The Poisson-exponential model for recurrent event data: an application to bowel motility data

Francisco Louzada\textsuperscript{a}, Márcia A.C. Macera\textsuperscript{b}\textsuperscript{*} and Vicente G. Cancho\textsuperscript{a}

\textsuperscript{a}Instituto de Ciências Matemáticas e de Computação, Universidade de São Paulo, Caixa Postal 668, São Carlos, SP, 13560-970, Brasil; \textsuperscript{b}Departamento de Estatística, Universidade Federal de São Carlos, Via Washington Luís, km 235, Caixa Postal 676, São Carlos, SP, 13565-905, Brasil

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This paper presents a new parametric model for recurrent events, in which the time of each recurrence is associated to one or multiple latent causes and no information is provided about the responsible cause for the event. This model is characterized by a rate function and it is based on the Poisson-exponential distribution, namely the distribution of the maximum among a random number (truncated Poisson distributed) of exponential times. The time of each recurrence is then given by the maximum lifetime value among all latent causes. Inference is based on a maximum likelihood approach. A simulation study is performed in order to observe the frequentist properties of the estimation procedure for small and moderate sample sizes. We also investigated likelihood-based tests procedures. A real example from a gastroenterology study concerning small bowel motility during fasting state is used to illustrate the methodology. Finally, we apply the proposed model to a real data set and compare it with the classical Homogeneous Poisson model, which is a particular case.

Keywords: recurrent event data; rate function; gap time; maximum likelihood estimation; Poisson-exponential distribution; latent complementary risks

1. Introduction

Recurrent event data are usually observed in longitudinal studies involving multiple subjects. This kind of data set arises in several areas, such as biomedical studies with reappearance of cancerous tumors, criminology studies with relapse of an offender in a crime, industrial studies with recurrent failures of an equipment, demographic studies with repeated migrations, among others.

In the literature, two types of time scale are often used to analyze recurrent event data, namely the event time of recurrence \cite{13,15} and the interval time (gap) between successive recurrences.
We can mention the nonhomogeneous Poisson processes as canonical models for the analysis of recurrent event data [8]. These models are often characterized through the properties of recurrence times, and in this context a variety of methods have been proposed [16, 26, 40, 42]. On the other hand, renewal processes are the canonical models for the gap times analysis [13, 28], being characterized through the distribution of gap times. The assumption of independence in a renewal process is a strong one, and thus more general models are often required. Hence, considerable attention has been devoted to the gap times providing a wide variety of models, including bivariate distribution for censored gap times [19], accelerated failure time models [34], proportional hazards models [12, 33] and additive hazards models [21, 35] for gap times based on renewal process, and more recently additive hazards models for gap times with multiple causes [32]. Another class of models includes the renewal Poisson processes [10, 17] and the hybrid scale models [22], which accommodate the two time scales, total time and interval time.

Full specification of a model for recurrent event data by intensity functions often does not adequately reflect certain practical situations. For instance, in some applications there are only a few individuals with more than one or two events, and in such cases there is naturally less information about the event processes, affecting the modeling [8]. In confronting these situations, many authors have been considered methods that focus on marginal features, such as rate function of the recurrent process [1, 7, 20]. This approach has the advantage of being easily interpretable, mainly to identifying risk factors, and enable the development of simple and robust methods [38]. This formulation is also attractive to gap time models. Recently, Zhao and Zhou [41] introduced a new model for gap times, based on a marginal rate function, which is derived from a nonhomogeneous Poisson process.

In several situations, the occurrence of a particular event can be given by one or multiple causes. In this context, Lawless et al. [18] discussed multiplicative hazard models for the gap time distribution of recurrent event data when there is a single cause of recurrence, and Sankaran and Anisha [31, 32] proposed, respectively, an additive hazard model and a shared frailty model for gap time distributions with multiple causes. However, we can also consider that the number of causes as well as the associated lifetime with each cause are often not observed, called latent causes, rather we observed only the maximum lifetime value among all causes. This can also be considered in situations where the event of interest may occur more than once for the same subject. In this case, we assume that the time of each occurrence is associated to one or several latent causes and there is no information about which cause was responsible for the event. We point out that complementary risk problems arise in several areas. An example of such problems are hospitalizations of patients infected with human immunodeficiency virus. Some opportunistic diseases as candidiasis, anemia, hepatitis, tuberculosis and esophagitis affect such patients [11, 24]. These infections can be considered as risk factors that compete, leading the repeated hospitalizations of these patients. In the tumor cases, clonogenic cells that survive a treatment may be considered as risk factors, leading to the development of new tumors. Another example can be seem in a gastroenterology study involving small bowel motility. Several systemic diseases such as myxedema, structural abnormalities of the gut from birth, amyloidosis, psychologic stress, Parkinson’s disease, myasthenia gravis, hyperthyroidism, systemic sclerosis, diabetes mellitus, hypothyroidism, and so on [14, 37, 39] can be regarded as competing causes that lead to intestinal dysmotility.

This paper proposes a model to analyze gap times of recurrent event data. This model is characterized by a baseline function fully parametric and it is based on the Poisson-exponential distribution, recently studied by Cancho et al. [4]. Furthermore, assuming this specific parametric form, our model is stated on a complementary risk scenario, and the time of each recurrence is then given by the maximum lifetime value among all latent causes. Hereafter, we will call our model as the PE recurrent event model or simply Poisson-exponential model.
The remainder of the paper is organized as follows. In Section 2, we present the proposed model and its properties. The likelihood function for statistical inference, model assessment and hypothesis testing are detailed in Section 3. Section 4 contains the results of a simulation study on the behavior of the maximum likelihood estimates when a possibly small or moderate number of recurrent events per subject is observed. Likelihood-based tests procedures for testing the adequacy of the proposed model and their particular case are also discussed in this section. A real data analysis on a gastroenterology study concerning small bowel motility during fasting state for 19 individuals are presented in Section 5. Finally, Section 6 concludes the paper with final comments.

2. Model formulation

The proposed model in this paper is described in the context of recurrent events and it is founded on a gap time model formulation. For explicit representation of our model, we denote $t$ as a calendar time (referred to as the event time) and $w$ as another time of interest, such as a gap (interevent) time. Motivated by the idea of Zhao and Zhou [41], we consider a model in which the general form of the rate function is given by

$$\lambda(w|t) = \lambda_0(t + w),$$  \hspace{1cm} (1)

where $\lambda(w|t)$ is the rate function for the recurrence process up to time $t + w$ and $\lambda_0(t)$ is a deterministic function describing the general behavior of a subject over time.

Hereafter, we suppose that $n$ independent subjects are submitted to experience an initial event and the recurrences of the same event are registered along the study period. Subjects are indexed by $i$, $i = 1, 2, \ldots, n$, and each subject’s recurrences are indexed by $j$, $j \geq 1$. For subject $i$, let $(W_{ij})_{j \geq 1}$ be the sequence of gap times between successive occurrences of the event. Let $0 < T_{i1} < T_{i2} < \cdots$ represent the times at which event occurs, where $T_{ij} = W_{i1} + \ldots + W_{ij}$ is the occurrence time of the $j$th event of subject $i$.

Specifically, conditional on $T_{i,j-1} = t_{i,j-1}$, we consider that the baseline rate function has a Poisson-exponential form and then the rate function of recurrence process $N_i(t_{i,j-1} + w)$ for subject $i$ is defined by

$$\lambda(w|t_{i,j-1}) = \frac{\theta \alpha e^{-\alpha(t_{i,j-1}+w)}}{e^{\theta}e^{-\alpha(t_{i,j-1}+w)} - 1},$$ \hspace{1cm} (2)

where $\theta, \alpha > 0$ and $w > 0$. The rate function increases with recurrence times but stabilizes at $\alpha$. Besides, when $\theta$ approaches zero the rate function will be close to $\alpha$, which is the upper bound of rate function, and hence the model reduces to the classical homogeneous Poisson process (HPP) with constant rate (i.e. the gap times $W_{ij}$ between successive events are independent and identically distributed exponential random variables with mean $\alpha^{-1}$). Figure 1 illustrates rate function shapes for some selected values of $\theta$ and fixed $\alpha$. The PEre parameters have a direct interpretation in terms of complementary risks. The $\theta/(1 - e^{\theta})$ represents the mean of the number of complementary risks, while $\alpha$ denotes the failure rate of the distribution of time-to-event due to individual complementary risks. It can be noted that the expected number of complementary risks tends to 1 as the parameter $\theta$ tends to zero.

We now consider the corresponding cumulative rate function over the interval $(t_{i,j-1}, t_{i,j-1} + w]$ given by

$$\Lambda(t_{i,j-1}, w) = \Lambda(t_{i,j-1} + w) - \Lambda(t_{i,j-1}) = \int_0^w \lambda(u|t_{i,j-1}) \, du$$

$$= \int_0^w \lambda_0(u) \, du = \int_{t_{i,j-1}}^{t_{i,j-1}+w} \lambda_0(u) \, du, \hspace{1cm} (3)$$
where $\Lambda(t) = \int_0^t \lambda(u) \, du$.

The recurrence process $N_i(t_{i,j-1}, t_{i,j-1} + w)$ of subject $i$ is assumed to be a nonhomogeneous Poisson process with rate function (2), and together with (3), we can write

$$E[N_i(t_{i,j-1} + w) - N_i(t_{i,j-1})] = \Lambda(t_{i,j-1}, w).$$

(4)

So for a process that is independent of the history of events prior to $t_{i,j-1}$, the conditional distributions of gap times $W_{ij}$ are given by Cook and Lawless [8]

$$\Pr(W_{ij} > w | T_{i,j-1} = t_{i,j-1}) = \Pr[N_i(t_{i,j-1} + w) - N_i(t_{i,j-1}) = 0]$$

$$= \exp\{-\Lambda(t_{i,j-1}, w)\}.\quad (5)$$

Let $S(w|t_{i,j-1})$ denote the survival function for subject $i$. Considering that the rate function expressed by Equation (2) is deterministic and integrable over $(t_{i,j-1}, t_{i,j-1} + w]$ and $\Lambda(t_{i,j-1}, w)$ is continuous, the survival function of $W_{ij}$, given $T_{i,j-1} = t_{i,j-1}$, for each subject is given by

$$S(w|t_{i,j-1}) = \frac{1 - e^{-\theta e^{-\alpha(t_{i,j-1} + w)}}}{1 - e^{-\theta e^{-\alpha(t_{i,j-1})}}}.\quad (6)$$

and thus the each subject’s gap times are not in general statistically independent.

Moreover, it follows from Equation (5) that conditional on $T_{i,j-1} = t_{i,j-1}$, the $j$th gap time $W_{ij}$ of subject $i$ has rate function (2) and density function given by

$$f_{W_{ij}}(w|t_{i,j-1}) = \lambda(w|t_{i,j-1}) \exp\{-\Lambda(t_{i,j-1}, w)\}$$

$$= \frac{\theta \alpha e^{-\alpha(t_{i,j-1} + w)} - \theta e^{-\alpha(t_{i,j-1})}}{1 - e^{-\theta e^{-\alpha(t_{i,j-1})}}}.$$

(7)

The proof that the function in Equation (7) is a probability density function is trivial and a known result, then it is omitted.
Hereafter, we present a general expression for the raw moments of the $j$th gap time $W_{ij}$ of subject $i$, given by Equation (8), which follow directly from the moments of Cancho et al. [4] considering Equation (7).

Then for $r \in \mathbb{N}$, the raw moments are given by

$$E(W_{ij}^r | t_{ij}^{-1}) = \frac{b_{ij} \Gamma(r + 1)}{\alpha^r (1 - e^{-b_{ij}})} F_{r+1,r+1}([1, 1], [2, 2], \ldots, [2], \ldots, [2, 1], [-b_{ij}], -b_{ij}),$$

where $b_{ij} := b_{ij}(\theta, \alpha) = \theta e^{-\alpha t_{ij-1}}$ and $F_{p,q}(n, d, b_{ij})$ is the generalized hypergeometric function (see [25, p. 405]).

Hence, considering Equation (8), the mean and variance of the $j$th gap time $W_{ij}$ of subject $i$ are given, respectively, by

$$E(W_{ij} | t_{ij}^{-1}) = \frac{b_{ij}}{\alpha (1 - e^{-b_{ij}})} F_{2,2}([1, 1], [2, 2], -b_{ij}),$$

$$\text{Var}(W_{ij} | t_{ij}^{-1}) = \frac{b_{ij}}{(1 - e^{-b_{ij}})\alpha^2} [2F_{3,3}([1, 1, 1], [2, 2, 2], -b_{ij}) - \frac{b_{ij}}{(1 - e^{-b_{ij}})} F_{2,2}^{2}([1, 1], [2, 2], -b_{ij})].$$

Finally, a method for data generation is presented below. The numerical study of the inferential method properties requires the simulation of the gap times, driven by the corresponding rate function (2), and of the times of events.

The gap times $(w_{ij})_{i,j \geq 1}$ are simulated using the iterative inverse-transform algorithm [30, Chapter 2]. The idea of the inverse-transform method is that for a uniform random variable $U$ on the interval $(0, 1)$, and for any continuous distribution function $F$, the random variable $X$, defined as $X = F^{-1}(U)$, has distribution function $F$.

Consider a random variable $W_{ij}$, the gap time between the $(j - 1)$st and the $j$th recurrent event times of a subject $i$. The conditional distribution function $F$ of $W_{ij}$ may be used for inversion. Specifically,

$$F_{W_{ij}}(w | T_{i,j-1} = t_{ij-1}) = 1 - \exp \left\{- \int_{t_{ij-1}}^{t_{ij-1}+w} \lambda_0(u) \, du \right\}. \quad (9)$$

Then the gap times and times of events are generated through the following steps:

1. Draw $u_{ij} \sim \text{uniform}(0, 1)$;
2. Use the Equations (9) and (2) and obtain the distribution of gap time $W_{ij}$

   $$F_{W_{ij}}(w | T_{i,j-1} = t_{ij-1}) = 1 - \exp \left\{- \int_{t_{ij-1}}^{t_{ij-1}+w} \frac{\theta \alpha e^{-\alpha u}}{e^\theta e^{-\alpha u} - 1} \, du \right\}$$

   $$= \frac{e^{-\theta e^{-\theta u_{ij-1}+w}} - e^{-\theta e^{-\theta u_{ij-1}}}}{1 - e^{-\theta e^{-\theta u_{ij-1}}}} = u_{ij}, \quad (10)$$

3. Solve Equation (10) for $w$, and obtain $w_{ij}$, a realization of the random variable $W_{ij}$. Then the general expression for generated gap times is easily obtained:

   $$w_{ij} = \frac{\log(\theta) - \alpha t_{ij-1} - \log[- \log(u_{ij} + (1 - u_{ij})e^{-\theta e^{-\theta u_{ij-1}}})]}{\alpha}; \quad (11)$$

4. Get the times of events by doing $t_{ij} = t_{ij-1} + w_{ij}$, for $i = 1, \ldots, n$ and $j \geq 1$, with $t_{i0} = 0$. 

3. Statistical inference

The parameters \((\alpha, \theta)\) of the model are estimated using the maximum likelihood method, described in the current section. We assume that the recurrences of subjects are driven by a rate function as defined in Section 2. Let \(i\) be a subject observed over the interval time \((0, \tau_i]\), \(i = 1, \ldots, n\), where \(t = 0\) corresponds to the start of the recurrence process. More precisely, for subject \(i\), if \(m_i\) recurrences are observed at times \(0 < t_{i1} < \cdots < t_{im_i} \leq \tau_i\), define \(w_{ij} = t_{ij} - t_{ij-1}\) for \(j = 1, 2, \ldots, m_i\) and \(t_0 = 0\). We assume that the stopping time \(\tau_i\) coincides with the occurrence time of the \(m_i\) failure, that is, \(\tau_i = t_{im_i}\).

Assuming that each subject’s gap times, \(W_{11}, \ldots, W_{im_i}\), are associated with a censoring variable, and the censoring mechanism is noninformative, the contribution to the likelihood from each individual with respect to all occurrences and all intervals is

\[
L(\cdot) = \left\{ \prod_{i=1}^{n} \prod_{j=1}^{m_i} \lambda(w_{ij}|t_{ij-1})^{\nu_{ij}} \exp\left\{ -\sum_{i=1}^{n} \sum_{j=1}^{m_i} \Lambda(t_{ij-1}, w_{ij}) \right\} \right\},
\]

where \(c_{ij}\) is a censoring indicator, which is equal to 0 if the gap time is censored or 1 if the gap time is completely observed.

Then, from Equation (6) we obtain the log-likelihood function as

\[
\ell(\alpha, \theta) = \sum_{i=1}^{n} \sum_{j=1}^{m_i} c_{ij} \left[ \log(\theta\alpha) - \alpha(t_{ij-1} + w_{ij}) - \theta e^{-\alpha(t_{ij-1} + w_{ij})} \right]
+ (1 - c_{ij}) \log(1 - e^{-\alpha(t_{ij-1} + w_{ij})}) - \log(1 - e^{-\alpha(t_{ij-1})}).
\]

The maximum likelihood estimates (MLEs) of the parameters can be obtained by direct maximization of the log-likelihood function (13) using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) optimization procedure of the R system [29].

Considering the usual large-sample approximation, inference for the parameters can be based on the MLEs and their estimated variances, which are available from Fisher information matrix. Then, considering appropriate conditions on the model, to obtain interval estimates for the MLEs \((\hat{\alpha}, \hat{\theta})\), we can act as though \((\hat{\alpha}, \hat{\theta}) \sim N(\theta, I^{-1}(\theta))\), where \(I(\theta)\) denotes the observed information matrix and \(I^{-1}(\hat{\theta}) = I^{-1}(\theta)|_{\theta=(\hat{a},\hat{b})}\). The components of the observed information are given by \(I_{kl} = -\partial^2 \ell/\partial \alpha_k \partial \theta_l\), \(k, l = 1, 2\), and they are provided in Appendix A.

Assessment of fit and model selection is also a important issue. The PEre model (2) includes as particular case the HPP. We may be interested in verify if such simpler model could be considered. Thus, we may test the hypotheses \(H_0 : \theta = 0\) versus \(H_1 : \theta > 0\), which leads to the particular case of Equation (2). Note that, for the \(H_0\), \(\theta = 0\) is on the boundary of the parameter space of \(\theta\).

We consider the likelihood ratio and the score tests. Let \(\hat{\theta} = \arg \max_{(\alpha, \theta)} L(\alpha, \theta)\) the MLEs obtained from fitting full model and \(\hat{\theta}_0 = \arg \max_{(\alpha, \theta=0)} L(\alpha, \theta)\) the corresponding MLE obtained under the restricted hypothesis \(H_0\), both under a sample of size \(n\). The likelihood ratio statistic (LRS) is defined by

\[
D^2 = 2(\ell(\hat{\theta}) - \ell(\hat{\theta}_0)),
\]

where \(\ell(\theta)\) is the log-likelihood function. Following Maller and Zhou [23], since the test is performed in the boundary of the parameter space, the LRS, \(D^2\), is assumed to be asymptotically distributed as a symmetric mixture of a chi-squared random variable with one degree of freedom \((\chi^2_1)\) and a mass at zero. This result can be written as \(\lim_{n \to \infty} P(D^2 \leq x) = \frac{1}{2} + 1/2P(\chi^2_1 \leq x)\), for \(x \geq 0\). Then, large positive values of \(D^2\) provide evidence against \(H_0\).
The score test is defined by Peng and Xu [27] as

$$Z^2 = \left( \frac{\partial^2 \ell(\theta)}{\partial \theta^2} \right)^2 \left( \frac{- \partial^2 \ell(\theta)}{\partial \theta^2} - \frac{A^2 B^{-1}}{\hat{\theta}_0} \right),$$

(15)

where \( A = -\partial^2 \ell(\theta)/\partial \theta \partial \alpha \) and \( B = -\partial^2 \ell(\theta)/\partial \alpha^2 \). The null distribution of the score test can be approximated by the chi-square distribution with one degree of freedom. Again, large values of this statistic, \( Z^2 \), provide evidence against \( H_0 \).

In addition, checking the model fit is also critical to ensure that assumptions underlying the model are plausible to the available data. However, informal graphical methods can provide information, and in this sense we consider the Cox–Snell residuals to the assessment of fit. These residuals are defined as

$$\hat{E}_{ij} = \hat{\Lambda}(t_{ij-1}, w_{ij}), \quad i = 1, \ldots, n \quad \text{and} \quad j = 1, \ldots, m_i,$$

where \( \hat{\Lambda}(\cdot) \) is the cumulative rate function obtained from the fitted model [8]. The Cox–Snell residuals for the PEre model are defined, with the estimates being the MLEs, as

$$\hat{E}_{ij} = \log \left[ \frac{1 - \exp(-\hat{\theta}e^{-\hat{\alpha}(t_{ij-1})})}{1 - \exp(-\hat{\theta}e^{-\hat{\alpha}(t_{ij-1}+w_{ij})})} \right].$$

(16)

The Cox–Snell goodness-of-fit plot is a visual diagnostic tool where the Nelson–Aalen estimate of the cumulative hazard function is generated based on the Cox–Snell residuals, which are used as the lifetimes failure and the original censoring used as failures [6].

4. Simulation study

In this section we describe the results of a simulation study performed in order to assess the applicability of asymptotic results of the estimation procedure previously described. In addition, we also conducted a simulation study to investigate the empirical power of the hypothesis tests and the behavior of Cox–Snell residuals for recurrent events. The study was based on the generation of data set as described in Section 2, assuming initially that each one of \( n \) subjects experienced the same number of event occurrences \( m_i = m = 2, 5, 7, 15 \) with \( n = 30, 50 \) and 100. In the simulation we fixed \( \alpha = 3 \), but the assessment of the inferential procedure does not depend on the specific value of \( \alpha \) selected for data generation. We considered different values of \( \theta, \theta \in \{0.75, 2, 4\} \), which correspond to different degrees of inclination of the rate function. Then we simulated 36 different cases, each one with 1000 samples. Besides, to address the impact of censoring, the study was repeated with right-censored samples with \( m = 5, 7 \) and 15. For \( m = 5 \) we consider one censored observation, for \( m = 7 \) we consider two censored observations and for \( m = 15 \) we consider four censored observations, which correspond approximately to 25%, 30% and 30% of censoring.

Then, we first evaluate the accuracy of the approximation of the variance and covariance of the MLEs obtained from the Fisher information matrix. Table 1 shows the simulated values of \( \text{Var}(\hat{\theta}), \text{Var}(\hat{\alpha}) \) and \( \text{Cov}(\hat{\theta}, \hat{\alpha}) \) as well as the approximate values from the average the corresponding values determined through the observed information matrix. It is noted that the approximated values obtained from the observed information matrix are close to the simulated ones for a small and moderate numbers of recurrence. Moreover, it is observed that the approximation becomes quite accurate when the sample size and the number of recurrences per subject increase.

In addition, simulation studies have been performed in order to analyze the frequentist properties of the estimation procedure. To examine the frequentist properties, we constructed the 95% confidence intervals for the model parameters and calculated their coverage probabilities (CP). The averages of the 1000 MLEs as well as their standard errors and the empirical CP for different sets of parameters, different sample sizes and different numbers of recurrence are condensate in
Table 1. Mean of variances and covariances of the MLEs.

| n   | m | \((\theta, \alpha)\) | Simulated | From observed information |
|-----|---|-------------------|-----------|------------------------|
|     |    | \(\text{Var}(\hat{\theta})\) | \(\text{Var}(\hat{\alpha})\) | \(\text{Cov}(\hat{\theta}, \hat{\alpha})\) | \(\text{Var}(\hat{\theta})\) | \(\text{Var}(\hat{\alpha})\) | \(\text{Cov}(\hat{\theta}, \hat{\alpha})\) |
| 30  | 2  | (0.75, 3.0)       | 0.605     | 0.261                  | 0.270                  | 0.782                  | 0.297                  | 0.359                  |
|     |    | (2.00, 3.0)       | 0.917     | 0.200                  | 0.299                  | 0.896                  | 0.198                  | 0.299                  |
|     |    | (4.00, 3.0)       | 1.698     | 0.138                  | 0.333                  | 1.610                  | 0.135                  | 0.325                  |
| 5   |    | (0.75, 3.0)       | 0.395     | 0.079                  | 0.098                  | 0.472                  | 0.083                  | 0.117                  |
|     |    | (2.00, 3.0)       | 0.630     | 0.068                  | 0.121                  | 0.592                  | 0.066                  | 0.114                  |
|     |    | (4.00, 3.0)       | 1.200     | 0.058                  | 0.155                  | 1.121                  | 0.055                  | 0.143                  |
| 7   |    | (0.75, 3.0)       | 0.352     | 0.050                  | 0.062                  | 0.417                  | 0.053                  | 0.077                  |
|     |    | (2.00, 3.0)       | 0.558     | 0.045                  | 0.080                  | 0.538                  | 0.046                  | 0.079                  |
|     |    | (4.00, 3.0)       | 1.062     | 0.042                  | 0.117                  | 0.999                  | 0.040                  | 0.104                  |
| 15  |    | (0.75, 3.0)       | 0.262     | 0.021                  | 0.026                  | 0.345                  | 0.022                  | 0.032                  |
|     |    | (2.00, 3.0)       | 0.427     | 0.020                  | 0.039                  | 0.448                  | 0.020                  | 0.035                  |
|     |    | (4.00, 3.0)       | 0.766     | 0.018                  | 0.048                  | 0.828                  | 0.019                  | 0.050                  |
| 50  | 2  | (0.75, 3.0)       | 0.404     | 0.183                  | 0.194                  | 0.464                  | 0.179                  | 0.216                  |
|     |    | (2.00, 3.0)       | 0.546     | 0.133                  | 0.191                  | 0.520                  | 0.118                  | 0.175                  |
|     |    | (4.00, 3.0)       | 0.982     | 0.091                  | 0.209                  | 0.900                  | 0.080                  | 0.187                  |
| 5   |    | (0.75, 3.0)       | 0.222     | 0.047                  | 0.054                  | 0.277                  | 0.049                  | 0.069                  |
|     |    | (2.00, 3.0)       | 0.319     | 0.041                  | 0.064                  | 0.345                  | 0.039                  | 0.066                  |
|     |    | (4.00, 3.0)       | 0.674     | 0.035                  | 0.092                  | 0.630                  | 0.032                  | 0.082                  |
| 7   |    | (0.75, 3.0)       | 0.210     | 0.030                  | 0.036                  | 0.246                  | 0.032                  | 0.046                  |
|     |    | (2.00, 3.0)       | 0.300     | 0.027                  | 0.042                  | 0.314                  | 0.027                  | 0.047                  |
|     |    | (4.00, 3.0)       | 0.564     | 0.024                  | 0.062                  | 0.568                  | 0.024                  | 0.060                  |
| 15  |    | (0.75, 3.0)       | 0.192     | 0.012                  | 0.018                  | 0.208                  | 0.013                  | 0.019                  |
|     |    | (2.00, 3.0)       | 0.268     | 0.012                  | 0.022                  | 0.268                  | 0.012                  | 0.021                  |
|     |    | (4.00, 3.0)       | 0.466     | 0.010                  | 0.026                  | 0.482                  | 0.011                  | 0.029                  |
| 100 | 2  | (0.75, 3.0)       | 0.204     | 0.083                  | 0.096                  | 0.229                  | 0.088                  | 0.107                  |
|     |    | (2.00, 3.0)       | 0.245     | 0.057                  | 0.084                  | 0.251                  | 0.058                  | 0.086                  |
|     |    | (4.00, 3.0)       | 0.415     | 0.039                  | 0.090                  | 0.417                  | 0.039                  | 0.090                  |
| 5   |    | (0.75, 3.0)       | 0.131     | 0.025                  | 0.036                  | 0.137                  | 0.024                  | 0.034                  |
|     |    | (2.00, 3.0)       | 0.177     | 0.021                  | 0.038                  | 0.171                  | 0.020                  | 0.033                  |
|     |    | (4.00, 3.0)       | 0.326     | 0.017                  | 0.047                  | 0.303                  | 0.016                  | 0.040                  |
| 7   |    | (0.75, 3.0)       | 0.110     | 0.015                  | 0.021                  | 0.121                  | 0.016                  | 0.022                  |
|     |    | (2.00, 3.0)       | 0.147     | 0.013                  | 0.023                  | 0.154                  | 0.013                  | 0.023                  |
|     |    | (4.00, 3.0)       | 0.254     | 0.012                  | 0.030                  | 0.273                  | 0.012                  | 0.029                  |
| 15  |    | (0.75, 3.0)       | 0.100     | 0.007                  | 0.010                  | 0.103                  | 0.006                  | 0.009                  |
|     |    | (2.00, 3.0)       | 0.134     | 0.006                  | 0.011                  | 0.132                  | 0.006                  | 0.010                  |
|     |    | (4.00, 3.0)       | 0.230     | 0.006                  | 0.013                  | 0.234                  | 0.006                  | 0.014                  |

Table 2. It can be observed that the empirical CP are closer to the nominal coverage level for a larger sample size and moderate numbers of recurrence. Moreover, as the number of observations increase the estimates approaching the real value of the parameter and the standard errors of MLEs decrease, which allows us to conclude that the established estimators of parameters are consistent. Thus, we can guarantee the form of data generation given by Equation (11). The results are similar for all sets of parameters.

We also analyze the likelihood ratio test and the score test under the null hypotheses, \(H_0: \theta = 0\), and their power to detect the alternative hypothesis. The results are summarized in Tables 3 and 4, which report, respectively, the observed proportions of type I error and the empirical powers from the likelihood ratio test and the score test at a 5% nominal significance level. The rejection regions are obtained from a symmetric mixture of a chi-squared random variable with one degree of freedom and a point-mass at zero for the likelihood ratio test \(D^2\) and from the chi-square distribution with one degree of freedom for the score test \(Z^2\).

It can be seen that empirical significance levels of the likelihood ratio test are very close to the nominal level while those from the score test are slightly greater than the nominal level under
sizes also correspond to larger power for the tests, but small and moderate numbers of recurrence increases, the empirical levels of the tests all approaching the nominal level. The larger sample sizes, particularly for recurrence numbers lower than 15. As the sample size increases, the empirical levels of the tests all approaching the nominal level. The larger sample sizes also correspond to larger power for the tests, but small and moderate numbers of recurrence

| n  | m | (θ, α)     | Av(θ̂, ˆα)     | Sd(θ̂, ˆα)     | CP(θ, α)     |
|----|---|-----------|---------------|---------------|--------------|
| 30 | 2 | (0.75, 3.0) | (0.938, 3.098) | (0.882, 0.540) | (0.973, 0.962) |
|    |   | (2.00, 3.0) | (2.162, 3.049) | (0.941, 0.442) | (0.961, 0.953) |
|    |   | (4.00, 3.0) | (4.310, 3.048) | (1.238, 0.366) | (0.975, 0.954) |
| 5  |   | (0.75, 3.0) | (0.801, 3.005) | (0.686, 0.287) | (0.979, 0.955) |
|    |   | (2.00, 3.0) | (2.024, 2.977) | (0.766, 0.257) | (0.957, 0.942) |
|    |   | (4.00, 3.0) | (4.246, 3.030) | (1.041, 0.233) | (0.958, 0.946) |
| 7  |   | (0.75, 3.0) | (0.832, 2.995) | (0.644, 0.230) | (0.976, 0.957) |
|    |   | (2.00, 3.0) | (2.081, 2.990) | (0.730, 0.213) | (0.963, 0.946) |
|    |   | (4.00, 3.0) | (4.194, 3.020) | (0.986, 0.199) | (0.956, 0.939) |
| 15 |   | (0.75, 3.0) | (0.753, 2.975) | (0.586, 0.148) | (0.982, 0.951) |
|    |   | (2.00, 3.0) | (1.981, 2.974) | (0.667, 0.143) | (0.953, 0.942) |
|    |   | (4.00, 3.0) | (4.129, 3.006) | (0.901, 0.139) | (0.963, 0.954) |
| 50 | 2 | (0.75, 3.0) | (0.892, 3.091) | (0.680, 0.420) | (0.966, 0.950) |
|    |   | (2.00, 3.0) | (2.143, 3.060) | (0.719, 0.342) | (0.961, 0.937) |
|    |   | (4.00, 3.0) | (4.243, 3.052) | (0.936, 0.283) | (0.964, 0.934) |
| 5  |   | (0.75, 3.0) | (0.816, 3.010) | (0.526, 0.221) | (0.984, 0.959) |
|    |   | (2.00, 3.0) | (2.012, 2.986) | (0.586, 0.198) | (0.965, 0.938) |
|    |   | (4.00, 3.0) | (4.139, 3.016) | (0.787, 0.180) | (0.952, 0.946) |
| 7  |   | (0.75, 3.0) | (0.778, 2.992) | (0.495, 0.178) | (0.980, 0.957) |
|    |   | (2.00, 3.0) | (2.036, 2.993) | (0.559, 0.165) | (0.965, 0.951) |
|    |   | (4.00, 3.0) | (4.112, 3.012) | (0.748, 0.154) | (0.962, 0.949) |
| 15 |   | (0.75, 3.0) | (0.771, 2.987) | (0.455, 0.115) | (0.962, 0.954) |
|    |   | (2.00, 3.0) | (2.026, 2.987) | (0.517, 0.111) | (0.962, 0.955) |
|    |   | (4.00, 3.0) | (4.085, 3.003) | (0.690, 0.107) | (0.958, 0.967) |
| 100| 2 | (0.75, 3.0)  | (0.806, 3.034) | (0.478, 0.296) | (0.968, 0.965) |
|    |   | (2.00, 3.0)  | (2.069, 3.025) | (0.500, 0.240) | (0.957, 0.957) |
|    |   | (4.00, 3.0)  | (4.117, 3.023) | (0.643, 0.198) | (0.953, 0.960) |
| 5  |   | (0.75, 3.0)  | (0.765, 2.991) | (0.370, 0.156) | (0.954, 0.947) |
|    |   | (2.00, 3.0)  | (2.020, 2.991) | (0.413, 0.140) | (0.948, 0.944) |
|    |   | (4.00, 3.0)  | (4.081, 3.006) | (0.548, 0.127) | (0.947, 0.939) |
| 7  |   | (0.75, 3.0)  | (0.749, 2.991) | (0.348, 0.126) | (0.958, 0.954) |
|    |   | (2.00, 3.0)  | (2.001, 2.992) | (0.392, 0.116) | (0.955, 0.949) |
|    |   | (4.00, 3.0)  | (4.046, 3.003) | (0.520, 0.108) | (0.957, 0.949) |
| 15 |   | (0.75, 3.0)  | (0.758, 2.993) | (0.320, 0.081) | (0.949, 0.953) |
|    |   | (2.00, 3.0)  | (2.008, 2.993) | (0.364, 0.078) | (0.948, 0.950) |
|    |   | (4.00, 3.0)  | (4.039, 3.001) | (0.483, 0.078) | (0.963, 0.941) |

Table 2. The averages of the 1000 MLEs, Av(θ̂, ˆα), their standard errors, Sd(θ̂, ˆα), and the CP of the 95% confidence intervals for the model parameters, CP(θ, α).

Table 3. Empirical proportions of type I error of the likelihood ratio test and score test with 5% nominal significance level.

| m   | LRS n = 30 | LRS n = 50 | LRS n = 100 | Score n = 30 | Score n = 50 | Score n = 100 |
|-----|------------|------------|-------------|--------------|--------------|--------------|
| 2   | 0.057      | 0.056      | 0.053       | 0.060        | 0.058        | 0.052        |
| 5   | 0.063      | 0.055      | 0.049       | 0.066        | 0.064        | 0.054        |
| 7   | 0.049      | 0.052      | 0.050       | 0.043        | 0.059        | 0.052        |
| 15  | 0.051      | 0.050      | 0.051       | 0.049        | 0.049        | 0.051        |
Table 4. Empirical powers of the likelihood ratio test and score test with 5% nominal significance level.

| Test | $\theta = 0.75$ | $\theta = 1.5$ | $\theta = 3.0$ |
|------|----------------|----------------|----------------|
|      | $n = 30$ | $n = 50$ | $n = 100$ | $n = 30$ | $n = 50$ | $n = 100$ | $n = 30$ | $n = 50$ | $n = 100$ |
| LRS  | 2  0.229 | 0.331 | 0.489 | 0.564 | 0.754 | 0.955 | 0.966 | 0.998 | 0.999 |
|      | 5  0.283 | 0.425 | 0.656 | 0.706 | 0.897 | 0.990 | 0.994 | 0.999 | 0.999 |
|      | 7  0.332 | 0.449 | 0.707 | 0.755 | 0.927 | 0.998 | 0.997 | 0.999 | 0.999 |
|      | 15  0.337 | 0.513 | 0.769 | 0.800 | 0.950 | 0.998 | 0.997 | 0.999 | 0.999 |
| Score | 2  0.141 | 0.213 | 0.267 | 0.443 | 0.590 | 0.844 | 0.936 | 0.993 | 0.999 |
|      | 5  0.158 | 0.230 | 0.406 | 0.508 | 0.782 | 0.947 | 0.975 | 0.997 | 0.999 |
|      | 7  0.169 | 0.258 | 0.447 | 0.578 | 0.800 | 0.980 | 0.992 | 0.999 | 0.999 |
|      | 15  0.184 | 0.313 | 0.544 | 0.626 | 0.865 | 0.984 | 0.992 | 0.999 | 0.999 |

do not harm the empirical powers. Furthermore, it can be concluded that the empirical power of the likelihood ratio test is greater than those from the score test for values of $\theta$ closer to zero, and this difference decreases when the parameter $\theta$ is farther to zero. When $\theta = 1.5$, a larger power than 90% is achieved, for both tests, when the sample size is 100. However, for $\theta = 3$ an even larger power than 90% is achieved even for a small sample size.

Figure 2. Overall goodness-of-fit plots generated using cumulative Cox–Snell residuals for sample sizes $n = 30$ (top panel), $n = 50$ (middle panel) and $n = 100$ (bottom panel).
Finally, we also assess the fit of the proposed model, based on the simulated data, using the Cox–Snell residuals. Figure 2 presents the Cox–Snell goodness-of-fit plots for the proposed model, for different numbers of occurrences $m = 2, 7$ and $15$ and sample sizes $n = 30, 50$ and $100$. Similar results hold for $k = 5$ recurrences. To obtain these residuals, we have calculated the cumulative Cox–Snell residual. This is necessary since the recurrent event data require a cumulative residual for each occurrence, given that the last recurrence of each subject is recorded a cumulative residual total. A good fit is observed when the points have a closely fitting to the diagonal.

The results presented in Figure 2 have no departure from linearity, even with a small or moderate number of recurrences and the presence of censored observations, reflecting a satisfactory fit of the proposed model. Again, we can also ensure the form of data generation given by Equation (11).

5. Bowel motility data

In this section, the methodology is illustrated in a real data set which concerns the occurrence of certain cyclic movements in the small bowel during the fasting state. We consider the data discussed by Aalen and Husebye [2], which describe a study of small bowel motility (muscular activity) involving 19 healthy human subjects. Initially, catheters were positioned nearby the small bowel to monitor intraluminal pressure. Afterward, the individuals were examined continuously from 5:45 p.m. to 7:25 a.m. on the next day, giving a total of 13 h and 40 min observation. Then, a standardized mixed meal was given to each individual at 6:00 p.m. to induce a fed state. After a time period in which irregular bowel contractions occur, a fasting (interdigestive) state begins, with a cyclical bowel activity pattern. The time between two consecutive fasting cycles is also called the migrating motor complex (MMC) period. The lengths of successive motility (or MMC) cycles make up the data set, so that the motility cycle patterns are not associated with the duration of the fed state. In this study, events are associated with the beginning of a motility cycle and the length of the last cycle for each individual is censored by the end of the monitoring period.

Intestinal dysmotility is an alteration in bowel functions and occurs due abnormalities in the muscles and nervous of the bowels. As pointed out in Section 1, even though the complementary risks are unobserved, one may speculate on some possible complementary risks for the bowel motility data. For example, the bowel motility can be affected by diet, drugs, diseases, such as neuropathy, autonomic neuropathy, amyloidosis, myopathies, and other causes that even unobserved lead to the intestinal dysmotility [39]. In this context, the PEr model allows to analyze the effect of these factors as latent complementary risks for a better interpretation and adaptation to the situation.

Then the PEr model (2) was fitted to the bowel motility data, as well as its HPP particular case. Furthermore, by fitting the submodel of (2) we can evaluate whether the gap times for an individual are possibly independent. Table 5 presents the MLEs and the corresponding 95% confidence intervals (in parenthesis) of the parameters, which were based on the observed information matrix, for both PEr and HPP models. The last column of this table provides the log-likelihood for both models.

The results of Table 5 show that both PEr and HPP models are well supported by the data. However, the HPP model assumes that the gap times of an individual are independent. Thus, for the considered data, where the assumption of independence between events may be inappropriate, it is expected that the PEr model is more advantageous with respect to its particular case (HPP model), as can be seen in Table 5.

Therefore, the advantage of the proposed model is that it can be used both in situations where the events are independent as those in which there is no certainty of independence between
Table 5. MLEs and corresponding 95% confidence intervals (in parenthesis).

| Model | Parameter | θ        | α            | ℓ(·)          |
|-------|-----------|----------|--------------|---------------|
| PEre  |           | 4.119    | 0.727 (0.571, 0.883) | −124.101     |
| HPP   |           | 0.532    | 0.649 (0.416, 0.649)  | −130.457     |

Figure 3. Cox–Snell residuals to assess the fit of the PEre model (left panel) and HPP model (right panel).

... recurrent events of an individual, providing a wider applicability relative to the classical HPP model and also to other renewal processes.

Testing of independence between gap times can be done based on likelihood ratio and score tests by considering the null hypothesis is $H_0 : \theta = 0$. The LRS, of the hypothesis that $\theta = 0$ gives an observed value for the $D^2$ of 12.713. The 95th percentile, $x_{0.95}$, of the asymptotic distribution of the LRS can be calculated from

$$1 + \frac{1}{2}P(\chi^2_1 \leq x_{0.95}) = 0.95,$$

so $P(\chi^2_1 \leq x_{0.95}) = 0.9$, giving $x_{0.95} = 2.71$ [23]. Since $12.713 > 2.71$, we reject $H_0$, with a $p$-value < 0.001, and considered there is evidence in favor of the proposed model. Similarly, the score test provides a value for the $Z^2$ equal to 13.710, which is compared with a chi-square distribution with one degree of freedom, $\chi^2_{1,0.05} = 3.841$ and $13.710 > 3.841$, we reject $H_0$, with a $p$-value < 0.001, and again we considered there is evidence in favor of the PEre model. Therefore, the value of $\hat{\theta} = 4.119$ is significantly greater than zero, with $p$-value < 0.001 for both tests.

In order to verify the overall goodness of fit of the PEre model we calculated the Cox–Snell residuals. Figure 3 shows the Cox–Snell goodness-of-fit plots for the PEre and HPP models based on the bowel motility data. Again, the advantage of the PEre model is demonstrated by closely fitting to the diagonal.

In addition, the proposed model is a satisfactory option for data analysis, pointing out the importance of marginal features on the modeling of recurrent event data and the effect of unobservable causes that also contributes to the occurrence of the event.

6. Final comments

In this paper, we consider situations where individuals in a longitudinal study are subject to recurrences of an event of interest. The proposed model is an application of the Poisson-exponential
model, proposed by Cancho et al. [4], for recurrent event data, where we have investigated the gap times between events. We obtained the conditional distributions of gap times from the rate function, which is an attractive formulation for recurrent event data with direct interpretations frequently preferred by professionals on medical and biostatistical areas [41]. The parameters of PEre model have a direct interpretation in terms of complementary risks. Moreover, its specific parametric form is analytically convenient and easily interpretable. We discussed MLEs, obtained by direct maximization of the log-likelihood function. The inferential procedure based on the maximum likelihood approach is implemented straightforwardly. The results of simulation study showed the effectiveness of the parameter estimation approach, allowing us to conclude that small and moderate numbers of recurrences do not affect the estimates of the parameters, even in presence of censoring. The PEre model allowed a straightforwardly nested hypothesis testing procedures for comparison with its HPP particular case. The Cox–Snell residual plots allowed to assess the model fit and ensure that assumptions underlying the model are plausible to the available data. The applicability of the PEre model was demonstrated in a real data set.

The analysis considered in this paper is a preliminary step for the development of a more complete model, and our modeling may be generalized in some directions. An immediate extension of this model is to consider the effects of covariates for each subject and also a possible heterogeneity between them. As an alternative to the Poisson-exponential distribution other distributions, such as Weibull-geometric [3], beta-Weibull geometric [9], Geometric Birnbaum-Saunders [5], can be considered for modeling. These issues are of interest and will be investigated in future.

Disclosure statement

No potential conflict of interest was reported by the authors.

Supplemental data and research materials

We provide further details on the observed information matrix and codes of the simulation and case study described in this paper. Appendix A displays the components of the Fisher information matrix of Section 3. Appendix B provides additional functions required for the simulation and case study codes. The code to reproduce Figure 1 of Section 2 is provided in Appendix C. The codes to reproduce the results of the simulation study of Section 4 and the results of the case study of Section 5 are presented in Appendices D and E, respectively. Supplemental data for this article can be accessed at 10.1080/02664763.2015.1030369.

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