal{H}_i(t)) = e^{\beta z_i(t)} \rho_0(t;\boldsymbol{\gamma}) E\left\{\alpha_i|\mathcal{H}_i(t)\right\}. \tag{3.14}$$

Note that when $\beta = 0$ the unconditional process $\{N_i(t); t \geq 0\}$ is not a Poisson process.

The probability of the outcome that "n_i events are observed at times $t_{i1} < \ldots < t_{in_i}$, $i = 1, \ldots, m$", is

$$\prod_{i=1}^{m} \int_0^\infty \Pr\{n_i, t_{i1}, \ldots, t_{in_i}|\alpha_i\}\, dG(\alpha_i;\phi), \tag{3.15}$$

where

$$\Pr\{n_i, t_{i1}, \ldots, t_{in_i}|\alpha_i\} = \prod_{j=1}^{n_i} \alpha_i \rho_0(t_{ij};\boldsymbol{\gamma}) e^{\beta z_i(t_{ij})} \exp\left\{-\int_0^{\tau_i} \alpha_i \rho_0(t;\boldsymbol{\gamma}) e^{\beta Z_i(u)}\, du\right\}. \tag{3.16}$$

Therefore, the likelihood function is given by

$$L(\boldsymbol{\gamma}, \beta, \phi) = \prod_{i=1}^{m} \int_0^\infty \left\{\prod_{j=1}^{n_i} \alpha_i \rho_0(t_{ij};\boldsymbol{\gamma}) e^{\beta z_i(t_{ij})}\right\} e^{-\alpha_i R_i(\boldsymbol{\gamma},\beta)}\, dG(\alpha_i;\phi), \tag{3.17}$$

where $R_i(\boldsymbol{\gamma}, \beta)$ is given by (3.6). After simplifications, we obtain the log likelihood function (Cook and Lawless, 2007, Section 3.5.3)

$$\begin{aligned} \ell(\boldsymbol{\gamma}, \beta, \phi) \;=\; & \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} [\log \rho_0(t_{ij};\boldsymbol{\gamma}) + \beta z_i(t_{ij})] + \log\Gamma\left(n_i + \phi^{-1}\right) - \log\Gamma(\phi^{-1}) \right. \\ & \left. + n_i \log\phi - (n_i + \phi^{-1}) \log\left[1 + \phi R_i(\boldsymbol{\gamma}, \beta)\right] \right\}. \end{aligned} \tag{3.18}$$

The derivatives of (3.18) with respect to $\boldsymbol{\gamma}$, β and ϕ give (cf. Section 1.4.3)

$$\boldsymbol{U}_{\boldsymbol{\gamma}}(\boldsymbol{\gamma},\beta,\phi) = \sum_{i=1}^{m}\left\{\sum_{j=1}^{n_i}\left[\frac{\partial \log \rho_0(t_{ij};\boldsymbol{\gamma})}{\partial \boldsymbol{\gamma}}\right] - \left(n_i + \frac{1}{\phi}\right)\frac{\phi[\partial R_i(\boldsymbol{\gamma},\beta)/\partial \boldsymbol{\gamma}]}{1+\phi R_i(\boldsymbol{\gamma},\beta)}\right\}, \tag{3.19}$$

$$U_{\beta}(\boldsymbol{\gamma},\beta,\phi) = \sum_{i=1}^{m}\left\{\sum_{j=1}^{n_i} z_i(t_{ij}) - \left(n_i + \frac{1}{\phi}\right)\frac{\phi[\partial R_i(\boldsymbol{\gamma},\beta)/\partial \beta]}{1+\phi R_i(\boldsymbol{\gamma},\beta)}\right\} \tag{3.20}$$

and

$$\begin{aligned} U_{\phi}(\boldsymbol{\gamma},\beta,\phi) &= \sum_{i=1}^{m}\left\{\frac{\partial}{\partial \phi}\left[\sum_{k=1}^{n_i}\log\left(\phi^{-1}+n_i-k\right)\right] + \frac{1}{\phi^2}\log\left(1+\phi R_i(\boldsymbol{\gamma},\beta)\right)\right. \\ &\left. + \frac{n_i}{\phi} - \left(n_i+\frac{1}{\phi}\right)\frac{R_i(\boldsymbol{\gamma},\beta)}{1+\phi R_i(\boldsymbol{\gamma},\beta)}\right\}, \end{aligned} \tag{3.21}$$

respectively. The negative Hessian matrix for the log likelihood (3.18) is given by

$$\boldsymbol{I}(\boldsymbol{\gamma},\beta,\phi) = \begin{pmatrix} \boldsymbol{I}_{\gamma\gamma}(\boldsymbol{\gamma},\beta,\phi) & \boldsymbol{I}_{\gamma\beta}(\boldsymbol{\gamma},\beta,\phi) & \boldsymbol{I}_{\gamma\phi}(\boldsymbol{\gamma},\beta,\phi) \\ \boldsymbol{I}_{\beta\gamma}(\boldsymbol{\gamma},\beta,\phi) & I_{\beta\beta}(\boldsymbol{\gamma},\beta,\phi) & I_{\beta\phi}(\boldsymbol{\gamma},\beta,\phi) \\ \boldsymbol{I}_{\phi\gamma}(\boldsymbol{\gamma},\beta,\phi) & I_{\phi\beta}(\boldsymbol{\gamma},\beta,\phi) & I_{\phi\phi}(\boldsymbol{\gamma},\beta,\phi) \end{pmatrix}, \tag{3.22}$$

where $\boldsymbol{I}_{\gamma\gamma}(\boldsymbol{\gamma},\beta,\phi) = -\partial^2\ell(\boldsymbol{\gamma},\beta,\phi)/\partial\boldsymbol{\gamma}\partial\boldsymbol{\gamma}'$, $\boldsymbol{I}_{\beta\gamma}(\boldsymbol{\gamma},\beta,\phi) = -\partial^2\ell(\boldsymbol{\gamma},\beta,\phi)/\partial\beta\partial\boldsymbol{\gamma}'$, $\boldsymbol{I}_{\phi\gamma}(\boldsymbol{\gamma},\beta,\phi) = -\partial^2\ell(\boldsymbol{\gamma},\beta,\phi)/\partial\phi\partial\boldsymbol{\gamma}'$, and so on. The components of (3.22) are given by

$$\begin{aligned} \boldsymbol{I}_{\gamma\gamma} &= \sum_{i=1}^{m}\left\{-\sum_{j=1}^{n_i}\frac{\partial^2\log\rho_0(t_{ij};\boldsymbol{\gamma})}{\partial\boldsymbol{\gamma}\partial\boldsymbol{\gamma}'}\right. \\ &\left. + \left(n_i+\frac{1}{\phi}\right)\left[\frac{\phi[\partial^2 R_i/\partial\boldsymbol{\gamma}\partial\boldsymbol{\gamma}']}{1+\phi R_i} - \frac{\phi^2[\partial R_i/\partial\boldsymbol{\gamma}][\partial R_i/\partial\boldsymbol{\gamma}']}{(1+\phi R_i)^2}\right]\right\}, \\ \boldsymbol{I}_{\phi\gamma} &= \sum_{i=1}^{m}\left\{\frac{(n_i-R_i)[\partial R_i/\partial\boldsymbol{\gamma}]}{(1+\phi R_i)^2}\right\}, \\ \boldsymbol{I}_{\beta\gamma} &= \sum_{i=1}^{m}\left(n_i+\phi^{-1}\right)\left\{\frac{[\phi^{-1}+R_i]\,[\partial^2 R_i/\partial\beta\partial\boldsymbol{\gamma}'] - [\partial R_i/\partial\beta]\,[\partial R_i/\partial\boldsymbol{\gamma}']}{[\phi^{-1}+R_i]^2}\right\}, \\ I_{\beta\beta} &= \sum_{i=1}^{m}\left(n_i+\phi^{-1}\right)\left\{\frac{[\phi^{-1}+R_i]\,[\partial R_i/\partial\beta] - [\partial R_i/\partial\beta]^2}{[\phi^{-1}+R_i]^2}\right\}, \\ I_{\beta\phi} &= \sum_{i=1}^{m}\left\{\frac{\phi^{-2}\,(\partial R_i/\partial\beta)\,[2\phi^{-1}+n_i+R_i]}{[\phi^{-1}+R_i]^2}\right\}, \end{aligned}$$

and

$$I_{\phi\phi} = \sum_{i=1}^{m} \left\{ \frac{\partial^2}{\partial \phi^2} \left[\sum_{k=1}^{n_i} \log\left(\phi^{-1} + n_i - k\right) \right] + \frac{n_i}{\phi^2} + \frac{2}{\phi^3} \log(1 + \phi R_i) \right.$$
$$\left. - \frac{2R_i}{\phi^2(1 + \phi R_i)} - \left(n_i + \frac{1}{\phi}\right) \left(\frac{R_i}{1 + \phi R_i}\right)^2 \right\},$$

where $R_i = R_i(\boldsymbol{\gamma}, \beta)$ and $\boldsymbol{I}_{\gamma\gamma} = \boldsymbol{I}_{\gamma\gamma}(\boldsymbol{\gamma}, \beta, \phi)$, $\boldsymbol{I}_{\phi\gamma} = \boldsymbol{I}_{\gamma\beta}(\boldsymbol{\gamma}, \beta, \phi)$ etc.

Likelihood ratio tests of $H_0 : \beta = 0$ require maximum likelihood estimates $\hat{\boldsymbol{\gamma}}, \hat{\beta}, \hat{\phi}$ and $\tilde{\boldsymbol{\gamma}}, \tilde{\phi}$ (when $\beta = 0$); these are readily obtained with general optimization software. Therefore, the likelihood ratio statistic $\Lambda_2 = 2\ell(\hat{\boldsymbol{\gamma}}, \hat{\beta}, \hat{\phi}) - 2\ell(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi})$ can be used for testing $H_0 : \beta = 0$. Score tests can also be used, and they require only that we obtain $\tilde{\boldsymbol{\gamma}}$ and $\tilde{\phi}$. The score statistic is given by

$$S_2 = U_\beta(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi}) / \widehat{Var} \left[U_\beta(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi}) \right]^{1/2}, \tag{3.23}$$

where

$$U_\beta(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi}) = \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} z_i(t_{ij}) - \frac{(1 + \tilde{\phi} n_i)[\partial R_i(\tilde{\boldsymbol{\gamma}}, 0)/\partial \beta]}{1 + \tilde{\phi} R_i(\tilde{\boldsymbol{\gamma}}, 0)} \right\}, \tag{3.24}$$

and

$$\widehat{Var}\left(U_\beta(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi} \right) = \tilde{I}_{\beta\beta} - \begin{pmatrix} \tilde{\boldsymbol{I}}_{\gamma\beta} & \tilde{I}_{\phi\beta} \end{pmatrix} \begin{pmatrix} \tilde{\boldsymbol{I}}_{\gamma\gamma} & \tilde{\boldsymbol{I}}_{\gamma\phi} \\ \tilde{\boldsymbol{I}}_{\phi\gamma} & \tilde{I}_{\phi\phi} \end{pmatrix}^{-1} \begin{pmatrix} \tilde{\boldsymbol{I}}_{\beta\gamma} \\ \tilde{I}_{\beta\phi} \end{pmatrix}, \tag{3.25}$$

where $\tilde{\boldsymbol{I}}_{\gamma\gamma} = \boldsymbol{I}_{\gamma\gamma}(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi})$, $\tilde{\boldsymbol{I}}_{\gamma\beta} = \boldsymbol{I}_{\gamma\beta}(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi})$, $\tilde{\boldsymbol{I}}_{\gamma\phi} = \boldsymbol{I}_{\gamma\phi}(\tilde{\boldsymbol{\gamma}}, 0, \tilde{\phi})$, and so on.

It is instructive to consider the numerators of (3.23) and (3.9) for homogeneous Poisson processes. In this case $\rho_0(t; \gamma) = \gamma$ in (3.1) for the random effects case and $R_i(\gamma, \beta) = \int_0^{\tau_i} \gamma \exp(\beta z_i(t))\, dt = \left(e^\beta - 1\right) \gamma E_i(\Delta) + \gamma \tau_i$. From (3.24), the numerator of (3.23), therefore, becomes

$$U_\beta(\tilde{\gamma}, 0, \tilde{\phi}) = O(\Delta) - \sum_{i=1}^{m} \left\{ \frac{\left(n_i + \tilde{\phi}^{-1}\right) \tilde{\gamma}}{\tilde{\phi}^{-1} + \tilde{\gamma} \tau_i} \right\} E_i(\Delta). \tag{3.26}$$

This differs from the numerator of (3.9) only in the coefficients applied to the $E_i(\Delta)$. The fixed effects case (3.9) corresponds to the limit of (3.23) as $\tilde{\phi}^{-1}$ approaches zero (that is, the estimated variance of the α_i becomes arbitrarily large).

Assuming that the gamma distribution for the α_i is correct, the statistic S_2 in (3.23) is asymptotically $N(0, 1)$ as $m \to \infty$, unlike the fixed effects statistic. In practice, of course, the gamma distribution will never be exactly correct, so it is important to consider the performance of (3.23) under departures from the gamma. We consider this in Section 3.3.

3.2.3 Power and Consistency of Tests

The tests of no carryover effect in fixed effects and random effects model are developed under the alternative family of models of the form (3.1) with (3.2). However, simulations of the following chapter indicate that tests considered here are also consistent against some carryover alternatives that are not in this specific family of models. In other words, the probability of rejection of H_0 approaches one under the alternative as $m \to \infty$. Therefore, we also have some flexibility in the choice of Δ which will never be exactly known even if the form of (3.2) is correct. A discussion about Δ is given in Section 2.3.3. It should be noted that, in the following section, we also discuss the use of the tests of this chapter when the processes are identical as well as when the α_i are misspecified in the random effects model.

3.3 Simulation Studies

We present the results of simulation studies for tests based on heterogeneous processes in this section. We first consider the fixed effects case, and then the random effects model. In the first case, results of the simulation studies show that the normal distribution is not suitable for large m values. However, in certain finite sample settings, p-values may still be computed from the standard normal distribution. In the random effects case, normal approximation becomes more accurate as m gets larger. In both cases, the tests provide overall high power in testing for no carryover effects, and are robust with respect to misspecification of carryover periods. In random effects case, we also show that the test is robust when the random effects are misspecified.

We consider the fixed effects model (3.1) where $\rho_0(t;\gamma) = \gamma$, and the hypothesis of no carryover effect is tested by using the statistic S_1 in (3.9). In simulations we took $\gamma = 1$, and generated the α_i from the gamma distribution with mean 1 and variance $\phi = 0.3$ or 0.6. The α_i were generated once for each scenario, so that $\alpha_1, \ldots, \alpha_m$ are fixed across the repeated samples. To examine the asymptotic normal approximation for the null distribution of (3.9), we generated 10,000 realizations of the m processes under the null HPP model with rates α_i. In simulations reported below, scenarios with various combinations of m, τ, Δ were considered, with $m = 10, 20, 50, 100$; $\tau = 5, 10, 20$; and $\Delta = 0.0202, 0.0513, 0.1054$. Normal quantile-quantile plots of the 10,000 values of S_1 are shown in Figure 3.1 and Figure 3.2 for scenarios when $\tau = 5$ and the α_i are generated from the gamma distribution with mean 1 and variance $\phi = 0.3$ or 0.6, respectively. We consider similar scenarios with $\tau = 10$ in Figure 3.3 and Figure 3.4. The standard normal approximation is not suitable for each case, and goes off as m increases. As additional information, Table 3.1 presents the values of $\hat{Q}_p$ and $\hat{P}(S > Q_p)$ analogous to those in Table 2.1, where $p = 0.950$, 0.975 and 0.990. The results indicate that the normal

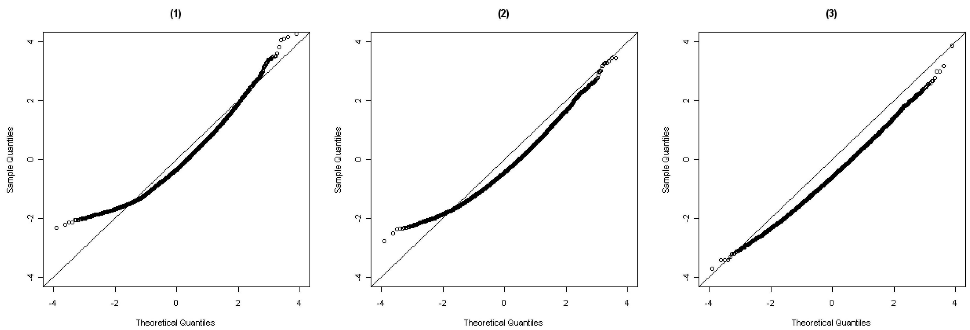

Figure 3.1: Normal Q-Q plot of S_1 in (3.9) from 10,000 samples with $\tau = 5$, $\phi = 0.3$, $\Delta = 0.0513$, and (1) $m = 10$, (2) $m = 20$, (3) $m = 50$.

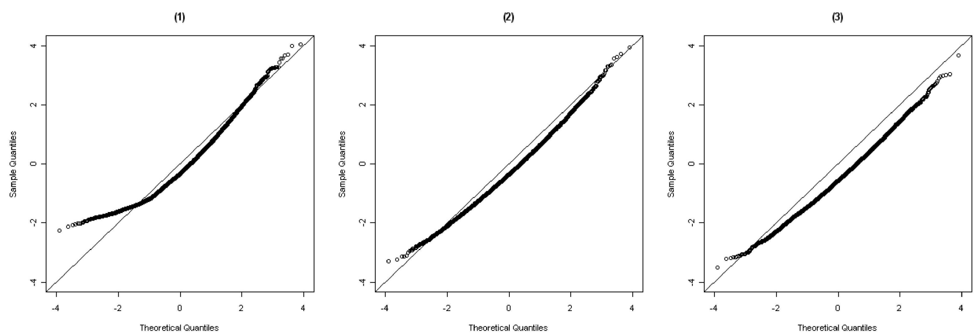

Figure 3.2: Normal Q-Q plot of S_1 in (3.9) from 10,000 samples with $\tau = 5$, $\phi = 0.6$, $\Delta = 0.0513$, and (1) $m = 10$, (2) $m = 20$, (3) $m = 50$.

approximation is not suitable for the distribution of the score statistic (3.9) as m gets larger. This reflects the fact that for fixed τ and increasing m, regular asymptotics do not apply to maximum likelihood estimation under (3.1) since the α_i are not consistently estimated. In Section 3.2.1, we mentioned that in cases where m is not too large and the numbers of events per process are fairly large then the normal approximation may be used. This can be seen in Figure 3.5 where the normal approximation is satisfactory when $\tau = 100$. The approximation is also fairly good when m is small and τ exceeds 10.

The statistic S_1 in (3.9) can be used along with simulation to obtain p-values when the normal approximation is unsatisfactory, so its power was also investigated. In each scenario we used 10,000 realizations of the m processes, as presented in Figures 3.1 to 3.5, to obtain 5% critical values. We estimated the power of the test statistics (3.9) by 1,000 simulation runs under alternative Models A and B below. For Model A we used the model ($i = 1, \ldots, m$)

$$\text{Model A:} \quad \lambda_i(t|\mathcal{H}_i(t)) = \alpha \exp\{\beta I(N_i(t^-) > 0))I(B_i(t) \leq \Delta_0)\}. \tag{3.27}$$

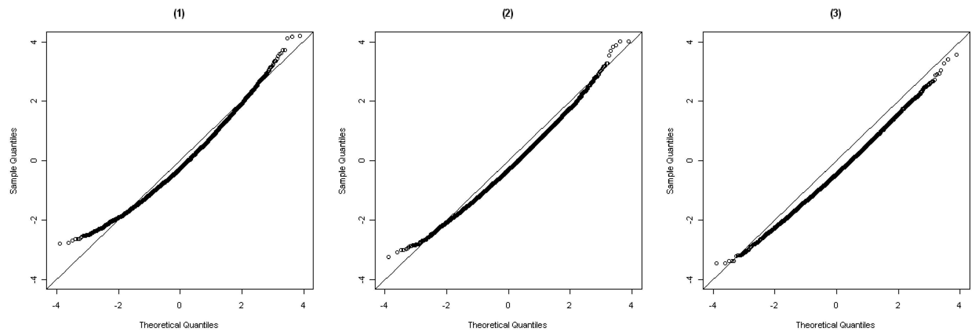

Figure 3.3: Normal Q-Q plot of S_1 (3.9) from 10,000 samples with $\tau = 10$, $\phi = 0.3$, $\Delta = 0.0513$, and (1) $m = 10$, (2) $m = 20$, (3) $m = 50$.

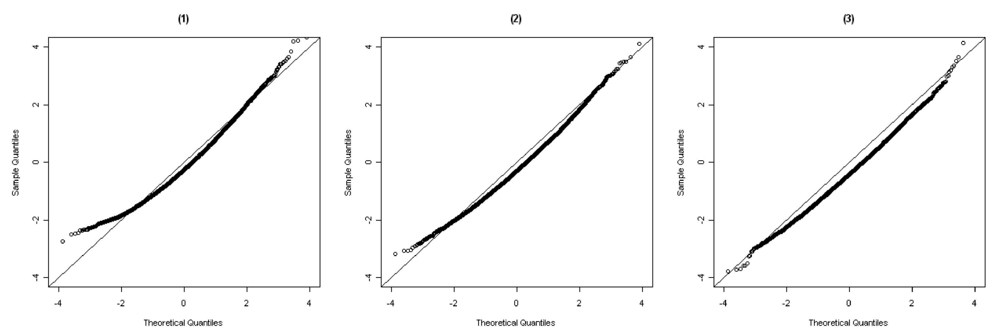

Figure 3.4: Normal Q-Q plot of S_1 in (3.9) from 10,000 samples with $\tau = 10$, $\phi = 0.6$, $\Delta = 0.0513$, and (1) $m = 10$, (2) $m = 20$, (3)$m =$ 50.

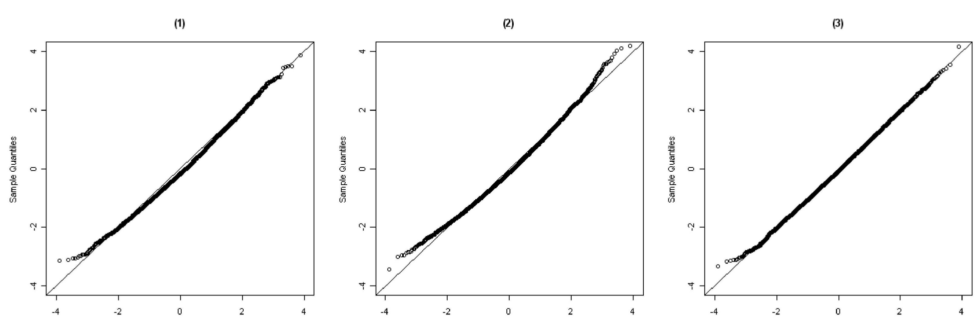

Figure 3.5: Normal Q-Q plot of S_1 in (3.9) from 10,000 samples with $m = 10$, $\phi = 0.6$, $\Delta = 0.0513$, and (1) τ=20, (2) $\tau = 50$, (3) $\tau = 100$.

Δ	m	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\hat{P}(S > 1.645)$	$\hat{P}(S > 1.960)$	$\hat{P}(S > 2.326)$
0.0202	10	1.658	2.090	2.632	0.0515	0.0301	0.0174
	20	1.569	1.950	2.426	0.0433	0.0248	0.0115
	50	1.362	1.720	2.095	0.0292	0.0148	0.0067
	100	1.243	1.591	1.990	0.0226	0.0107	0.0049
0.0513	10	1.469	1.873	2.289	0.0367	0.0206	0.0090
	20	1.418	1.781	2.166	0.0319	0.0168	0.0072
	50	1.234	1.511	1.932	0.0192	0.0096	0.0024
	100	0.988	1.265	1.622	0.0094	0.0045	0.0017
0.1054	10	1.361	1.685	2.139	0.0276	0.0142	0.0074
	20	1.242	1.599	1.981	0.0220	0.0104	0.0045
	50	1.013	1.365	1.703	0.0117	0.0059	0.0026
	100	0.751	1.047	1.417	0.0062	0.0027	0.0008

Table 3.1: $\hat{Q}_p$ is the empirical pth quantile of S_1 in (3.9) computed from 10,000 samples when $m > 1$ and $\tau = 10$. $\hat{P}(S > Q_p)$ is the proportion of the values of S_1 in 10,000 samples which are larger than the pth quantile of a $N(0, 1)$. The α_i are generated once from $Gamma(1, 0.3)$.

(m, τ)	Δ_0	$e^\beta = 1$	$e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$
	$\frac{2}{3}\Delta$	0.055	0.243	0.856	0.990
(10, 20)	Δ	0.044	0.433	0.982	0.999
	$\frac{4}{3}\Delta$	0.046	0.420	0.978	1.000
	$\frac{2}{3}\Delta$	0.049	0.219	0.830	0.986
(20, 10)	Δ	0.044	0.433	0.972	1.000
	$\frac{4}{3}\Delta$	0.048	0.421	0.980	1.000

Table 3.2: Power of S_1 in (3.9) with $\Delta = 0.0202$: Null model is Model A with $\beta = 0$; data are generated from Model A.

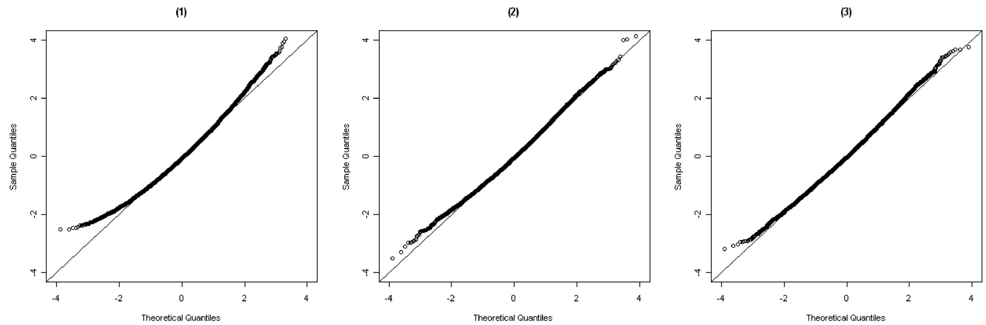

Figure 3.6: Normal Q-Q plot of S_2 in (3.23) from 10,000 samples with $\tau = 10$, $\alpha_i \sim Gamma(1, 0.3)$, $\Delta = 0.0202$, and (1) $m = 20$, (2) $m = 50$, (3) $m = 100$.

where $\alpha = 1$, that is, the m processes are actually identical. Results are given in Table 3.2 for various (m, τ, Δ_0) combinations when $\Delta = 0.0202$. In the simulation section of Chapter 2, we showed by simulation that when there is heterogeneity between the processes, the tests based on identical processes lead to an inflated Type 1 error, Table 3.2 indicates that using S_1 based on nonidentical processes give the correct Type 1 error as seen in the table under the columns with $e^{\beta} = 1$, and S_1 is still powerful for testing carryover effects. Comparing Table 3.2 to Tables 2.5 and 2.6 of Section 2.4, the powers of the corresponding scenarios are similar. In some cases, there may be a slight loss of power relative to the test S in (2.70), due to fact that m values $\alpha_1, \ldots, \alpha_m$ are estimated instead of a single common value α. However, in view of the Type 1 error seen in Table 2.9, S_1 remains preferable to the test statistic (2.70) when homogeneity in the event rates of the processes is not certain.

We next consider the model ($i = 1, \ldots, m$)

$$\text{Model B:} \quad \lambda_i(t|\mathcal{H}_i(t)) = \alpha_i \exp\{\beta I(N_i(t^-) > 0) I(B_i(t) \leq \Delta_0)\}, \tag{3.28}$$

where the α_i ($i = 1, \ldots, m$) are unknown parameters. We used the α_i values that were generated from the gamma distribution with mean 1 and variances $\phi = 0.3$ or 0.6 to obtain critical values under the null model $\lambda_i(t) = \alpha_i$ ($i = 1, \ldots, m$) as repeated in Figures 3.1 to 3.5. We then generated 1,000 realizations of m processes under Model B using the same α_i's and non-zero values for β. Power results are presented for various (m, τ, Δ_0, e^{β}) scenarios in Table 3.3 where the entries are the proportion of the 1,000 samples in which S_1 exceeded its 5% critical value. The power of the test is high when $e^{\beta} = 4$ and 6. Power increases as τ and m increase. There is a slight increase in the power when ϕ changes from 0.3 to 0.6. Once again, when Δ_0 is bigger than Δ (i.e. equivalent to choosing Δ a little too small), there is little effect on power. However, there is some loss in the power when Δ_0 is smaller than Δ.

We also investigated the random effects test statistic S_2 in (3.23) for the case where

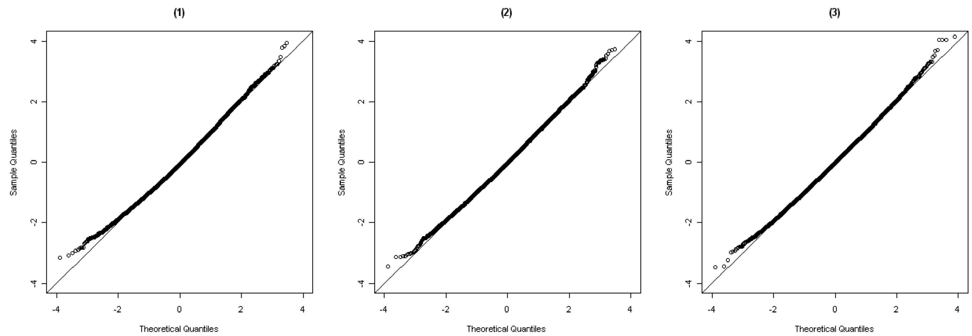

Figure 3.7: Normal Q-Q plot of S_2 in (3.23) from 10,000 samples with $\tau = 10$, $\alpha_i \sim Gamma(1,\, 0.3)$, $\Delta = 0.0513$, and (1) $m = 20$, (2) $m = 50$, (3) $m = 100$.

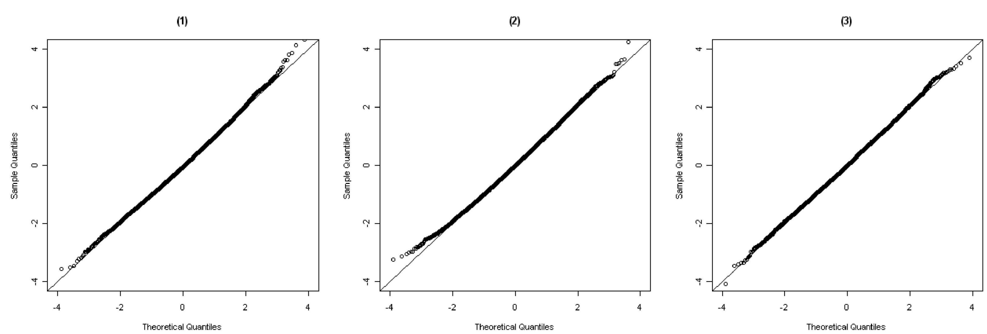

Figure 3.8: Normal Q-Q plot of S_2 in (3.23) from 10,000 samples with $\tau = 10$, $\alpha_i \sim Gamma(1,\, 0.3)$, $\Delta = 0.1054$, and (1) $m = 20$, (2) $m = 50$, (3) $m = 100$.

(m, τ)	Δ_0	$\phi = 0.3$ $e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$	$\phi = 0.6$ $e^\beta = 2$	$e^\beta = 4$	$e^\beta = 6$
	$\frac{2}{3}\Delta$	0.188	0.686	0.910	0.202	0.713	0.916
(10, 10)	Δ	0.294	0.885	0.987	0.354	0.888	0.978
	$\frac{4}{3}\Delta$	0.287	0.850	0.977	0.349	0.892	0.980
	$\frac{2}{3}\Delta$	0.174	0.675	0.938	0.213	0.745	0.943
(20, 5)	Δ	0.294	0.874	0.990	0.360	0.916	0.995
	$\frac{4}{3}\Delta$	0.298	0.889	0.989	0.352	0.919	0.993
	$\frac{2}{3}\Delta$	0.303	0.889	0.988	0.297	0.895	0.983
(10, 20)	Δ	0.504	0.976	1.000	0.515	0.982	0.998
	$\frac{4}{3}\Delta$	0.516	0.980	1.000	0.507	0.969	0.999
	$\frac{2}{3}\Delta$	0.290	0.908	0.996	0.320	0.925	0.991
(20, 10)	Δ	0.481	0.983	1.000	0.517	0.988	0.998
	$\frac{4}{3}\Delta$	0.473	0.988	1.000	0.504	0.991	0.999

Table 3.3: Power of S_1 in (3.9) with $\Delta = 0.0202$: Null model is Model B with $\beta = 0$; data were generated from Model B. The α_i are generated once from $Gamma(1, \phi)$.

$\rho_0(t; \gamma) = \gamma$. The α_i were assumed to be independent gamma random variables with mean 1 and variance $\phi = 0.3$ or 0.6. We generated 10,000 replicates of m Poisson processes for different combinations of (Δ, m, τ, ϕ), to evaluate the distribution and critical values of S_2. We generated a new set of α_i ($i = 1, \ldots, m$) in each simulation run. Figures 3.6, 3.7, 3.8 and Table 3.4 indicate that the standard normal distribution is accurate for large m and reasonably satisfactory (absolute errors about 1% for right tail probabilities of 0.05 or less) even for scenarios with $m = 10$. We then generated 1,000 samples from versions of Model B in (3.28) to calculate the power of the test. In each simulation run, we generated a new set of α_i from the gamma distribution with mean 1 and variance ϕ. Tables 3.5 and 3.6 shows the results for different (Δ_0, e^β, m, τ) combinations when $\phi = 0.3$ and 0.6, respectively. In both tables, the power is generally high when $e^\beta = 3$ or 4, with a little decrease when Δ is chosen too large. Also, the power is a little higher when $\phi = 0.6$.

A final simulation study was conducted to examine the performance of S_2 in (3.23) when the assumption that the α_i have a gamma distribution is not true. To do that, we generated the α_i from a lognormal distribution with mean 1 and variance ϕ. We then generated 1,000 realizations of m processes when $\tau = 10$, $\Delta = 0.0202$, and $e^\beta = 1$, 2, 3, 4 and calculated proportion of the time that S_2 exceeded the 0.05 critical value. The results are given in Table 3.7. The column under $e^\beta = 1$ shows the empirical Type 1 errors based on the 1,000 samples. They are close to the nominal significance level 0.05. In addition, S_2 maintains high power in this case, and we conclude that mild misspecification of the distribution of random effects is not a problem; this agrees with similar results for estimation of rate functions in mixed Poisson processes without carryover effects (Lawless, 1987).

Δ	m	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\hat{P}(S > 1.645)$	$\hat{P}(S > 1.960)$	$\hat{P}(S > 2.326)$
0.0202	10	1.835	2.263	2.735	0.0479	0.0303	0.0171
	20	1.785	2.177	2.707	0.0625	0.0370	0.0196
	50	1.725	2.099	2.589	0.0573	0.0326	0.0159
	100	1.703	2.020	2.434	0.0561	0.0284	0.0124
0.0513	10	1.779	2.179	2.656	0.0627	0.0357	0.0192
	20	1.694	2.080	2.458	0.0562	0.0312	0.0146
	50	1.691	2.027	2.404	0.0554	0.0289	0.0120
	100	1.665	1.997	2.361	0.0515	0.0268	0.0111
0.1054	10	1.682	2.049	2.456	0.0534	0.0291	0.0126
	20	1.669	2.016	2.366	0.0523	0.0285	0.0110
	50	1.642	2.008	2.345	0.0497	0.0280	0.0105
	100	1.631	1.942	2.359	0.0479	0.0238	0.0107

Table 3.4: $\hat{Q}_p$ is the empirical pth quantile of S_2 in (3.23) computed from 10,000 samples when $m > 1$ and $\tau = 10$. $\hat{P}(S > Q_p)$ is the proportion of the values of S_2 in 10,000 samples which are larger than the pth quantile of a $N(0,1)$. The α_i are generated from $Gamma(1, 0.3)$ in each simulation run.

		$m = 20$, $\tau = 10$			$m = 40$, $\tau = 5$			$m = 40$, $\tau = 10$		
Δ	Δ_0	$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$	$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$	$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$
	$\frac{2}{3}\Delta$	0.282	0.693	0.888	0.316	0.692	0.912	0.493	0.936	0.995
0.0202	Δ	0.437	0.912	0.991	0.496	0.924	0.995	0.781	0.994	1.000
	$\frac{4}{3}\Delta$	0.460	0.886	0.987	0.498	0.914	0.984	0.776	0.994	1.000
	$\frac{2}{3}\Delta$	0.565	0.959	0.996	0.527	0.949	1.000	0.805	0.999	1.000
0.0513	Δ	0.828	0.997	1.000	0.809	0.998	1.000	0.979	1.000	1.000
	$\frac{4}{3}\Delta$	0.776	0.997	1.000	0.806	0.996	1.000	0.972	1.000	1.000
	$\frac{2}{3}\Delta$	0.785	0.999	1.000	0.808	0.996	1.000	0.959	1.000	1.000
0.1054	Δ	0.968	1.000	1.000	0.968	1.000	1.000	1.000	1.000	1.000
	$\frac{4}{3}\Delta$	0.961	1.000	1.000	0.942	1.000	1.000	0.997	1.000	1.000

Table 3.5: Power of S_2 in (3.23): Model B, $\phi = 0.3$.

Δ	Δ_0	$m = 20,\ \tau = 10$			$m = 40,\ \tau = 5$			$m = 40,\ \tau = 10$		
		$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$	$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$	$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$
	$\frac{2}{3}\Delta$	0.322	0.766	0.924	0.327	0.752	0.944	0.557	0.940	0.997
0.0202	Δ	0.566	0.923	0.991	0.537	0.937	0.992	0.846	0.995	1.000
	$\frac{4}{3}\Delta$	0.551	0.938	0.989	0.553	0.918	0.996	0.813	0.999	1.000
	$\frac{2}{3}\Delta$	0.633	0.964	0.996	0.623	0.976	1.000	0.857	1.000	1.000
0.0513	Δ	0.871	0.996	1.000	0.856	0.999	1.000	0.981	1.000	1.000
	$\frac{4}{3}\Delta$	0.844	0.998	0.999	0.837	0.998	1.000	0.981	1.000	1.000
	$\frac{2}{3}\Delta$	0.815	0.998	1.000	0.854	0.998	1.000	0.977	1.000	1.000
0.1054	Δ	0.966	1.000	1.000	0.976	1.000	1.000	1.000	1.000	1.000
	$\frac{4}{3}\Delta$	0.950	1.000	1.000	0.957	1.000	1.000	0.998	1.000	1.000

Table 3.6: Power of S_2 in (3.23): Model B, $\phi = 0.6$.

(m, τ)	$\phi = 0.3$				$\phi = 0.6$			
	$e^\beta = 1$	$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$	$e^\beta = 1$	$e^\beta = 2$	$e^\beta = 3$	$e^\beta = 4$
(20, 10)	0.044	0.607	0.965	0.999	0.055	0.652	0.953	0.996
(40, 5)	0.052	0.630	0.964	0.997	0.045	0.618	0.966	0.999
(40, 10)	0.057	0.868	1.000	1.000	0.058	0.674	0.999	1.000

Table 3.7: Empirical Type 1 error and power of S_2 in (3.23) under misspecification of the distribution of α_i: $\Delta = 0.0202$. The α_i are generated from the log normal distribution with mean 1 and variance ϕ, but tests assume the α_i have a gamma distribution.

3.4 Example: Asthma Prevention Trial

Duchateau et al. (2003) discussed data from a prevention trial in infants with a high risk of asthma, but without a prior attack. The subjects were 6 months of age on entry to the study. The followup period for each subject was approximately 18 months, and started after random allocation to a placebo control group or an active drug treatment group. The main aim of the study was to assess the effect of the drug on the occurrence of asthma attacks. Here, we consider the interesting secondary question as to whether the occurrence of an event (asthma attack) influences the future event rate.

The Nelson-Aalen estimates of the mean function for treatment group and control group are given in Figure 3.9 and Figure 3.10, respectively. Both plots are close to linear and suggest roughly constant rates of event. In addition, we fitted the model $\alpha_i\gamma_1\gamma_2 t^{\gamma_2-1}e^{\beta z_i(t)}$, where the α_i are i.i.d. gamma random variables with mean 1 and variance ϕ and $z_i(t)$ is given in (3.2), and tested $H_0 : \gamma_2 = 1$ against $H_1 : \gamma_2 \neq 1$. We did not reject the null hypothesis by a likelihood ratio test for each group at 0.05 level of significance when $\Delta = 5$, 7, 10 and 14 days; p-values based on $\chi^2_{(1)}$ are 0.366, 0.345, 0.321 and 0.281 for control group and 0.081, 0.103, 0.135 and 0.152 for treatment group, respectively. Therefore, we consider here the tests for carryover effects based on homogeneous processes. There were 483 asthma attacks among 119 children in the control group and 336 asthma attacks among 113 children in the treatment group, during the 18 month followup. Distributions of the numbers of attacks are given in Table 3.8 for both groups.

A point concerning the event rate, which we return to later, is that Duchateau et al. (2003) do not provide the trial entry dates for each subject, so it is not possible to assess whether there might be a seasonal effect in the rate. Also, an asthma attack lasts an average of 6–7 days, and a patient is not considered at-risk for a new attack over that time; the at-risk indicator $Y_i(t)$ takes value 1 if subject i at risk of an asthma attack at time t. The intensity model for subject i that we consider is

$$\lambda_i\left(t|\mathcal{H}_i\left(t\right)\right) = Y_i(t)\alpha_i\gamma\exp\{\beta z_i(t)\}, \qquad t \geq 0, \tag{3.29}$$

where $z_i(t) = I\{N_i(t^-) > 0\}I\{B_i(t) \leq \Delta\}$ and $B_i(t) = t - \max(s : s \leq t, Y_i(s) = 0)$. That is, $B_i(t)$ is the time since subject i started their current at-risk period.

We continue our analysis by testing for extra-Poisson variation in the numbers of events in treatment and control groups separately. We use the random effects model (3.29), where $\alpha_i \sim Gamma(1, \phi)$. The model under the null hypothesis ($\phi = 0$ or $\alpha_i = 1$) is $Y_i(t)\gamma\exp\{\beta z_i(t)\}$. A likelihood ratio statistic $\Lambda = 2\ell(\hat{\gamma}, \hat{\beta}, \hat{\phi}) - 2\ell(\tilde{\gamma}, \tilde{\beta}, 0)$ for testing $H_0 : \phi = 0$ is computed. A choice of Δ of interest here could be between 5–14 days. Results from fitting Model (3.29) are given in Tables 3.9 and 3.10 with the estimates of parameters and their standard errors in parentheses for treatment and control groups,

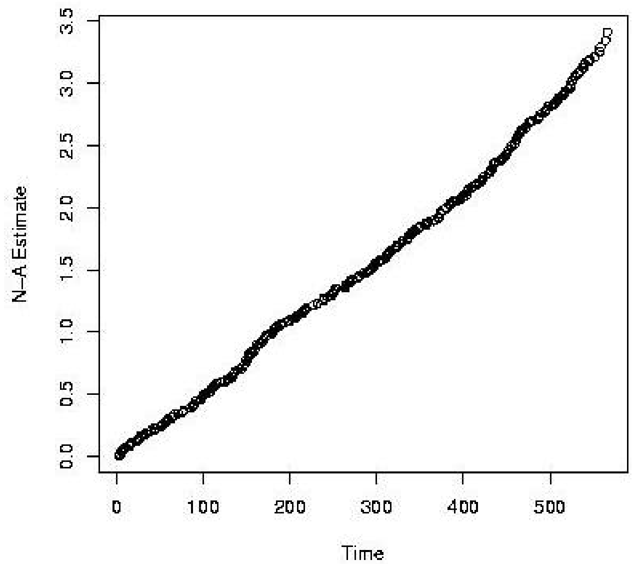

Figure 3.9: Nelson-Aalen (N-A) estimate of the mean function of asthma attacks of subjects in the treatment group versus time on study (in days).

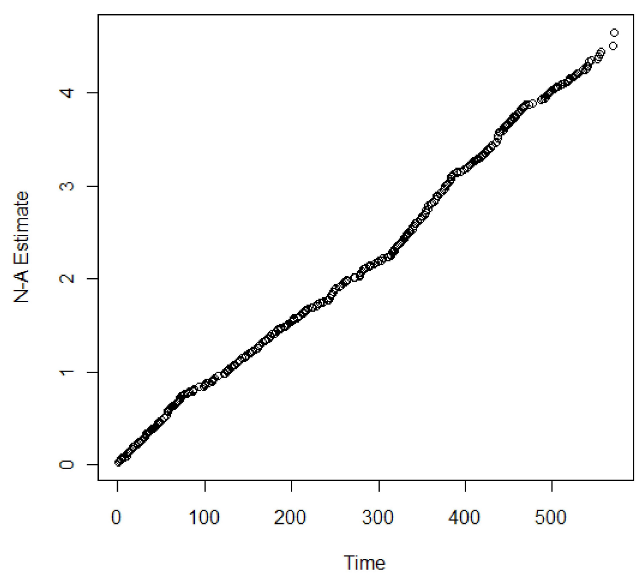

Figure 3.10: Nelson-Aalen (N-A) estimate of the mean function of asthma attacks of subjects in the control group versus time on study (in days).

Number of	*Number of Children*	
Asthma Attacks	*Control Group*	*Treatment Group*
1	37	50
2	20	25
3	17	11
4	8	7
5	9	3
6	6	2
7	4	3
8	7	3
9	0	1
10	3	5
11+	8	3
Total	119	113

Table 3.8: Distribution of the numbers of asthma attacks for children in the control group and treatment group.

respectively. Note that since ϕ is on the boundary under the null hypothesis ($\phi = 0$), and the true values of γ and β are not on the boundary, the correct limiting distribution of Λ is $\Pr\{\Lambda \leq q\} = 0.5 + 0.5\Pr\{\chi_1^2 \leq q\}$ (Self and Liang, 1987). Therefore, we obtain the p-values as $0.5\Pr\{\chi_1^2 \geq \Lambda\} \approx 0$ for both groups and each Δ. In other words, there is highly significant extra-Poisson variation within the treatment and control groups.

We, therefore, consider the random effects model (3.29), where the $\alpha_i \sim Gamma(1, \phi)$ independently, for testing $H_0 : \beta = 0$. When $\beta = 0$, the maximum likelihood estimation gives for the treatment group that $\tilde{\phi} = 0.5517$ with standard error (s.e.) 0.10799 and $\tilde{\gamma} = 0.00608$ with s.e. 0.000543, and for the control group that $\tilde{\phi} = 0.5898$ with s.e. 0.10167

Δ	$\hat{\gamma}$	$\hat{\beta}$	$\hat{\phi}$	$\ell(\hat{\gamma}, \hat{\beta}, \hat{\phi})$	$\ell(\tilde{\gamma}, \tilde{\beta}, 0)$	Λ
5	0.006	0.359	0.525	-2014.511	-2054.239	79.456
	(0.001)	(0.224)	(0.107)			
7	0.006	0.681	0.476	-2009.406	-2039.622	60.433
	(0.001)	(0.180)	(0.102)			
10	0.005	0.903	0.416	-2000.992	-2018.167	34.349
	(0.001)	(0.155)	(0.096)			
14	0.005	0.904	0.388	-1998.522	-2012.535	28.026
	(0.0004)	(0.146)	(0.094)			

Table 3.9: Estimation results for Model (3.29) for the treatment group.

Δ	$\hat{\gamma}$	$\hat{\beta}$	$\hat{\phi}$	$\ell(\hat{\gamma},\hat{\beta},\hat{\phi})$	$\ell(\tilde{\gamma},\tilde{\beta},0)$	Λ
5	0.008	0.354	0.552	-2729.326	-2794.637	130.622
	(0.001)	(0.164)	(0.099)			
7	0.008	0.486	0.521	-2726.178	-2783.308	114.259
	(0.001)	(0.143)	(0.097)			
10	0.007	0.569	0.489	-2722.382	-2769.688	94.611
	(0.001)	(0.128)	(0.094)			
14	0.007	0.637	0.455	-2717.954	-2751.922	67.936
	(0.001)	(0.118)	(0.091)			

Table 3.10: Estimation results for Model (3.29) for the control group.

Group	Δ	$O(\Delta)$	$E(\Delta)$	$U_\beta(\tilde{\gamma},0,\tilde{\phi})$	$\widehat{Var}[U_\beta(\tilde{\gamma},0,\tilde{\phi})]$	S	p–value
Treatment	5	23	16.763	6.237	12.878	1.738	0.085
	7	40	22.858	17.142	16.954	4.163	0
	10	61	30.908	30.092	21.941	6.424	0
	14	76	40.464	35.536	27.244	6.808	0
Control	5	47	35.298	11.702	25.187	2.332	0.023
	7	68	47.173	20.827	32.160	3.673	0
	10	93	62.495	30.505	40.688	4.782	0
	14	121	80.302	40.698	49.644	5.776	0

Table 3.11: The results of the no carryover test based on S_2 in (3.23) for various Δ values; p-values were obtained from 1,000 simulated samples in each case.

and $\tilde{\gamma} = 0.00822$ with s.e. 0.000695. Table 3.11 shows results for the test statistic S_2 in (3.23) as well as the values of $O(\Delta)$ and $E(\Delta) = \sum_{i=1}^{m}\{[(n_i + \tilde{\phi}^{-1})\tilde{\gamma}]/(\tilde{\phi}^{-1} + \tilde{\gamma}\tau_i)\}E_i(\Delta)$ for various Δ values. We carried out a parametric bootstrap procedure to obtain the p–value for testing the null model for each Δ. To represent the data more accurately, we used 1,000 bootstrap samples with at least one event per individual, as in the original data set. The results are presented in Table 3.11, and suggest strong evidence against the null hypothesis when $\Delta = 7$, 10 and 14 days. Therefore, a carryover effect is suggested in both groups. Note that here we can also test $H_0 : \beta = 0$ using $\hat{\beta}$ and its standard error from Tables 3.9 and 3.10. This gives results very similar to those based on S_2.

Duchateau et al. (2003) consider models based on calendar and gap times for the asthma event data, and note that in their parametric gap time models the hazard function $h(w)$ is decreasing in w. However, they use a proportional hazards model for treatment, which is not checked. In their analysis, a gap time model where the first gap time W_{i1} is allowed to have a different distribution than the other gap times W_{i2}, W_{i3}, …, fit the

	Control Group	*Treatment Group*
$\hat{\gamma}$	0.002 (0.0002)	0.002 (0.0002)
$\hat{b}_1$	696.246 (68.987)	790.531 (106.312)
$\hat{b}_2$	0.876 (0.032)	0.809 (0.039)
$\hat{\phi}$	4.841 (0.469)	3.95 (0.395)
$\ell(\hat{\boldsymbol{\theta}})$	-3361.959	-2465.011

Table 3.12: Estimates for the gap time model of Duchateau et al. (2003) for asthma event data. Standard error of the estimate is given in parenthesis.

data best. In particular, they considered the W_{i1} to have an exponential distribution with the rate function $\alpha_i\gamma$, where the α_i are i.i.d. gamma random variables with mean 1 and variance ϕ, and the other gap times to have a Weibull distribution with the hazard function $h(w) = \alpha_i w^{b_2-1}/b_1^{b_2}$, where the α_i are i.i.d. gamma random variables with mean 1 and variance ϕ. We now consider their model for treatment and control groups separately, and compare it to the carryover model (3.29) with random effects. In this case, the likelihood function is given by (cf. Section 1.4.1)

$$L(\boldsymbol{\theta}) = \prod_{i=1}^{m} \int_0^\infty \alpha_i \gamma e^{-\alpha_i \gamma w_{i1}} \left[\prod_{j=2}^{n_i} \left(\frac{\alpha_i b_2 w_{ij}^{b_2-1}}{b_1^{b_2}} \right)^{\delta_{ij}} e^{-\frac{\alpha_i w_{ij}^{b_2}}{b_1^{b_2}}} \right] \frac{\alpha_i^{\frac{1}{\phi}-1} e^{-\frac{\alpha_i}{\phi}}}{\Gamma(\frac{1}{\phi})\phi^{\frac{1}{\phi}}} \, d\alpha_i, \tag{3.30}$$

where $\boldsymbol{\theta} = (\gamma, b_1, b_2, \phi)'$, n_i is the number of at-risk intervals for subject i, and $\delta_{i1} = \ldots = \delta_{i,n_{i-1}} = 1$; $\delta_{in_i} = 0$ or 1 ($i = 1, \ldots, m$). Table 3.12 shows the m.l.e. of γ, b_1, b_2, ϕ, and their standard errors, and values of the log likelihood function $\ell(\boldsymbol{\theta}) = \log L(\boldsymbol{\theta})$ at $\hat{\boldsymbol{\theta}} = (\hat{\gamma}, \hat{b}_1, \hat{b}_2, \hat{\phi})'$ for treatment and control groups. The estimates $\hat{b}_2$ are less than one, indicating that the probability of a new attack decreases as the time since the last attack increases. Comparing the corresponding log likelihood values in Table 3.12 to those of Tables 3.9 and 3.10, the log likelihood values are higher in the carryover effect model (random effects model (3.29)) even though the number of parameters is less than the gap time random effects model. Thus, the carryover effect model that we considered here is a better fit for the recurrent asthma event data.

A final note about the asthma data set should be given, about the lack of the trial entry dates for each subject. In a study related to asthma events, the patients may be subject to seasonal effects such as air pollution and weather conditions, although this may perhaps be less of a factor for infants. An approach in this case is to include a trend term for seasonality, and consider a modulated nonhomogeneous Poisson process model which includes trend and carryover effetcs at the same time. Since the data here were not given with the entry dates for each subject, neither we nor Ducheatau et al. (2003) could consider seasonality. However, it should be noted that the conclusion of an analysis considering seasonality might be different than the conclusion of this section.

Chapter 4

Testing for Trend in Identical Recurrent Event Processes

In the previous two chapters, we discussed a feature of recurrent event processes called carryover effects. In the current and following chapter we discuss testing for trends in recurrent event data. We investigate settings where the processes are identical in this chapter, and the case where the processes are nonidentical in the next chapter.

The remainder of this chapter is organized as follows. We introduce the problems and the definition of trend in Section 4.1. We review some models and tests for trend in Section 4.2. Section 4.3 introduces robust tests for trend. We also consider settings with covariates. We present results of simulation studies in Section 4.4. For convenience, an example is deferred to Chapter 5.

4.1 Introduction

A much-studied aspect of processes where individuals or systems experience recurrent events is the existence or non-existence of time trends (Cox and Lewis, 1966, Chapter 3; Ascher and Feingold, 1984, Chapter 5). We discuss definitions of trend below but, broadly speaking, the term refers to systematic variation in either event occurrence rates or times between events. Trends can be related either to the ages of individual processes or to external factors operating on a calendar time scale, and can be monotonic (increasing or decreasing) or non-monotonic. Examples of monotonic trends are the increasing rate of failures seen as repairable systems age (Ascher and Feingold, 1984, Chapter 2) and the tendency for times between repeated hospitalizations for psychiatric patients to decrease (Kvist et al., 2008); examples of non-monotonic trends are the U-shaped rate functions seen in systems observed from new to old (Kvaloy and Lindqvist, 1998) and the seasonal fluctuations in pulmonary infections for persons with chronic bronchitis (Cook and

Lawless, 2007, Section 6.7.2).

According to Cox and Lewis (1966, p. 37), there are two general reasons why there is interest in the analysis of trends in a recurrent event setting. Firstly, the main aim of a study may be to reveal any kind of trends in the failures that occur in time. For example, in some reliability settings, the rate of failure in a process is monitored in order to reveal problems or plan maintenance if there is an increase in the rate of failure (Cook and Lawless, 2007, p. 88). Secondly, the use of statistical methods may depend on the absence or presence of trends. In the first type of a problem, as it is discussed by Cox and Lewis (1966, Chapter 3), the interest is usually not only of testing the null hypothesis of no trend but also of revealing the shape of the trend.

Models that incorporate time trends include nonhomogeneous Poisson processes, renewal processes in which the distributions of successive gap times stochastically increase, decrease or otherwise fluctuate systematically, and generally, models in which the intensity function depends on time in some systematic way. Tests for absence of trend can be carried out within such models, but it is useful to have simple and robust tests which can be employed as a prelude to more detailed modeling. This was first considered by Cox and Lewis (1996, Chapter 3), which remains an excellent discussion of trend testing. They considered tests based on both nonhomogeneous Poisson process and more general renewal process models. Other tests for departures from a renewal process have subsequently been proposed (e.g. Lewis and Robinson, 1974; Kvaloy and Lindqvist, 2003), and many authors have considered tests based on nonhomogeneous Poisson processes (e.g. Bain et al., 1985; Cohen and Sackrowitz, 1993). Many of these tests are based on conditioning on the number of failures observed over a fixed period or observing a fixed number of events, and mostly consider the case when $m = 1$. Bhattacharjee et al. (2004) develop an unconditional test for monotonic trend in a nonhomogenous Poisson process observed over a fixed period when $m = 1$. Since the literature on tests of trend in Poisson processes is vast when $m = 1$, we will focus on cases in which $m > 1$.

In spite of previous work, there remain limitations on current trend tests. In particular, most tests rely on the assumption that the null (no trend) model is a renewal process and in some cases, that it is a homogenous Poisson process. In addition, the computation of p-values for many tests is based on an assumption that observation of a process ceases after some specified number of event occurrences, which is rarely the case in practice. Our purpose is to study tests based on robust inference methods for rate and mean functions (Pepe and Cai, 1993; Lawless and Nadeau, 1995), and compare them to other tests. Cook and Lawless (2007, Problems 3.13 and 3.15) outlined such an approach but to our knowledge this has not been followed up or studied. We show here that such tests are flexible, easily implemented and powerful in a range of settings. Our focus is on situations where recurrent event processes for multiple individuals or systems are observed, though we comment on the case of long single processes in the final section.

Definition of Trend

Consider an individual process which starts at time $t = 0$, and let $N(t)$ denote the number of events in $(0, t]$. The times of events are denoted $T_1 < T_2 < \ldots$, and the gap times between successive events are denoted by $W_j = T_j - T_{j-1}$, $(j = 1, \ldots, n)$, where $T_0 = 0$. In some clearly identified cases discussed later, we will assume a process is observed over a time period $[\tau_0, \tau]$ and in that case, we define $T_0 = \tau_0$ and let $N(\tau_0, t)$ represent the number of events in $(\tau_0, t]$, for $\tau_0 \leq t \leq \tau$. As previously, we define the mean and rate functions as $\mu(t) = E\{N(t)\}$ and $\rho(t) = d\mu(t)/dt$, respectively.

There is no single definition of time trend or the absence of trend. Cook and Lawless (2007, p. 10) define a *time trend* in a process as a tendency for the rate of event occurrence to change over time in some systematic way. Although this definition is comprehensive enough to include various cases, it is not that easy to give a mathematically comprehensive definition of a time trend. A discussion of this issue is given by Ascher and Feingold (1984, p. 169); also, see Lawless and Thiagarajah (1996). The most frequent definition for absence of trend is that the process is a renewal process. In this case the W_j $(j = 1, 2, \ldots)$ are independent and identically distributed random variables; equivalently, $\lambda(t|\mathcal{H}(t)) = h(B(t))$ for some positive-valued function $h(w)$, where $B(t) = t - T_{N(t-)}$ is the time since the most recent event. A second definition of absence of trend is that $\rho(t) = \alpha$ (or $\mu(t) = \alpha t$) for some constant $\alpha > 0$; that is, the rate of event occurrence is constant over time. Other definitions could, however, be given; for example, any process that is stationary in certain respects (e.g. Cox and Lewis, 1966, Chapter 4; Cox and Isham, 1980, Section 2.2) could be said to have no trend. If a monotonic trend is present, the shape of the mean function should be either convex when the events tend to occur more frequently in time or concave when the events tend to occur less frequently in time. A statistical trend test is then a test of the null hypothesis that events occur according to a stationary process against the alternative hypothesis that events occur according to another process specified by the type of trend.

4.2 Models and Tests for Trend

We suppose that $m > 1$ independent and identical processes are under study. We provide here a brief review of important trend tests, dividing them into (i) tests of a homogeneous Poisson process, and (ii) tests of a general renewal process. We focus on tests which can be carried out without elaborate model fitting, as indicated in the previous section, and for now, do not consider covariates.

4.2.1 Tests Based on Identical Poisson Processes

Likelihood methods can be applied for analysis of trends in specified models such as models based on Poisson processes. In this case, a very useful family of models for testing the absence trend in the rate function is given by

$$\rho(t;\alpha,\beta) = \alpha e^{\beta g(t)}, \qquad t \geq 0, \tag{4.1}$$

where the function $g(t)$ specifies the shape of the trend, α is a positive-valued parameter, and β is a real-valued parameter. Then, a test of no trend in the rate function of the Poisson processes can be obtained by testing the null hypothesis $H_0 : \beta = 0$ against the alternative hypothesis $H_1 : \beta \neq 0$.

Suppose that the process i ($i = 1, \ldots, m$) with rate function (4.1) is observed over the time interval $[\tau_{0i}, \tau_i]$. As outlined by Cook and Lawless (2007, Problem 3.13), a score test can be developed by considering the likelihood function $L(\alpha, \beta)$ for data set $\{(N_i(\tau_{0i}, \tau_i) = n_i; t_{i1}, \ldots, t_{in_i}); i = 1, \ldots, m\}$. In this case, the log likelihood function is given by

$$\ell(\alpha,\beta) = n.\log\alpha + \beta\sum_{i=1}^{m}\sum_{j=1}^{n_i} g(t_{ij}) - \sum_{i=1}^{m}\int_{\tau_{0i}}^{\tau_i}\alpha e^{\beta g(s)}\,ds, \tag{4.2}$$

where $n. = \sum_{i=1}^{m} n_i$. Then, the score functions are

$$U_\alpha(\alpha,\beta) = \frac{\partial\ell(\alpha,\beta)}{\partial\alpha} = \frac{n.}{\alpha} - \sum_{i=1}^{m}\int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\,ds \tag{4.3}$$

and

$$U_\beta(\alpha,\beta) = \frac{\partial\ell(\alpha,\beta)}{\partial\beta} = \sum_{i=1}^{m}\sum_{j=1}^{n_i} g(t_{ij}) - \alpha\sum_{i=1}^{m}\int_{\tau_{0i}}^{\tau_i} g(s)e^{\beta g(s)}\,ds. \tag{4.4}$$

Solving $U_\alpha(\alpha, 0) = 0$ gives $\tilde{\alpha} = n./\tau.$, where $\tau. = \sum_{i=1}^{m}(\tau_i - \tau_{0i})$. Plugging $(\tilde{\alpha}, 0)$ in (4.4), we obtain

$$U_\beta(\tilde{\alpha},0) = \sum_{i=1}^{m}\sum_{j=1}^{n_i} g(t_{ij}) - \frac{n.}{\tau.}\sum_{i=1}^{m}\int_{\tau_{0i}}^{\tau_i} g(s)\,ds. \tag{4.5}$$

A variance estimate for $U_\beta(\tilde{\alpha}, 0)$ is given by (cf. Section 1.4.3)

$$\widehat{Var}[U_\beta(\tilde{\alpha},0)] = I_{\beta\beta}(\tilde{\alpha},0) - I_{\beta\alpha}(\tilde{\alpha},0)I_{\alpha\alpha}^{-1}(\tilde{\alpha},0)I_{\alpha\beta}(\tilde{\alpha},0). \tag{4.6}$$

A test statistic for testing the absence of trend is then

$$S_1 = \frac{U_\beta(\tilde{\alpha},0)}{\widehat{Var}[U_\beta(\tilde{\alpha},0)]^{1/2}}. \tag{4.7}$$

The standardized score statistic (4.7) can be used for testing H_0. However, a simple but efficient procedure is to use a score test based on a conditional likelihood function for

β (Cox and Lewis, 1966, Section 3.3). Since processes are assumed to be independently distributed, $\sum_{i=1}^{m} N_i(\tau_{0i}, \tau_i)$ has a Poisson distribution with mean $\sum_{i=1}^{m} \mu_i(\tau_{0i}, \tau_i)$, where $\mu_i(\tau_{0i}, \tau_i) = \int_{\tau_{0i}}^{\tau_i} \alpha e^{g(s)}\, ds$. From this result and (4.2), the log likelihood function based on the conditional distribution of the event times T_{ij} ($i = 1, \ldots, m$; $j = 1, \ldots, n_i$) given $n.$, where $\sum_{i=1}^{m} N_i(\tau_{0i}, \tau_i) = n. > 0$, is then proportional to

$$\ell_c(\beta) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} \beta g(t_{ij}) - n. \log \left(\sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\, ds \right). \tag{4.8}$$

Therefore, the conditional score function is

$$U_c(\beta) = \frac{\partial \ell_c(\beta)}{\partial \beta} = \sum_{i=1}^{m} \sum_{j=1}^{n_i} g(t_{ij}) - n. \frac{\sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} g(s) e^{\beta g(s)}\, ds}{\sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\, ds}, \tag{4.9}$$

and the variance of $U_c(\beta)$ conditional on $n.$ is

$$Var[U_c(\beta)] = -\frac{\partial^2 \ell_c(\beta)}{\partial \beta^2} = n. \left\{ \frac{\sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} g^2(s)\, e^{\beta g(s)}\, ds}{\sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\, ds} - \left(\frac{\sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} g(s)\, e^{\beta g(s)}\, ds}{\sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\, ds} \right)^2 \right\}. \tag{4.10}$$

A test of $H_0 : \beta = 0$ is given by

$$S_2 = \frac{U_c(0)}{Var[U_c(0)]^{1/2}}. \tag{4.11}$$

Cook and Lawless (2007, p. 89) considered the test statistic (4.11) when $g(t) = t$. In this case, $U_\beta(\tilde{\alpha}, 0)$ and $U_c(0)$ are the same. The distribution of (4.11) is asymptoticaly normal as $m \to \infty$ and p-values for H_0 can be computed using this approximation. In cases where m and $n.$ are small, we can alternatively obtain the p-value based on (4.11) by simulation.

A major limitation of these tests is the assumption the processes are homogeneous Poisson processes in the absence of trend. The tests are sensitive to departures from this assumption and one can, for example, falsely conclude there is a trend when the processes are renewal processes but not HPPs (e.g. Lawless and Thiagarajah, 1996; Lindqvist et al., 1994). The same criticism applies to similar tests based on total time on test (TTT) statistics (e.g. Kvaloy and Lindqvist, 1998; Kvist et al., 2008). Consequently, there has been considerable recent emphasis on tests for which the null hypothesis is that each individual process is an arbitrary renewal process. We review such tests next.

4.2.2 Tests Based on Identical Renewal Processes

In the previous section, we considered tests for absence of trend in identical Poisson processes. When processes are trend-free, the intervals between events are i.i.d. exponential random variables. It is, however, possible to give tests for the null hypothesis that the intervals between events are i.i.d. with an arbitrary distribution.

Tests of the renewal process hypothesis H_0 : The W_{ij} $(i = 1, \ldots, m;\ j = 1, 2, \ldots)$ are i.i.d. can be formed in various ways. It is desirable to avoid making parametric assumptions about the gap time distribution for each process, and we focus on tests that do this. We consider the case where $\tau_{0i} = 0$ for the observation period for process i, and the values n_i are prespecified, rather than the lengths τ_i of the observation periods. This is standard in the literature on these tests; we discuss the limitations of this below.

The simplest procedure is, for the ith process, to use a linear rank test of no association between the gap time W_{ij} and a specified covariate x_{ij} that is designed to reflect the type of trend to be considered. In using a rank test we replace the W_{ij} with scores and use the fact that all $n_i!$ permutations of the ranks of $W_{i1}, \ldots, W_{in_i}$ are equally probable under H_0. This approach was introduced by Cox and Lewis (1966, Section 3.4), who used exponential ordered scores α_{ij} and $x_{ij} = j$ to illustrate the method. They indicated that a test which is not efficient when the true distribution of the W_{ij} is exponential is of a little interest. The exponential ordered scores give high efficiency for the test of the null hypothesis of no trend in exponentially distributed observations (Cox and Lewis, 1966, p. 55) as well as good power in other cases. This test uses statistics

$$U_i = \sum_{j=1}^{n_i} \alpha_{ij} \left(x_{ij} - \bar{x}_i \right), \qquad i = 1, \ldots, m, \tag{4.12}$$

where α_{ij} is a function of the rank r_{ij} of W_{ij} among $W_{i1}, \ldots, W_{in_i}$. The exponential ordered score is

$$\alpha_{ij} = \frac{1}{n_i} + \ldots + \frac{1}{n_i - r_{ij} + 1}, \qquad j = 1, \ldots, n_i. \tag{4.13}$$

The mean and variance of U_i under H_0 are zero and

$$Var(U_i) = \left\{ \sum_{j=1}^{n_i} (x_{ij} - \bar{x})^2 \right\} \left\{ \sum_{j=1}^{n_i} \frac{(\alpha_{ij} - \bar{\alpha}_i)^2}{n_i - 1} \right\}, \tag{4.14}$$

and a combined test of H_0 can be based on the statistic

$$R = \sum_{i=1}^{m} U_i / \left\{ \sum_{i=1}^{m} Var(U_i) \right\}^{1/2}, \tag{4.15}$$

which under H_0 is asymptotically normal as $m \to \infty$ or, for fixed m as the $n_i \to \infty$. Other scores besides (4.13) can be used; see for example Hajek and Sidak (1967) or Kalbfleisch and Prentice (2002, Section 7.2) for a general discussion of linear rank tests.

We mention two other tests which have been shown to have good power against monotonic trend alternatives (Kvaloy and Lindqvist, 2003). The first is the well-known Lewis-Robinson test (Lewis and Robinson, 1974), which uses the statistic

$$Z = \frac{1}{\sqrt{m}} \sum_{i=1}^{m} Z_i = \frac{1}{\sqrt{m}} \sum_{i=1}^{m} \frac{\bar{W}_i}{\hat{\sigma}_i} \left\{ \frac{\sum_{j=1}^{n_i-1} T_{ij} - \frac{(n_i-1)}{2} T_{in_i}}{T_{in_i} \left(\frac{n_i-1}{12}\right)^{1/2}} \right\}, \tag{4.16}$$

where $\hat{\sigma}_i$ is an estimate of the standard deviation of the $W_{ij}(j = 1, \ldots, n_i)$. Under H_0, the statistic Z is asymptotically normal for m fixed and the $n_i \to \infty$. A second test, developed by Kvaloy and Lindqvist (2003), effectively uses an Anderson-Darling statistic to test that the mean of a continuous version of the discrete processes $\{(T_{ij}/T_{in_i} - j/n_i), j = 1, \ldots, n_i\}$ is zero. This test is rather awkward to compute when the n_i are unequal.

Limitations of the renewal process based tests are the need for the no trend case to be a renewal process; p-values computed under this assumption may be off when the processes are stationary, but not renewal processes. A second and more serious limitation is the requirement for fixed n_i in the observation of processes. Although it has been claimed (e.g. Kvaloy and Lindqvist, 2003) that the tests readily generalize to fixed observation intervals $[0, \tau_i]$, it is not clear that this is the case. Intuitively, the rank statistic (4.12) should still be suitable, since the $W_{ij}(j = 1, \ldots, n_i)$ are exchangeable under H_0 and given that $N_i(\tau_i) = n_i$; the variance estimate (4.14), which can be obtained from permutation arguments, should also be valid. The Lewis-Robinson statistic (4.16) and the Kvaloy-Lindqvist (2003) statistic do not, however, have the stated limiting distributions as $m \to \infty$. We investigate these points in Section 4.4. One last note is that the test statistics (4.15) and (4.16) can be used for testing the absence of trend when there is heterogeneity between processes. Therefore, we will return to these tests in Chapter 5.

4.3 Robust Trend Tests Based on Rate Functions

The trend tests of Section 4.2.1 are based on methods for the Poisson process models. It is, however, possible to relax the model assumptions, and develop simple robust tests. We discussed robust methods for rate functions in Section 1.4.4. The main target of this section is to discuss the robust tests for trend in identical processes. We will discuss their properties, and compare them to other tests in Section 4.4 by simulation.

Let the rate functions be $\rho_i(t)$ for independent processes $i = 1, \ldots, m$. We consider tests of the null hypothesis ($i = 1, \ldots, m$)

$$H_0 : \rho_i(t) = \alpha, \qquad t \geq 0, \tag{4.17}$$

where α is an unknown positive value. To develop tests we consider models of the form (4.1), where $\rho(t) = \alpha \exp(\beta g(t))$. An important difference with Section 4.2.1, however, is that we do not assume here that the processes are Poisson; no assumption is made about the processes beyond their rate functions.

We assume as in Section 4.2.1 that the ith process is observed over the time interval $[\tau_{0i}, \tau_i]$ and that n_i events at times $T_{i1} < \ldots < T_{in_i}$ are observed. An important requirement for the development of robust tests is that the τ_{0i} and τ_i are determined independently of the event processes. With the notation of Section 1.4.4, this means that the observable processes $\{Y_i(t); t \geq 0\}$ and the event proceses are independent. This excludes observation schemes where n_i is prespecified. In addition, we will for simplicity ignore processes with $n_i = 0$ (since they contain no information about the shape of $\rho(t)$) and assume that all of processes 1, …, m have $n_i > 0$. This does not pose any restrictions; terms in score test statistics below are zero for any process with $n_i = 0$.

A little algebra shows that $U_\beta(\tilde{\alpha}, 0)$ in (4.5) (or $U_c(0)$ in (4.9)) can be rewritten as

$$U_\beta(\tilde{\alpha}, 0) = \sum_{i=1}^{m} U_{\beta i}(\tilde{\alpha}, 0) = \sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} \left(g(s) - \frac{g.}{\tau.} \right) [dN_i(s) - \alpha\, ds]\,, \tag{4.18}$$

where $g. = \sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} g(u)\, du$ and $\tilde{\alpha} = n./\tau.$(Cook and Lawless, 2007, Problem 3.13). Under the assumption of a homogeneous Poisson process with rate function α, the expectation of (4.18) is zero. However, this result holds even when the correct model is not a homogeneous Poisson process so long as the rate function is correctly specified. This is because of the fact that $E\{dN_i(t)\} = \rho_i(t)dt$, where $dN_i(t) = \lim_{\Delta t \downarrow 0}[N(t + \Delta t^-) - N(t^-)]$ represents the number of events in an arbitrarily short interval $(t - dt, t]$. It is easily seen that under H_0, $E\{U_\beta(\tilde{\alpha}, 0)\} = 0$ and that under alternatives of the form (4.1), $E\{U_\beta(\tilde{\alpha}, 0)\}$ will be bigger or smaller than zero when $g(t)$ is increasing and decreasing, respectively. In addition, the terms $U_{\beta i}(0)$ in (4.18) for $i = 1, \ldots, m$ are independent and so $\mathrm{Var}\{U_\beta(\tilde{\alpha}, 0)\}$ can be estimated under H_0 by

$$\widehat{Var}\,\{U_\beta(\tilde{\alpha}, 0)\} = \sum_{i=1}^{m} U_{\beta i}(\tilde{\alpha}, 0)^2, \tag{4.19}$$

leading to the standardized statistic

$$S_{R1} = \sum_{i=1}^{m} U_{\beta i}(\tilde{\alpha}, 0) \Big/ \left\{ \sum_{i=1}^{m} U_{\beta i}(\tilde{\alpha}, 0)^2 \right\}^{1/2} \tag{4.20}$$

for testing H_0. The variance estimate (4.19) is different than the Poisson estimate (4.6), and is robust to stationary departures from a Poisson process (cf. Section 1.4.4).

In Section 4.2.1, we also mentioned that a similar procedure can be followed to develop a score test for testing H_0 by conditioning on n_1, …, n_m, instead of $\sum_{i=1}^{m} n_i$. In this case, we obtain the score function (see, Section 5.2.1) as

$$U(0) = \sum_{i=1}^{m} U_i(0) = \sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} \left(g(t) - \frac{\int_{\tau_{0i}}^{\tau_i} g(t)\, dt}{\tau_{0i} - \tau_i} \right) dN_i(t). \tag{4.21}$$

We observe that $E\{U(0)\} = 0$ under $H_0 : \rho_i(t) = \alpha$, whether the Poisson assumption is true or not. This gives

$$S_{R2} = \sum_{i=1}^{m} U_i(0) / \left\{ \sum_{i=1}^{m} U_i(0)^2 \right\}^{1/2}, \tag{4.22}$$

which is another standardized score test statistic for testing H_0. In general, the test statistic (4.22) is different than (4.20), but is still robust.

As $m \to \infty$, the distribution of S_{R1} is asymptotically standard normal under H_0 as long as the integrals in (4.18) are finite. When the normal approximation is not accurate, p-values can be obtained by simulation. Other details about S_{R1} are discussed in Section 4.4.

For the special case $g(t) = t$, the numerator of (4.20) is given by (4.18) or (4.5), which can be shown to equal

$$\sum_{i=1}^{m} \sum_{j=1}^{n_i} t_{ij} - \frac{n.}{\tau.} \sum_{i=1}^{m} \frac{(\tau_i - \tau_{0i})^2}{2}, \tag{4.23}$$

where $n. = \sum_{i=1}^{m} n_i$ and $\tau. = \sum_{i=1}^{m} (\tau_i - \tau_{0i})$. It should be noted that, when the observation periods are equal for all processes (i.e. $\tau_i - \tau_{0i} = \tau$; $i = 1, \ldots, m$) and $g(t) = t$, the tests S_{R1} and S_{R2} are equal, and the numerator simplifies to

$$\sum_{i=1}^{m} \sum_{j=1}^{n_i} t_{ij} - \frac{n.\tau}{2}. \tag{4.24}$$

When $g(t) = t$, the test statistic S_{R2} is called the generalized Laplace test. A further discussion of the Laplace statistic is given in Chapter 5.

4.3.1 Settings with Covariates

Most trend tests proposed in the literature do not allow covariates to be incuded in the model. We now introduce covariates into the models where the baseline rate functions of the processes are the same for each process. We consider models with rate functions of the form ($i = 1, \ldots, m$)

$$\rho_i(t) = \alpha e^{\beta g(t) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t) + \boldsymbol{\delta}' \boldsymbol{v}_i}, \qquad , t > 0, \tag{4.25}$$

where $\boldsymbol{x}_i(t)$ is a vector of time-varying external covariates and $\boldsymbol{v}_i$ is a vector of fixed covariates for process i. We develop a score test for testing the null hypothesis $H_0 : \beta = 0$.

Note that the model (4.25) is not identical for each process anymore, only the baseline rates are assumed to be identical. A generalization of this model where the baseline rate functions are assumed to be different for each process is considered in the next chapter. In this section, we only develop a score test for H_0, and defer a more detailed discussion to the next chapter.

A test for trend can be based on the distribution of the observed data $\{(N_i(\tau_{0i}, \tau_i) = n_i; t_{i1} < \ldots < t_{n_i}); i = 1, \ldots, m\}$, but a simpler approach is based on the conditional distribution of $\{(N_i(\tau_{0i}, \tau_i) = n_i; t_{i1} < \ldots < t_{n_i}); i = 1, \ldots, m\}$ given either $n. = \sum_{i=1}^{m} n_i$ or $n_1, \ldots, n_m$, where $N_i(\tau_{0i}, \tau_i) = n_i > 0$. Although this test is based on a Poisson process, we show that the estimating functions are unbiased under the more general assumption that (4.25) represents the process rate functions. Here, we give the score test for the "given $n_1, \ldots, n_m$" case, which is also considered in the next chapter. In this case, the conditional likelihood function is given by

$$L_c(\beta, \boldsymbol{\gamma}) = \prod_{i=1}^{m} \left\{ \frac{n_i! \prod_{j=1}^{n_i} e^{\beta g(t_{ij}) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t_{ij})}}{\left(\int_{\tau_{0i}}^{\tau_i} e^{\beta g(t) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t)} \, dt \right)^{n_i}} \right\}, \tag{4.26}$$

which is free of parameters α and $\boldsymbol{\delta}$. Although $L_c(\beta, \boldsymbol{\gamma})$ has been obtained under a Poisson process assumption, the estimating functions for β and $\boldsymbol{\gamma}$ based on it are valid more generally. In particular, these are

$$\begin{aligned} U_\beta(\beta, \boldsymbol{\gamma}) &= \partial \log L_c(\beta, \boldsymbol{\gamma}) / \partial \beta \\ &= \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} g(t_{ij}) - \frac{n_i D_i^\beta(\beta, \boldsymbol{\gamma})}{D_i(\beta, \boldsymbol{\gamma})} \right\}, \end{aligned} \tag{4.27}$$

and

$$\begin{aligned} U_{\boldsymbol{\gamma}}(\beta, \boldsymbol{\gamma}) &= \partial \log L_c(\beta, \boldsymbol{\gamma}) / \partial \boldsymbol{\gamma} \\ &= \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} \boldsymbol{x}_i(t_{ij}) - \frac{n_i D_i^{\boldsymbol{\gamma}}(\beta, \boldsymbol{\gamma})}{D_i(\beta, \boldsymbol{\gamma})} \right\}, \end{aligned} \tag{4.28}$$

where for convenience we define

$$\begin{aligned} D_i(\beta, \boldsymbol{\gamma}) &= \int_{\tau_{0i}}^{\tau_i} e^{\beta g(t) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t)} \, dt \\ D_i^\beta(\beta, \boldsymbol{\gamma}) &= \partial D_i / \partial \beta = \int_{\tau_{0i}}^{\tau_i} g(t) \, e^{\beta g(t) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t)} \, dt \\ D_i^{\boldsymbol{\gamma}}(\beta, \boldsymbol{\gamma}) &= \partial D_i / \partial \boldsymbol{\gamma} = \int_{\tau_{0i}}^{\tau_i} \boldsymbol{x}_i(t) \, e^{\beta g(t) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t)} \, dt \end{aligned}$$

and for use below,

$$
\begin{aligned}
D_i^{\beta\boldsymbol{\gamma}} &= \left(D_i^{\gamma\beta}\right)' = \partial^2 D_i\left(\beta,\boldsymbol{\gamma}\right)/\partial\beta\partial\gamma' = \int_{\tau_{0i}}^{\tau_i} g(t)x_i(t)'e^{\beta g(t)+\gamma x_i(t)}dt \\
D_i^{\beta\beta} &= \partial^2 D_i\left(\beta,\boldsymbol{\gamma}\right)/\partial\beta^2 = \int_{\tau_{0i}}^{\tau_i} g(t)^2 e^{\beta g(t)+\gamma x_i(t)}dt \\
D_i^{\gamma\gamma} &= \partial^2 D_i\left(\beta,\boldsymbol{\gamma}\right)/\partial\gamma\partial\gamma' = \int_{\tau_{0i}}^{\tau_i} x_i(t)x_i(t)'e^{\beta g(t)+\gamma x_i(t)}dt.
\end{aligned}
$$

By noting that $n_i = \int_{\tau_{0i}}^{\tau_i} dN_i(t)$, rewriting (4.27) as

$$
U_\beta(\beta,\gamma) = \sum_{i=1}^{m}\left\{\int_{\tau_{0i}}^{\tau_i}\left[g(t) - \frac{D_i^\beta(\beta,\gamma)}{D_i(\beta,\gamma)}\right]dN_i(t)\right.
$$

and using the fact that $E\{dN_i(t)\} = \rho_i(t)dt$, we see that $E\{U_\beta(\beta,\gamma)\} = 0$ provided (4.25) is true and the $[\tau_{0i},\tau_i]$ are independent of the event processes. It is seen similarly that $E\{U_\gamma(\beta,\gamma)\} = 0$. Thus, solving $U_\beta(\beta,\gamma) = 0$ and $U_\gamma(\beta,\gamma) = 0$ will produce consistent estimates (as $m \to \infty$) of β and γ under mild conditions on $g(t)$ and the $\boldsymbol{x}_i(t)$.

Our interest here is in testing $H_0 : \beta = 0$ and to that end we let $\tilde{\gamma}$ be the solution to $U_\gamma(0,\gamma) = 0$. The pseudo score statistic for H_0 is then

$$
U_i(0,\tilde{\gamma}) = \sum_{i=1}^{m} U_{\beta i}(0,\tilde{\gamma}) = \sum_{i=1}^{m}\left\{\sum_{j=1}^{n_i} g(T_{ij}) - \frac{n_i D_i^\beta(0,\tilde{\gamma})}{D_i(0,\tilde{\gamma})}\right\}. \tag{4.29}
$$

A variance estimate $\tilde{V}$ for $U_i(0,\tilde{\gamma})$ is given by results in Section 4.1 of Boos (1992). This takes the form

$$
\tilde{V} = \tilde{A}\ \tilde{B}\ \tilde{A} \tag{4.30}
$$

where

$$
\tilde{A} = \tilde{I}_{11} - \tilde{I}_{12}\tilde{I}_{22}^{-1}\tilde{I}_{21}, \quad \tilde{B} = \left(\tilde{I}^{-1}\tilde{C}\tilde{I}^{-1}\right)_{11},
$$

with

$$
\begin{aligned}
\tilde{I}_{11} &= \sum_{i=1}^{m} n_i\left\{\frac{D_i(0,\tilde{\gamma})D_i^{\beta\beta}(0,\tilde{\gamma}) - D_i^\beta(0,\tilde{\gamma})^2}{D_i(0,\tilde{\gamma})^2}\right\} \\
\tilde{I}_{12} &= \tilde{I}_{21}' = \sum_{i=1}^{m} n_i\left\{\frac{D_i(0,\tilde{\gamma})D_i^{\beta\gamma}(0,\tilde{\gamma}) - D_i^\beta(0,\tilde{\gamma})D_i^\gamma(0,\tilde{\gamma})}{D_i(0,\tilde{\gamma})^2}\right\} \\
\tilde{I}_{22} &= \sum_{i=1}^{m} n_i\left\{\frac{D_i(0,\tilde{\gamma})D_i^{\gamma\gamma}(0,\tilde{\gamma}) - D_i^\gamma(0,\tilde{\gamma})D_i^\gamma(0,\tilde{\gamma})'}{D_i(0,\tilde{\gamma})^2}\right\} \\
\tilde{C} &= \sum_{i=1}^{m} U_{\beta i}(0,\tilde{\gamma})^2
\end{aligned}
$$

The test statistic $Z = U_1(0, \tilde{\gamma})/\tilde{V}^{1/2}$ is asymptotically standard normal under H_0, as $m \to \infty$. When m is not sufficiently large for the normal approximation to be accurate, there is at present no alternative approach to obtaining p-values unless additional assumptions about the process are made.

4.4 Simulation Studies

We present here the results of simulation studies undertaken to assess the accuracy of large sample approximations to the null distributions of test statistics for trend, and to compare the power of several tests under various trend alternatives. We consider three types of "no trend" null hypothesis, as follows:

(a) H_0 : Process i ($i = 1, \ldots, m$) is a HPP with rate α,

(b) H_0 : Process i ($i = 1, \ldots, m$) is a renewal process with gap times W_{ij} ($j = 1, \ldots, n_i$) following a gamma distribution with scale a and shape b,

(c) H_0 : Process i ($i = 1, \ldots, m$) has intensity function $\alpha \exp\{\beta z_i(t)\}$, where $z_i(t) = I(N_i(t^-) > 0)I(B_i(t) \leq \Delta)$.

Note that case (a) is the special case of (b) when $b = 1$ and $a = \alpha^{-1}$ but because of its importance we designate it separately. In simulations, we consider $b = 0.75$ and 1.5 for case (b). Case (c) is a carryover model as in Chapter 2. We note that it is in fact a delayed renewal process in which the hazard function is α for W_{i1} and for W_{i2}, W_{i3}, ..., it is $h_2(w) = \alpha(e^\beta - 1)I(w \leq \Delta) + \alpha$. We consider $\exp(\beta) = 5$ and $\Delta = 0.05$ throughout this section. We take $\alpha = 1$ in (a) and (c) and $a = (\alpha b)^{-1}$ in (b) so that the average gap time ab is α^{-1}, which gives an event rate approaching α as $t \to \infty$ in case (b). For simplicity, we take $\tau_i = \tau$ ($i = 1, \ldots, m$), with τ taking values 5 and 20. We consider $m = 10$, 20 or 50 processes. This gives approximately (exactly, in case (a)) $m\tau$ expected total events under each null hypothesis setting. We consider the following test statistics for "no trend":

(1) the standardized robust score statistic S_{R1} in (4.20) with $g(t) = t$,

(2) the linear rank statistic R in (4.15),

(3) Z^*, a corrected version of the generalized Lewis-Robinson statistic, where $Z^* = \frac{1}{\sqrt{m}} \sum_{i=1}^{m} \sqrt{\frac{n_i}{n_i+1}} Z_i$ and Z_i is given in (4.16).

Since the observation periods are equal for all processes and $g(t) = t$, the statistics S_{R1} and S_{R2} given in (4.22) are the same. In the case of (2) and (3), we ignore the final censored gap between t_{n_i} and τ. To mimic how fixed-n_i statistics are used in practice when τ_i is actually fixed, we use $\hat{\sigma}_i^2 = \sum_{j=1}^{n_i}(w_{ij} - \bar{w}_i)^2/(n_i - 1)$, where $\bar{w}_i = \sum_{j=1}^{n_i} w_{ij}/n_i$, in Z^*, and only consider systems with $n_i \geq 2$. The correction in (3) is useful when τ and the $E(N_i(\tau))$ are small but has a small effect for a large τ. We simulated 10,000 runs for each of the "no trend" scenarios (a), (b) and (c) and (m, τ) combinations. For each test statistic (1), (2) and (3), we report on its distribution and the adequacy of the standard normal approximation. For convenience, results are collected in Section 4.4.1 below.

Normal quantile-quantile (Q-Q) plots of the 10,000 values of the test statistics are given for case (a) in Figures 4.1, 4.2 and 4.3 when $\tau = 5$ and $m = 10$, 20 or 50, respectively. The standard normal approximation is suitable for R and Z^* in each setting but is not adequate for S_{R1} in the extreme tails when $m = 10$. This is likely because S_{R1} uses a robust variance estimate effectively based on m values $U_i(\Delta)$, and some departure from normality when $m = 10$ is unsurprising. In Figures 4.4, 4.5 and 4.6, we consider the case (a) when $\tau = 20$, and obtain similar results. Table 4.1 gives additional details of the results in the normal Q-Q plots.

In case (b), we generate data from a renewal process where the W_{ij} have a gamma distribution with scale a and shape b parameters. Strictly speaking, a renewal process is not (strongly) stationary. Although $\rho_i(t) \to \alpha = (1/E(W_{ij}))$ as $t \to \infty$, $\rho_i(t)$ can vary quite a lot for smaller t, depending on the distribution of the W_{ij}. Thus, the S_{R1} test can show bias (i.e. $E(U_{\beta i}(\tilde{\alpha}, 0)) \neq 0$) when the process is a renewal process, especially for smaller τ. The bias disappears as τ increases. This can be seen in Figure 4.7 where we generated the W_{ij} from the gamma distribution with scale parameter a and shape parameter $b = 1.5$. Our preliminary studies showed that the bias is negative when $b < 1$ and positive when $b > 1$, and increasing as $|b|$ increases. When we have a renewal process that is not an HPP, one approach is to use S_{R1} by taking $\tau_i = t_{n_i}$ ($i = 1, \ldots, m$). Another approach is to note that, with τ_i fixed, $(w_{i1}, \ldots, w_{in_i})$ are exchangeable under H_0, given $N_i(\tau_i) = n_i$. In other words, the joint distributions of $(W_{i1}, \ldots, W_{in_i})$ and any permutation of $(W_{i1}, \ldots, W_{in_i})$, given $N_i(\tau_i) = n_i$, are the same. Thus we could estimate a mean adjustment for each $U_{\beta i}(\tilde{\alpha}, 0)$ as follows: Take B permutations of $W_{i1}, \ldots, W_{in_i}$ and define, for permutation b (call it, $w_{i1}^b, \ldots, w_{in_i}^b$), the new event times $t_{ij}^b = w_{i1}^b + \cdots + w_{ij}^b$ ($j = 1, \ldots, n_i$). Then, compute

$$U_{\beta i}^b(\tilde{\alpha}, 0) = \sum_{j=1}^{n_i} t_{ij}^b - \frac{n_i \tau_i}{2}, \qquad b = 1, \ldots, B,$$

and estimate $E\{U_{\beta i}(\tilde{\alpha}, 0)\}$ by

$$\bar{U}_{\beta i}(\tilde{\alpha}, 0) = \frac{\sum_{b=1}^{B} U_{\beta i}^b(\tilde{\alpha}, 0)}{B}.$$

Then, replace $U_{\beta i}(\tilde{\alpha},0)$ with $U_{\beta i}^{\text{new}}(\tilde{\alpha},0) = U_{\beta i}(\tilde{\alpha},0) - \bar{U}_{\beta i}(\tilde{\alpha},0)$, and use the statistic

$$S_{R1}^{\text{new}} = \sum_{i=1}^{m} U_{\beta i}^{\text{new}}(\tilde{\alpha},0) \Big/ \left\{ \sum_{i=1}^{m} U_{\beta i}^{\text{new}}(\tilde{\alpha},0)^2 \right\}^{1/2}.$$

A third way involving less computation is as follows: Since $W_{i1}, \ldots, W_{in_i}$ are exchangeable , given $N_i(\tau_i) = n_i$, we have $E\{W_{ij}|N_i(\tau_i) = n_i\} = \mu(n_i)$. Then,

$$U_{\beta i}(\tilde{\alpha},0) = \sum_{j=1}^{n_i} t_{ij} - \frac{n_i \tau_i}{2} = \sum_{j=1}^{n_i} (n_i - j + 1) W_{ij} - \frac{n_i \tau_i}{2}$$

and

$$\begin{aligned} E\{U_{\beta i}(\tilde{\alpha},0)|N_i(\tau_i) = n_i\} &= \sum_{j=1}^{n_i} (n_i - j + 1)\mu(n_i) - \frac{n_i \tau_i}{2} \\ &= \frac{n_i(n_i+1)}{2}\mu(n_i) - \frac{n_i \tau_i}{2}. \end{aligned} \tag{4.31}$$

Replacing $\mu(n_i)$ with $\bar{W}_i = \frac{1}{n_i}\sum_{j=1}^{n_i} W_{ij} = t_{in_i}/n_i$, we estimate (4.31) by

$$\bar{U}_{\beta i}(\tilde{\alpha},0) = \left(\frac{n_i+1}{2}\right) t_{in_i} - \frac{n_i \tau_i}{2}. \tag{4.32}$$

Now, let $U_{\beta i}^{*}(\tilde{\alpha},0) = U_{\beta i}(\tilde{\alpha},0) - \bar{U}_{\beta i}(\tilde{\alpha},0)$ and use the statistic

$$S_{R1}^{*} = \sum_{i=1}^{m} U_{\beta i}^{*}(\tilde{\alpha},0) \Big/ \left\{ \sum_{i=1}^{m} U_{\beta i}^{*}(\tilde{\alpha},0)^2 \right\}^{1/2}. \tag{4.33}$$

Figure 4.8 shows normal Q-Q plots of S_{R1} and S_{R1}^{*} statistics based on 10,000 realizations. The test statistic S_{R1}^{*} works well when $E\{U_{\beta i}(\tilde{\alpha},0)\} \neq 0$. Therefore, we used it for case (b). It should be noted that using it does not change the results when $E\{U_{\beta i}(\tilde{\alpha},0)\} = 0$ as well; for example, in case (a).

We next generated 10,000 realizations of m processes for case (b) by generating the W_{ij} from a gamma distribution with scale parameter a and shape parameter $b = 0.75$, and consider S_{R1}^{*} in place of S_{R1}. The normal Q-Q plots of the test statistics are given in Figures 4.9, 4.10 and 4.11 when $\tau = 5$ and $m = 10$, 20 and 50, respectively. We now observe similar results to those of case (a) (see Figures 4.1, 4.2 and 4.3). When $m = 10$, the expected number of events is approximately 5 for each process, and in this case the normal approximation for S_{R1}^{*} is not good in the extreme tails. The normal approximation is , however, adequate when $m = 20$ or 50. This can be seen in Table 4.2 as well, which summarizes features of Figures 4.9–4.11. Figures 4.12, 4.13 and 4.14 show the normal Q-Q plots when $\tau = 20$. Increasing τ from 5 to 20 does not have a significant effect on the normal approximations of the test statistics. We conducted a similar simulation study when $b = 1.5$. The normal Q-Q plots are not given here but Table 4.3 summarizes the results, which are similar to the results when $b = 0.75$.

In case (c), we generate data from a delayed renewal process where W_{i1} ($i = 1, \ldots, m$) has the hazard function $h_1(w) = \alpha$ and the W_{ij} ($i = 1, \ldots, m$; $j = 2, 3, \ldots$) have the hazard function $h_j(w) = \alpha(e^{\beta} - 1)I(w < \Delta) + \alpha$ ($j = 2, 3, \ldots$), $w > 0$. Normal Q-Q plots based on the 10,000 simulated values of the test statistics S_{R1}, R and Z^* are given in Figure 4.15, 4.16 and 4.17 when $\tau = 5$ and $m = 10$, 20 or 50, respectively. In this case, the standard normal approximation is not adequate for R and Z^*, and for $m = 5$, it is off for extreme tails in the distribution of S_{R1}, as in case(a). The bias in the mean of R and Z^* gets worse as m increases. The effect of the W_{i1} disappears as τ increases. This can be seen in Figures 4.18, 4.19 and 4.20 where we present the normal Q-Q plots of 10,000 realizations of S_{R1}, R and Z^* when $\tau = 20$ and $m = 10$, 20 and 50. Tables 4.4 summarizes key features of the figures.

We also conducted power studies with the three test statistics under trend alternatives. The following families of models were taken for processes exhibiting an increasing trend.

(d) Process i ($i = 1, \ldots, m$) is a NHPP with rate function $\rho_i(t) = \alpha^* \exp(\gamma t)$,

(e) Process i ($i = 1, \ldots, m$) is a semi-Markov process where the gap times W_{ij} ($j = 1, \ldots, n_i$)are independent, and follow a gamma distribution with scale $a^* \exp(\gamma j)$ for W_{ij} and shape b,

(f) Process i ($i = 1, \ldots, m$) has intensity function

$$\lambda_i(t|\mathcal{H}_i(t)) = \alpha^* \exp(\gamma t) \exp(\beta z_i(t)), \qquad t \geq 0,$$

where $z_i(t) = I(N_i(t^-) > 0)I(B_i(t) \leq \Delta)$.

We report below on the power of tests based on S_{R1} (or S^*_{R1}, for case (e)), R and Z^* when $e^{\gamma\tau} = 2$ or 4. The values used for α^* in case (d) and (f) and a^* in case (e) were selected so as to give roughly the same expected total numbers of events as in the null cases (a), (b) and (c). Thus, for case (e), we chose $a^* = (\alpha^* b)^{-1}$.

We consider the power of tests with size (Type 1 error) 0.05. To compare the power of the statistics independent of the adequacy of their normal approximations under the null hypotheses, we used in each case the empirical 0.95 quantile of the test statistic in the 10,000 simulation runs corresponding to the null hypothesis that matches each alternative. That is, we used quantiles based on (a), (b) and (c) for alternatives of the form (d), (e) and (f), respectively. We considered $\tau = 5$, 10 and 20 and $m = 10$, 20 and 50, and generated 1,000 samples in each case. We used the same generated data with S_{R1}, R and Z^*.

For case (d), the proportions of rejection of no trend (i.e. $H_0 : \gamma = 0$) are given in Table 4.5. To obtain approximately the same number of events obtained in case (a), we chose $\alpha^* = \alpha\gamma\tau/(e^{\gamma\tau} - 1)$, where $\alpha = 1$. In each scenario, S_{R1} is more powerful than R and Z^*, though as τ increases the difference becomes small. The power of Z^* is slightly higher than R. Note that, if we used the variance estimate based on the Poisson process instead of the robust variance estimate (i.e. tests of Section 4.2.1) in S_{R1}, the test would be optimum against the alternative model given in case (d) (Cox and Lewis, 1966). However, the test S_{R1} maintains high power with the robust variance estimate when $m \geq 10$. The powers of test statistics in case (e) are presented in Tables 4.6 and 4.7 when $b = 0.75$ and 1.5, respectively. This case is the match of case (b) so we used S^*_{R1} in (4.33) instead of S_{R1}. When $\tau = 5$, the power of S^*_{R1} is slightly higher than Z^*. However, when $\tau = 20$ or 50, Z^* is slightly more powerful than S^*_{R1}. Note that, although the test Z^* is based on the renewal processes, the differences between the powers of S^*_{R1} and Z^* are small. Both statistics are more powerful than R. Also, the powers are higher when $b = 1.5$ than the powers when $b = 0.75$ for all test statistics. In case (f), we consider a model that incorporates monotonic trend and a carryover effect. We generated data from the model in (f) when $\alpha = 1$, $e^\beta = 5$ and $\Delta = 0.05$. To obtain approximately same number of events per process as in case (c), we chose α^* so that the numbers of events $N_i(\tau)$ per process is approximately same to those of the case (c). Table 4.8 gives results, and it shows that S_{R1} is more powerful than R and Z^*.

Section 4.4.2 summarizes results of the simulation studies, whose outputs are given in Section 4.4.1 below.

4.4.1 Figures and Tables

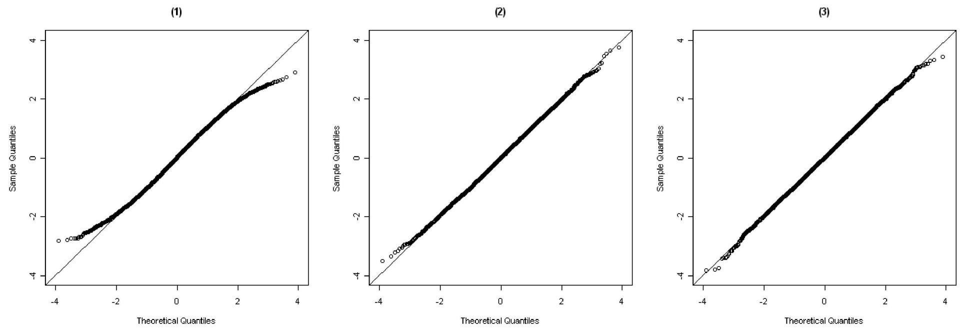

Figure 4.1: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (a), $\tau = 5$, $m = 10$.

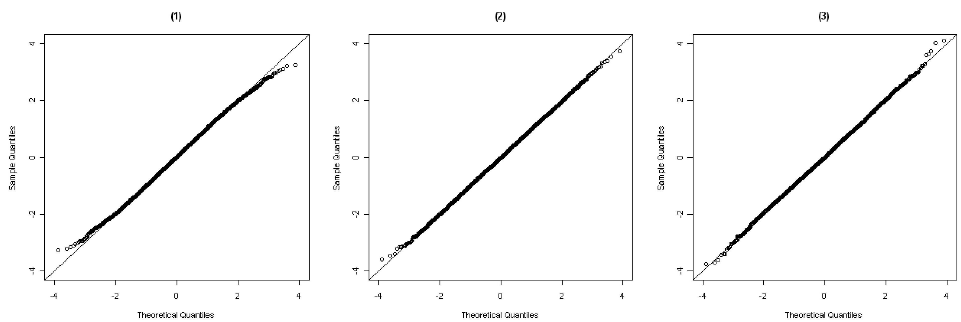

Figure 4.2: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (a), $\tau = 5$, $m = 20$.

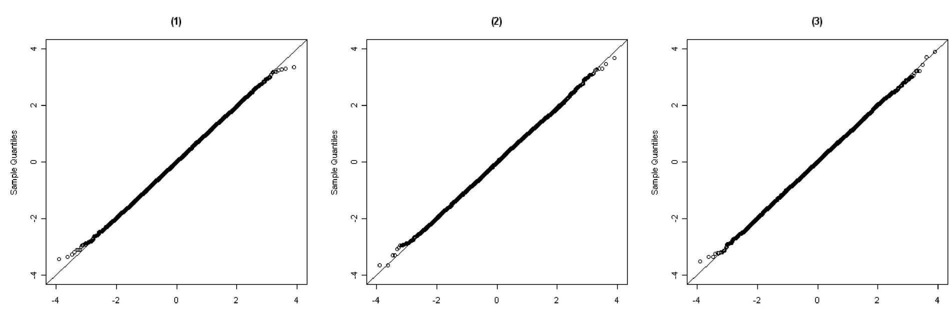

Figure 4.3: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (a), $\tau = 5$, $m = 50$.

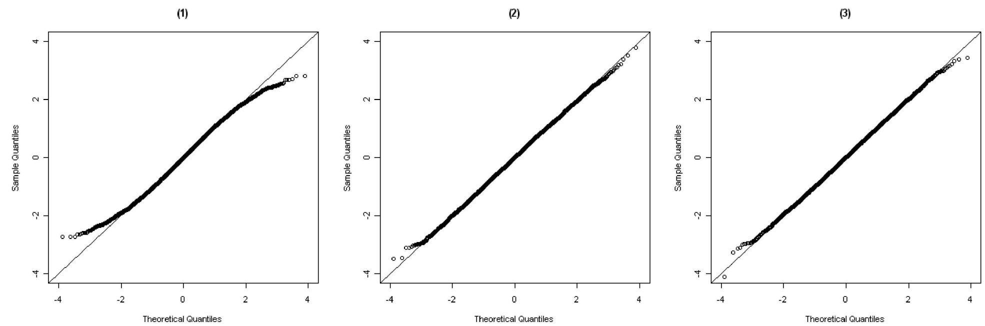

Figure 4.4: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^{*}: Case (a), $\tau = 20$, $m = 10$.

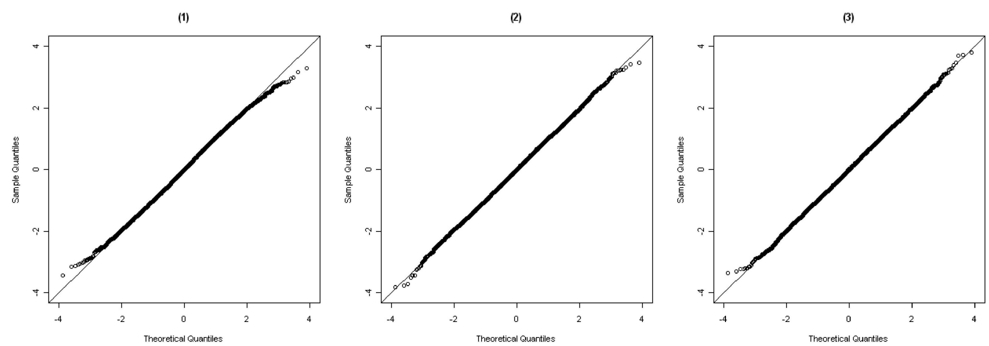

Figure 4.5: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^{*}: Case (a), $\tau = 20$, $m = 20$.

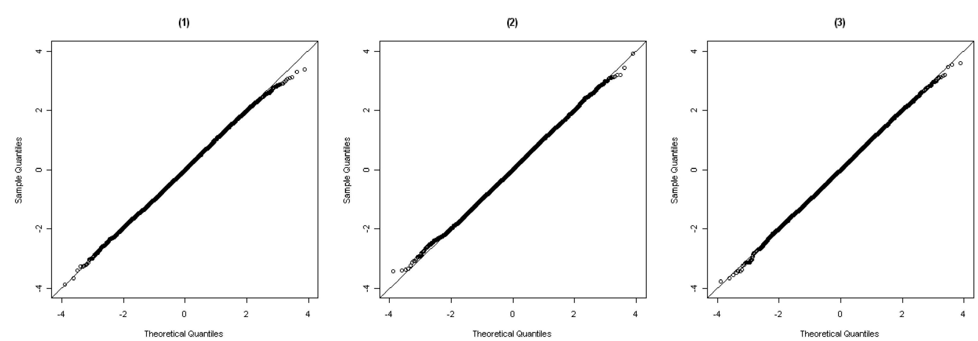

Figure 4.6: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^{*}: Case (a), $\tau = 20$, $m = 50$.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S_{R1}	1.643	1.892	2.146	0.050	0.021	0.004
		R	1.636	1.939	2.306	0.049	0.024	0.009
		Z^*	1.671	1.958	2.333	0.052	0.025	0.010
	20	S_{R1}	1.661	1.942	2.258	0.052	0.025	0.007
		R	1.605	1.909	2.299	0.046	0.022	0.009
		Z^*	1.668	1.992	2.374	0.052	0.027	0.011
	50	S_{R1}	1.639	1.931	2.302	0.049	0.023	0.009
		R	1.579	1.862	2.230	0.042	0.020	0.008
		Z^*	1.654	1.993	2.308	0.051	0.027	0.010
20	10	S_{R1}	1.653	1.899	2.143	0.051	0.021	0.005
		R	1.631	1.922	2.277	0.048	0.022	0.009
		Z^*	1.647	1.976	2.309	0.050	0.027	0.010
	20	S_{R1}	1.634	1.934	2.218	0.049	0.023	0.007
		R	1.625	1.916	2.328	0.048	0.023	0.010
		Z^*	1.629	1.947	2.326	0.049	0.024	0.010
	50	S_{R1}	1.656	1.941	2.282	0.051	0.024	0.009
		R	1.638	1.946	2.383	0.050	0.024	0.011
		Z^*	1.658	1.961	2.285	0.051	0.025	0.009

Table 4.1: $\hat{Q}_p$ is the empirical pth quantile of S_{R1}, R and Z^* computed from 10,000 samples under case (a). $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S_{R1}, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

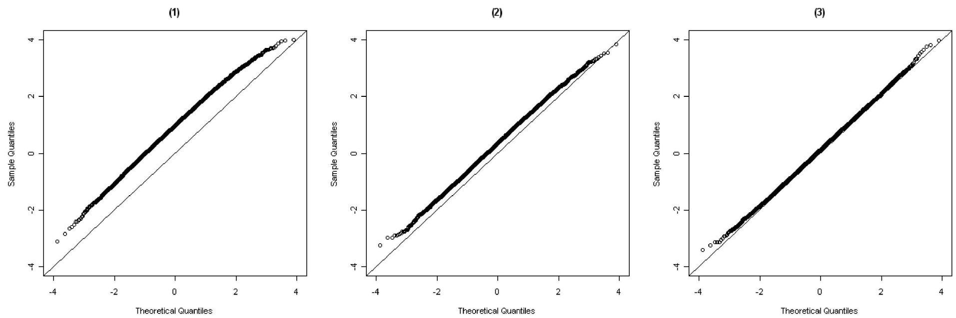

Figure 4.7: Normal Q-Q plots of simulated values of S_{R1} when (1) $\tau = 5$, (2) $\tau = 50$, and (3) $\tau = 500$: Case (b), $m = 50$, $W_{ij} \sim Gamma(a, b = 1.5)$.

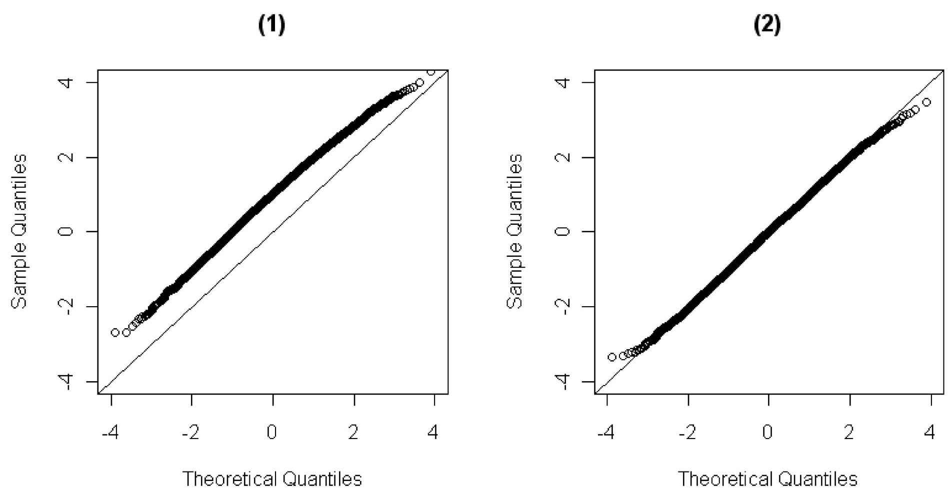

Figure 4.8: Normal Q-Q plots of simulated values of (1) S_{R1} and (2) S^*_{R1} in (4.33): Case (b), $\tau = 5$, $m = 50$, $W_{ij} \sim Gamma(a, b = 1.5)$.

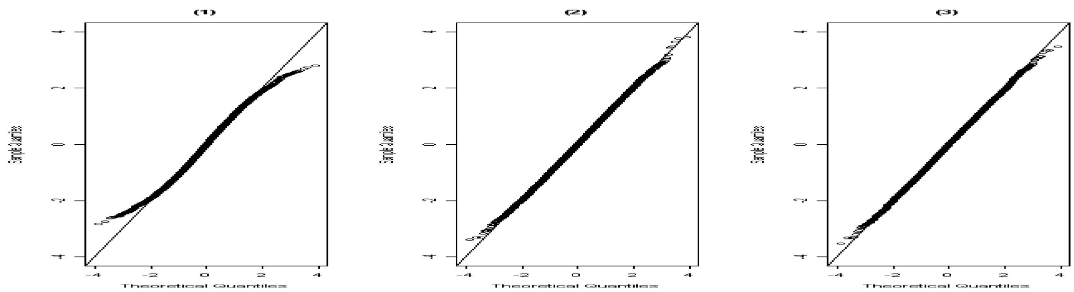

Figure 4.9: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 10$, $W_{ij} \sim Gamma(a, b = 0.75)$.

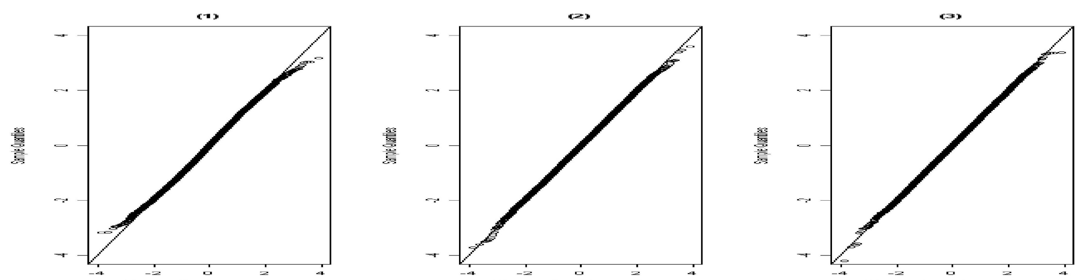

Figure 4.10: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 20$, $W_{ij} \sim Gamma(a, b = 0.75)$.

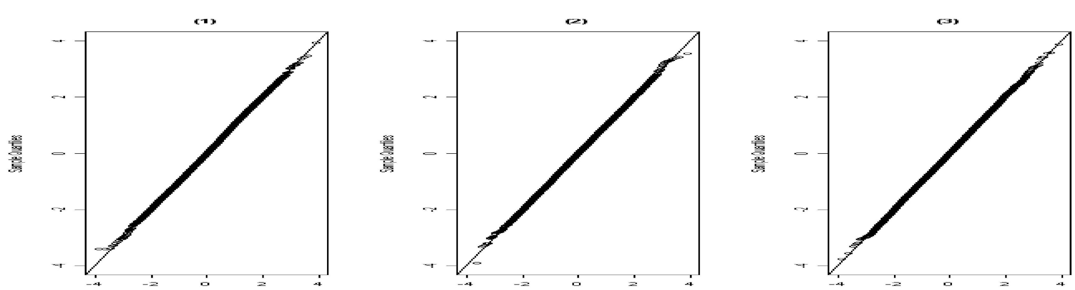

Figure 4.11: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 50$, $W_{ij} \sim Gamma(a, b = 0.75)$.

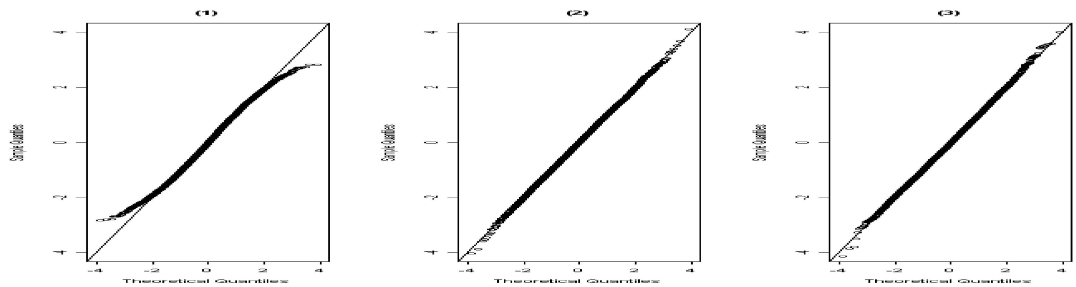

Figure 4.12: Normal Q-Q plots of simulated values of the test statistics (1) S^*_{R1}, (2) R and (3) Z^*: Case (b), $\tau = 20$, $m = 10$, $W_{ij} \sim Gamma(a, b = 0.75)$.

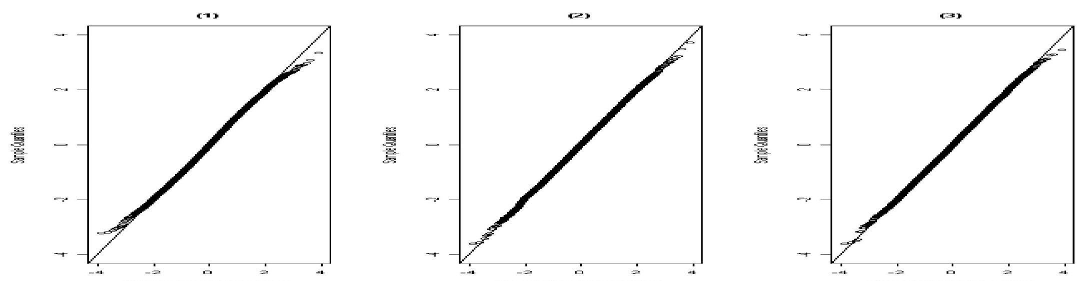

Figure 4.13: Normal Q-Q plots of simulated values of the test statistics (1) S^*_{R1}, (2) R and (3) Z^*: Case (b), $\tau = 20$, $m = 20$, $W_{ij} \sim Gamma(a, b = 0.75)$.

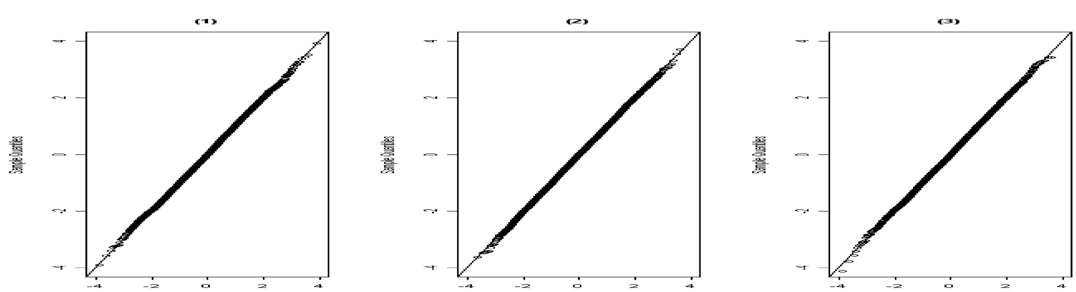

Figure 4.14: Normal Q-Q plots of simulated values of the test statistics (1) S^*_{R1}, (2) R and (3) Z^*: Case (b), $\tau = 20$, $m = 50$, $W_{ij} \sim Gamma(a, b = 0.75)$.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S^*_{R1}	1.643	1.868	2.092	0.050	0.018	0.004
		R	1.674	1.978	2.346	0.054	0.026	0.011
		Z^*	1.629	1.905	2.319	0.049	0.022	0.010
	20	S^*_{R1}	1.642	1.918	2.246	0.050	0.022	0.009
		R	1.624	1.954	2.304	0.048	0.025	0.009
		Z^*	1.638	1.942	2.317	0.049	0.024	0.009
	50	S^*_{R1}	1.665	1.978	2.340	0.053	0.026	0.010
		R	1.633	1.948	2.313	0.049	0.024	0.010
		Z^*	1.662	2.019	2.362	0.052	0.028	0.011
20	10	S^*_{R1}	1.648	1.895	2.187	0.050	0.020	0.006
		R	1.613	1.933	2.354	0.046	0.024	0.011
		Z^*	1.642	1.973	2.354	0.050	0.026	0.011
	20	S^*_{R1}	1.652	1.919	2.259	0.051	0.023	0.008
		R	1.669	1.978	2.291	0.053	0.027	0.009
		Z^*	1.641	1.942	2.319	0.050	0.024	0.010
	50	S^*_{R1}	1.666	1.974	2.299	0.053	0.026	0.009
		R	1.663	1.961	2.306	0.051	0.025	0.010
		Z^*	1.662	1.971	2.338	0.052	0.026	0.010

Table 4.2: $\hat{Q}_p$ is the empirical pth quantile of S^*_{R1}, R and Z^* computed from 10,000 samples under case (b) when $b = 0.75$. $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S^*_{R1}, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S^*_{R1}	1.656	1.894	2.134	0.051	0.020	0.004
		R	1.668	2.001	2.321	0.052	0.027	0.010
		Z^*	1.635	1.936	2.260	0.049	0.023	0.008
	20	S^*_{R1}	1.666	1.975	2.266	0.052	0.026	0.008
		R	1.668	1.989	2.371	0.053	0.027	0.012
		Z^*	1.649	1.971	2.334	0.051	0.026	0.011
	50	S^*_{R1}	1.647	1.953	2.301	0.050	0.025	0.009
		R	1.656	1.973	2.375	0.051	0.026	0.012
		Z^*	1.651	1.947	2.318	0.050	0.025	0.010
20	10	S^*_{R1}	1.648	1.897	2.191	0.051	0.021	0.006
		R	1.631	1.924	2.294	0.049	0.023	0.009
		Z^*	1.639	1.957	2.349	0.050	0.025	0.010
	20	S^*_{R1}	1.667	1.931	2.235	0.052	0.024	0.007
		R	1.615	1.890	2.289	0.047	0.021	0.009
		Z^*	1.672	1.975	2.328	0.052	0.026	0.010
	50	S^*_{R1}	1.642	1.959	2.317	0.050	0.025	0.010
		R	1.661	1.964	2.389	0.051	0.025	0.013
		Z^*	1.660	1.954	2.365	0.051	0.025	0.011

Table 4.3: $\hat{Q}_p$ is the empirical pth quantile of S^*_{R1}, R and Z^* computed from 10,000 samples under case (b) when $b = 1.5$. $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S^*_{R1}, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

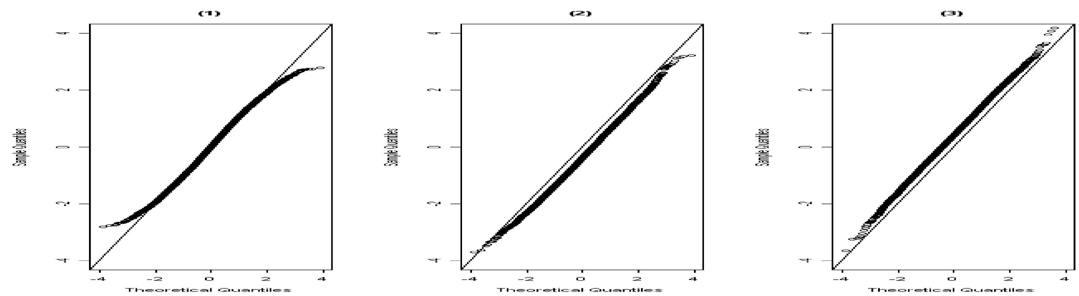

Figure 4.15: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (c), $\tau = 5$, $m = 10$.

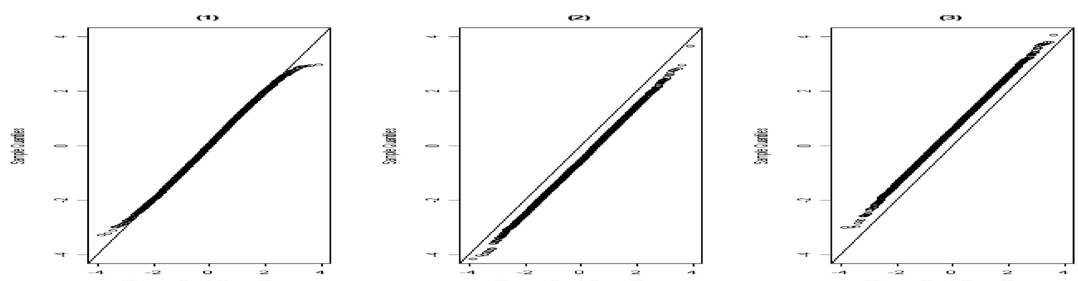

Figure 4.16: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (c), $\tau = 5$, $m = 20$.

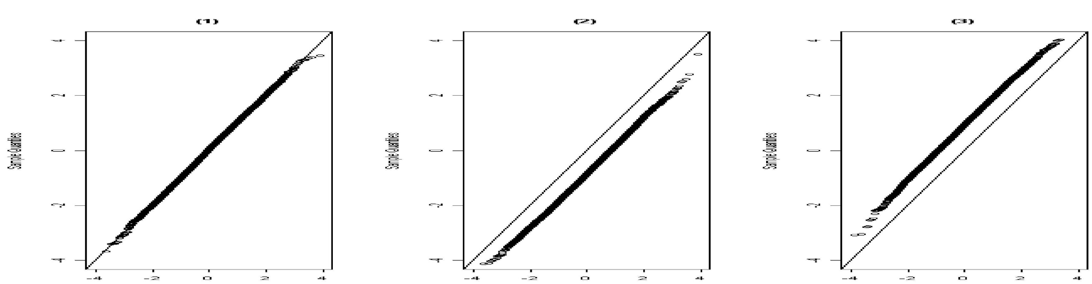

Figure 4.17: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (c), $\tau = 5$, $m = 50$.

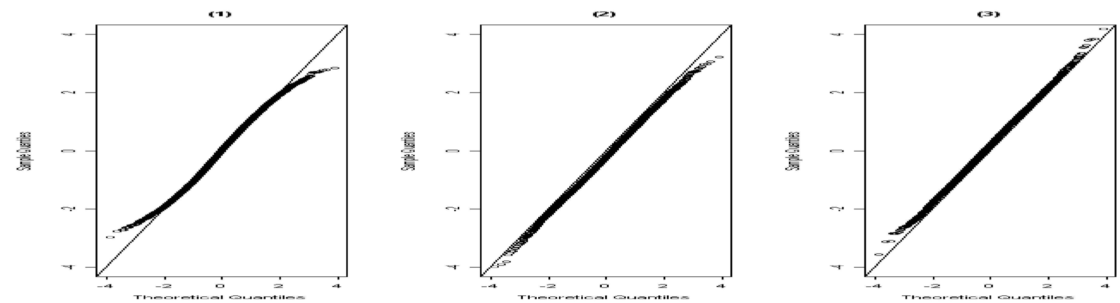

Figure 4.18: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (c), $\tau = 20$, $m = 10$.

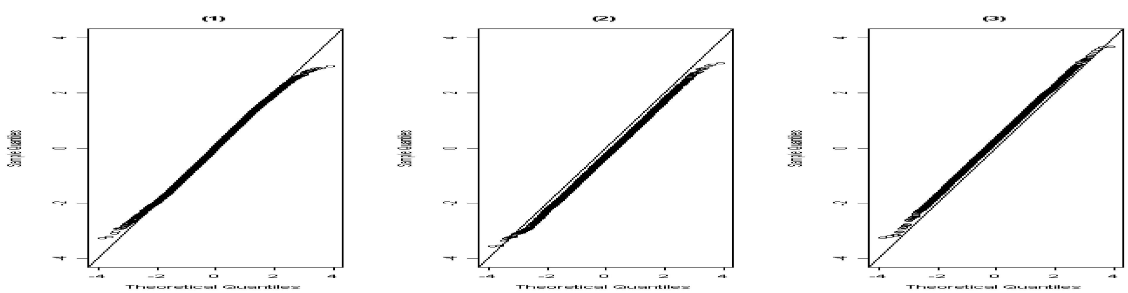

Figure 4.19: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (c), $\tau = 20$, $m = 20$.

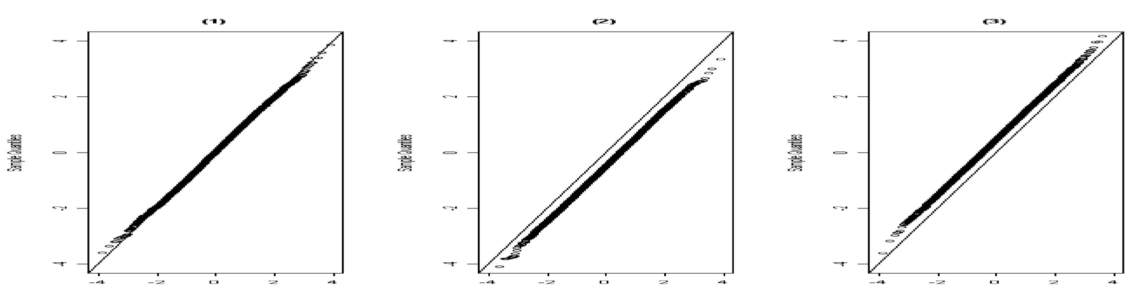

Figure 4.20: Normal Q-Q plots of simulated values of the test statistics (1) S_{R1}, (2) R and (3) Z^*: Case (c), $\tau = 20$, $m = 50$.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S_{R1}	1.637	1.888	2.168	0.049	0.020	0.005
		R	1.258	1.579	1.939	0.022	0.010	0.004
		Z^*	2.059	2.349	2.664	0.111	0.061	0.027
	20	S_{R1}	1.684	1.974	2.282	0.055	0.026	0.009
		R	1.106	1.431	1.781	0.014	0.006	0.002
		Z^*	2.223	2.519	2.886	0.142	0.083	0.039
	50	S_{R1}	1.659	1.991	2.346	0.052	0.027	0.011
		R	0.811	1.170	1.521	0.007	0.002	0.001
		Z^*	2.579	2.835	3.160	0.238	0.151	0.083
20	10	S_{R1}	1.651	1.903	2.162	0.051	0.020	0.005
		R	1.442	1.732	2.088	0.031	0.015	0.004
		Z^*	1.816	2.127	2.497	0.072	0.038	0.015
	20	S_{R1}	1.663	1.916	2.261	0.052	0.023	0.008
		R	1.360	1.674	2.049	0.026	0.013	0.004
		Z^*	1.939	2.200	2.577	0.089	0.047	0.019
	50	S_{R1}	1.658	1.942	2.306	0.052	0.024	0.009
		R	1.178	1.501	1.835	0.017	0.007	0.002
		Z^*	2.096	2.412	2.769	0.123	0.067	0.031

Table 4.4: $\hat{Q}_p$ is the empirical pth quantile of S_{R1}, R and Z^* computed from 10,000 samples under case (c). $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S_{R1}, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

τ	m	$e^{\gamma\tau}$	S_{R1}	R	Z^*
5	10	2	0.229	0.168	0.163
		4	0.706	0.514	0.506
	20	2	0.485	0.271	0.261
		4	0.958	0.796	0.793
	50	2	0.896	0.583	0.622
		4	1.000	0.994	0.995
10	10	2	0.415	0.359	0.387
		4	0.931	0.845	0.901
	20	2	0.750	0.630	0.676
		4	1.000	0.998	0.997
	50	2	0.993	0.942	0.960
		4	1.000	1.000	1.000
20	10	2	0.672	0.673	0.689
		4	0.999	0.998	0.999
	20	2	0.972	0.950	0.959
		4	1.000	1.000	1.000
	50	2	1.000	0.999	1.000
		4	1.000	1.000	1.000

Table 4.5: Proportion of rejection of $H_0 : \gamma = 0$ under the case (d), based on 1,000 samples.

τ	m	$e^{\gamma\tau}$	a^*	S^*_{R1}	R	Z^*
5	10	2	0.863	0.105	0.087	0.100
		4	0.538	0.314	0.260	0.310
	20	2	0.863	0.188	0.155	0.162
		4	0.538	0.581	0.441	0.500
	50	2	0.863	0.402	0.323	0.343
		4	0.538	0.951	0.856	0.913
10	10	2	0.893	0.247	0.254	0.273
		4	0.575	0.721	0.697	0.761
	20	2	0.893	0.463	0.431	0.485
		4	0.575	0.971	0.953	0.981
	50	2	0.893	0.864	0.778	0.829
		4	0.575	1.000	1.000	1.000
20	10	2	0.908	0.521	0.534	0.591
		4	0.595	0.982	0.985	0.992
	20	2	0.908	0.843	0.819	0.857
		4	0.595	1.000	1.000	1.000
	50	2	0.908	0.997	0.995	0.999
		4	0.595	1.000	1.000	1.000

Table 4.6: Proportion of rejection of $H_0 : \gamma = 0$ under the case (e) when $b = 0.75$, based on 1,000 samples.

τ	m	$e^{\gamma\tau}$	a^*	S^*_{R1}	R	Z^*
5	10	2	0.431	0.218	0.160	0.195
		4	0.269	0.602	0.527	0.596
	20	2	0.431	0.359	0.293	0.337
		4	0.269	0.919	0.847	0.899
	50	2	0.431	0.831	0.701	0.747
		4	0.269	1.000	0.998	1.000
10	10	2	0.446	0.486	0.490	0.514
		4	0.288	0.968	0.967	0.978
	20	2	0.446	0.820	0.791	0.836
		4	0.288	1.000	1.000	1.000
	50	2	0.446	0.997	0.993	0.999
		4	0.288	1.000	1.000	1.000
20	10	2	0.454	0.819	0.842	0.878
		4	0.298	1.000	1.000	1.000
	20	2	0.454	0.996	0.998	0.998
		4	0.298	1.000	1.000	1.000
	50	2	0.454	1.000	1.000	1.000
		4	0.298	1.000	1.000	1.000

Table 4.7: Proportion of rejection of $H_0 : \gamma = 0$ under the case (e) when $b = 1.5$, based on 1,000 samples.

τ	m	$e^{\gamma\tau}$	S_{R1}	R	Z^*
5	10	2	0.281	0.080	0.093
		4	0.713	0.309	0.333
	20	2	0.509	0.123	0.132
		4	0.973	0.541	0.613
	50	2	0.902	0.222	0.281
		4	1.000	0.890	0.951
10	10	2	0.412	0.215	0.246
		4	0.921	0.735	0.796
	20	2	0.755	0.378	0.485
		4	1.000	0.957	0.981
	50	2	0.993	0.787	0.869
		4	1.000	1.000	1.000
20	10	2	0.716	0.593	0.649
		4	0.993	0.989	0.995
	20	2	0.960	0.878	0.917
		4	1.000	1.000	1.000
	50	2	1.000	0.999	1.000
		4	1.000	1.000	1.000

Table 4.8: Proportion of rejection of $H_0 : \gamma = 0$ under the case (f), based on 1,000 samples.

4.4.2 Summary

The simulation studies were conducted to assess the accuracy of the $N(0,1)$ approximations for S_{R1}, S^*_{R1}, R and Z^* statistics under the null hypothesis, in different scenarios. Based on 10,000 samples of each statistic, normal Q-Q plots as well as a detailed table showed that, when the null model is an HPP (case (a)), p-values for the linear rank and Lewis-Robinson tests can be found from standard normal approximations in all scenarios considered (i.e. $m = 10$, 20, 50 and $\tau = 5$, 20). The standard normal approximation is suitable for S_{R1}, but a little off in the extreme tails when $m = 10$. In case (b), we generated data from a renewal process with gap times following a gamma distribution with shape parameter 0.75 or 1.5. In this case, S_{R1} is biased so we proposed a mean correction for S_{R1}. Normal Q-Q plots and tables suggested that the normal approximations for S^*_{R1} is off in the extreme tails when $m = 10$, but is satisfactory otherwise. In all scenarios, normal approximations are suitable for R and Z^*. In case (c), we considered a delayed renewal process as the null model. The normal approximation is adequate for S_{R1} especially when $m > 10$, but not for the R and Z^* statistics, which are biased. We also conducted simulation studies to compare the powers of the tests in three different cases. In all cases, S_{R1} (S^*_{R1} in case (e)) is the overall most powerful test for monotonic trend.

We recommend using S_{R1} as a routine check for monotonic trends in identical processes when $m \geq 10$. It is easy to implement, powerful against different types of monotonic trend alternatives, and can be used with covariates. A good idea is to look at S^*_{R1} as well. If the results of S_{R1} and S^*_{R1} are too different, S^*_{R1} can be used instead of S_{R1}. When m is small but the τ_i are large, either R or Z^* can be used. However, it should be noted that these tests assume the processes are renewal processes. Research is needed regarding tests when this assumption is unsatisfactory.

Chapter 5

Testing for Trend in Nonidentical Recurrent Event Processes

A general introduction and definition of trends was given in Section 4.1, and after that trends were considered in identical processes throughout Chapter 4. It has been, however, stressed by several authors that it is important to allow for any heterogeneity in the form of variation in event rates or gap time distributions across the m processes (e.g. Cox and Lewis, 1966, p. 49; Kvaloy and Lindqvist, 2003). Failure to recognize such heterogeneity can lead to improper rejection of a hypothesis of no trend in cases where the m processes are each actually trend-free. Hence, in this chapter we allow for heterogeneity between processes in the tests for trend of Chapter 4.

In Section 5.1, we review some specific models and tests for trend, with which we will make comparisons. Section 5.2 gives robust tests for trend in nonidentical processes in settings with and without covariates. Section 5.3 presents simulation studies on the behavior and power of robust tests and others, and Section 5.4 illustrates the tests.

5.1 Models and Tests for Trend

In this section, we consider the trend tests of Chapter 4 in nonidentical processes settings. As in Section 4.1, we divide the important trend tests into (i) tests of a homogeneous Poisson process, and (ii) tests of a general renewal process, and focus on tests which are practical in usage. The models with covariates are consider in Section 5.2.3.

Suppose that m independent processes are under observation. Consider an individual process i ($i = 1, \ldots, m$) which starts at time $t = 0$, and let $N_i(t)$ denote the number of events in $[0, t]$. The gap times between successive events are denoted by $W_{ij} = T_{ij} - T_{i,j-1}$, ($j = 1, \ldots, n_i$), where $T_{i0} = 0$. The process $\{N_i(t); t > 0\}$ is assumed to be under observation over a time period $[\tau_{0i}, \tau_i]$ and in that case, we define $T_{i0} = \tau_{0i}$ and let $N_i(\tau_{0i}, t)$ represent the number of events in $(\tau_{0i}, t]$, for $\tau_{0i} \le t \le \tau_i$. Unless otherwise stated, we assume that processes are under observation continuously throughout this chapter; that is, $Y_i(t) = I(\tau_{0i} \le t \le \tau_i)$. The history of events $\mathcal{H}_i(t)$ consists of the number $N_i(t) = n_i$ of events and their times $0 < T_{i1} < \ldots < T_{in} < t$ as well as all information on $Y_i(t)$, $t \in [\tau_{0i}, \tau_i]$.

5.1.1 Tests Based on Nonidentical Poisson Processes

The model (4.1) based on nonhomogeneous Poisson processes where the rate function for the ith process is extended here so the rate function fot the ith process is ($i = 1, \ldots, m$)

$$\rho_i(t) = \alpha_i e^{\beta g(t)}, \qquad t \ge 0, \tag{5.1}$$

where $g(t)$ is a specified function, $\alpha_1, \ldots, \alpha_m$ are positive-valued parameters, and β is a real-valued parameter. A test of no trend is based on the hypothesis $H_0 : \beta = 0$, under which the ith process is a homogeneous Poisson process with event rate α_i.

As in Section 4.2.1, a score test based on a conditional likelihood function for β can be used for testing no trend in Poisson processes (Cox and Lewis, 1966, Section 3.3). We consider the case where the ith process is observed over the time interval $[\tau_{0i}, \tau_i]$, where τ_{0i} and τ_i are independent of the event process; this is the most common observation scheme in practice. The likelihood function for $(\boldsymbol{\alpha}, \beta)$, where $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m)'$, based on data set $\{N_i(\tau_{0i}, \tau_i);\, t_{i1}, \ldots, t_{in_i};\, i = 1, \ldots, m\}$ is (cf. Section 1.4.1)

$$L(\boldsymbol{\alpha}, \beta) = \prod_{i=1}^{m} \left\{ \alpha_i^{n_i} \exp\left[\beta \sum_{j=1}^{n_i} g(t_{ij}) - \int_{\tau_{0i}}^{\tau_i} \alpha_i e^{\beta g(s)}\, ds \right] \right\}. \tag{5.2}$$

From (5.2) and the fact that $N_i(\tau_{0i}, \tau_i)$ has a Poisson distribution with mean $\mu_i(\tau_{0i}, \tau_i) = \int_{\tau_{0i}}^{\tau_i} \rho_i(s)\, ds$, the conditional distribution of the event times T_{ij} ($i = 1, \ldots, m; j = 1, \ldots, n_i$) given the n_i, where $N_i(\tau_{0i}, \tau_i) = n_i > 0$, is

$$L_c(\beta) = \prod_{i=1}^{m} \prod_{j=1}^{n_i} \left\{ \frac{n_i!\, e^{\beta g(t_{ij})}}{\int_{a_i}^{b_i} e^{\beta g(t)}\, dt} \right\}. \tag{5.3}$$

From (5.3), we obtain the conditional score function

$$\begin{aligned} U_c(\beta) &= \frac{\partial}{\partial \beta} \log L_c(\beta) \\ &= \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} g(t_{ij}) - \sum_{j=1}^{n_i} \frac{\int_{\tau_{0i}}^{\tau_i} g(s)\, e^{\beta g(s)}\, ds}{\int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\, ds} \right\}, \end{aligned} \tag{5.4}$$

and the variance of $U_c(\beta)$ based on Poisson model as

$$\begin{aligned} Var\{U_c(\beta)\} &= -\frac{\partial^2}{\partial\beta^2}\log L_c(\beta) \\ &= \sum_{i=1}^{m} n_i \left\{ \frac{\int_{\tau_{0i}}^{\tau_i} g^2(s)e^{\beta g(s)}\,ds}{\int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\,ds} - \left(\frac{\int_{\tau_{0i}}^{\tau_i} g(s)e^{\beta g(s)}\,ds}{\int_{\tau_{0i}}^{\tau_i} e^{\beta g(s)}\,ds} \right)^2 \right\}. \end{aligned} \tag{5.5}$$

A test of $H_0 : \beta = 0$ can be based on the conditional score statistic $U_c(0)$. A little algebra shows that

$$U_c(0) = \sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} g\left(t_{ij}\right) - \frac{n_i}{\tau_i - \tau_{0i}} \int_{\tau_{0i}}^{\tau_i} g(s)\,ds \right\}, \tag{5.6}$$

and that, under H_0, the variance of $U_c(0)$ conditional on $n_1, \ldots, n_m$ is

$$Var\left\{U_c(0)\right\} = \sum_{i=1}^{m} n_i \left\{ \frac{\int_{\tau_{0i}}^{\tau_i} g(s)^2\,ds}{\tau_i - \tau_{0i}} - \left[\frac{\int_{\tau_{0i}}^{\tau_i} g(s)\,ds}{\tau_i - \tau_{0i}} \right]^2 \right\}. \tag{5.7}$$

The standardized score statistic for testing H_0 is given by

$$S_c = \frac{U_c(0)}{Var\left\{U_c(0)\right\}^{1/2}}. \tag{5.8}$$

The asymptotic distribution for the test statistic S_c is standard normal as $m \to \infty$ so p-values for H_0 can be obtained from this approximation. When m and the n_i are small, we can obtain p-values based on (5.7) by simulation. Since S_c is defined by conditioning on the observed values of $n_1, \ldots, n_m$, the appropriate simulation procedure under H_0 is, for each process, to generate the times t_{ij} ($j = 1, \ldots, n_i$) as a random sample of size n_i from the uniform distribution on $[\tau_{0i}, \tau_i]$.

The best known test of this type is the Laplace test, which comes from taking $g(t) = t$. It has been considered by many authors (e.g. Cox and Lewis, 1966, Section 3.3) and simplification of (5.6) and (5.7) in this case gives the test statistic (e.g. Kvaloy and Lindqvist, 1998)

$$S_{LA} = \frac{\sum_{i=1}^{m} \left\{ \sum_{j=1}^{n_i} T_{ij} - n_i(\tau_i + \tau_{0i})/2 \right\}}{\left\{ \sum_{i=1}^{m} n_i(\tau_i - \tau_{0i})^2/12 \right\}^{1/2}}. \tag{5.9}$$

Another well known test (e.g. Kvaloy and Lindqvist 1998, Section 2.6) corresponds to $g(t) = \log t$. Various authors (e.g. Bain et al., 1985; Cohen and Sackrowitz, 1993) have conducted power studies for these tests. Most attention has been paid to monotonic trends, where $g(t)$ is either an increasing or decreasing function of t but in principle $g(t)$

could be nonmonotonic. For example, if a seasonal trend in events was a possibility, $g(t)$ could be defined accordingly. It is also possible to make $g(t)$ and β in (5.1) vectors, with $g(t)$ chosen to reflect different types of trends (e.g. Augustin and Pena, 2005), but we focus here on single functions $g(t)$.

As explained in Section 4.2.2, an important limitation of tests based on Poisson processes is that processes are assumed to be HPP in the absence of trend. Therefore, we consider tests based on renewal processes next.

5.1.2 Tests Based on Renewal Processes

In this section, we consider tests of the renewal process hypothesis H_0 : For each $i = 1, \ldots, m$ on the W_{ij} ($j = 1, 2, \ldots$) are i.i.d. The tests were introduced in Section 4.2.2 for identical processes, but we can use them for testing no trend in nonidentical processes as well. In particular, tests considered are the linear rank test R given in (4.15) and the Lewis-Robinson test Z given in (4.16). Simulation studies in nonidentical processes including R and Z are given in Section 5.3.

5.2 Robust Trend Tests Based on Rate Functions

5.2.1 Pseudo Score Tests

Robust estimating function procedures are explained in Section 1.4.4, and robust tests for testing trend in identical processes are discussed in Section 4.3. In this section, we extend the tests in Section 4.3 to the nonidentical case.

Let the rate functions be $\rho_i(t)$ for independent processes $i = 1, \ldots, m$. We consider tests of the null hypothesis ($i = 1, \ldots, m$)

$$H_0 : \rho_i(t) = \alpha_i, \qquad t \geq 0, \tag{5.10}$$

where $\alpha_1, \ldots, \alpha_m$ are unknown positive values. A robust test for H_0 can be developed by considering the models with rate functions $\rho_i(t) = \alpha_i \exp(\beta g(t))$. As in Section 4.3, we do not assume that the processes are Poisson. In the following development, it is required that the τ_i and τ_{0i} are independent of the event processes.

We now show that the statistic $U_c(0)$ in (5.6) derived under the assumption of a Poisson process can in fact be applied more generally. We define $\bar{g}_i = \int_{\tau_{0i}}^{\tau_i} g(t)\, dt/(\tau_i - \tau_{0i})$. Then, noting that $n_i = \int_{\tau_{0i}}^{\tau_i} dN_i(t)$, we can rewrite (5.6) as

$$U(0) = \sum_{i=1}^{m} U_i(0) = \sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} [g(t) - \bar{g}_i]\ dN_i(t). \tag{5.11}$$

It is easily seen that under H_0 of (5.10), $E\{U(0)\} = 0$ and that under alternatives of the form (5.1), $E\{U(0)\}$ will be bigger or smaller than zero when $g(t)$ is increasing and decreasing, respectively. In addition, the terms $U_i(0)$ in (5.11) for $i = 1, \ldots, m$ are independent and so $Var\{U(0)\}$ can be estimated under H_0 by

$$\widehat{Var}\,\{U(0)\} = \sum_{i=1}^{m} U_i(0)^2, \tag{5.12}$$

leading to the standardized statistic

$$S = \sum_{i=1}^{m} U_i(0) / \left\{ \sum_{i=1}^{m} U_i(0)^2 \right\}^{1/2} \tag{5.13}$$

for testing H_0. The variance estimate (5.12) is different than the Poisson estimate (5.7), and is robust to stationary departures from a Poisson process.

Provided $g(t)$ is integrable over the intervals $[\tau_{0i}, \tau_i]$, which have some positive minimum length, the distribution of S is asymptotically standard normal under H_0 as $m \to \infty$. The speed of approach to normality depends on the values of $\alpha_i(\tau_i - \tau_{0i})$ and, especially when m is small or moderate in size, a normal approximation used to obtain p-values may be somewhat inaccurate. A possible alternative is to use a permutation approach to obtain a p-value, by considering the distribution of (5.13) under random permutation of the W_{ij} ($j = 1, \ldots, n_i$) for each $i = 1, \ldots, m$. Another caveat about (5.13), is that when m is small the variability in (5.12) may be larger than the variability of model-based variance estimates such as (5.7). This can affect the power to detect trends and so, as usual, we may face a robustness-efficiency tradeoff. These points are examined in Section 5.3.

A final important point is that the statistic (5.13) will have good power for trend alternatives of the form (5.1), but will also have reasonable power against alternative $\rho_i(t)$ with broadly similar shapes to (5.1). In particular, note from (5.11) that if $\rho_i(t)$ is the true rate for process i, then

$$E\{U(0)\} = \sum_{i=1}^{m} \int_{\tau_{0i}}^{\tau_i} [g(t) - \bar{g}_i]\, \rho_i(t)\, dt, \tag{5.14}$$

so that if the terms in (5.14) are bounded away from zero, say $|E\{U_i(0)\}| > C > 0$, then a two-sided test based on S will reject H_0 of (5.10) with probability approaching one as m increases. This feature has been observed in previous empirical studies of tests based on Poisson processes (e.g. Bain et al., 1985).

5.2.2 The Generalized Laplace Test

For the special case $g(t) = t$ the test statistic S in (5.13) has numerator terms

$$U_i(0) = \sum_{j=1}^{n_i} T_{ij} - \frac{n_i\,(\tau_{0i} + \tau_i)}{2}, \qquad i = 1, \ldots, m. \tag{5.15}$$

The Poisson process-based statistic S_c in (5.8) has the same numerator but a different denominator. The denominators will tend to differ according to how much the T_{ij} depart from an ordered uniform random sample, which affects how much $\text{Var}(\sum_{j=1}^{n_i} T_{ij})$ differs from $n_i(\tau_i - \tau_{0i})^2$.

It is of interest that the Lewis-Robinson test statistic Z in (4.16) has the same form as a Laplace statistic S_{LA} in (5.9) modified for observation with the n_i fixed, and with variances based on a general renewal process. It is possible to make ad hoc adjustments to Z for the case of fixed observation periods $[\tau_{0i}, \tau_i]$, but as noted above, component pseudo scores (5.15) do not in general have means equal to zero under a renewal process model. However, the adjustment in Section 4.4 (see p. 118) can be used. This is considered in Section 5.3. In fact, a renewal process starting, say, at $t = 0$ does not in general have a constant rate function though as t increases, the rate function approaches the constant $E(W_{ij})^{-1}$ (e.g. Cook and Lawless, 2007, Problem 2.8). Thus, if one observes renewal processes which started a sufficiently long time prior to τ_{0i}, then the rate function over $[\tau_{0i}, \tau_i]$ will be approximately constant. It is important to bear in mind, however, that the families of "no trend" processes represented by either a constant rate function or a renewal process, overlap only for homogeneous Poisson processes, when we observe the processes from their time origins.

5.2.3 Settings with Covariates

Kvist et al. (2008) give tests for trend in the presence of covariates but assume homogeneous Poisson processes in the null hypothesis. We remove this restriction and allow external time-varying covariates in the model. In this way, we provide tests for determining whether a trend exists after adjustment for external factors that may result in variations in the rate of events.

Let $\boldsymbol{x}_i(t)$ be a vector of time-varying external covariates and let $\boldsymbol{v}_i$ be a vector of fixed covariates for process i ($i = 1, \ldots, m$). We consider models where the rate functions are

$$\rho_i(t) = \alpha_i e^{\beta g(t) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t) + \boldsymbol{\delta}' \boldsymbol{v}_i}, \qquad t \geq 0, \tag{5.16}$$

and consider the null hypothesis $H_0 : \beta = 0$. A conditional likelihood based on Poisson processes with rate functions (5.16) is given by the distribution of the event times T_{ij} ($j = 1, \ldots, n_i$), given $N_i(\tau_{0i}, \tau_i) = n_i$. Corresponding to $L_c(\beta)$ in Section 5.1.1, we now have

$$L_c(\beta, \boldsymbol{\gamma}) = \prod_{i=1}^{m} \left\{ \frac{n_i! \prod_{j=1}^{n_i} e^{\beta g(t_{ij}) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t_{ij})}}{\left(\int_{\tau_{0i}}^{\tau_i} e^{\beta g(t) + \boldsymbol{\gamma}' \boldsymbol{x}_i(t)} \, dt \right)^{n_i}} \right\}, \tag{5.17}$$

and neither the α_i or $\boldsymbol{\delta}$ in (5.16) are present. Note that (5.17) and (4.26) given in Section 4.3.1 are exactly the same. Therefore, a test of H_0 can be develop following the procedure of Section 4.3.1.

5.3 Simulation Studies

In this section, we present the results of simulation studies conducted for nonidentical processes to assess when asymptotic normal approximations for trend test statistics of this chapter are satisfactory, and to discuss their power. To be consistent with the simulation studies presented in Section 4.4 for identical processes, we consider similar models under null and alternative hypothesis. Hence, we consider the following three types of "no trend" null hypothesis:

(a) H_0 : Process i ($i = 1, \ldots, m$) is a HPP with rate α_i,

(b) H_0 : Process i ($i = 1, \ldots, m$) is a renewal process with gap times W_{ij} ($j = 1, \ldots, n_i$) following a gamma distribution with scale a_i and shape b,

(c) H_0 : Process i ($i = 1, \ldots, m$) has intensity function $\alpha_i \exp\{\beta z_i(t)\}$, where $z_i(t) = I(N_i(t^-) > 0)I(B_i(t) \leq \Delta)$.

We will follow a similar approach to Section 4.4. Once again case (a) is the special case of (b) when $b = 1$ and $a_i = \alpha_i^{-1}$. We consider $b = 0.75$ and 1.5 for case (b). Case (c) includes a term for a carryover effect, and is a delayed renewal process. In simulations, we consider $\exp(\beta) = 5$ and $\Delta = 0.05$. We take the α_i in (a) and (c) and the a_i in (b) to have fixed values, as follows: $\alpha_i = 0.5 + (i-1)/(m-1)$ for $i = 1, \ldots, m$ so that the α_i range from 0.5 to 1.5, with an average of 1 in (a) and (c); for (b) we take $a_i = (\alpha_i b)^{-1}$, which gives average gap time $a_i b = \alpha_i^{-1}$ and thus an event rate approaching α_i as $t \to \infty$. We take $\tau_i = \tau$ ($i = 1, \ldots, m$), with τ taking values 5 and 20 and $m = 10$, 20 or 50 processes so that the expected total number of events under each null hypothesis setting is approximately (exactly, in case (a)) $m\tau$. We consider the following test statistics for "no trend":

(1) the generalized Laplace statistic S in (5.13) with $U_i(0)$ as in (5.15),

(2) the linear rank statistic R in (4.15),

(3) Z^*, a corrected version of the generalized Lewis-Robinson statistic, where $Z^* = \frac{1}{\sqrt{m}} \sum_{i=1}^{m} \sqrt{\frac{n_i}{n_i+1}} Z_i$ and Z_i is given in (4.16).

In the calculation of R and Z^*, we ignore the final censored gap between t_{n_i} and τ, and only use the processes with $n_i \geq 2$. We simulated 10,000 runs for each of the "no trend" scenarios (a), (b) and (c) and (m, τ) combinations. For each test statistic (1), (2) and (3) we used the same generated data, and report on its distribution and the adequacy of the standard normal approximation.

In case (a), we present results as Normal quantile-quantile (Q-Q) plots of the 10,000 values of the test statistics in (1), (2) and (3) in Figures 5.1, 5.2 and 5.3; see Section 5.3.1. We show results when $\tau = 5$ and $m = 10$, 20 or 50. The standard normal approximation is accurate for all statistics when $m = 20$ and 50, but off in extreme tails for S when $m = 10$. This can also be seen in Table 5.1, which summarizes features of the plots, for $\tau = 10$ as well as for $\tau = 20$.

As we discussed in Section 4.4, S shows bias (i.e. $E\{U_i(0)) \neq 0\}$) in case (b) where we generated data from a renewal process where the W_{ij} have a gamma distribution with scale a_i and shape $b \neq 1$. As in the identical processes case, the bias disappears as τ increases. The permutation method explained in Section 4.4 can be used for a mean adjustment in S. However, we consider the analytic method of Section 4.4, and use the following test statistic in case (b):

$$S^* = \sum_{i=1}^{m} U_i^*(0) / \left\{ \sum_{i=1}^{m} U_i^*(0)^2 \right\}^{1/2}, \tag{5.18}$$

where $U_i^*(0) = U_i(0) - \bar{U}_i(0)$, $\bar{U}_i(0) = [(n_i+1)t_{in_i} - n_i\tau_i]/2$ and $U_i(0)$ is given in (5.15). We generated 10,000 realizations of m processes by generating the W_{ij} from the distribution in (b) with $b = 0.75$. The normal Q-Q plots in Figures 5.4, 5.5 and 5.6 show that normal approximation is adequate for S^*, R and Z^* when $m = 20$ or 50. Table 5.2 summarizes features of the plots and supports these remarks. We also conducted a simulation study by generating data from the renewal process given in (b) with $b = 1.5$. As seen from the normal Q-Q plots in Figures 5.7, 5.8 and 5.9 and in Table 5.3, the results for $b = 1.5$ are similar to those for $b = 0.75$. It should be noted that the normal approximation is suitable for S^* in case (b), where $E\{U_i(0)\} \neq 0$, as well as in case (a), where $E\{U_i(0)\} = 0$.

In case (c), we consider a delayed renewal process where W_{i1} $(i = 1, \ldots, m)$ has the hazard function $h_{i1}(w) = \alpha_i$ and the W_{ij} $(i = 1, \ldots, m;\ j = 2, 3, \ldots)$ have the hazard function $h_{ij}(w) = \alpha_i(e^{\beta} - 1)I(w < \Delta) + \alpha_i$, $w > 0$, as in case (c) of Section 4.4. Normal Q-Q plots based on the 10,000 simulated values of the test statistics S, R and Z^* are given in Figure 5.10, 5.11 and 5.12 when $\tau = 5$ and $m = 10$, 20 or 50, respectively. As discussed in the identical processes case, the normal approximation is not suitable for R and Z^*, but our preliminary studies showed that normal approximation becomes adequate as τ increases, when m is fixed. This can also be seen in Table 5.4 where we display the results for $m = 10$, 20 and 50 when $\tau = 5$ as well as when $\tau = 20$. Note that the results for S are very similar to those given in Tables 5.2 and 5.3 for cases (a) and (b).

We next consider power of the three test statistics, and introduce the following families of models to incorporate an increasing trend.

(d) Process i ($i = 1, \ldots, m$) is a NHPP with rate function $\rho_i(t) = \alpha_i^* \exp(\gamma t)$,

(e) Process i ($i = 1, \ldots, m$) is a renewal process where the gap times W_{ij} ($j = 1, 2, \ldots$) are independent random variables, with W_{ij} having a gamma distribution with scale $a_i^* \exp(\gamma j)$ and shape b,

(f) Process i ($i = 1, \ldots, m$) has intensity function

$$\lambda_i(t|\mathcal{H}_i(t)) = \alpha_i^* \exp(\gamma t) \exp(\beta z_i(t)), \qquad t \geq 0,$$

where $z_i(t) = I(N_i(t^-) > 0) I(B_i(t) \leq \Delta)$.

Note that once again the cases (d), (e) and (f) above are in agreement with the cases (d), (e) and (f) of Section 4.4. The power of tests S (S^* in case (e)), R and Z^* was investigated by simulation. We used 10,000 realizations of the m processes to obtain 5% critical values for each statistic. We consider the "matches" of case (d), (e) and (f) with their corresponding "null model-matches" cases (a), (b) and (c), respectively; and so, chose α_i^* in (d) and (f) and a_i^* in (e) so that we obtained roughly the same expected total numbers of events as in the corresponding null cases. For case (e), we thus chose $a_i^* = (\alpha_i^* b)^{-1}$. We took $e^{\gamma\tau} = 2$ or 4. We considered $\tau = 5$, 10 and 20 and $m = 10$, 20 and 50, and generated 1,000 realizations of m processes in each case. We used the same generated data with all of the three tests.

In case (d), we used the empirical 0.95 quantiles of the test statistics obtained in case (a) as critical values. The proportions of rejection of $H_0 : \gamma = 0$ are given in Table 5.5. The power of the generalized Laplace test S is higher than R and Z^* in each scenario. The powers of Z^* and R are very close, but Z^* is slightly higher in general. This is the case where we expect the Laplace test based on the Poisson model would excel, but using a robust variance estimate also gives good power results. Tables 5.6 and 5.7 shows power of the tests under case (e) with $b = 0.75$ and $b = 1.5$, respectively. We used the modified version of the generalized Laplace statistic S^*, R and Z^*. In both cases, overall R is more powerful than S^* and Z^*, especially for smaller m and larger τ. However, for $m \geq 20$ the robust Laplace test is very good. The powers of the tests are higher when $b = 1.5$, as seen in Table 5.7. In case (f), we used $e^{\beta} = 5$ and $\Delta = 0.05$, and chose α_i^* so that we obtain roughly same n_i for each process as in case (c). Results are given in Table 5.8. The generalized Laplace test S has higher power than the other statistics in each scenario, with the advantage decreasing as τ increases.

Results of simulations are given in Section 5.3.1 below. In Section 5.3.2, we summarize results and give recommendations for trend testing.

5.3.1 Figures and Tables

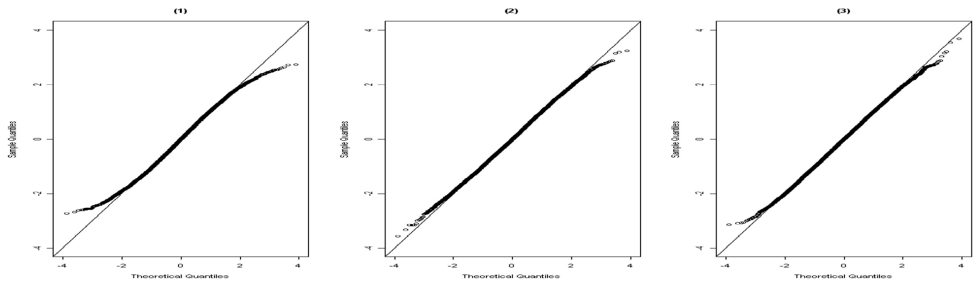

Figure 5.1: Normal Q-Q plots of simulated values of the test statistics (1) S, (2) R and (3) Z^*: Case (a), $\tau = 5$, $m = 10$.

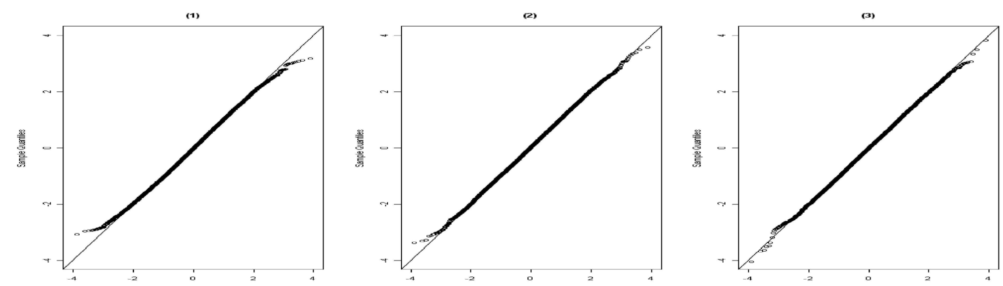

Figure 5.2: Normal Q-Q plots of simulated values of the test statistics (1) S, (2) R and (3) Z^*: Case (a), $\tau = 5$, $m = 20$.

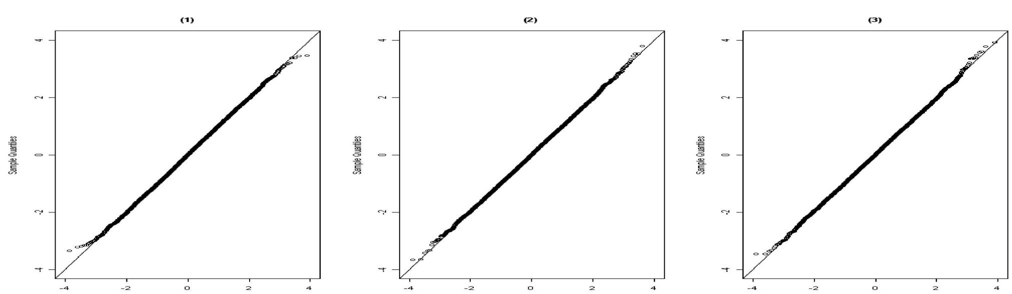

Figure 5.3: Normal Q-Q plots of simulated values of the test statistics (1) S, (2) R and (3) Z^*: Case (a), $\tau = 5$, $m = 50$.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S	1.636	1.882	2.123	0.049	0.018	0.004
		R	1.623	1.911	2.232	0.048	0.022	0.007
		Z^*	1.624	1.921	2.194	0.048	0.022	0.007
	20	S	1.632	1.960	2.261	0.049	0.025	0.008
		R	1.687	2.016	2.336	0.055	0.028	0.010
		Z^*	1.644	1.941	2.291	0.050	0.023	0.009
	50	S	1.657	1.944	2.310	0.052	0.024	0.010
		R	1.638	1.923	2.335	0.049	0.023	0.011
		Z^*	1.614	1.928	2.333	0.048	0.023	0.010
20	10	S	1.644	1.887	2.138	0.050	0.021	0.004
		R	1.609	1.918	2.232	0.047	0.022	0.008
		Z^*	1.685	1.976	2.294	0.055	0.026	0.009
	20	S	1.622	1.906	2.221	0.048	0.022	0.007
		R	1.620	1.918	2.281	0.047	0.022	0.009
		Z^*	1.618	1.971	2.380	0.048	0.026	0.011
	50	S	1.677	1.963	2.336	0.053	0.026	0.010
		R	1.672	1.985	2.305	0.053	0.027	0.009
		Z^*	1.666	1.981	2.325	0.052	0.027	0.010

Table 5.1: $\hat{Q}_p$ is the empirical pth quantile of S, R and Z^* computed from 10,000 samples under case (a). $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

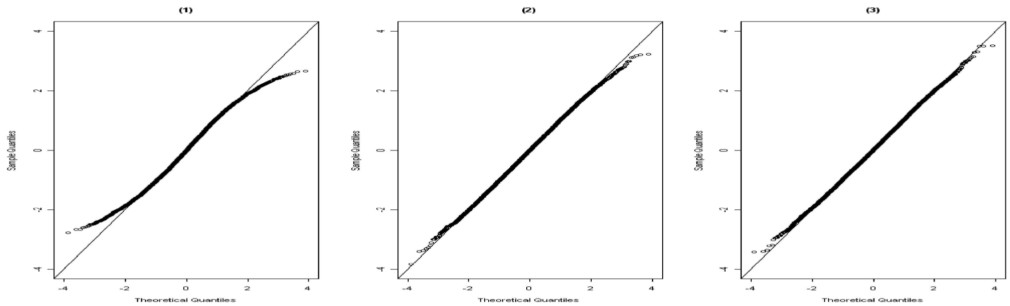

Figure 5.4: Normal Q-Q plots of simulated values of the test statistics (1) S^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 10$, $W_{ij} \sim Gamma(a, b = 0.75)$.

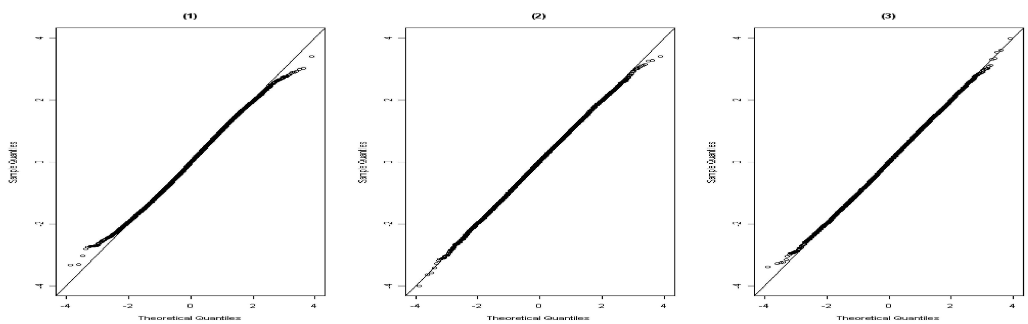

Figure 5.5: Normal Q-Q plots of simulated values of the test statistics (1) S^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 20$, $W_{ij} \sim Gamma(a, b = 0.75)$.

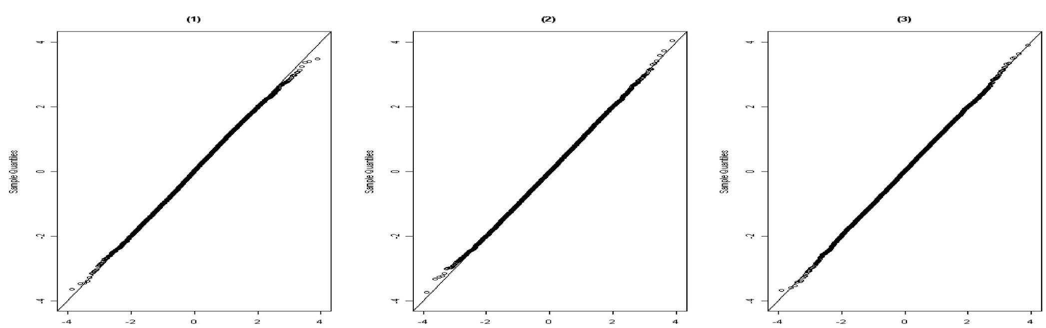

Figure 5.6: Normal Q-Q plots of simulated values of the test statistics (1) S^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 50$, $W_{ij} \sim Gamma(a, b = 0.75)$.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S^*	1.630	1.875	2.090	0.048	0.017	0.003
		R	1.650	1.924	2.239	0.051	0.023	0.008
		Z^*	1.665	1.965	2.272	0.053	0.025	0.008
	20	S^*	1.658	1.923	2.255	0.052	0.023	0.008
		R	1.665	1.944	2.262	0.053	0.024	0.008
		Z^*	1.639	1.949	2.308	0.050	0.024	0.010
	50	S^*	1.650	1.945	2.262	0.051	0.024	0.008
		R	1.651	1.963	2.308	0.051	0.025	0.010
		Z^*	1.652	1.968	2.271	0.051	0.026	0.009
20	10	S^*	1.641	1.869	2.123	0.050	0.020	0.004
		R	1.640	1.964	2.354	0.049	0.026	0.011
		Z^*	1.650	1.945	2.284	0.050	0.024	0.009
	20	S^*	1.680	1.968	2.313	0.054	0.026	0.010
		R	1.626	1.931	2.243	0.049	0.023	0.008
		Z^*	1.657	1.985	2.382	0.052	0.026	0.011
	50	S^*	1.660	1.943	2.275	0.052	0.024	0.009
		R	1.591	1.933	2.271	0.046	0.023	0.009
		Z^*	1.673	1.967	2.276	0.052	0.026	0.009

Table 5.2: $\hat{Q}_p$ is the empirical pth quantile of S^*, R and Z^* computed from 10,000 samples under case (b) nonidentical processes when $b = 0.75$. $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S^*, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

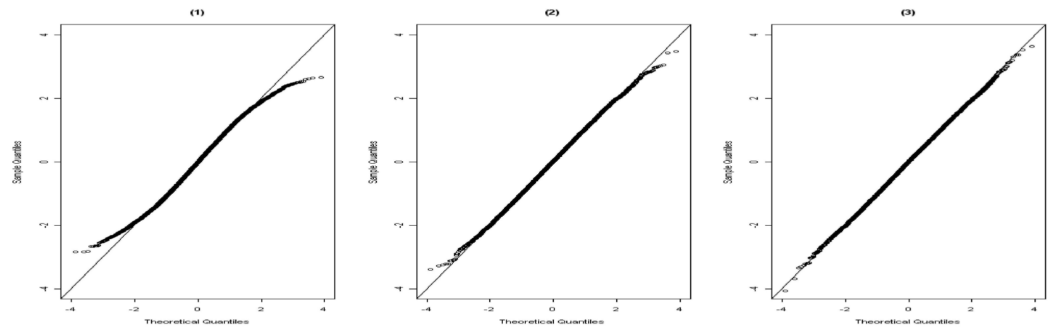

Figure 5.7: Normal Q-Q plots of simulated values of the test statistics (1) S^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 10$, $W_{ij} \sim Gamma(a, b = 1.5)$.

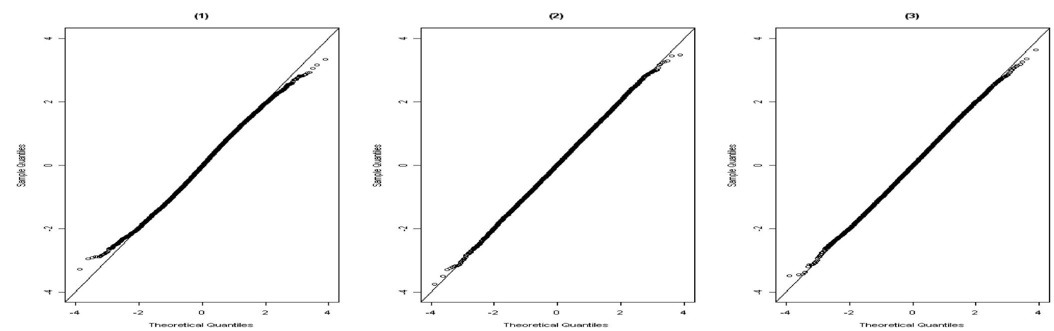

Figure 5.8: Normal Q-Q plots of simulated values of the test statistics (1) S^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 20$, $W_{ij} \sim Gamma(a, b = 1.5)$.

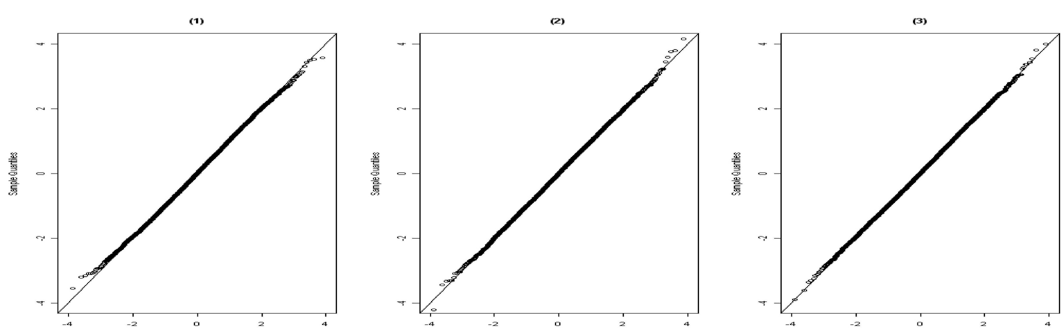

Figure 5.9: Normal Q-Q plots of simulated values of the test statistics (1) S^*, (2) R and (3) Z^*: Case (b), $\tau = 5$, $m = 50$, $W_{ij} \sim Gamma(a, b = 1.5)$.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S^*	1.651	1.866	2.093	0.051	0.018	0.004
		R	1.669	1.954	2.252	0.054	0.025	0.008
		Z^*	1.608	1.908	2.227	0.047	0.022	0.007
	20	S^*	1.635	1.926	2.224	0.049	0.022	0.007
		R	1.672	1.996	2.381	0.053	0.027	0.012
		Z^*	1.659	1.966	2.287	0.051	0.025	0.009
	50	S^*	1.661	1.982	2.305	0.052	0.026	0.009
		R	1.633	1.917	2.292	0.048	0.023	0.009
		Z^*	1.647	1.959	2.332	0.051	0.025	0.010
20	10	S^*	1.671	1.911	2.165	0.054	0.021	0.004
		R	1.622	1.948	2.287	0.047	0.024	0.009
		Z^*	1.651	1.934	2.319	0.051	0.024	0.010
	20	S^*	1.638	1.929	2.255	0.050	0.023	0.008
		R	1.639	1.964	2.319	0.050	0.025	0.010
		Z^*	1.620	1.952	2.295	0.048	0.025	0.009
	50	S^*	1.669	1.984	2.310	0.053	0.026	0.010
		R	1.653	1.951	2.336	0.051	0.025	0.010
		Z^*	1.666	1.971	2.346	0.053	0.026	0.011

Table 5.3: $\hat{Q}_p$ is the empirical pth quantile of S^*, R and Z^* computed from 10,000 samples under case (b) nonidentical processes when $b = 1.5$. $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S^*, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

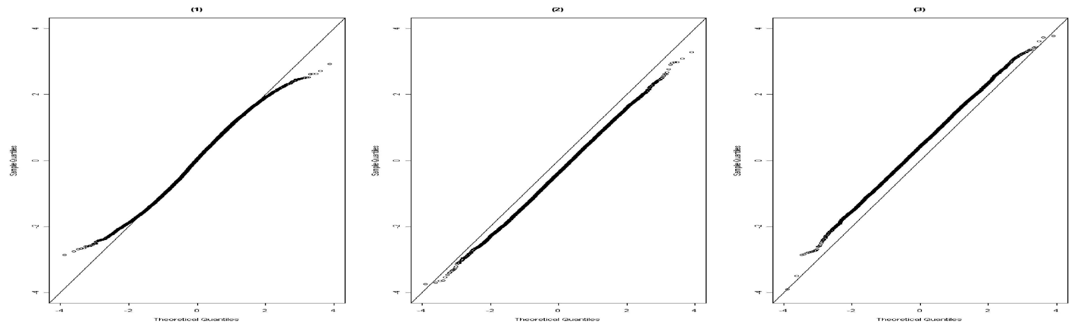

Figure 5.10: Normal Q-Q plots of simulated values of the test statistics (1) S, (2) R and (3) Z^*: Case (c), $\tau = 5$, $m = 10$.

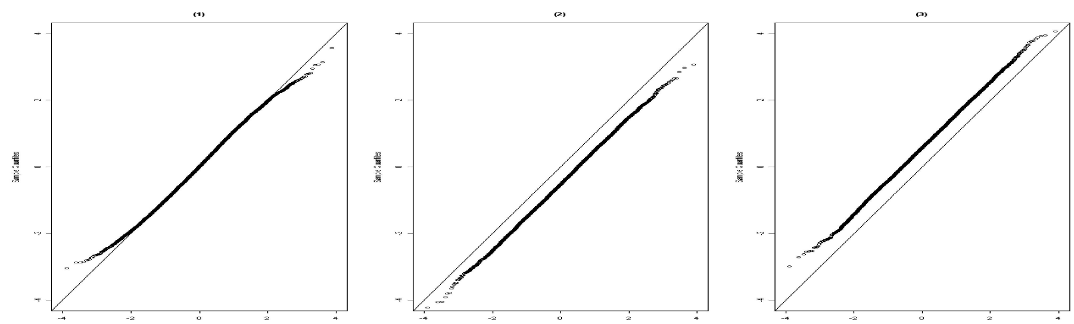

Figure 5.11: Normal Q-Q plots of simulated values of the test statistics (1) S, (2) R and (3) Z^*: Case (c), $\tau = 5$, $m = 20$.

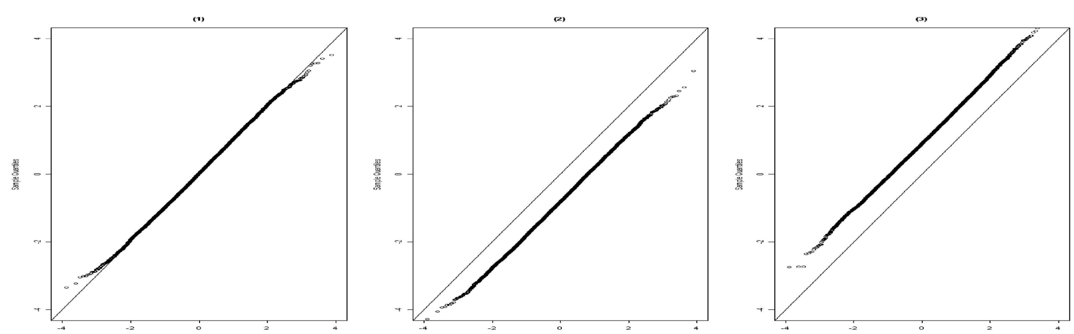

Figure 5.12: Normal Q-Q plots of simulated values of the test statistics (1) S, (2) R and (3) Z^*: Case (c), $\tau = 5$, $m = 50$.

τ	m	Test	$\hat{Q}_{.950}$	$\hat{Q}_{.975}$	$\hat{Q}_{.990}$	$\widehat{\Pr}(\cdot > 1.645)$	$\widehat{\Pr}(\cdot > 1.960)$	$\widehat{\Pr}(\cdot > 2.326)$
5	10	S	1.643	1.887	2.127	0.050	0.019	0.004
		R	1.257	1.555	1.882	0.021	0.008	0.003
		Z^*	2.019	2.317	2.675	0.110	0.058	0.024
	20	S	1.660	1.939	2.233	0.053	0.024	0.006
		R	1.129	1.456	1.784	0.015	0.005	0.002
		Z^*	2.195	2.515	2.874	0.142	0.083	0.038
	50	S	1.657	1.988	2.327	0.052	0.027	0.010
		R	0.839	1.134	1.490	0.007	0.002	0.0003
		Z^*	2.559	2.873	3.283	0.226	0.146	0.077
20	10	S	1.652	1.898	2.173	0.051	0.020	0.004
		R	1.447	1.739	2.094	0.032	0.015	0.005
		Z^*	1.857	2.170	2.561	0.075	0.039	0.018
	20	S	1.657	1.930	2.222	0.052	0.023	0.008
		R	1.340	1.641	2.010	0.025	0.012	0.004
		Z^*	1.915	2.235	2.540	0.086	0.045	0.020
	50	S	1.713	2.003	2.326	0.056	0.029	0.010
		R	1.174	1.459	1.793	0.016	0.007	0.002
		Z^*	2.116	2.421	2.793	0.118	0.067	0.031

Table 5.4: $\hat{Q}_p$ is the empirical pth quantile of S, R and Z^* computed from 10,000 samples under case (c) nonidentical processes. $\widehat{\Pr}(\cdot > Q_p)$ is the proportion of the values of S, R and Z^* in 10,000 samples which are larger than the pth quantile of a standard normal distribution.

τ	m	$e^{\gamma\tau}$	S	R	Z^*
5	10	2	0.234	0.183	0.146
		4	0.710	0.533	0.508
	20	2	0.472	0.282	0.273
		4	0.952	0.804	0.814
	50	2	0.884	0.628	0.623
		4	1.000	0.994	0.993
10	10	2	0.380	0.321	0.326
		4	0.914	0.866	0.896
	20	2	0.788	0.649	0.669
		4	1.000	0.996	0.998
	50	2	0.983	0.922	0.945
		4	1.000	1.000	1.000
20	10	2	0.701	0.669	0.687
		4	0.996	0.997	0.999
	20	2	0.962	0.930	0.945
		4	1.000	1.000	1.000
	50	2	1.000	1.000	1.000
		4	1.000	1.000	1.000

Table 5.5: Proportion of rejection of $H_0 : \gamma = 0$ under the case (d), nonidentical processes, based on 1,000 samples.

τ	m	$e^{\gamma\tau}$	S^*	R	Z^*
5	10	2	0.139	0.171	0.149
		4	0.353	0.536	0.381
	20	2	0.266	0.284	0.219
		4	0.738	0.792	0.671
	50	2	0.602	0.579	0.466
		4	0.994	0.984	0.948
10	10	2	0.284	0.476	0.363
		4	0.710	0.958	0.868
	20	2	0.645	0.689	0.625
		4	0.992	0.999	0.995
	50	2	0.976	0.971	0.931
		4	1.000	1.000	1.000
20	10	2	0.554	0.829	0.749
		4	0.956	1.000	1.000
	20	2	0.946	0.991	0.960
		4	1.000	1.000	1.000
	50	2	1.000	1.000	1.000
		4	1.000	1.000	1.000

Table 5.6: Proportion of rejection of $H_0 : \gamma = 0$ under the case (e), nonidentical processes, when $b = 0.75$ based on 1,000 samples.

τ	m	$e^{\gamma\tau}$	S^*	R	Z^*
5	10	2	0.235	0.365	0.262
		4	0.553	0.897	0.715
	20	2	0.537	0.598	0.477
		4	0.969	0.990	0.938
	50	2	0.935	0.916	0.829
		4	1.000	1.000	1.000
10	10	2	0.511	0.791	0.667
		4	0.915	1.000	0.995
	20	2	0.923	0.960	0.913
		4	1.000	1.000	1.000
	50	2	1.000	1.000	1.000
		4	1.000	1.000	1.000
20	10	2	0.816	0.992	0.968
		4	0.997	1.000	1.000
	20	2	1.000	1.000	0.999
		4	1.000	1.000	1.000
	50	2	1.000	1.000	1.000
		4	1.000	1.000	1.000

Table 5.7: Proportion of rejection of $H_0 : \gamma = 0$ under the case (e), nonidentical processes, when $b = 1.5$ based on 1,000 samples.

τ	m	$e^{\gamma\tau}$	S	R	Z^*
5	10	2	0.272	0.085	0.093
		4	0.694	0.277	0.348
	20	2	0.485	0.101	0.119
		4	0.970	0.500	0.605
	50	2	0.911	0.208	0.259
		4	1.000	0.874	0.925
10	10	2	0.421	0.226	0.257
		4	0.902	0.686	0.775
	20	2	0.738	0.359	0.440
		4	1.000	0.937	0.977
	50	2	0.991	0.717	0.836
		4	1.000	1.000	1.000
20	10	2	0.709	0.523	0.601
		4	0.995	0.980	0.993
	20	2	0.971	0.816	0.894
		4	1.000	1.000	1.000
	50	2	1.000	0.994	0.998
		4	1.000	1.000	1.000

Table 5.8: Proportion of rejection of $H_0 : \gamma = 0$ under the case (f), nonidentical processes, based on 1000 samples.

5.3.2 Summary

We conducted simulation studies to investigate the adequacy of the normal approximations (under the null hypothesis H_0) for the generalized Laplace statistic S, the mean corrected generalized Laplace statistic S^*, the linear rank statistic R and the Lewis-Robinson statistic Z^* in nonidentical processes. Results are similar to those obtained in simulation studies of Chapter 4. Based on 10,000 samples of each scenario for H_0, normal Q-Q plots as well as detailed tables were used. We considered $m = 10$, 20, 50 and $\tau = 5$, 20. In case (a), the null model is an HPP. The normal approximations for R and Z^* are suitable. The normal approximation for S is a little off in the extreme tails when $m = 10$, but is adequate when $m > 10$. In case (b), S is biased. Instead of S, we then used S^*, a mean corrected version of S. The normal approximation is adequate for S^* when $m = 20$ or 50, but it is a little off in the extreme tails when $m = 10$. The p-values for R and Z^* can be found from the standard normal distribution. In case (c), we considered a delayed renewal process as the null model. In this case, the normal approximations for R and Z^* are off. The results for S are similar to results for case (a).

Powers of the tests were considered under three different alternatives which are in concordance with the null hypotheses. In case (d), the alternative model is an NHPP. In this case, the S test is the most powerful. R and Z^* are close in power. In case (e), we generated 1,000 realizations of a semi-Markov model where we generated independent gap times from a gamma distribution with shape parameter 0.75 or 1.5. The R test is the most powerful test in this case, especially when $m = 10$. In case (f), the alternative model is a delayed modulated renewal process, and S is superior.

In conclusion, the generalized Laplace test is recommended when $m \geq 10$ as in Chapter 4. It is easy to implement, powerful in a range of settings, flexible, and does not involve crucial model assumptions. Also, it can be used when covariates are present. The S^* test can be used along with the S test to guard against the cases where the S statistic is biased. When the result of S and S^* are too different, S^* can be preferable, and R can be used to support the conclusion. For small values of m, other tests such as R or Z^* can be used when the τ_i are large enough to provide moderate numbers of events. However, these tests are based on certain assumptions which may need to be checked.

5.4 Example: Hydraulic systems of LHD machines

Load-haul-dump (LHD) machines data were introduced in Section 1.1.1, and investigated in Section 2.6.2 for carryover effects. As discussed previously, Figure 2.10 suggests presence of trend in the rate of occurrence of events of some LHD machines; in particular, in LHD 3, 9 and 17. To illustrate the methods of this chapter, we now consider testing for trend in the LHD data set.

$\hat{\alpha}_1$	$\hat{\alpha}_2$	$\hat{\alpha}_3$	$\hat{\alpha}_4$	$\hat{\alpha}_5$	$\hat{\alpha}_6$	$\hat{\beta}$	$\ell(\hat{\boldsymbol{\alpha}}, \hat{\beta})$
6.231	4.027	2.607	6.062	4.811	4.098	0.295	-163.62
(1.4905)	(1.0643)	(0.8089)	(1.4229)	(1.2067)	(1.0789)	(0.0837)	

Table 5.9: Estimates of the parameters in model (5.19), and the maximum value of the log likelihood function. The numbers in the parentheses are the standard errors of parameter estimates.

$\hat{\alpha}$	$\hat{\beta}$	$\ell(\hat{\alpha}, \hat{\beta}^*)$
5.363	0.181	-157.80
(0.8734)	(0.0712)	

Table 5.10: Estimates of the parameters in model $\rho_i(t) = \alpha e^{\beta^* t}$ and the maximum value of the log likelihood function. The numbers in the parentheses are the standard errors of parameter estimates.

We first consider the model ($i = 1, \ldots, 6$)

$$\rho_i(t) = \alpha_i e^{\beta t}, \qquad t \geq 0, \tag{5.19}$$

and test the null hypothesis $H_0 : \alpha_1 = \alpha_2 = \ldots = \alpha_6 = \alpha$ against the alternative H_1 : *at least one differs*. The maximum likelihood estimates, their standard errors obtained from the inverse of the observed information matrix, and the maximum value of $\ell(\boldsymbol{\alpha}, \beta)$, where $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_6)'$, are given in Table 5.9. The reduced model is given by $\rho_i(t) = \alpha \exp\{\beta^* t\}$, $t \geq 0$ ($i = 1, \ldots, 6$). Table 5.10 shows the m.l.e. of α and β^*, and maximum value of $\ell(\alpha, \beta^*)$. A likelihood ratio test of H_0 gives $\Lambda = 2\ell(\hat{\boldsymbol{\alpha}}, \hat{\beta}) - 2\ell(\hat{\alpha}, \hat{\beta}^*) = 11.63$. The p-value based on $\chi^2_{(5)}$ is 0.04 indicating some evidence against H_0. Therefore, we now conduct a trend test for LHD data for the case of heterogeneous processes.

We consider tests of $H_0 : \beta = 0$ in the model (5.19). The tests used are the generalized Laplace test S, the modified generalized Laplace test S^*, linear rank test R and the corrected Lewis-Robinson test Z^*. The average number of failures per machine is 25. Simulation results in Section 5.3 showed that the $N(0, 1)$ approximation is quite accurate for the p-values for R and Z^*, but not for S and S^*, for which we used a parametric bootstrap based on 5,000 runs. The R statistic gives -2.146. Using $N(0, 1)$, we obtain a two-sided p-value of 0.032. The Lewis-Robinson statistic Z^* is 2.5532, gives a two-sided p-value of 0.011. Similarly, we obtain that $S = 2.017$ and $S^* = 1.864$ with the two-sided p-values 0.037 and 0.046, respectively. According to these results, we conclude that trend is significant in the model at 0.05 level of significance. Note that using $N(0, 1)$ gives a two-sided p-value 0.044 for S and 0.062 for S^*.

There is an indication in Figure 2.10 that β in (5.19) might be β_i (different for each

Machine	$\hat{\alpha}$	$\hat{\beta}$	$\tilde{\alpha}$
LHD 1	-5.6794 (0.537547)	0.000697 (0.000311)	-4.6870 (0.208514)
LHD 3	-5.3485 (0.442624)	0.000213 (0.000199)	-4.9490 (0.200000)
LHD 9	-6.1239 (0.491414)	0.000354 (0.000150)	-5.1686 (0.192450)
LHD 11	-4.8357 (0.396553)	0.000127 (0.000226)	-4.6447 (0.188982)
LHD 17	-5.5385 (0.470913)	0.000401 (0.000219)	-4.8221 (0.196116)
LHD 20	-5.1379 (0.435105)	0.000099 (0.000219)	-4.9689 (0.208514)

Table 5.11: Estimates of α and β in the Model (5.20) and estimate of α when $\beta = 0$, for each machine. The numbers in the parentheses are the standard errors of parameter estimates.

Machine	$l(\hat{\boldsymbol{\theta}})$	$l(\tilde{\boldsymbol{\theta}})$	Λ	S_{LA}	$W = \hat{\beta}^2/s^2(\hat{\beta})$
LHD 1	-128.104	-130.800	5.390 (0.020)	2.294 (0.028)	5.016 (0.025)
LHD 3	-148.145	-148.726	1.162 (0.281)	1.075 (0.282)	1.146 (0.284)
LHD 9	-163.583	-166.552	5.937 (0.015)	2.410 (0.016)	5.552 (0.019)
LHD 11	-157.893	-158.053	0.319 (0.572)	0.565 (0.572)	0.318 (0.573)
LHD 17	-149.632	-151.376	3.488 (0.062)	1.855 (0.064)	3.349 (0.067)
LHD 20	-137.181	-137.285	0.206 (0.649)	0.455 (0.649)	0.206 (0.650)

Table 5.12: The maximized log likelihoods for expanded Model (5.20) and the reduced model $\rho(t) = e^{\alpha}$, the likelihood ratio statistic $\Lambda = 2l(\hat{\boldsymbol{\theta}}) - 2l(\tilde{\boldsymbol{\theta}})$, S_{LA} in (5.9) and the Wald type statistic W. The numbers in the parentheses are the p-values.

machine). Therefore, we now test the absence of monotonic trend separately in each machine. This can be done by considering the following model;

$$\lambda(t|\mathcal{H}(t)) = \exp\{\alpha + \beta t\}, \qquad t \geq 0, \tag{5.20}$$

and then by testing the null hypothesis $H_0 : \beta = 0$. Let $\boldsymbol{\theta} = (\alpha, \beta)'$ and $\tilde{\boldsymbol{\theta}} = (\tilde{\alpha}, 0)'$. The maximum likelihood estimates and their standard errors of the parameters of the expanded and reduced models are presented in Table 5.11. The Laplace test S_{LA} in (5.9), the likelihood ratio test statistic $\Lambda = 2l(\hat{\boldsymbol{\theta}}) - 2l(\tilde{\boldsymbol{\theta}})$, and a Wald type statistic W are used to test $H_0 : \beta = 0$. The computed values of S_{LA}, Λ and W are given in Table 5.12. A χ^2 based p-value for Λ and $N(0, 1)$ based two-sided p-values for S_{LA} and W indicate that there is a strong evidence against the null hypothesis $H_0 : \beta = 0$ for LHD 1 and LHD 9 machines, and some evidence for LHD 17. It should be pointed out that these results are in concordance with the results of Kumar and Klefso (1992).

Chapter 6

Summary and Future Research

In this last chapter of the thesis, we summarize outcomes of the previous chapters, recommend practical usage of the methods, and briefly discuss further research topics.

6.1 Summary and Practical Recommendations

We examined two important features of recurrent event processes; carryover effects and time trends. Formal tests for the absence of these features in the processes were developed, and their properties were discussed.

Carryover effects cause clustering of events together in time by increasing the probability of a new event for a limited period after occurrence of an event. Carryover effects may also cause a decrease in the probability. We did not consider such carryover effects in the thesis but the tests of Chapters 2 and 3 also apply to this case. Our objective for testing carryover effects was to propose a test which is simple, powerful and can be routinely applied before extensive model fitting and checking has been undertaken.

We investigated testing for carryover effects by considering a family of modulated Poisson processes with the intensity function given in (2.1), which includes internal time-dependent covariates. Model expansion is an effective way of model testing, and was applied to give score tests of absence of a carryover effect. We first considered the case in which the null model is an HPP. The tests introduced are easily interpreted. They are in a simple "Observed - Expected" form. What we mean by "Observed" is the number of events during the carryover period following the occurrence of an event and "Expected" is an estimate of the expected number of such occurrences under the null hypothesis. Asymptotic properties of the tests were examined analytically as well as by simulation under two different settings; (i) when the number of processes m increases, (ii) when one process is under observation and the observation period or a model parameter increases. We showed analytically that the standard normal approximation is suitable as m increases as well as when τ increases, when one process is under observation. These results were supported by simulation studies.

One problem about the tests considered is that they include a term for a carryover period, and we will never be sure of the exact form of it. Therefore, robustness of the tests with respect to misspecification of the form of a carryover period is an important issue. We examined this by simulation. Our studies showed that tests are robust and powerful with respect to small misspecfication of a carryover period. We considered the power of tests against various types of carryover alternatives, and found the powers are quite high overall. We also developed a score test for a carryover effect when the null model is an NHPP. We showed analytically that the score test has a normal limiting distribution.

Heterogeneity is often seen in studies involving multiple processes. As discussed in Chapter 2, if the tests developed for identical processes are used when significant heterogeneity is present, Type 1 errors can be greatly inflated, so tests for nonidentical processes are needed. We considered this in two different family of models in Chapter 3; (*i*) fixed effects models, and (*ii*) random effects models. Once again the tests are in the "Observed - Expected" form. In the fixed effects case, the maximum likelihood estimators are not consistent as $m \to \infty$ because of the nuisance parameters problem. Our simulation studies showed that the normal approximations for the score test are adequate in some cases where m is not too large and the numbers of events per process are fairly large, but in general not adequate. When the standard normal approximation is not adequate, we recommend obtaining p-values by simulation. In the random effects case, we introduce unobservable i.i.d. gamma random variables into the model. Under the assumption that the gamma distribution for random effects is correct, we showed by simulation that the score statistic given in (3.23) is asymptotically $N(0,1)$ as $m \to \infty$, unlike the fixed effects statistic (3.9). We also conducted a simulation study, and showed that it is safe to use the score test (3.23) under misspecification of the distribution of random effects. Our simulation studies showed that score tests in both cases maintain high power against various carryover alternatives as well as misspecification of the carryover periods.

In Chapter 4 and Chapter 5, we discussed tests for trend in Poisson and renewal models when the processes are identical and nonidentical, respectively. We focused on $m > 1$ case since $m = 1$ case is much-discussed in the literature. Most of the existing trend tests are based on the assumption that the "no trend" model is a renewal model, or many times an HPP as a special case of renewal processes. Another problem is, as discussed in Chapter 4, that the computation of p-values for many tests is based on an assumption that observation of a process ceases after some specified number of event occurrences but in practice different observation schemes are common. Our aim was to develop simple trend tests that are robust in the sense of retaining appropriate size and good power for more general processes than Poisson or renewal processes. We, therefore, developed robust score tests for time trends. The tests provided can be used with observation schemes in which observation is ceased after a prespecified time period, and can also be applied in the presence of external time-varying covariates. We focused on monotonic trend alternatives.

Monte Carlo simulation studies were conducted to assess the accuracy of large sample approximations, and to compare robust trend tests to other important tests. In particular, the generalized Laplace test, which is a special case of robust trend tests, the linear rank test and a corrected Lewis-Robinson trend tests were used. We considered three different types of null hypotheses in Chapters 4 and 5. When the null model is an HPP, p-values for the linear rank and Lewis-Robinson tests can be found from standard normal approximations in all cases considered. The normal approximation is suitable for the generalized Laplace test, but a little off in the extreme tails when $m = 10$. When we generated data from a renewal process with gap times following a gamma distribution with shape parameter 0.75 or 1.5, the generalized Laplace test is biased. We recommended a mean correction which also works fine in the cases where the generalized Laplace test is unbiased. When the null model is a delayed renewal process, the normal approximation is adequate for the generalized Laplace test especially when $m > 10$, but not for the linear rank test and the Lewis-Robinson test.

We also conducted power studies under three different alternatives which are in concordance with the null hypotheses, and we obtained similar results in Chapter 4 and Chapter 5. The generalized Laplace test is the most powerful when the alternative model is an NHPP as explained in simulation sections. The Lewis-Robinson and linear rank tests are close in power. We next considered semi-Markov process alternatives where we generated independent gap times from a gamma distribution with shape parameter 0.75 or 1.5. For identical processes, the modified generalized Laplace test is the most powerful overall. However, in nonidentical processes, the linear rank test has good power, especially when m is smaller. When the alternative model is a delayed modulated renewal process, the generalized Laplace test is superior.

As a conclusion, the generalized Laplace test as a robust test for absence of trend is recommended as a routine check for monotonic trends, provided m is 10 or bigger. It is easy to implement, flexible, powerful in a range of settings, and can be applied various type of trend alternatives. Standard normal approximation is suitable when $m \geq 10$. Robust trend tests considered in the thesis can also be used with covariates. When m is small but the τ_i are large enough to provide at least a moderate number of events, we have to rely on other tests, involving certain assumptions, such as the linear rank or Lewis-Robinson tests.

6.2 Two-State Models

Alternating two-state models are useful when the duration of an event is important along with the counting of events in a recurrent event process; for example, downtime periods in a nuclear power plant, repair times in a repairable systems, and at-risk free periods (i.e. attack periods) of asthma patients. Alternating two-state models can be effectively used for modeling and analyzing carryover effects where duration in each state is variable (see Cook and Lawless, 2007, Section 1.5.3). For example, let a machine be in an *active* state when it is in working condition and be in an *inactive* state when it has a failure after which a repair immediately takes place. Suppose that the observation of a process starts in the *active* state at $t = 0$. Then, a possible two-state model is defined with the transition (jump) intensities; (i) from *active* to *inactive* state, $\lambda_{12}(t|\mathcal{H}(t)) = Y_{i1}(t)\alpha_{12}(t)e^{\beta z_i(t)}$, where $Y_{i1}(t) = I($*active* at $t^-)$ and $z_i(t) = I(B_i(t) \leq \Delta)$ and $B_i(t)$ is the time since the last *inactive* to *active* transition, and (ii) from *inactive* to *active* state, $\lambda_{21}(t|\mathcal{H}(t)) = Y_{i2}(t)\alpha_{21}(t)$, where $Y_{i2}(t) = I($*inactive* at $t^-)$. Then, $dN_i(t) = 1$ if there is a failure which cause the process to jump from *active* to *inactive* state. With this model we are able to model the "being repaired" times and carryover effects. The alternating two-state model can also be used for analysis of trends. For example, a model with increasing trend can be developed by considering decreasing sojourn times in each new state visited.

6.3 Multiple Type Recurrent Events

We discussed the case where processes consist of a single type of event. However, in many settings, multitype recurrent events are of interest (Cook and Lawless, 2007, Chapter 6). For example, a machine may have downtime periods caused by different types of failures. Two different cases could be considered. In the first one, each type of event occurs independently. In this case, the tests for carryover effects and trends developed in this thesis can be still used for the individual event types. In the second case, the occurrence of an event may affect the probability of occurrence of another type of event. This type of carryover effects can be modeled by multivariate counting processes based on intensity functions like those in Chapters 2 and 3, with covariates for one type of event allowed to include event history for other event types. This is an interesting topic, and will be considered as future work.

6.4 More Complicated Processes

In many settings more complicated models and methods are needed. In this thesis, we did not consider covariates even though our models and methods allow us to include covariates. Similarly, we considered only monotonic trends. As discussed in Section 3.4, in the asthma prevention trial data, start times of observations for each individual were not presented, but could be very useful since seasonal trends may affect the occurrence of asthma attacks. A seasonal trend could then be incorporated into a model via covariates.

Cook and Lawless (2007, pp. 232–236) illustrate this with an example from exacerbations in patients with chronic bronchitis. Also, complex dependence on the previous history of a counting process can be useful in many applications. For example, an extra term for the previous number of events can be incorporated into carryover effect models as a covariate. Such a model is generally useful when the number of previous events is believed to have an effect on the course of a process. Aalen et al. (2008) give an example from a study on sleep patterns. A possible model is given by $\lambda_i(t|\mathcal{H}(t)) = \lambda_0(t)\exp\{\alpha N(t^-) + \beta z(t)\}$, where $z(t) = I(N(t^-) > 0)I(B(t) \leq \Delta)$. It is also possible to include a term for trend. Baker (2001), Lindqvist (2006) and Pena (2006) consider reliability settings, and the need for more complex models. We will examine such models in the future.

APPENDICES

Appendix A

Data Sets

A.1 Submarine Engine Data

The data presented in Table A.1 are taken from Lee (1980). Asterisk denotes times of scheduled engine overhaul. See Section 1.1.1 for details.

Table A.1: Cumulative operating hours until the occurrence of significant maintenance actions for the U.S.S. Grampus No. 4 main propulsion diesel engine.

860	2439	4411	6137	8498	10594*	13399	14173
1203*	3197*	4456	6221	8690	11511	13668	14357*
1258	3203	4517	6311	9042	11575	13780	14449
1317	3298	4899	6613	9330	12100	13877	14587
1442	3902	4910	6975	9394	12126	14007	14610
1897	3910	5414*	7335	9426	12368	14028	15070
2011	4000	5676	7723*	9872	12681	14035	15574*
2122	4247	5755	8158	10191	12795	14173	22000
							22575

A.2 LHD Machines Data

The data presented in Table A.2 are given by Kumar and Klefsjo (1992). See Section 1.1.1 for details.

Table A.2: Times between the successive failures of the hydraulic systems.

LHD 1	LHD 3	LHD 9	LHD 11	LHD 17	LHD 20
327	637	278	353	401	231
125	40	261	96	36	20
7	397	990	49	18	361
6	36	191	211	159	260
107	54	107	82	341	176
277	53	32	175	171	16
54	97	51	79	24	101
332	63	10	117	350	293
510	216	132	26	72	5
110	118	176	4	303	119
10	125	247	5	34	9
9	25	165	60	45	80
85	4	454	39	324	112
27	101	142	35	2	10
59	184	38	258	70	162
16	167	249	97	57	90
8	81	212	59	103	176
34	46	204	3	11	370
21	18	182	37	5	90
152	32	116	8	3	15
158	219	30	245	144	315
44	405	24	79	80	32
18	20	32	49	53	266
	248	38	31	84	
	140	10	259	218	
		311	283	122	
		61	150		
			24		

A.3 Asthma Prevention Trial Data

An excerpt of the asthma prevention trial data presented in Table A.3. See Duchateau et al. (2003) and Section 1.1.1 for details.

Column1 : id.w :identification number of the subject
Column2 : trt.w: treatment assignment: 0= control, 1=drug
Column3 : start.w: Start of the at risk period
Column4 : stop.w: End of the at risk period
Column5 : st.w: censoring indicator: 0=censored, 1=event
Column6 : nn: number of at risk periods for particular subject
Column7 : fevent: indicator for first event: 0= no, 1: yes

Table A.3: An excerpt from asthma prevention trial data.

id.w	trt.w	start.w	stop.w	st.w	nn	fevent
3	0	0	12	1	2	1
3	0	17	548	0	2	0
8	0	0	53	1	15	1
8	0	54	108	1	15	0
8	0	109	201	1	15	0
8	0	202	203	1	15	0
8	0	206	216	1	15	0
8	0	218	317	1	15	0
8	0	319	324	1	15	0
8	0	325	344	1	15	0

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