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Abstract

Recurrent event data arises in several areas, such as, biometrics, criminology, demography, industrial reliability and production. In this kind of data it is reasonable to presume that there is dependency among the observations related to the same subject. Such dependency can be modelled by allowing a random effect, usually called frailty term, in the modelling. In this paper the recurrent event problem is treated under the non homogeneous Poisson process approach, but with a frailty term. A Bayesian inference procedure based on Markov Chain Monte Carlo Methods is developed. The methodology is illustrated on a real data set.

Key Words: Bayesian Inference, Frailty Term, Poisson Process, Algorithm Metropolis-Hastings, Recurrent Events.

1 Introduction

Recurrent event data is is common in several areas, such as, biometrics, criminology, demography, industrial reliability and production. For instance, one infractor may go back to crime many times, several tumors may be observed in an individual, pneumonia episodes may reoccur in patients with immunodeficiency syndrome and an equipment may fail several times.

Although the initial techniques developed for handling recurrent event data suppose independence among the recurrent event times for the same individual, it is reasonable

to presume the existence of such dependence. A manner of incorporating the dependence among the recurrent event times for the same individual into the analysis is to introduce a random effect in the modelling, usually called frailty term (Clayton,1978; Aalen, 1978). The frailty term generates dependency between the lifetimes of a subject, which are assumed conditionally independent given the frailty. The first models with frailty term were considered by Clayton (1978), Vaupel, Manton and Stallard (1979), Oakes (1982), Lawless (1987), Lawless and Nadeans (1995) and Cook (1995) which considered a Poisson intensity model with a frailty term, while Follmann and Goldberg (1988) considered a renewal intensity model with random effects.

In this paper we develop a Bayesian approach for a non homogeneous Poisson process with a frailty term following a gamma distribution. We consider applications when there is a small or moderate number of recurrent events per individual with a moderate number of individuals in the experiment. The inferences for the model parameters are based on Markov Chain Monte Carlo Methods. In Section 2, we describe the intensity model with random effect and present a classical analysis for it. The Bayesian model formulation and analysis are presented in Section 3. Model selection is briefly discussed in Section 4. A real numeric example is presented in Section 4.

2 Model Formulation

Following Cox and Isham (1980) we shall model recurrent event data via intensity based models. Suppose that n individuals may experience a single type of recurrent event. Let m_i denotes the number of events occurring for the ith subject in the interval $(0, T_i]$, where T_i is determined independently of m_i and let $0 \leq t_{i1} < t_{i2} < \cdots < t_{im_i} \leq T_i$ denote the continuous failure times for the ith subject. Also, consider that, for each individual, there is a covariate vector $\mathbf{x}_i$, representing the observed heterogeneity among the individuals.

The intensity function for a non homogeneous Poisson process is given by (Lawless and Nadeans, 1995)

$$\lambda_{x_i}(t) = \lambda_0(t) \exp(\mathbf{x}_i'\beta), \quad t \geqslant 0, i = 1, 2, \ldots, n, \tag{1}$$

where $\lambda_0(t)$ is the baseline intensity function, β is an unknown regression coefficient vector and $\mathbf{x}_i$ is a covariate vector for the i-th individual.

A simple way of composing the intensity model with a frailty term is to introduce a multiplicative random effect in (1). Hence, the homogeneous Poisson process with a frailty term is given by

$$\lambda_{x_i}(t) = \lambda_0(t)\, \nu_i \exp(\mathbf{x}_i'\beta), \quad t \geqslant 0, i = 1, 2, \ldots, n, \tag{2}$$

where $\lambda_0(t)$, β and $\mathbf{x}_i$ are defined in (1) and ν_i is the frailty variable with a knew distribution function. The frailty term represents the information that may not be observed

such as, environment and genetics factors or information that, by some reason, were not considered at the planning.

We shall asume that the frailty term have a gamma distribution, with mean 1 and variance α, where α quantifies the amount of heterogeneity among subjects. The choice of the gamma distribution is essentially made by mathematical convenience, but as the frailty variable may not be negative, other distributions, such as the log-normal and Weibull could be considered. Interested readres can refer to Hougaard (2000) for a comprehensive discussion about the choice of the frailty term distribution.

From (2), the likelihood function for the individual i having m_i events observed by the time t_{ij} $(j = 1, 2, \ldots, m_i)$ is given by

$$L_i = \prod_{j=1}^{m_i} \left\{ \frac{\lambda_0 (t_{ij})}{\Lambda_0 (T_i)} \right\} \times \int_0^\infty \left[\nu_i \Lambda_0 (T_i) e^{\mathbf{x}_i' \beta} \right]^{m_i} \exp \left[-\nu_i \Lambda_0 (T_i) e^{\mathbf{x}_i' \beta} \right] dP (\nu_i), \tag{3}$$

where $\Lambda_0 (T_i) = \int_0^\infty \lambda_0 (u) \, du$ is the integrated baseline intensity, and the second term in L_i is the likelihood kernel for a mixed Poisson regression model (Hinde, 1982).

Assuming than a gamma distribution with mean 1 and variance α for ν_i the second term in (3) becomes

$$\frac{\Gamma (m_i + \alpha^{-1})}{\Gamma (\alpha^{-1})} \frac{\left[\alpha \Lambda_0 (T_i) e^{\mathbf{x}_i' \beta} \right]^{m_i}}{\left[1 + \alpha \Lambda_0 (T_i) e^{\mathbf{x}_i' \beta} \right]^{m_i + \alpha^{-1}}}, \tag{4}$$

which is a negative binomial regression model (Lawless 1995).

We shall focus our analysis further by assuming $\lambda_0 (t)$ having a Weibull form given by

$$\lambda_0 (t) = \kappa \delta t^{\delta - 1}, \; k > 0, \; \delta > 0, \tag{5}$$

where κ and δ are parameters unknown. The specific form (5)has been used extensively due to its simplicity and flexibility (Lawless 1995).

So the likelihood function for a sample of n independent individual is composed as the product of the terms $L_1, L_2, \ldots, L_n$, that is,

$$L (\alpha, \delta, \beta_0, \beta) = \prod_{i=1}^{n} \left\{ \prod_{j=1}^{m_i} \left(\frac{\delta t_{ij}^{\delta - 1}}{T_i^{\delta}} \right) \right\} \times \prod_{i=1}^{n} \frac{\Gamma (m_i + \alpha^{-1})}{\Gamma (\alpha^{-1})} \frac{\left[\alpha T_i^{\delta} e^{\beta_0 + \mathbf{x}_i' \beta} \right]^{m_i}}{\left[1 + \alpha T_i^{\delta} e^{\beta_0 + \mathbf{x}_i' \beta} \right]^{m_i + \alpha^{-1}}}. \tag{6}$$

The maximum likelihood estimates for the parameters can be obtained by direct maximization of $LogL$ in(6) or also by solving the system of nonlinear equations given by the partial derivatives of $LogL$ with respect to the parameters. Intervals estimates and hypothesis tests for the parameters can be based on the asymptotic normal distribution of the MLEs and the asymptotic chi-squared distribution of the likelihood ratio statistics respectively. However, the asymptotic theory can not be very accurate for small or moderate samples sizes, and then we turn to the Bayesian approach.

3 A Bayesian Approach

Consider the joint prior density for α, δ, β_0 and β is given by

$$\pi(\alpha, \beta, \beta_0) = \pi(\alpha)\,\pi(\beta)\,\pi(\beta_0)\,\pi(\delta). \tag{7}$$

In what follows, combining the likelihood function (6) and the prior distribution (7), the joint posterior distribution for α, δ, β_0 and β is given by,

$$\pi(\alpha, \delta, \beta_0, \beta | D) \propto \pi(\alpha)\,\pi(\beta)\,\pi(\beta_0)\,\pi(\delta) \prod_{i=1}^{n} \left\{ \prod_{j=1}^{m_i} \left(\frac{\delta t_{ij}^{\delta-1}}{T_i^{\delta}} \right) \right\} \times \tag{8}$$
$$\times \prod_{i=1}^{n} \frac{\Gamma(m_i + \alpha^{-1})}{\Gamma(\alpha^{-1})} \frac{\left[\alpha T_i^{\delta} e^{\mathbf{x}_i'\beta}\right]^{m_i}}{\left[1 + \alpha T_i^{\delta} e^{\mathbf{x}_i'\beta}\right]^{m_i + \alpha^{-1}}}.$$

Bayesian inferences for the parameters are based on their marginal posterior densities, which, in our case, can not be obtained explicitly. We overcome this difficulty by making use of the Markov Chain Monte Carlo (MCMC) methodology to obtain approximations for such densities.

Assuming the following prior distributions for the parameters,

$$\pi(\alpha) = \frac{\eta^{\tau}}{\Gamma(\tau)} \alpha^{\tau-1} e^{-\alpha\eta}, \tag{9}$$

$$\pi(\delta) = \frac{\phi^{\xi}}{\Gamma(\xi)} \delta^{\xi-1} e^{-\delta\phi}, \tag{10}$$

$$\pi(\beta_0) = \frac{1}{\sqrt{2\pi R_2}} \exp\left\{ -\frac{1}{2R_2} (\beta_0 - \mu_2)^2 \right\}, \tag{11}$$

and

$$\pi(\beta) = \frac{1}{\sqrt{2\pi}\,|\mathbf{R}_1|} \exp\left\{ -\frac{1}{2} (\beta - \mu_1)' \mathbf{R}_1 (\beta - \mu_1) \right\}, \tag{12}$$

and substituting (9), (10) (11) and (12) in (7) the joint posterior distribution (8) is rewritten as,

$$\pi\left(\alpha,\delta,\beta_0,\beta|D\right)=\exp\left\{n\log\delta+(\delta-1)\sum_{i=1}^{n}\sum_{j=1}^{m_i}\log\left(t_{ij}\right)+\right.$$
$$+\sum_{i=1}^{n}\log\Gamma\left(m_i+\alpha^{-1}\right)-n\log\Gamma\left(\alpha^{-1}\right)+\sum_{i=1}^{n}m_i\log(\alpha)+\sum_{i=1}^{n}m_i\beta_0+$$
$$\left.+\sum_{i=1}^{n}m_i\mathbf{x}'\beta-\left(m_i+\alpha^{-1}\right)\sum_{i=1}^{n}\log(1+\alpha T_i e^{\beta_0+\mathbf{x}_i'\beta})\right\}\times \tag{13}$$
$$\times\alpha^{\tau-1}e^{-\alpha\eta}\times\exp\left\{-\tfrac{1}{2}\left(\beta-\mu_1\right)'\mathbf{R}_1\left(\beta-\mu_1\right)\right\}\times$$
$$\times\exp\left\{-\tfrac{1}{2R_2}\left(\beta_0-\mu_2\right)^2\right\}\times\delta^{\xi-1}e^{-\delta\phi}.$$

In order to implement the MCMC methodology we consider the Gibbs within Metropolis sampler, which requeres the derivation of the complete set of conditional posterior densities. In our case, after some algebraic manipulations, the full conditional distributions for α, β_0 and β are given by

$$\pi\left(\alpha|\ \beta,\beta_0,\delta\right)\propto\alpha^{\tau-1}e^{-\alpha\eta}\times\Psi\left(\alpha,\beta,\beta_0,\delta\right), \tag{14}$$

where

$$\Psi\left(\alpha,\beta_0,\beta\right)=\exp\left\{\sum_{i=1}^{n}\log\Gamma\left(m_i+\alpha^{-1}\right)-n\log\Gamma\left(\alpha^{-1}\right)+\right.$$
$$\left.+\sum_{i=1}^{n}m_i\log\left(\alpha\right)-\left(m_i+\alpha^{-1}\right)\sum_{i=1}^{n}\log(1+\alpha T_i^{\delta}e^{\beta_0+\mathbf{x}_i'\beta})\right\}, \tag{15}$$

$$\pi\left(\delta|\ \beta,\beta_0,\alpha\right)\propto\delta^{\xi-m-1}e^{-\delta\eta}\times\Psi\left(\alpha,\beta,\beta_0,\delta\right), \tag{16}$$

where,

$$\Psi\left(\beta_0,\alpha,\beta,\delta\right)=\exp\left\{n\log\delta+\delta\sum_{i=1}^{n}\sum_{j=1}^{m_i}\log\left(t_{ij}\right)-\right.$$
$$\left.-\left(m_i+\alpha^{-1}\right)\sum_{i=1}^{n}\log(1+\alpha T_i^{\delta}e^{\beta_0+\mathbf{x}_i'\beta})\right\}, \tag{17}$$

$$\pi\left(\beta_0|\alpha,\beta,\delta\right)\propto\exp\left\{-\frac{1}{2R_2}\left(\beta_0-\mu_1\right)^2\right\}\times\Psi\left(\beta_0,\alpha,\beta\right), \tag{18}$$

where,

$$\Psi\left(\beta_0,\alpha,\beta,\delta\right)=\exp\left\{\sum_{i=1}^{n}m_i\beta_0-\right.$$
$$\left.-\left(m_i+\alpha^{-1}\right)\sum_{i=1}^{n}\log(1+\alpha T_i^{\delta}e^{\beta_0+\mathbf{x}_i'\beta})\right\} \tag{19}$$

and

$$\pi\left(\beta|\alpha,\beta_0,\delta\right) \propto \exp\left\{-\frac{1}{2}\left(\beta-\mu_1\right)'\mathbf{R}_1\left(\beta-\mu_1\right)\right\} \times \Psi\left(\beta,\alpha,\beta_0,\delta\right), \tag{20}$$

where,

$$\begin{aligned}\Psi\left(\beta,\alpha,\beta_0,\delta\right) = \exp\Bigg\{&\sum_{i=1}^{n} m_i \mathbf{x}'\beta - \\ &-\left(m_i+\alpha^{-1}\right)\sum_{i=1}^{n}\log(1+\alpha T_i^{\delta} e^{\beta_0+\mathbf{x}_i'\beta})\Bigg\}.\end{aligned} \tag{21}$$

As above conditional posteriors do not present standard forms, we consider the Metropolis-Hastings algorithm (Hastings,1970; Chib and Greenberg,1995), which allows us to simulate observations from complex joint distributions by generating random samples successively from the full conditional distributions for the unknown parameters.

To generate samples of α,δ, β_0 and β from the conditional distributions above we proceed as follows:

(a) Start with the values $\theta_1^{(0)} = (\alpha^{(0)}, \beta^{(0)}, \delta^{(0)}, \beta_0^{(0)})$

(b) Generate α^* from the gamma prior distribution mentioned above.

(c) Generate the value u from the uniform distribution $U(0,1)$

(d) Verify that $u \leq min\left(1, \frac{\pi\left(\alpha^{(1)}|\beta^{(0)},\beta_0^{(0)},\delta^{(0)}\right)}{\pi\left(\alpha^{(0)}|\beta^{(0)},\beta_0^{(0)},\delta^{(0)}\right)}\right)$. If the inequality is true accept $\alpha^{(1)} = \alpha$

else set $\alpha^{(1)} = \alpha^{(0)}$. Similarly, generate $\delta^{(1)}$, $\beta_0^{(1)}$, and $\beta^{(1)}$. Then repeat the process now using $\left(\alpha^{(1)}, \beta^{(1)}, \delta^{(1)}, \beta_0^{(1)}\right)$ as the starting values and so on until to obtain the desired sample.

4 Model Selection

In order to chose between two parametric models M_1 and M_2 we can use the Bayes factor, which is is the relative weight of evidence for model M_1 compared to model M_2, given by

$$B_{12} = \frac{f\left(t_{obs}|M_1\right)}{f\left(t_{obs}|M_2\right)}, \tag{22}$$

where t_{obs} denotes the actual observations and $f\left(t_{obs}|M_k\right)$ denotes the marginal density under model M_k, $k = 1, 2$ (Gelfand, 1996). It can be useful to consider twice the logarithm of the (22), which is on the same scale as the deviance and the likelihood ratio test statistics. According to the rough classification in Section 3.2 of Kass and Raftery (1995),

the twice of the logarithms of the Bayes factors between 0 and 1/2 give no evidence, between 1/2 and 1 positive evidence, between 1 and 2 strong evidence, and bigger than 2 very strong evidence against model M_1. We approximate the marginal densities in (18) by their Monte Carlo estimates, obtained from the S generated Gibbs samples, given by

$$\widehat{f}(t_{obs}|M_k) = \sum_{s=1}^{S} f\left(t_{obs}|\theta_i^{(s)}, M_i\right). \tag{23}$$

5 The Animal Carcinogenesis Data

In this section we illustrate the methodology on an animal carcinogenesis data extracted from Gail et.al.(1980). The experiment used 48 female rats to the development of tumor mammary, 23 rats in Group 1 (Retinoid) and 25 in Group 2 (Control). The data are days on which new tumors occurred for each animal. A given animal may experience any number of tumors. The main objective of analysis is to assess the difference between treatment Groups 1 and 2 regarding to the development of tumors. The rats were induced to remain tumor-free for 60 days and were observed over the period from 60 to 182 days.

Suppose that the ith rat has tumors occurring according to a Poisson process with intensity function, $\lambda_0(t)\exp(\alpha_i + \mathbf{x}\beta)$, where α_i is a frailty term and $\mathbf{x}_i$ is a centered covariate indicating whether an individual is in Group 1 $(x_i = 1)$ or Group 2 $(x_i = -1)$. The time t is defined as the number of days from the start minus 60, so that the observation intervals $(0, T_i)$ are $(0, 122)$ for all animals.

We fixed the values of the hyperparameters at $\eta = 5$, $\tau = 5$, $\xi = 15$ and $\phi = 15$ for the gamma priors for α and δ, respectively. For the normal priors of the parameters β_0 and β we fixed $\mu_1 = \mu_2 = 0$ and $\sigma_1 = \sigma_2 = 10^4$, respectively. Other hyperparameters values were also considered but their choice do not lead to substantial changes in the posteriors.

Characteristics of the posterior distributions of the parameters α, δ, β_0 and β were calculated from the samples generated by the Metropolis-Hastings technique and the convergence of the chains were tested by using the Gelman and Rubin method (e.g., Gelman, et. al 1995). A number of iterations were considered sufficient for approximate convergence if the estimate potential scale reduction was $\sqrt{\widehat{R}} < 1.1$. The software MATLAB was used to generate five chains of 5000 iterations each for the three parameters. The first 2500 were ignored. For each parameter we considered the $2501^{th}, 2506^{th}, \ldots, 2511^{th}$ iterations, which for five chains yields a sample size of 12500 elements for analysis. The posterior results are summarized in Table 1, where it is presented characteristics such as the posterior means and posterior medians, standard deviation and the 95% credible intervals of the parameters of interest. The estimated hypothesis scale reductions $\widehat{R}$ for the parameters are also shown in Table 2. The convergence was observed for all parameters since $\sqrt{\widehat{R}} < 1.1$ for all of them. It is important to note that there is significant

difference between Groups 1 and 2 regarding to the development of tumors indicated by the estimated β which is equal to -0.47 with standard deviation equals to 0.15. This result is corroborated by the value of the twice the logarithm of (22), of the full model (M_2) with respect to the the model without covariate (M_1), which is 3.40, given strong support to model M_2. This result is in abroad agreement with the result obtained by Lawless (1995).

Table 1: Posterior Summaries

Parameters	Mean	Sd	IC(95%)	$\widehat{R}$
α	0.37	0.15	[0.148 ; 0.594]	1.0003
δ	0.92	0.07	[0.806 ; 1.024]	1.0008
β_0	-3.41	0.22	[-3.742 ; -3.084]	1.0013
β	-0.47	0.15	[-0.699 ; -0.246]	1.0000

The Figure 1 shows the scatterplots of the pairs (α, β),(α, β_0) , (α, δ), (β, β_0), (β, δ) and (δ, β_0), where we observe that the five chains with different start conditions converge to the same region. Figure 2 shows the plots of the generated samples. The empirical marginal posterior densities based on the generated chains are presented in Figure 3.

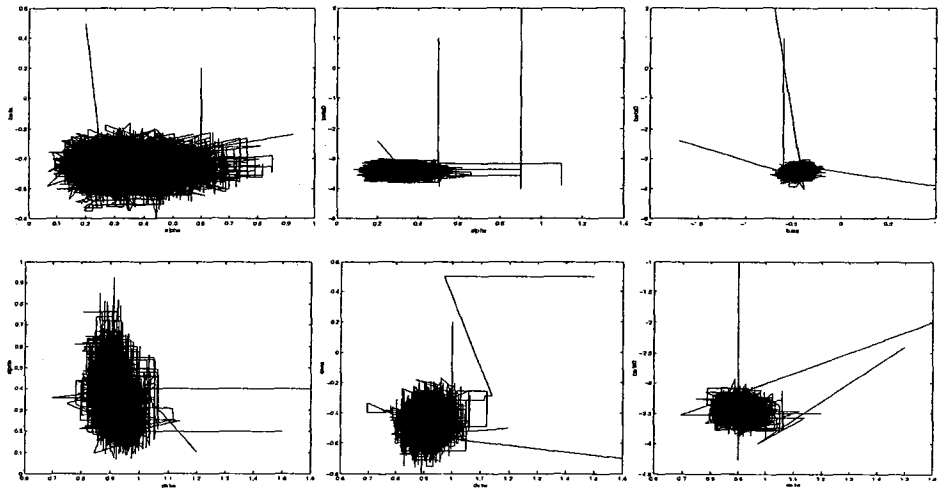

Figura 1: Scatterplot of the samples generated.

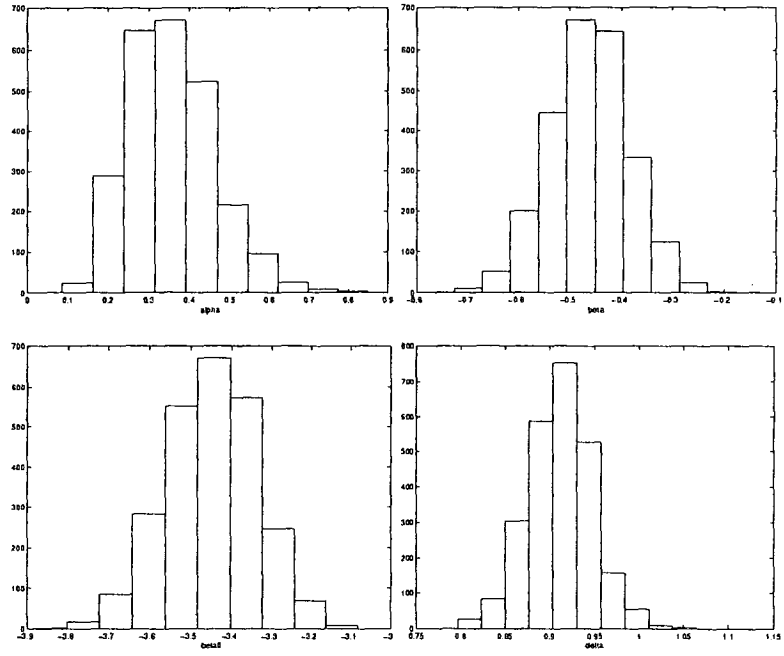

Figure 2: Histograms of the samples to α, β, δ and β_0.

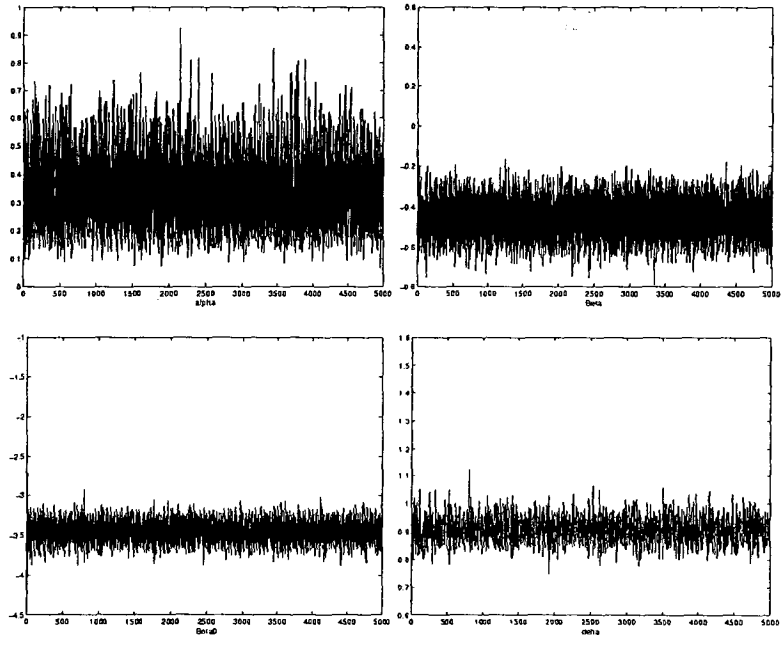

Figura 3: plot of the sample to α, β, δ and β_0.

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