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A class of multi-sample nonparametric tests for panel count data

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Abstract This paper considers the problem of multi-sample nonparametric comparison of mean functions of point processes with panel count data, which arise naturally when recurrent events are considered. Such data frequently occur in medical follow-up studies and reliability experiments, for example. For the problem considered, we construct a class of nonparametric test statistics based on the integrated weighted differences between the estimated mean functions of the point processes. The asymptotic distributions of the proposed statistics are rigorously derived when the monotonicity assumptions for weight processes are removed, and their finite-sample properties are examined through Monte Carlo simulations. The simulation results show that the proposed methods are good for practical use and are slightly powerful than the existing tests. A set of panel count data from a cancer study is analyzed and presented as an illustrative example.

Keywords Medical follow-up study · Nonparametric comparison · Panel count data · Point processes

1 Introduction

Consider a study that concerns some recurrent event and suppose that each subject in the study gives rise to a point process $N(t)$, denoting the total number of occurrences

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of the event of interest up to time t. Also suppose that for each subject, observations include only the values of $N(t)$ at discrete observation times or the numbers of occurrences of the event between the observation times. Such data are usually referred to as *panel count data* (Sun and Kalbfleisch 1995; Wellner and Zhang 2000). Our focus here will be on the situation when such a study involves k groups. Let $\Lambda_l(t)$ denote the mean function of $N(t)$ corresponding to the lth group for $l = 1, \ldots, k$. The problem of interest is then to test the hypothesis $H_0 : \Lambda_1(t) = \cdots = \Lambda_k(t)$.

Several authors have discussed the analysis of recurrent event data when each subject in the study is observed continuously over an interval or when the exact times of occurrences of the recurrent event are known. For example, the book by Andersen et al. (1993) presents many of the commonly used statistical methods for the analysis of recurrent event data. In contrast, there exists limited research on the analysis of panel count data. Sun and Kalbfleisch (1995) and Wellner and Zhang (2000) studied estimation of the mean function of $N(t)$. Sun and Wei (2000) and Zhang (2002) discussed regression analysis for such data. To test the hypothesis H_0, Thall and Lachin (1988) suggested to transform the problem to a multivariate comparison problem and then apply a multivariate Wilcoxon-type rank test. Sun and Fang (2003) proposed a nonparametric procedure for this problem, but their procedure depends on the assumption that treatment indicators can be regarded as independent and identically distributed random variables, which may not be the case in practice. Park et al. (2007) removed this assumption and proposed a class of nonparametric tests for the two-sample comparison problem. Also, Zhang (2006) presented some multi-sample nonparametric tests based on panel count data, but the selection of weight processes given in the test statistics is somewhat restrictive.

The remainder of the paper is organized as follows. Section 2 discusses a nonparametric test for the hypothesis H_0 when only panel count data are available and then presents a class of nonparametric test statistics. The statistics, motivated by similar statistics in survival analysis, are formulated as the integrated weighted difference between the estimated mean functions corresponding to the pooled data and each group. To estimate the mean function, the isotonic regression estimate is used (Sun and Kalbfleisch 1995; Wellner and Zhang 2000). In Sect. 3, the asymptotic normality of these test statistics is established. In Sect. 4, finite-sample properties of the proposed test statistics are examined through Monte Carlo simulations. In Sect. 5, we apply the proposed methods to a data from a bladder tumor study. Finally, in Sect. 6, some concluding remarks are made.

2 Statistical methods

Consider a longitudinal study that is concerned with some recurrent event and involves n independent subjects, n_l in the lth group with $n_1 + \cdots + n_k = n$. Let $N_i(t)$ denote the point process arising from subject i and $\Lambda_l(t)$ $(l = 1, \ldots, k)$ be defined as before, for $i = 1, \ldots, n$. Suppose that each subject is observed only at discrete time points $0 < t_{i,1} < \cdots < t_{i,k_i}$ and that no information is available about $N_i(t)$ between observation times; that is, only panel count data are available. Let $n_{i,j} = N_i(t_{i,j})$ be the observed value of N_i at $t_{i,j}$, $j = 1, \ldots, k_i$, $i = 1, \ldots, n$.

To propose the test statistics, we first introduce the isotonic regression estimator of the mean functions (Sun and Kalbfleisch 1995; Wellner and Zhang 2000). For simplicity, assume that H_0 is true, and let $\Lambda_0(t)$ denote the common mean function of the $N_i(t)$'s. Further, let $s_1, \ldots, s_m$ denote the ordered distinct observation times in the set $\{ t_{i,j} ; \ j = 1, \ldots, k_i, \ i = 1, \ldots, n \}$ and w_ℓ and $\bar{n}_\ell$ be the number and mean value, respectively, of observations made at time s_ℓ, $\ell = 1, \ldots, m$. Then, the isotonic regression estimator $\hat{\Lambda}_n(t)$ is defined as a nondecreasing step function with possible jumps at the s_ℓ's, and is given by

$$\hat{\Lambda}_n(s_\ell) = \max_{r \le \ell} \min_{s \ge \ell} \frac{\sum_{v=r}^{s} w_v \bar{n}_v}{\sum_{v=r}^{s} w_v} = \min_{s \ge \ell} \max_{r \le \ell} \frac{\sum_{v=r}^{s} w_v \bar{n}_v}{\sum_{v=r}^{s} w_v}, \quad \ell = 1, \ldots, m,$$

the isotonic regression of the $\bar{n}_\ell$'s with weights w_ℓ's (Robertson et al. 1988).Wellner and Zhang (2000) established its consistency and also derived its asymptotic distribution at a fixed time point. Note that the well-known Nelson–Aalen estimator is not available here, since it is applicable only for recurrent event data (Andersen et al. 1993).

Let $\hat{\Lambda}_{n_l}$ denote the isotonic regression estimate of Λ_l based on samples from all the subjects in the lth group. To test the hypothesis H_0, motivated by an idea commonly used in survival analysis (Pepe and Fleming 1989; Cook et al. 1996; Zhang et al. 2001; Park et al. 2007), we propose the statistic

$$U_n^{(l)} = \sqrt{n} \int_0^\tau W_n^{(l)}(t) \{ \hat{\Lambda}_n(t) - \hat{\Lambda}_{n_l}(t) \} \, \mathrm{d}\, G_n(t), \quad l = 1, \ldots, k,$$

where τ is the largest observation time, $W_n^{(l)}(t)$'s are bounded weight processes, and $G_n(t)$ is defined by

$$G_n(t) = \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{k_i} 1_{\{t_{i,j} \le t\}},$$

where $1_{\{s \le t\}} = 1$, if $t \ge s$; otherwise, $1_{\{s \le t\}} = 0$. The statistic $U_n^{(l)}$ is the integrated weighted difference between $\hat{\Lambda}_n$ and $\hat{\Lambda}_{n_l}$. It is important to mention that some statistics similar to $U_n^{(l)}$ are commonly used in survival analysis. For the two-sample survival comparison with right-censored data, for example, Pepe and Fleming (1989) proposed some test statistics that have a form similar to $U_n^{(l)}$ with $\hat{\Lambda}_n$ and $\hat{\Lambda}_{n_l}$ replaced by the corresponding estimated survival functions. Petroni and Wolfe (1994) and Zhang et al. (2001) used similar methods for the comparison of treatments based on interval-censored data. Cook et al. (1996) presented similar tests for treatment comparisons based on recurrent event data.

When we rewrite the test statistic $U_n^{(l)}$ as

$$U_n^{(l)} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \sum_{j=1}^{k_i} W_n^{(l)}(t_{i,j}) \{\hat{\Lambda}_n(t_{i,j}) - \hat{\Lambda}_{n_l}(t_{i,j})\},$$

we observe that $U_n^{(l)}$ is also a Wilcoxon-type statistic. Similar statistics are often used in the analysis of repeated measurement data; see, for example, Davis and Wei (1988).

Based on Zhang (2006), we can consider a class of test statistics as follows

$$V_n^{(l)} = \sqrt{n} \int_0^\tau W_n^{(l)}(t) \{ \hat{\Lambda}_{n_1}(t) - \hat{\Lambda}_{n_l}(t) \} \, \mathrm{d}\, G_n(t), \quad l = 2, \ldots, k.$$

Zhang (2006) obtained the asymptotic distribution of $V_n^{(l)}$ when $W_n^{(l)} = W_n$ and W_n satisfies stronger condition (the limit process $W(t)$ of $W_n(t)$ is monotone). In addition, the proof of Theorem 1 of Zhang (2006) may not be rigorous. These will be discussed with more details in the next section.

For the selection of the weight process $W_n^{(l)}(t)$, a simple and natural choice is $W_n^{(1,l)}(t) = 1$, $l = 1, \ldots, k$. Another natural choice is $W_n^{(2,l)}(t) = Y_n(t) = \sum_{i=1}^n I(t \le t_{i,k_i})/n$, $l = 1, \ldots, k$, in which case weights are proportional to the number of subjects under observation. Yet another choice for the weight process $W_n^{(l)}(t)$ is

$$W_n^{(3,l)}(t) = g(Y_{n_l}(t), Y_n(t)),$$

where g is a fixed function, and $Y_{n_l}(t)$ $(l = 1, \ldots, k)$ are defined as $Y_n(t)$ with the summation being only over subjects in the lth group. Some weight processes similar to $W_n^{(3)}$ have been used when recurrent event data are observed; see Andersen et al. (1993).

In the next section, we will present the asymptotic distributions of $\mathbf{U}_n = (U_n^{(1)}, \ldots, U_n^{(k)})^T$ as well as $\mathbf{V}_n = (V_n^{(2)}, \ldots, V_n^{(k)})^T$ in order to construct the tests for the null hypothesis.

3 Asymptotic results

Let $\Lambda_0(t)$ denote the true mean function of the $N_i(t)$'s under H_0. Suppose that K is an integer-valued random variable and $T = \{T_{k,j},\ j = 1, \ldots, k,\ k = 1, 2, \ldots\}$ is a random triangular array, and that k_i and $t_{i,j} = t_{k_i,j}$'s are realizations of them. We assume that $\{(K_i; T_{K_i,1}, \ldots, T_{K_i,K_i})\,;\ i = 1, \ldots, n\}$ are independent and identically distributed, and are independent of the N_i's. Let $\mathbf{X} = (K, T_K, N_K)$, where T_k is the kth row of the triangular array T and $N_k = \big(N(T_{k,1}), \ldots, N(T_{k,k})\big)$. Then, $\mathbf{X}_i = (K_i, T_{K_i}, N_{i,K_i})$, $i = 1, \ldots, n$, is a random sample of size n from the distribution of $\mathbf{X}$. For establishing asymptotic results on $\hat{\Lambda}_n(t)$ and $\mathbf{U}_n$, we need the following regularity conditions:

A. The mean function Λ_0 is strictly increasing such that $\Lambda_0(\tau) \le M$ for some constant $M \in (0, \infty)$;
B. There exists a constant K_0 such that $\Pr\{K \le K_0\} = 1$ and that the random variables $T_{k,j}$'s take values in a bounded set $[\tau_0, \tau]$ and $\Pr\{T_{K,1} = \tau_0\} > 0$, where $0 < \tau_0 < \tau < \infty$;

C. $\Pr\left\{\limsup_{n\to\infty} \max_i N_i(\tau) < \infty\right\} = 1$ and $E\left((N_i(t))^2\right) \le M_1$ for all $t \le \tau$, where M_1 is a constant.

Now, let $\hat{\Lambda}_n(t)$ be the isotonic regression estimate of $\Lambda_0(t)$ under H_0 given in Sect. 1. Also let Λ_0^{-1} denote the inverse function of Λ_0, and let $W \circ \Lambda_0^{-1}$ denote composition of two functions W and Λ_0^{-1}. First, we present the asymptotic normality of functional of $\hat{\Lambda}_n$.

Theorem 1 *Suppose that Conditions A, B and C hold. Further, suppose that $W(t)$ is a bounded weight process such that $W \circ \Lambda_0^{-1}$ is a bounded Lipschitz function. Let $G(t) = E\left[\sum_{j=1}^{K} 1_{\{T_{K,j}\le t\}}\right]$. Then as $n \to \infty$,*

$$\sqrt{n}\int_0^\tau W(t)\,\{\hat{\Lambda}_n(t) - \Lambda_0(t)\}\,\mathrm{d}G(t) \longrightarrow U_w$$

in distribution, where U_w has a normal distribution with mean zero and variance that can be consistently estimated by

$$\hat{\sigma}_w^2 = \frac{1}{n}\sum_{i=1}^{n}\left[\sum_{j=1}^{K_i} W(T_{K_i,j})\left\{N_i(T_{K_i,j}) - \hat{\Lambda}_n(T_{K_i,j})\right\}\right]^2.$$

Proof First, note that

$$\sqrt{n}\int_0^\tau W(t)\{\hat{\Lambda}_n(t) - \Lambda_0(t)\}\,\mathrm{d}G(t) = I_{1n} + I_{2n} + I_{3n},$$

where

$$I_{1n} = \sqrt{n}(P_n - P)\left[\sum_{j=1}^{K} W(T_{K,j})\{\Lambda_0(T_{K,j}) - \hat{\Lambda}_n(T_{K,j})\}\right],$$

$$I_{2n} = \sqrt{n}P_n\left[\sum_{j=1}^{K} W(T_{K,j})\{\hat{\Lambda}_n(T_{K,j}) - N(T_{K,j})\}\right],$$

and

$$I_{3n} = \sqrt{n}P_n\left[\sum_{j=1}^{K} W(T_{K,j})\{N(T_{K,j}) - \Lambda_0(T_{K,j})\}\right],$$

where P_n is the empirical measure corresponding to (N, T, K), P is the corresponding underlying true measure, $P_n f = \frac{1}{n}\sum_{i=1}^{n} f_i$ and $Pf = \int f\,dP$. It is easy to see that I_{3n} is a U statistic and has an asymptotic normal distribution with mean zero and variance that can be consistently estimated by $\hat{\sigma}_w^2$ in the theorem. Hence, it is sufficient to show that both I_{1n} and I_{2n} converge in probability to zero.

We will show the convergence of I_{1n} first. Note that Condition C implies

$$\limsup_{n\to\infty} \hat{\Lambda}_n(\tau) < \infty$$

almost surely. Note that $\hat{\Lambda}_n(\tau_0) \to \Lambda_0(\tau_0)$ a.s. So, for every $0 < \varepsilon < \Lambda_0(\tau_0)$, there exist two positive constants $M_\varepsilon > \Lambda_0(\tau)$ and $L_\varepsilon < \Lambda_0(\tau_0)$ such that

$$\sup_n \Pr\{\hat{\Lambda}_n(\tau_0) < L_\varepsilon\} + \sup_n \Pr\{\hat{\Lambda}_n(\tau) > M_\varepsilon\} < \varepsilon.$$

Let

$$\mathcal{F} = \{\Lambda : [0, \tau] \longrightarrow [0, \infty) \,|\Lambda \text{ is nondecreasing}, \ \Lambda(0) = 0\}$$

and

$$\mathcal{F}_\varepsilon = \{\Lambda : \Lambda \in \mathcal{F}, \ \Lambda(\tau_0) \geq L_\varepsilon, \ \Lambda(\tau) \leq M_\varepsilon\}.$$

Define $\hat{\Lambda}_{n,\varepsilon}$ as

$$\hat{\Lambda}_{n,\varepsilon} = \text{argmax}_{\Lambda\in\Omega\cap\mathcal{F}_\varepsilon} \left\{ \sum_{i=1}^{n} \sum_{j=1}^{K_i} \left\{ N_i(T_{K_i,j}) \log \Lambda(T_{K_i,j}) - \Lambda(T_{K_i,j}) \right\} \right\},$$

where Ω is the class of nondecreasing step functions with possible jumps only at the observation time points $\{T_{K_i,j}, \ j = 1, \ldots, K_i, \ i = 1, \ldots, n\}$. Let $I_{1n,\varepsilon}$ denote the version of I_{1n} obtained by replacing $\hat{\Lambda}_n$ with $\hat{\Lambda}_{n,\varepsilon}$. Then, to prove that I_{1n} converges to zero in probability, it is sufficient to show that $I_{1n,\varepsilon} = o_p(1)$ since

$$\Pr\{I_{1n,\varepsilon} \neq I_{1n}\} \leq \Pr\{\hat{\Lambda}_n(\tau_0) < L_\varepsilon\} + \Pr\{\hat{\Lambda}_n(\tau) > M_\varepsilon\} < \varepsilon.$$

By using arguments similar to those in Sun and Fang (2003), it can be shown that $I_{1n,\varepsilon} = o_p(1)$.

Next, we show the convergence of I_{2n}. By using the same block argument as in Proposition 1.2 in Part II of Groeneboom and Wekkner (1992), we have for any real function h,

$$\sum_{\ell=1}^{m} h(\hat{\Lambda}_n(s_\ell)) w_\ell \{\bar{N}_\ell - \hat{\Lambda}_n(s_\ell)\} = 0,$$

where the s_ℓ's, w_ℓ's and $\bar{N}_\ell = \bar{n}_\ell$ are as defined in Sect. 2. Hence, we can rewrite I_{2n} as

$$I_{2n} = \sqrt{n} P_n \left[\sum_{j=1}^{K} \{W_0(\Lambda_0(T_{K,j})) - W_0(\hat{\Lambda}_n(T_{K,j}))\} \{\hat{\Lambda}_n(T_{K,j}) - N(T_{K,j})\} \right],$$

where $W_0 = W \circ \Lambda_0^{-1}$. By Condition C, there exists a constant N_ε such that

$$\sup_n \Pr\left\{\max_{1 \le i \le n} N_i(\tau) > N_\varepsilon\right\} < \varepsilon.$$

Let

$$A_n = \{\max_{1 \le i \le n} N_i(\tau) \le N_\varepsilon\},$$

and for $\Lambda \in \mathcal{F}_\varepsilon$, let

$$f_\Lambda(\mathbf{X}) = \sum_{j=1}^{K} \{W_0(\Lambda_0(T_{K,j})) - W_0(\Lambda(T_{K,j}))\}\{\Lambda(T_{K,j}) - N(T_{K,j})\},$$
$$g_\Lambda(\mathbf{X}) = \sum_{j=1}^{K} \{W_0(\Lambda_0(T_{K,j})) - W_0(\Lambda(T_{K,j}))\}\{\Lambda(T_{K,j}) - \Lambda_0(T_{K,j})\},$$

and

$$h_\Lambda(\mathbf{X}) = \sum_{j=1}^{K} \{W_0(\Lambda_0(T_{K,j})) - W_0(\Lambda(T_{K,j}))\}\{\Lambda_0(T_{K,j}) - N(T_{K,j})\}.$$

Then, we have

$$I_{2n} = (\Delta_{1n} + \Delta_{2n} + \Delta_{3n}) 1_{A_n} + \Delta_{4n},$$

where

$$\begin{aligned}
\Delta_{1n} &= \sqrt{n}(P_n - P)\left[f_{\hat{\Lambda}_n}(\mathbf{X}) 1_{\{N(\tau) \le N_\varepsilon\}}\right], \\
\Delta_{2n} &= \sqrt{n} P\left[g_{\hat{\Lambda}_n}(\mathbf{X}) 1_{\{N(\tau) \le N_\varepsilon\}}\right], \\
\Delta_{3n} &= \sqrt{n} P\left[h_{\hat{\Lambda}_n}(\mathbf{X}) 1_{\{N(\tau) \le N_\varepsilon\}}\right] \\
&= \sqrt{n} P\left[h_{\hat{\Lambda}_n}(\mathbf{X})\right] - \sqrt{n} P\left[h_{\hat{\Lambda}_n}(\mathbf{X}) 1_{\{N(\tau) > N_\varepsilon\}}\right] \\
&= -\sqrt{n} P\left[h_{\hat{\Lambda}_n}(\mathbf{X}) 1_{\{N(\tau) > N_\varepsilon\}}\right],
\end{aligned}$$

and

$$\Delta_{4n} = \sqrt{n} P_n\left[f_{\hat{\Lambda}_n}(\mathbf{X})\right] 1_{A_n^c}.$$

For Δ_{3n} and Δ_{4n}, we have $\forall \delta > 0$,

$$P\{|\Delta_{3n}| > \delta\} \le P\{N(\tau) > N_\varepsilon\} < \varepsilon$$

and

$$P\left\{|\varDelta_{4n}| > \delta\right\} \leq P\left(A_n^c\right) < \varepsilon\ .$$

Let $\varDelta_{1n,\varepsilon}$ denote the version of $\varDelta_{1n}$ obtained by replacing $\hat{\varLambda}_n$ by $\hat{\varLambda}_{n,\varepsilon}$. Since W_0 is a bounded Lipschitz function, it can be shown that

$$\mathcal{H}_\varepsilon = \left\{f_\varLambda(\mathbf{X})1_{\{N(\tau)\leq N_\varepsilon\}} : \varLambda \in \mathcal{F}_\varepsilon\right\}$$

is P-Donsker using thebracket entropy theorem of Van der Vaart and Wellner (1996, pp. 127–159) and arguments similar to those in Huang and Wellner (1995). Moreover, Theorem 4.1 of Wellner and Zhang (2000) yields

$$d(\hat{\varLambda}_{n,\varepsilon}, \varLambda_0) \leq d(\hat{\varLambda}_n, \varLambda_0) \longrightarrow 0,$$

where

$$d(\varLambda_1, \varLambda_2) = \left\{\int_0^\tau |\varLambda_1(t) - \varLambda_2(t)|^2\, \mathrm{d}G(t)\right\}^{1/2}.$$

Hence, it follows from the uniform asymptotic equicontinuity of the empirical process (Van der Vaart and Wellner, 1996, pp. 168–171) that $\varDelta_{1n,\varepsilon} = o_p(1)$. Then, we have $\varDelta_{1n} = o_p(1)$ since

$$P\{\varDelta_{1n} \neq \varDelta_{1n,\varepsilon}\} \leq P\{\hat{\varLambda}_n(\tau) > M_\varepsilon\} < \varepsilon.$$

For $\varDelta_{2n}$, since W_0 is a bounded Lipschitz function, it follows that

$$\begin{aligned}|\varDelta_{2n}| &= \left|\sqrt{n}\int_0^\tau \{W_0(\varLambda_0(t) - W_0(\hat{\varLambda}_n(t))\}\{\hat{\varLambda}_n(t) - \varLambda_0(t)\}\, \mathrm{d}G(t)\right| \\ &\leq c_1\sqrt{n}\, d^2(\hat{\varLambda}_n, \varLambda_0),\end{aligned}$$

where c_1 is a constant. To prove that $\sqrt{n}\, d^2(\hat{\varLambda}_n, \varLambda_0) = o_p(1)$, we only need to show that $\sqrt{n}\, d^2(\hat{\varLambda}_{n,\varepsilon}, \varLambda_0) = o_p(1)$. We shall now show that $d(\hat{\varLambda}_{n,\varepsilon}, \varLambda_0) = O_p(n^{-\frac{1}{3}})$.

To establish the rate of convergence for $\hat{\varLambda}_{n,\varepsilon}$, we shall apply Theorem 3.2.5 of Van der Vaart and Wellner (1996). Define

$$m_\varLambda(X) = \sum_{j=1}^K \{N(T_{K,j}) \log \varLambda(T_{K,j}) - \varLambda(T_{K,j})\}$$

and $\mathbb{M}(\Lambda) = Pm_{\Lambda}(X)$. Let $h(x) = x(\log x - 1) + 1$. Then $h(x) \geq \frac{1}{5}(x-1)^2$ for x in a neighbourhood of $x = 1$. Thus, in a neighbourhood of Λ_0,

$$\begin{aligned}\mathbb{M}(\Lambda_0) - \mathbb{M}(\Lambda) &= P\left[\sum_{j=1}^{K} \Lambda(T_{K,j}) h\left(\frac{\Lambda_0(T_{K,j})}{\Lambda(T_{K,j})}\right)\right] \\ &= \int \Lambda(t) h\left(\frac{\Lambda_0(t)}{\Lambda(t)}\right) \mathrm{d}G(t) \\ &\geq \frac{1}{5}\int \frac{(\Lambda_0(t) - \Lambda(t))^2}{\Lambda(t)} \mathrm{d}G(t) \\ &\geq \frac{1}{5M_\varepsilon} d^2(\Lambda, \Lambda_0),\end{aligned}$$

and hence the separation condition of the theorem is satisfied. Also, let

$$\mathcal{F}_{\delta,\varepsilon} = \{\Lambda : d(\Lambda, \Lambda_0) \leq \delta,\, \Lambda \in \mathcal{F}_\varepsilon\}\ (\delta > 0)$$

and

$$\mathcal{M}_{\delta,\varepsilon} = \{m_\Lambda(X) - m_{\Lambda_0}(X) : \Lambda \in \mathcal{F}_{\delta,\varepsilon}\}.$$

For $\Lambda \in \mathcal{F}_{\delta,\varepsilon}$, it is easily shown that $P|m_\Lambda(X) - m_{\Lambda_0}(X)|^2 \leq c_2\delta^2$ and $||m_\Lambda(X) - m_{\Lambda_0}(X)||_\infty \leq c_3$ for some constatnts c_2 and c_3. Since we have

$$\log N_{[]}\left(\eta, \mathcal{M}_{\delta,\varepsilon}, L_2(P)\right) \leq c_4\eta^{-1},$$

where c_4 is a constant which depends only on M_ε, then

$$\int_0^\delta \sqrt{1 + \log N_{[]}\left(\eta, \mathcal{M}_{\delta,\varepsilon}, L_2(P)\right)}\, \mathrm{d}\eta \leq c_5\delta^{\frac{1}{2}}.$$

for some constant c_5. Hence, by applying Lemma 3.4.2 of Van der Vaart and Wellner (1996), we have

$$E^*||\sqrt{n}(P_n - P)||_{\mathcal{M}_{\delta,\varepsilon}} \leq c_6\phi_n(\delta)$$

for some constant c_6, where E^* denotes the outer expectation, and $\phi_n(\delta) = \delta^{\frac{1}{2}} + \delta^{-1}n^{-\frac{1}{2}}$. Now, upon using Theorem 3.2.5 of Van der Vaart and Wellner (1996), $d(\hat{\Lambda}_{n,\varepsilon}, \Lambda_0)$ converges in probability to zero of order at least $n^{-\frac{1}{3}}$. This shows that $\Delta_{2n} = o_p(1)$ which completes the proof of the theorem. □

Remark For the proof of Theorem 1 of Zhang (2006), the author claimed that $||m_i^r(X) - m_i^l(X)||_{P,B}^2 \leq C\varepsilon^2$ where $m_i^r(X)$, and $m_i^l(X)$ are as defined in Zhang (2006, pp. 786). From

$$m_i^r(X) - m_i^l(X) = \sum_{j=1}^{K} \left\{ N(T_{K,j}) \log \frac{\Lambda_i^r(T_{K,j})}{\Lambda_i^l(T_{K,j})} - \Lambda_i^r(T_{K,j}) + \Lambda_i^l(T_{K,j}) \right\},$$

one can see that a positive lower bound for $\Lambda_i^l(t)$ is required to derive $||m_i^r(X) - m_i^l(X)||_{P,B}^2 \le C\varepsilon^2$. However, this property may not be obtained by the setting of $\Lambda_i^l(X)$ given in Zhang (2006, pp. 786). It is for this reason we have considered a smaller class $\mathcal{F}_\varepsilon$ and $\hat{\Lambda}_{n,\varepsilon}$ instead of $\hat{\Lambda}_n$.

Now, we derive the asymptotic distributions of $\mathbf{U}_n$ and $\mathbf{V}_n$. Let S_l denote the set of indices for subjects in group l, $l = 1, \ldots, k$.

Theorem 2 *Suppose that Conditions A, B and C hold. Further, suppose that $W_n^{(l)}(t)$'s are bounded weight processes and that there exists a bounded function $W(t)$ such that $W \circ \Lambda_0^{-1}$ is a bounded Lipschitz function, and*

$$\left[\int_0^\tau \{W_n^{(l)}(t) - W(t)\}^2 \, \mathrm{d}G(t) \right]^{1/2} = o_p(n^{-1/6}), \quad l = 1, \ldots, k.$$

Also suppose that $n_l/n \to p_l$ as $n \to \infty$, where $0 < p_l < 1$, $l = 1, \ldots, k$, and $p_1 + \cdots + p_k = 1$. Then under $H_0 : \Lambda_1 = \cdots = \Lambda_k = \Lambda_0$,

(i) $\mathbf{U}_n$ *has an asymptotic normal distribution with mean vector* $\mathbf{0}$ *and covariance matrix that can be consistently estimated by*

$$\hat{\Sigma}_{U_n} = \Gamma_n \, \mathbf{diag}(\hat{\sigma}_1^2, \hat{\sigma}_2^2, \ldots, \hat{\sigma}_k^2) \, \Gamma_n',$$

where

$$\Gamma_n = \begin{pmatrix} \sqrt{\frac{n_1}{n}} - \sqrt{\frac{n}{n_1}} & \sqrt{\frac{n_2}{n}} & \cdots & \sqrt{\frac{n_k}{n}} \\ \sqrt{\frac{n_1}{n}} & \sqrt{\frac{n_2}{n}} - \sqrt{\frac{n}{n_2}} & \cdots & \sqrt{\frac{n_k}{n}} \\ \cdots & \cdots & \cdots & \cdots \\ \sqrt{\frac{n_1}{n}} & \sqrt{\frac{n_2}{n}} & \cdots & \sqrt{\frac{n_k}{n}} - \sqrt{\frac{n}{n_k}} \end{pmatrix}$$

and

$$\hat{\sigma}_l^2 = \frac{1}{n_l} \sum_{i \in S_l} \left[\sum_{j=1}^{K_i} W_n^{(l)}(T_{K_i,j}) \left\{ N_i(T_{K_i,j}) - \hat{\Lambda}_{n_l}(T_{K_i,j}) \right\} \right]^2, \quad l = 1, \ldots, k.$$

(ii) $\mathbf{V}_n$ *has an asymptotic normal distribution with mean vector* $\mathbf{0}$ *and covariance matrix that can be consistently estimated by*

$$\hat{\Sigma}_{V_n} = \mathbf{H}_n \, \mathbf{diag}(\hat{\sigma}_1^2, \hat{\sigma}_2^2, \ldots, \hat{\sigma}_k^2) \, \mathbf{H}_n',$$

where

$$\mathbf{H}_n = \begin{pmatrix} -\sqrt{\frac{n}{n_1}} & \sqrt{\frac{n}{n_2}} & 0 & \cdots & 0 \\ -\sqrt{\frac{n}{n_1}} & 0 & \sqrt{\frac{n}{n_3}} & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ -\sqrt{\frac{n}{n_1}} & 0 & 0 & \cdots & \sqrt{\frac{n}{n_k}} \end{pmatrix}$$

and $\hat{\sigma}_l^2$*,* $l = 1, \ldots, k$ *are as given in* (i)*.*

Proof (i) Let

$$G_{n_l}(t) = \frac{1}{n_l} \sum_{i \epsilon S_l} \sum_{j=1}^{K_i} I(T_{K_i,j} \leq t)$$

for $l = 1, \ldots, k$. To obtain the asymptotic distribution of $\mathbf{U}_n$, we first note that $U_n^{(l)}$ can rewritten as

$$U_n^{(l)} = U_{1n}^{(l)} - \sqrt{\frac{n}{n_l}} U_{2n}^{(l)},$$

where, for $l = 1, \ldots, k$,

$$U_{1n}^{(l)} = \sqrt{n} \int_0^\tau W_n^{(l)}(t)\{\hat{\Lambda}_n(t) - \Lambda_0(t)\} \mathrm{d}G_n(t)$$

and

$$U_{2n}^{(l)} = \sqrt{n_l} \int_0^\tau W_n^{(l)}(t)\{\hat{\Lambda}_{n_l}(t) - \Lambda_0(t)\} \mathrm{d}G_n(t).$$

Further

$$U_{1n}^{(l)} = I_{1n}^{(l)} + I_{2n}^{(l)} + I_{3n}^{(l)},$$

where

$$\begin{aligned} I_{1n}^{(l)} &= \sqrt{n} \int_0^\tau \{W_n^{(l)}(t) - W(t)\}\{\hat{\Lambda}_n(t) - \Lambda_0(t)\} \, \mathrm{d}G_n(t) \\ &= \sqrt{n} \int_0^\tau \{W_n^{(l)}(t) - W(t)\}\{\hat{\Lambda}_n(t) - \Lambda_0(t)\} \, \mathrm{d}G(t) + o_p(1), \\ I_{2n}^{(l)} &= \sqrt{n}(P_n - P) \left[\sum_{j=1}^{K} W(T_{K,j})\{\hat{\Lambda}_n(T_{K,j}) - \Lambda_0(T_{K,j})\} \right], \end{aligned}$$

and

$$I_{3n}^{(l)} = \sqrt{n} \int_0^{\tau} W(t)\{\hat{\Lambda}_n(t) - \Lambda_0(t)\} \, \mathrm{d}G(t).$$

First, we show that $I_{1n}^{(l)} = o_p(1), l = 1, \ldots, k$. Using Cauchy–Schwarz inequality and the proof of Theorem 1, we have

$$\begin{aligned}
&\left| \sqrt{n} \int_0^{\tau} \{W_n^{(l)}(t) - W(t)\}\{\hat{\Lambda}_n(t) - \Lambda_0(t)\} \, \mathrm{d}G(t) \right| 1_{\{\hat{\Lambda}_n(\tau) \le M_\varepsilon\}} \\
&\le \sqrt{n} \left\{ \int_0^{\tau} (W_n^{(l)}(t) - W(t))^2 \, \mathrm{d}G(t) \right\}^{1/2} \left\{ \int_0^{\tau} (\hat{\Lambda}_{n,\varepsilon}(t) - \Lambda_0(t))^2 \, \mathrm{d}G(t) \right\}^{1/2} \\
&\longrightarrow 0
\end{aligned}$$

in probability, since

$$\left\{ \int_0^{\tau} (\hat{\Lambda}_{n,\varepsilon}(t) - \Lambda_0(t))^2 \, \mathrm{d}G(t) \right\}^{1/2} = O_p(n^{-1/3}).$$

Hence, $I_{1n}^{(l)} = o_p(1), l = 1, \ldots, k$. Now, as in the proof of Theorem 1, it can be shown that $I_{2n}^{(l)} = o_p(1), l = 1, \ldots, k$. Also, it follows from Theorem 1 that

$$I_{3n}^{(l)} = \sqrt{n} \int_0^{\tau} W(t)\{N(t) - \Lambda_0(t)\} \, \mathrm{d}G_n(t) + o_p(1)$$

for $l = 1, \ldots, k$. Hence, we have

$$U_{1n}^{(l)} = \sqrt{n} \int_0^{\tau} W(t)\{N(t) - \Lambda_0(t)\} \, \mathrm{d}G_n(t) + o_p(1), \quad l = 1, \ldots, k.$$

Similarly, we can show that

$$U_{2n}^{(l)} = \sqrt{n_l} \int_0^{\tau} W(t)\{N(t) - \Lambda_0(t)\} \, \mathrm{d}G_{n_l}(t) + o_p(1), \quad l = 1, \ldots, k.$$

Let

$$Y_n = \sqrt{n} \int_0^{\tau} W(t)\{N(t) - \Lambda_0(t)\} \, \mathrm{d}G_n(t)$$

and

$$Y_n^{(l)} = \sqrt{n_l} \int_0^{\tau} W(t)\{N(t) - \Lambda_0(t)\} \, \mathrm{d}G_{n_l}(t), \quad \text{for} \quad l = 1, \ldots, k.$$

Evidently, $Y_n^{(l)}$'s are i.i.d., and $\sqrt{n}Y_n = \sum_{l=1}^k \sqrt{n_l}Y_n^{(l)}$. Then,

$$\begin{aligned} U_n^{(l)} &= Y_n - \sqrt{\frac{n}{n_l}}Y_n^{(l)} + o_p(1) \\ &= \sum_{i=1}^k \sqrt{\frac{n_i}{n}}Y_n^{(i)} - \sqrt{\frac{n}{n_l}}Y_n^{(l)} + o_p(1), \quad l = 1, \ldots, k, \end{aligned}$$

and so

$$\mathbf{U}_n = \Gamma_n \mathbf{Y}_n + o_p(1) = \Gamma \mathbf{Y}_n + o_p(1),$$

where

$$\Gamma = \begin{pmatrix} \sqrt{p_1} - \frac{1}{\sqrt{p_1}} & \sqrt{p_2} & \cdots & \sqrt{p_k} \\ \sqrt{p_1} & \sqrt{p_2} - \frac{1}{\sqrt{p_2}} & \cdots & \sqrt{p_k} \\ \cdots & \cdots & \cdots & \cdots \\ \sqrt{p_1} & \sqrt{p_2} & \cdots & \sqrt{p_k} - \frac{1}{\sqrt{p_k}} \end{pmatrix}$$

and

$$\mathbf{Y}_n = \left(Y_n^{(1)}, \ldots, Y_n^{(k)}\right)^T$$

converges in distribution to $\mathbf{Y}_w$ having a k-dimensional normal distribution with mean vector $\mathbf{0}$ and covariance matrix $\mathbf{diag}(\sigma_1^2, \ldots, \sigma_k^2)$, where σ_l^2 can be consistently estimated by $\hat{\sigma}_l^2$ in the theorem. Thus, we have $\mathbf{U}_n$ converging in distribution to a random variable $\mathbf{U}_w$ that has a normal distribution $N(\mathbf{0}, \Sigma_w)$, in which Σ_w can be estimated by $\hat{\Sigma}_{U_n}$ presented in part (i) in the theorem.
(ii) We note that $V_n^{(l)} = U_n^{(1,l)} - U_n^{(l)}$, $l = 2, \ldots, k$, where $U_n^{(1,l)}$ is defined as $U_n^{(1)}$ by replacing $W_n^{(1)}$ with $W_n^{(l)}$ for $l = 2, \ldots, k$. Then, (ii) follows from (i).
Hence, the proof of the theorem is completed. □

Clearly,

$$\left[\int_0^\tau \{W_n^{(l)}(t) - W(t)\}^2 \, \mathrm{d}G(t)\right]^{1/2} = d(W_n^{(l)}, W)$$

where the metric d is as defined in the proof of Theorem 1. Here, we need

$$n^{1/6} d(W_n^{(l)}, W) \to_p 0.$$

For example, $W_n^{(1,l)}$ and $W_n^{(2,l)}$ given in Sect. 2, $1 - W_n^{(2,l)}$, Y_{n_l} and $1 - Y_{n_l}$ all satisfy this condition. The weight processes $Y_{n_1}Y_{n_l}/Y_n$ and $(1 - Y_{n_1})(1 - Y_{n_l})/(1 - Y_n)$ also satisfy the condition.

Remark For the two-sample comparison problem, the condition on the weight process W_n required by Park et al. (2007)

$$\sup_n E \int_0^\tau |\sqrt{n}\{W_n(t) - W(t)\}|^2 \mathrm{d}G_n(t) < \infty$$

implies

$$n^{1/6} d(W_n, W) \to_p 0.$$

Now, we are ready to present the nonparametric k-sample tests for panel count data. Let $\mathbf{U}_0$ denote the first $(k-1)$ components of $\mathbf{U}_n$ and $\hat{\Sigma}_0$ the matrix obtained by deleting the last row and column of $\hat{\Sigma}_{U_n}$. Then, using Theorem 2, two tests of the hypothesis H_0 can be carried out by means of the statistics $T_1 = \mathbf{U}_0^T \hat{\Sigma}_0^{-1} \mathbf{U}_0$ and $T_2 = \mathbf{V}_n^T \hat{\Sigma}_{V_n}^{-1} \mathbf{V}_n$, which have asymptotically a central χ^2-distribution with $(k-1)$ degrees of freedom. This can be seen readily from the proof of the theorem.

4 Simulation study

To examine the finite-sample properties of the proposed test statistic T_1 and compare its power with T_2, we carry out a simulation study for the three-sample comparison problem. To generate panel count data $\{k_i, t_{ij}, n_{ij}, j = 1, \ldots, k_i, i = 1, \ldots, n\}$, we mimic medical follow-up studies such as the example discussed in the next section. We first generate the number of observation times k_i from the uniform distribution $U\{1, \ldots, 10\}$, and then, given k_i, we generate observation times t_{ij}'s from $U\{1, \ldots, 10\}$, for simplicity. To generate n_{ij}'s, we assume that N_i's are nonhomogeneous Poisson or mixed Poisson processes. In particular, let $\{\nu_i, i = 1, \ldots, n\}$ be i.i.d. random variables, and given ν_i, let $N_i(t)$ be a Poisson process with mean function $\Lambda_i(t) = \nu_i t$ for $i \in S_1$, $\Lambda_i(t) = \nu_i t \exp(\beta_1)$ for $i \in S_2$ and $\Lambda_i(t) = \nu_i t \exp(\beta_2)$ for $i \in S_3$.

We consider two cases: $\nu_i = 1$ and $\nu_i \sim Gamma(2, 1/2)$. For each case, we consider two sample sizes, $n_1 = n_2 = n_3 = 50$ and 100, respectively. As mentioned earlier in Sect. 2, we choose the three weight processes: $W_n^{(1,l)}(t) = 1$, $l = 1, \ldots, k$, $W_n^{(2,l)}(t) = Y_n(t) = \sum_{i=1}^n I(t \le t_{i,k_i})/n$, $l = 1, \ldots, k$, and $W_n^{(3,l)}(t) = 1 - Y_n(t)$. Let

$$W_n^{(j)}(t) = \left(W_n^{(j,1)}(t), \ldots, W_n^{(j,k)}(t)\right), \quad j = 1, 2, 3.$$

All the results reported here are based on 1,000 Monte Carlo replications.

Tables 1 and 2 present the estimated sizes and powers of the tests T_1 and T_2 at significance level $\alpha = 0.05$ for different values of β and the three weight processes based on the simulated data for the two cases, respectively. In the first case, the $N_i(t)$'s are Poisson processes. In the second case, the $N_i(t)$'s are mixed Poisson processes. The first part of the table is for the situation with the total sample size of 150 and the second part is for the situation with the total sample size of 300. For the situation considered

Table 1 Percentage of null hypothesis rejection at significance level 5% based on 1,000 replications for Poisson processes

(β_1, β_2)	T_1			T_2		
	$W_n^{(1)}(t)$	$W_n^{(2)}(t)$	$W_n^{(3)}(t)$	$W_n^{(1)}(t)$	$W_n^{(2)}(t)$	$W_n^{(3)}(t)$
$n_1 = n_2 = n_3 = 50$						
(−0.5,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(−0.3,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(−0.3,−0.3)	0.969	0.936	0.949	0.968	0.931	0.949
(−0.1,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(−0.1,−0.3)	0.903	0.853	0.870	0.898	0.851	0.867
(−0.1,−0.1)	0.224	0.195	0.203	0.218	0.187	0.193
(0.0,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.0,−0.3)	0.974	0.950	0.959	0.965	0.946	0.953
(0.0,−0.1)	0.253	0.214	0.229	0.239	0.205	0.217
(0.0,0.0)	0.053	0.049	0.048	0.052	0.050	0.047
(0.0,0.1)	0.267	0.234	0.247	0.266	0.233	0.244
(0.0,0.3)	0.993	0.981	0.987	0.993	0.980	0.987
(0.0,0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.1,0.1)	0.273	0.223	0.236	0.270	0.221	0.236
(0.1,0.3)	0.963	0.939	0.952	0.960	0.934	0.949
(0.1,0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.3,0.3)	0.995	0.985	0.989	0.995	0.984	0.986
(0.3,0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.5,0.5)	1.000	1.000	1.000	1.000	1.000	1.000
$n_1 = n_2 = n_3 = 100$						
(−0.5,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(−0.3,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(−0.3,−0.3)	1.000	1.000	1.000	1.000	1.000	1.000
(−0.1,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(−0.1,−0.3)	0.997	0.993	0.996	0.996	0.993	0.995
(−0.1,−0.1)	0.466	0.373	0.394	0.463	0.373	0.390
(0.0,−0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.0,−0.3)	1.000	1.000	1.000	1.000	1.000	1.000
(0.0,−0.1)	0.438	0.388	0.403	0.434	0.382	0.403
(0.0,0.0)	0.056	0.049	0.054	0.055	0.056	0.055
(0.0,0.1)	0.491	0.432	0.449	0.488	0.429	0.447
(0.0,0.3)	1.000	1.000	1.000	1.000	1.000	1.000
(0.0,0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.1,0.1)	0.450	0.371	0.388	0.450	0.368	0.388
(0.1,0.3)	0.999	0.999	0.999	0.999	0.999	0.999
(0.1,0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.3,0.3)	1.000	1.000	1.000	1.000	1.000	1.000
(0.3,0.5)	1.000	1.000	1.000	1.000	1.000	1.000
(0.5,0.5)	1.000	1.000	1.000	1.000	1.000	1.000

Table 2 Percentage of null hypothesis rejection at significance level 5% based on 1,000 replications for mixed Poisson processes

(β_1, β_2)	T_1			T_2		
	$W_n^{(1)}(t)$	$W_n^{(2)}(t)$	$W_n^{(3)}(t)$	$W_n^{(1)}(t)$	$W_n^{(2)}(t)$	$W_n^{(3)}(t)$
$n_1 = n_2 = n_3 = 50$						
(−0.5,−0.5)	0.773	0.761	0.769	0.779	0.763	0.772
(−0.3,−0.5)	0.635	0.629	0.615	0.617	0.614	0.615
(−0.3,−0.3)	0.348	0.344	0.342	0.348	0.332	0.337
(−0.1,−0.5)	0.657	0.642	0.654	0.648	0.637	0.645
(−0.1,−0.3)	0.251	0.244	0.243	0.250	0.246	0.243
(−0.1,−0.1)	0.088	0.085	0.083	0.077	0.081	0.076
(0.0,−0.5)	0.715	0.706	0.722	0.713	0.709	0.708
(0.0,−0.3)	0.331	0.326	0.334	0.327	0.321	0.314
(0.0,−0.1)	0.074	0.075	0.077	0.068	0.070	0.069
(0.0,0.0)	0.060	0.059	0.057	0.056	0.060	0.057
(0.0,0.1)	0.082	0.086	0.074	0.078	0.075	0.078
(0.0,0.3)	0.381	0.386	0.357	0.379	0.369	0.372
(0.0,0.5)	0.815	0.811	0.805	0.814	0.813	0.791
(0.1,0.1)	0.086	0.086	0.073	0.085	0.086	0.068
(0.1,0.3)	0.317	0.312	0.300	0.300	0.303	0.285
(0.1,0.5)	0.741	0.736	0.723	0.731	0.727	0.729
(0.3,0.3)	0.323	0.325	0.296	0.317	0.324	0.308
(0.3,0.5)	0.654	0.655	0.630	0.647	0.650	0.629
(0.5,0.5)	0.769	0.767	0.745	0.765	0.764	0.744
$n_1 = n_2 = n_3 = 100$						
(−0.5,−0.5)	0.976	0.971	0.970	0.976	0.973	0.972
(−0.3,−0.5)	0.902	0.901	0.894	0.901	0.899	0.892
(−0.3,−0.3)	0.609	0.598	0.617	0.603	0.595	0.615
(−0.1,−0.5)	0.933	0.929	0.932	0.931	0.926	0.930
(−0.1,−0.3)	0.501	0.487	0.494	0.493	0.481	0.493
(−0.1,−0.1)	0.119	0.123	0.118	0.119	0.121	0.116
(0.0,−0.5)	0.966	0.961	0.961	0.961	0.957	0.960
(0.0,−0.3)	0.593	0.579	0.577	0.583	0.578	0.576
(0.0,−0.1)	0.105	0.106	0.099	0.097	0.097	0.096
(0.0,0.0)	0.053	0.056	0.054	0.054	0.057	0.052
(0.0,0.1)	0.109	0.108	0.109	0.103	0.105	0.104
(0.0,0.3)	0.676	0.668	0.655	0.668	0.659	0.656
(0.0,0.5)	0.989	0.987	0.982	0.988	0.985	0.982
(0.1,0.1)	0.117	0.116	0.097	0.117	0.116	0.098
(0.1,0.3)	0.539	0.534	0.513	0.535	0.533	0.491
(0.1,0.5)	0.956	0.953	0.958	0.956	0.949	0.955
(0.3,0.3)	0.606	0.600	0.575	0.602	0.599	0.573
(0.3,0.5)	0.937	0.934	0.938	0.935	0.933	0.929
(0.5,0.5)	0.976	0.975	0.976	0.979	0.975	0.977

here, the tests seem to have good powers, the powers of two tests are close for the three weight processes with the weight process $W_n^{(1)}$ showing a little higher power, and T_1 is slightly powerful than T_2. As expected, the power increases when the sample size increases, and the power decreases in the presence of variability. To evaluate the asymptotic result given in Theorem 2, the quantile plots of the test statistic T_1 against the chi-square distribution with 2 degrees of freedom were constructed under different set-ups, and all of them clearly reveal that the asymptotic approximation is quite good.

In the above simulation study, we did examine all three weight processes suggested earlier in Sect. 2, and in all situations considered here, the weight process $W_n^{(1)}$ yielded slightly higher power than the other two weight processes. This may not always be true as one can see from the next section and simulation results presented by Zhang (2006). In general, one should select appropriate weight processes based on the behavior of the mean functions to improve power. Zhang (2006) provided a detailed discussion about the roles of these weight processes through Monte Carlo simulations. In addition to the three processes considered here, some other weight processes can be found in Andersen et al. (1993), which discusses nonparametric treatment comparison based on recurrent event data. It would, therefore, be of great interest to investigate the problem of the selection of a weight process based on data.

5 An illustrative example

To illustrate the proposed method, we consider the data from a bladder tumor study conducted by the Veterans Administration Co-operative Urological Research Group (VACURG), and the data are presented in Andrew and Herzberg (1985). For some analyses of these data, one may refer to Byar et al. (1977); Byar (1980); Wellner and Zhang (2000); Sun and Wei (2000), and Zhang (2002, 2006). The data were obtained from a randomized clinical trial. All patients had superficial bladder tumors when they entered the trial, and they were assigned randomly to one of three treatments: placebo, thiotepa and pyridoxine. The study included 116 patients, of which there were 47 in placebo group, 38 in thiotepa group and 31 in pyridoxine. At subsequent follow-up visits, any tumors noticed were removed and treatment was continued. We can get a set of panel count data $\{k_i, t_{ij}, n_{ij}, j = 1, \ldots, k_i, i = 1, \ldots, n\}$ where for the ith patient, k_i is the number of visits, t_{ij}'s are all visit times, and n_{ij} is total number of tumors until t_{ij} $(j = 1, \ldots, k_i)$. The objective of the study is to determine the effect of treatment on the frequency of tumor recurrence.

Now, let

$$\mathbf{Z}^{(l)} = \left(K^{(l)}, T^{(l)}_{K^{(l)},j}, j = 1, \ldots, K^{(l)}\right)$$

and

$$\mathbf{Z}_i^{(l)} = \left(K_i^{(l)}, T^{(l)}_{K_i^{(l)},j}, j = 1, \ldots, K_i^{(l)}\right), \quad i = 1, \ldots, n_l,$$

and let Q_l and Q_{n_l} be the probability measure and the empirical measure of $\mathbf{Z}^{(l)}$ and $\mathbf{Z}_i^{(l)}$'s, respectively, for group l, $l = 1, 2, 3$. We wish to test

(i) $H_0 : Q_1 = Q_2$ against $H_1 : Q_1 \neq Q_2$;
(ii) $H_0 : Q_1 = Q_3$ against $H_1 : Q_1 \neq Q_3$;
(iii) $H_0 : Q_2 = Q_3$ against $H_1 : Q_2 \neq Q_3$.

These can be done by the two-sample Kolmogorov–Smirnov test discussed by Van der Vaart and Wellner (1996, pp. 360–365). Define the two-sample Kolmogrov–Smirnov test statistics as follows

$$D_{n_1,n_2} = \sqrt{\frac{n_1 n_2}{n_1 + n_2}} ||Q_{n_1} - Q_{n_2}||_{\mathcal{F}},$$
$$D_{n_1,n_3} = \sqrt{\frac{n_1 n_3}{n_1 + n_3}} ||Q_{n_1} - Q_{n_3}||_{\mathcal{F}},$$

and

$$D_{n_2,n_3} = \sqrt{\frac{n_2 n_3}{n_2 + n_3}} ||Q_{n_2} - Q_{n_3}||_{\mathcal{F}},$$

where

$$\mathcal{F} = \left\{ f_t(Z) = \sum_{j=1}^{K} 1_{\{T_{K,j} \leq t\}} : 0 \leq t \leq \tau \right\}.$$

Let $G_1(t)$, $G_2(t)$ and $G_3(t)$ be as defined in Theorem 1 for the placebo, thiotepa and pyridoxine groups, respectively, and

$$G_{n_l}(t) = \frac{1}{n_l} \sum_{i=1}^{n_l} \sum_{j=1}^{K_i} 1_{\{T_{K_i,j} \leq t\}},$$

which is the empirical estimator of $G_l(t)$, $l = 1, 2, 3$, where $n_1 = 48$, $n_2 = 38$, $n_3 = 31$ and $n = 116$. Then, D_{n_1,n_2}, D_{n_1,n_3} and D_{n_2,n_3} can be rewritten as

$$D_{n_1,n_2} = \sqrt{\frac{n_1 n_2}{n_1 + n_2}} \sup_{0 \leq t \leq \tau} |G_{n_1}(t) - G_{n_2}(t)|,$$
$$D_{n_1,n_3} = \sqrt{\frac{n_1 n_3}{n_1 + n_3}} \sup_{0 \leq t \leq \tau} |G_{n_1}(t) - G_{n_3}(t)|,$$

and

$$D_{n_2,n_3} = \sqrt{\frac{n_2 n_3}{n_2 + n_3}} \sup_{0 \leq t \leq \tau} |G_{n_2}(t) - G_{n_3}(t)|.$$

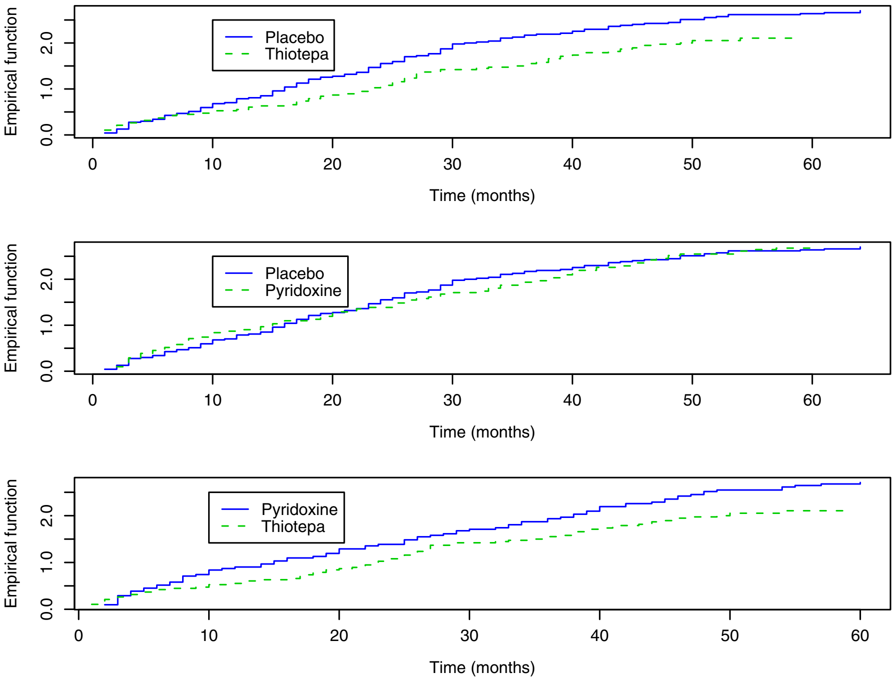


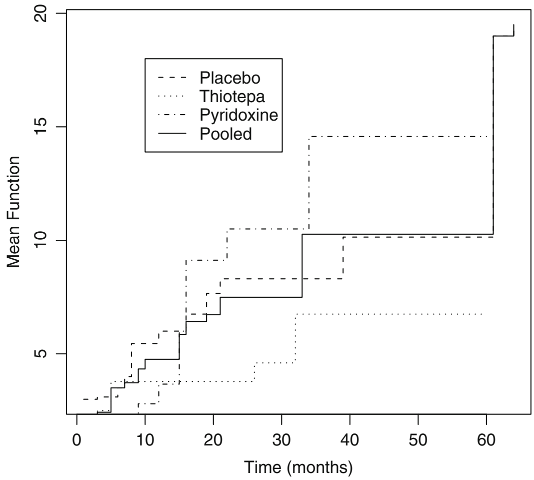
Fig. 1 Bladder tumor study. Empirical estimates of the mean functions of counting processes from observation times

Let us carry out the Kolmogorov–Smirnov test to check the equality of each pair. All three pairs of the empirical functions are shown in Fig. 1. Using two-sample bootstrap method presented by Van der Vaart and Wellner (1996, pp. 365), we obtain p values 0.213, 0.806 and 0.385 for three Kolmogorov–Smirnov tests under the null hypotheses $Q_1 = Q_2$, $Q_1 = Q_3$ and $Q_2 = Q_3$, respectively. These results suggest that the null hypotheses cannot be rejected. Sun and Wei (2000) and Hu et al. (2003) analyzed the data from the placebo and thiotepa groups using the regression model method and concluded that the mean function $G_l(t)$ of the counting process arising from observation times depends on the group indicator. However, their results depend on the expression of the model used and model checking is needed.

Now we can illustrate the application of our method to the bladder tumor study based on the Kolmogorov–Smirnov test results. Let $\Lambda_1(t)$, $\Lambda_2(t)$ and $\Lambda_3(t)$ be the mean functions corresponding to the three treatment groups: placebo, thiotepa and pyridoxine, respectively. The estimated mean functions from the three groups and from the pooled data are presented in Fig. 2.

We observe from Fig. 2 that the difference of the three groups becomes larger when the time increases. To test the null hypothesis $H_0 : \Lambda_1(t) = \Lambda_2(t) = \Lambda_3(t)$, we applied the proposed method to this panel count data and computed $T_1 = 6.139$ and p value $= 0.046$ with $W_n^{(l)}(t) = W_n^{(1,l)}(t)$, $T_1 = 4.768$ and p value $= 0.092$ with $W_n^{(l)}(t) = W_n^{(2,l)}(t)$, and $T_1 = 7.024$ and p value $= 0.030$ with $W_n^{(l)}(t) =$

Fig. 2 Bladder tumor study. Estimates of the mean functions



$W_n^{(3,l)}(t) = 1 - Y_{n_l}(t)$, respectively. These results suggest that the frequency of tumor recurrence are significantly different for the patients in the three groups at 10% level of significance. Incidentally, through a regression analysis of the data from two treatments, placebo and thiotepa, Sun and Wei (2000) and Zhang (2002) concluded that thiotepa effectively reduces the recurrence of tumors. Zhang (2006) obtained p values 0.0851, 0.1445 and 0.0840 by using weight processes $W_n = 1$, $Y_n(t)$ and $1 - Y_n(t)$, respectively. If we assume that treatment indicators are independent and identically distributed random variables, then the test presented by Sun and Fang (2003) would yield p value = 0.082 with the treatment indicators $z_i = -1, 1, 0$ for $i \in S_1, S_2, S_3$, p value = 0.696 with the treatment indicators $z_i = -1, 0, 1$ for $i \in S_1, S_2, S_3$, p value = 0.064 with the treatment indicators $z_i = 0, -1, 1$ for $i \in S_1, S_2, S_3$, p value = 0.139 with the treatment indicators $z_i = 0, 1, -1$ for $i \in S_1, S_2, S_3$, p value = 0.628 with the treatment indicators $z_i = 1, 0, -1$ for $i \in S_1, S_2, S_3$, and p value = 0.109 with the treatment indicators $z_i = 1, -1, 0$ for $i \in S_1, S_2, S_3$. One possible reason for such a difference between these p values is the assumption that treatment indicators are independent and identically distributed random variables, which may not be true if we look at the difference in sample sizes of the groups.

This example illustrates that different weights may result in different conclusions, and the tests with appropriate weight process could lead to better power of the test. Therefore, the selection of a suitable weight process would be important for detecting difference between groups.

6 Concluding remarks

This paper discusses the problem of the multi-sample comparison of point processes when only panel count data are available. A class of nonparametric tests are proposed for the problem and the asymptotic properties of the test statistics are derived. The proposed tests are generalizations of the two-sample tests given by Park et al. (2007).

Simulation studies are carried out and they suggest that the proposed method works well for practical situations. The proposed method applies to more general situations than the existing methods due to Thall and Lachin (1988) and Sun and Fang (2003).

A direction for future research is to study the properties of the test statistics under alternatives for selection of weight processes $W_n^{(l)}$'s. One can discuss the local asymptotic power of the tests and drive optimal tests along the lines of Andersen et al. (1993, pp. 372–379).

The proposed inferential procedures are established under the assumption that the observation scheme is the same for different treatment groups. This assumption may not be satisfied in many practical applications. Zhang (2006) discussed the problem and proposed alterative test statistic which involves the estimation of $G_l'(t)$, where $G_l(t)$ is the mean function of the count process arising from observation times for group l. For the problem, we prefer to construct some test statistics which do not involve the estimation of $G_l'(t)$ and are easily computable. This is in progress.

Further research is to replace the isotonic regression estimates by maximum likelihood estimates for the mean function in the statistic $\mathbf{U}_n$. Wellner and Zhang (2000) showed that the nonparametric maximum likelihood estimator (NPMLE) of the mean function is more efficient than the nonparametric maximum pseudo-likelihood estimator (NPMPLE, the isotonic regression estimator) by means of Monte Carlo simulations. From this, one would naturally expect that the tests based on the NPMLE could be more efficient than the proposed tests based on the NPMPLE. However, unlike the isotonic regression estimate, the maximum likelihood estimate has no closed form and its computation requires an iterative convex minorant algorithm.

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