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General joint frailty model for recurrent event data with a dependent terminal event: Application to follicular lymphoma data

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Many biomedical studies focus on delaying disease relapses and on prolonging survival. Usual methods only consider one event, often the first recurrence or death. However, ignoring the other recurrences may lead to biased results. The whole history of the disease should be considered for each patient. In addition, some diseases involve recurrences that can increase the risk of death. In this case, the death time may be dependent on the recurrent event history. We propose a joint frailty model to analyze recurrences and death simultaneously. Two gamma-distributed frailties take into account both the inter-recurrences dependence and the dependence between the recurrences and the survival times. We estimate separate parameters for disease recurrent event times and survival times in the joint frailty model to distinguish treatment effects and prognostic factors on these two types of events. We show how maximum penalized likelihood estimation can be applied to semiparametric estimation of the continuous hazard functions in the proposed joint frailty model with right censoring. We also propose parametrical approach. We evaluate the model by simulation studies and illustrate through a study of patients with follicular lymphoma. Copyright © 2012 John Wiley & Sons, Ltd.

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1. Introduction

Recurrent events are common in a wide variety of fields such as biomedical research and social sciences. In several medical studies, the focus is on relapses, which are considered as recurrent events. For instance, a subject can experience several breast cancer or follicular lymphoma relapses. In these contexts, it is necessary to take into account the dependence between the occurrences of these events and the heterogeneity across subjects. As a result, some individuals are more prone to disease, experiencing their relapses more quickly than others. This induces heterogeneity across individuals [1,2] and produces within-subject dependence. Moreover, the occurrence of one event may produce a biological weakening, a damage, or a strengthening. This implies that the risk of an event depends on the occurrences of previous events. Moreover, the observation of successive events across time for subjects in cohort studies could be complemented by loss to follow-up, end of study, or a major failure event such as death. The follow-up period is independent of the underlying recurrent process, when, for example, the follow-up stops at a prespecified study end point. In some instances, however, this may not be true, and the follow-up period may be determined by a terminal event that is dependent on the underlying recurrent process. A typical example is that the recurrent event is related to death, which would terminate the event process,

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with the result that the high recurrence rate of the events may indicate an increase in the risk of death. In this context, the major failure event and recurrent events can be dependent. Therefore, this dependence must be taken into account in the joint modeling of recurrent events and deaths. Treatment effects or prognostic factors on disease recurrence and survival are not necessarily the same. Some therapies may delay disease recurrence but not prolong survival. Hence, it is desirable to estimate two separate sets of parameters for disease recurrences and survival and to distinguish the patient frailty in terms of relapses and death.

In the presence of a dependent terminal event, several approaches have been developed for the analysis of recurrent event data. Various marginal models have been proposed [3–6]. They account for the dependence between observed times without estimating it directly. In addition, it is difficult to construct efficient estimators by using marginal models. Sun and Su [7] proposed a class of accelerated means regression models to offer more flexibility in formulating the effects of covariates on the mean functions. Zeng and Lin [8] proposed a class of semiparametric transformation models to allow for more flexible modeling of the recurrent event process.

An alternative approach is to use joint frailty models to analyze recurrent events with a dependent terminal event. Frailty models [9, 10], which are extensions of the Cox proportional hazards model [11], can be used to deal with such data and provide an explicit measure of the dependence between events. Joint frailty models for recurrent events and death have been proposed for different applications. Lancaster and Intrator [12] designed a joint semiparametric model where the dependence between the two rates is induced by an unobserved shared frailty. Liu *et al.* [13], Huang *et al.* [14], and Rondeau *et al.* [15] considered that the shared frailty did not apply equivalently for the two rates. Liu *et al.* and Huang *et al.* used a Monte Carlo Expectation–Maximization algorithm to estimate the hazard functions and the parameters, which could be time consuming. Furthermore, these methods proposed to estimate the cumulative hazard functions, but we cannot directly estimate a smooth hazard function, which often has a meaningful interpretation in epidemiological studies. Most of the time, the baseline intensity estimate is based on Breslow's estimate, leading to a piecewise-constant baseline hazard function or an unspecified baseline hazard function. Rondeau *et al.* [15] have proposed a semiparametric estimation method by using penalized likelihood.

In these approaches, a dependence between the two rates is considered, but it is not possible to deduce the origin of this dependence, whether it originates a little from the dependence between recurrences or it originates totally from the dependence between recurrent and terminal events. In this article, we develop a joint frailty model for recurrent events in the presence of a dependent terminal event, with right-censored survival data. Hence, the relationship between delayed disease recurrences and prolonged survival can be assessed with the random effects or frailties. The specificity of this model is that the inter-recurrences dependence and the dependence between the two rates are distinguished. We will show that it is important to consider the features of dependence of the data to avoid biased estimations of regression coefficients, that is, hazard ratios.

Our model considers the natural history of the disease beyond the first diagnosis and also accounts for covariates effects. For recurrent event data to be analyzed, the focus can be placed on time between events (i.e., gap times) or time to events (i.e., calendar times). The proposed approach can deal with both time scales. In the next section, we describe the new general joint frailty model. We provide details on estimation methods and log-likelihood expressions in Section 3. In Section 4, we conduct simulation studies, including a sensitivity analysis for the parametric frailty distribution assumption. In Section 5, we apply the model to a study of patients with follicular lymphoma. Section 6 is devoted to discussion.

2. The model

2.1. Notations

The considered event times are $T_{ij} = \min(X_{ij}, C_i, D_i)$, $i = 1, \ldots, N$, $j = 1, \ldots, n_i + 1$, where the last observed event times T_{in_i+1} is censored by $T_i^* = \min(C_i, D_i)$, which is the terminal event time. Let X_{ij} denote the jth recurrent event time for the individual i since the initiation of the recurrent events process. The number n_i of observed recurrent events is a random variable. We denote C_i as the independent right-censoring time and D_i as the death time. The time of study entry for each i is T_{i0}, which is assumed to be equal to 0; we are indeed interested in the history of the disease since the diagnosis. We denote the event indicator as $\delta_{ij} = \mathbb{1}_{(T_{ij}=X_{ij})}$ and the death indicator as $\delta_i^* = \mathbb{1}_{(T_i^*=D_i)}$. The recurrent

gap times S_{ij} represents the duration between two consecutive events: $S_{ij} = T_{ij} - T_{i(j-1)}$. We actually observe $\{T_{ij}$ (or S_{ij} if gap times), $T_i^*, \delta_{ij}, \delta_i^*\}$.

Let $N_i^{R^*}(t)$ count the number of recurrent events for i over the interval $(0, t], i = 1, \ldots, N$. Because of censoring, it is impossible to observe $N_i^{R^*}(.)$. We observe the process $N_i^R(t) = N_i^{R*}(\min(T_i^*, t))$, which counts the observed number of recurrent events. Similarly, denote by $N_i^{D^*}(t) = \mathbb{1}_{(D_i \leqslant t)}$ and $N_i^D(t) = \mathbb{1}_{(T_i^* \leqslant t, \delta_i^* = 1)}$ the actual death indicator and the observed death indicator by time t, respectively. Furthermore, let $Y_i(t) = \mathbb{1}_{(t \leqslant T_i^*)}$ denote whether or not the i is at risk of an event at t. The number of recurrent events that occurs for subject i over the small interval $[t, t + dt)$ is $dN_i^{R^*}(t) = N_i^{R^*}((t + dt)^-) - N_i^{R^*}(t^-)$, and we have $dN_i^R(t) = Y_i(t) dN_i^{R^*}(t)$. We can notice that $n_i = N_i^R(T_i^*)$. The history of the ith process up to t is denoted by

$$\mathcal{H}_{it} = \sigma\{Y_i(h), N_i^R(h), N_i^D(h), Z_i(h), 0 \leqslant h \leqslant t\}, \quad i = 1, \ldots, N,$$

where $Z_i(h)$ is a vector of possibly time-dependent covariates. We denote the following filtration:

$$\mathcal{F}_{it} = \sigma\{H_{it}, u_i, v_i\}, \quad i = 1, \ldots, N.$$

The random effect v_i accounts for the within-individual dependency, and the random effect u_i links the recurrent event intensity process and the terminal event intensity process. We assume that the recurrent, terminating, and censoring processes are continuous, which means that recurrent event and death cannot happen at the same time. We consider that death happens first in the small interval $[t, t + dt)$. We also consider that the actual recurrent event process $N_i^{R^*}(t)$ is constant after death time D_i but can increase after the censoring time C_i. This means that death precludes the observation of new recurrent events; but on the contrary, censoring, such as end of study or lost to follow-up, does not interrupt the occurrence of new recurrent events; they are simply not observed.

The recurrent event intensity process at t is

$$Y_i(t) r_i(t) dt = P(dN_i^R(t) = 1 | \mathcal{F}_{it^-}), \text{ where } r_i(t) dt = P(dN_i^{R^*}(t) = 1 | Z_i(t), u_i, v_i, D_i \geqslant t),$$

and the death intensity process at t is

$$Y_i(t) \lambda_i(t) dt = P(dN_i^D(t) = 1 | \mathcal{F}_{it^-}), \text{ where } \lambda_i(t) dt = P(dN_i^{D^*}(t) = 1 | Z_i(t), u_i, v_i, D_i \geqslant t).$$

We model the intensity functions for both recurrent event observed process and terminal event observed process, given that the individual is still alive.

2.2. *The joint frailty model with independent frailties*

The hazard function system for recurrent and terminal events is (in the calendar time scale or time to event) as follows:

$$\begin{cases} r_i(t|u_i, v_i) = u_i v_i r_0(t) \exp(\beta_1' Z_i(t)) = u_i v_i r_i(t) & \text{(recurrent)} \\ \lambda_i(t|u_i) = u_i \lambda_0(t) \exp(\{\beta_2' Z_i(t)) = u_i \lambda_i(t) & \text{(death)}, \end{cases} \tag{1}$$

where $r_0(t)$ ($\lambda_0(t)$) is the recurrent (terminal) event baseline hazard function and β_1 (β_2) is the regression coefficient vector associated with the covariate vector $Z_i(t)$. The covariates could be different for the recurrent event rate and death rate. The covariates may be time dependent with, for instance, a function of the number of previous events. These two components in the aforementioned joint model are coupled together by frailty terms u_i. The frailty v_i is specific to the recurrent event rate.

Our method acknowledges the fact that death stops further recurrent events in that, given $t > D$, $dN^{R*}(t)$ takes the value 0. This is different from the conventional censoring event, which only prevents us from observing further recurrent events but does not prevent their occurrence. Indeed, death is not an informative censoring. An individual cannot experience a relapse (recurrent event) after death, but it is possible after leaving the study due to deterioration of his or her health (informative censoring). Thus, the terminal and recurrent event processes are not independent, even conditional upon frailties and covariates. We consider the rate of recurrent events among individuals still alive.

We assume that u_i and v_i are two mutually independent and identically gamma-distributed frailties with

$$u_i \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right), \; v_i \sim \Gamma\left(\frac{1}{\eta}, \frac{1}{\eta}\right), \text{ i.e., } E(u_i) = E(v_i) = 1, \; \text{var}(u_i) = \theta, \; \text{var}(v_i) = \eta.$$

We chose the gamma distribution because it allows simplifications on the likelihood calculus. Moreover, Pickles and Crouchley [16] suggest that results should not be sensitive to the choice of the frailty distribution.

The variance η specifies the within-subject dependence between recurrent times. The variance θ assesses the dependence between recurrent and terminal events and informs whether the terminal event and the recurrent event are really dependent. A high value of θ illustrates strong dependence between recurrent and terminal events, and a high value of the variance η corresponds to strong dependence between recurrent events. Whereas $\eta = 0$ means that the recurrent times for the same subject are independent of each other, $\theta = 0$ means that the terminal and recurrent times are independent.

In the gap time scale, the joint frailty model for recurrent and terminal events is

$$\begin{cases} r_i(t|u_i, v_i) = u_i v_i r_0(t - T_{iN_i^R(t-)}) \exp(\beta_1' Z_i(t)) & \text{(recurrent)} \\ \lambda_i(t|u_i) = u_i \lambda_0(t) \exp(\beta_2' Z_i(t)) & \text{(death).} \end{cases} \tag{2}$$

Time t since the initiation of the recurrent event process is replaced by $t - T_{iN_i(t-)}$, the duration since the previous recurrent event time. We can notice that, conditional on frailties and covariates, recurrent gap times $S_{ij} = T_{ij} - T_{i(j-1)}$ are independent, with $T_{i0} = 0$, the time at entry into the study.

3. Estimation

Maximization of the penalized log-likelihood [17, 18] is the estimation method used to estimate the different parameters (β, θ, η) and the baseline hazard function $r_0(t)$ for recurrent events or $\lambda_0(t)$ for death times. Let Φ denote $(r_0(.), \lambda_0(.), \beta, \theta, \eta)$, the parameters to estimate.

3.1. Log-likelihood

We calculate the likelihood by integrating the conditional likelihood. We provide the details in Appendix A. Simplifications are possible because of the gamma frailty distributions. Contrary to the shared frailty model [18], the full log-likelihood does not adopt a simple form because the integrals do not have an analytical solution. We evaluate the integrals by using Gauss–Laguerre quadrature.

$$l(\Phi) = \sum_i \Bigg\{ \delta_i^* \log\left(\lambda_i(T_i^*)\right) + \sum_{j=1}^{n_i} \delta_{ij} \log\left(r_i(T_{ij})\right) + \log\left(\Gamma\left(n_i + \frac{1}{\eta}\right)\right) + n_i \log(\eta) - \log\left(\Gamma\left(\frac{1}{\eta}\right)\right)$$
$$+ \frac{1}{\theta}\ln(\theta) - \ln\Gamma\left(\frac{1}{\theta}\right) + \ln \int_0^\infty \frac{u_i^{n_i + \delta_i^* + \frac{1}{\theta} - 1} \exp\left(-u_i\left(\frac{1}{\theta} + \int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right)\right)}{\left(1 + u_i \eta \sum_{j=1}^{n_i+1} \int_{T_{i(j-1)}}^{T_{ij}} Y_i(t) r_i(t)\mathrm{d}t\right)^{n_i + \frac{1}{\eta}}} \mathrm{d}u_i \Bigg\}$$

In the previous expression, we consider recurrent event times from the beginning of the study (calendar time). We do not consider delayed entries that are meaningless in the application. We are more interested in the time to event since the diagnosis, and then for all individual, $T_{i0} = 0$. With left-truncating time due to delayed entries, we should have $T_{i0} > 0$, and the expression of the log-likelihood would have been different [19].

In the gap time scale formulation, the likelihood expression is the same, except that T_{ij} is replaced by S_{ij} and $\int_{T_i(j-1)}^{T_{ij}}$ by $\int_0^{S_{ij}}$, giving the following expression:

$$l(\Phi) = \sum_i \left\{ \delta_i^* \log\left(\lambda_i(T_i^*)\right) + \sum_{j=1}^{n_i} \delta_{ij} \log\left(r_i(S_{ij})\right) + \log\left(\Gamma\left(n_i + \frac{1}{\eta}\right)\right) + n_i \log(\eta) - \log\left(\Gamma\left(\frac{1}{\eta}\right)\right) \right.$$
$$\left. + \frac{1}{\theta}\ln(\theta) - \ln\Gamma\left(\frac{1}{\theta}\right) + \ln\int_0^\infty \frac{u_i^{n_i+\delta_i^*+\frac{1}{\theta}-1} \exp\left(-u_i\left(\frac{1}{\theta} + \int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right)\right)}{\left(1 + u_i\eta \sum_{j=1}^{n_i+1} \int_0^{S_{ij}} Y_i(t) r_i(t)\mathrm{d}t\right)^{n_i+\frac{1}{\eta}}} \mathrm{d}u_i \right\}.$$

3.2. *Penalized log-likelihood*

To avoid wide local variations of baseline hazard functions $\lambda_0(t)$ and $r_0(t)$, we introduce smoothness with a penalized log-likelihood of the form

$$pl(\Phi) = l(\Phi) - \kappa_1 \int_0^\infty r_0''(t)^2 \mathrm{d}t - \kappa_2 \int_0^\infty \lambda_0''(t)^2 \mathrm{d}t, \tag{3}$$

where $l(\Phi)$ is the full log-likelihood defined previously and κ_1 and κ_2 are the positive smoothing parameters that control the tradeoff between the data fit and the smoothness of the functions. The penalization is on hazard function fluctuations represented by $\int_0^\infty \lambda_0''(t)^2 \mathrm{d}t$ and $\int_0^\infty r_0''(t)^2 \mathrm{d}t$, which are the roughness terms based on the second derivative of the baseline hazard functions (approximated by a combination of polynomial functions of order 1). Maximization of $pl(\Phi)$ defines the maximum penalized likelihood estimator (MPnLE) $\hat{\Phi}$. We directly use $\hat{H}^{-1}$ as a variance estimator, where H is minus the converged Hessian of the penalized log-likelihood. Furthermore, to deal with the positivity constraints on the parameters ($\theta, \eta > 0$), we use a squared transformation and compute standard errors by using the delta method [20]. For a fixed value of the smoothing parameters, the maximization of the penalized likelihood provides estimators for Φ, the parameters of the model. We choose the smoothing parameters by fitting two shared frailty models [21], one for the recurrent event and the other for the terminal event, by using cross-validation estimation method with the R package *frailtypack* [22, 23].

3.3. *Maximization of the penalized log-likelihood estimation*

We obtain the estimated parameters by the robust Marquardt algorithm [24], which is a combination between a Newton–Raphson algorithm and a steepest descent algorithm. This algorithm has the advantage of being more stable than the Newton–Raphson algorithm while preserving its fast convergence property.

We update the vector Φ of the parameters until the convergence by using the following recurring expression:

$$\Phi^{(r+1)} = \Phi^{(r)} - \delta\left(\widetilde{H}^{(r)}\right)^{-1} \Delta\left(L(\Phi^{(r)})\right). \tag{4}$$

Step δ is equal to 1 by default but can be modified to ensure that the likelihood is improved at each iteration. The matrix $\widetilde{H}$ is a diagonal-inflated Hessian matrix to ensure positive definiteness. The term $\Delta(L(\Phi^{(r)}))$ corresponds to the penalized log-likelihood gradient at the rth iteration. The iterations stop when the difference between two consecutive log-likelihoods is small ($<10^{-3}$), when the coefficients are stable ($<10^{-3}$), and when the gradient is small enough ($<10^{-3}$). We calculate the first and second derivatives by using the finite differences method. After the convergence, we directly obtain the standard errors of the estimates from $\hat{H}^{-1}$.

3.4. Approximation of the baseline hazard functions by splines

B-splines are piecewise polynomial functions that are combined linearly to approximate a function on an interval. M-splines, which are variants of B-splines, are well adapted to model baseline hazard functions. Indeed, M-splines are non-negative functions that can approximate hazard functions $\lambda_0(.)$, $r_0(.)$ easy to integrate or differentiate. Ramsay *et al.* [25] and Joly *et al.* [26] have worked on the M-splines.

We denote by $t_1, \ldots, t_Q$ the sequence of the spline knots, and the order of the splines is $l = 4$ (cubic splines). On the basis of these knots Q, we define m-spline function $M_i(.)$, associated to coefficient η_i, from Ramsay's equations [25]. The number of parameters to estimate m is $Q+2$ (because $m = Q+l-2$). To be sure of having positive hazard functions, we impose the spline coefficients η_{Di}, η_{Ri} to be positive. If we denote $\tilde{r_0}(.)$ an approximation to the MPnLE $\hat{r_0}(.)$, the approximation error can be made as small as desired by increasing the number of knots Q. The more knots we use, the closer the approximation is to the true hazard function. The approximations $\widetilde{\lambda}_0(.)$, $\widetilde{r}_0(.)$ of the baseline hazard function estimators $\hat{\lambda}_0(.)$, $\hat{r}_0(t)$ are

$$\widetilde{\lambda}_0(.) = \sum_{i=1}^{m} \eta_{Di} M_i(.), \quad \widetilde{r}_0(.) = \sum_{i=1}^{m} \eta_{Ri} M_i(.).$$

Such approximation allows flexible shapes of the hazard functions while reducing the number of parameters. In our approach, although there are two different hazard functions (for recurrent event and for death), we use the same basis of splines for each function, but the spline coefficients are different for the distinct functions. We provide an approximation for the pointwise confidence intervals at 95% of $\widetilde{\lambda}_0(.)$:

$$\widetilde{\lambda}_0(.) \pm 1.96\sqrt{\mathbf{M}(.)^{\mathrm{T}} I^{-1}_{\hat{\eta}_{\mathrm{D}}} \mathbf{M}(.)\}}, \quad \widetilde{r}_0(.) \pm 1.96\sqrt{\mathbf{M}(.)^{\mathrm{T}} I^{-1}_{\hat{\eta}_{\mathrm{R}}} \mathbf{M}(.)\}},$$

where $\mathbf{M}(.) = (\mathrm{M_1}(.), \ldots, \mathrm{M_m}(.))$ is the M-splines vector, $I^{-1}_{\hat{\eta}_R} = \frac{\partial^2 pl(\hat{\Phi})}{\partial \eta_R^2}$, $I^{-1}_{\hat{\eta}_D} = \frac{\partial^2 pl(\hat{\Phi})}{\partial \eta_D^2}$, and pl is the penalized log-likelihood.

A function approximated by splines could have local fluctuations, in particular when the number of knots is big. A solution to limit these local variations is to penalize the likelihood of the model to have smooth estimation of the baseline hazard functions.

3.5. Considering Weibull baseline hazard functions

We propose this joint frailty with a parametric baseline hazard function: the Weibull function. In this case, we could use the maximum of likelihood method to estimate the parameters of the model. The advantage with such consideration is that we reduce the number of parameters to estimate. The main drawback is that Weibull function could be, in some cases, not enough flexible compared with an approximation by splines.

4. Simulation

We performed a simulation study of the proposed joint frailty model with two independent random effects (u_i, v_i) to evaluate the performance of the estimators and to compare it with the previous joint frailty model with one random effect (denoted by ω_i) proposed by Rondeau *et al.* [15]. Let $\tilde{\theta}$ denote the variance of the frailty ω_i shared by the two hazard functions in the model by Rondeau *et al.*. To investigate the effect of increased sample size on estimator performance, we considered three sample sizes with a variable number of subjects and a variable number of recurrent events per subject with a maximum of eight recurrent events. We generated 500 replicate data sets, with sample sizes $N = 100$, $N = 500$, and $N = 1000$. We report the results in Section 4.1. We also report the empirical standard errors and the estimator of standard error ($\sqrt{\hat{H}^{-1}}$). We treated the right-censored case only and used a gap time scale representation.

4.1. Generating data

We used the following joint independent gamma frailty model to generate data:

$$\begin{cases} r_i(s_{ij}|u_i, v_i) = u_i v_i r_0(s_{ij}) \exp(\beta_1 Z_{i1} + \beta_2 Z_{i2}) = u_i v_i r_i(s_{ij}) \\ \lambda_i(t_i^*|u_i) = u_i \lambda_0(t_i^*) \exp(\beta_3 Z_{i1}) = u_i \lambda_i(t_i^*). \end{cases} \tag{5}$$

For each subject i $(i = 1, \ldots, N)$, we generated the following two independent and identically gamma-distributed random variables: $u_i \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$, $v_i \sim \Gamma\left(\frac{1}{\eta}, \frac{1}{\eta}\right)$, where θ and η are the variances of the random effect. We used a fixed right-censoring variable $C_i = 0.8$ to have in average 40% of the censored data such as in the application. Death times and recurrent event times have in common one explanatory variable Z_{ij1}. We generated the binary explanatory variables Z_{ij1} and Z_{ij2} from a Bernoulli distribution with $p = 0.5$. We set $\beta_1 = 1.0$, $\beta_2 = -0.5$, and $\beta_3 = 0.7$.

- Firstly, we generated an exponential death time D_i by using the hazard function $\lambda_i(t_i^*|u_i)$ with $\lambda_0(t) = 2.0$. If $D_i \leqslant C_i$, then the terminal event time is a death time ($\delta_i^* = 1$ and $T_i^* = D_i$). If $D_i > C_i$, then it is a censoring time ($\delta_i^* = 0$ and $T_i^* = C_i$).
- Secondly, we generated the recurrent gap time S_{ij} by using the hazard function $r_i(s_{ij}|u_i, v_i)$ with $r_0(t) = 1.0$. The corresponding observed calendar times for recurrent events are $T_{ij} = \min(D_i, C_i, \sum_{k=1}^{j} S_{ik})$. If $T_{ij} < T_i^*$, then we observe a recurrent time, and $\delta_{ij} = 1$. The data generation continues until $T_{ij} < T_i^*$. If $T_{ij} > T_i^*$, then we consider that subject is censored at T_i^*, and $\delta_{ij} = 0$. The data generation stops.

4.2. *Scenarios*

We consider different settings for each parameter: η and θ. We present the following two more illustrative and interesting settings.

- In the first setting, we generated data with a significant dependence between recurrent event and terminal event $\theta = 0.5$ and with almost no inter-recurrence dependence $\eta = 0.01$. It is comparable with generating data according to the aforementioned model with $v_i \sim 1$. In this setting, the dependence between the two hazard functions is only due to the dependence between recurrent event and terminal event. Hence, we can compare, in the proposed model and in the model by Rondeau *et al.*, the regression coefficients, the variance parameters $\theta = \text{var}(u_i) \sim \tilde{\theta} = \text{var}(\omega_i)$. We expected the power coefficient α, in the model by Rondeau *et al.*, to be close to 1.
- In the second setting, we introduced a significant inter-recurrence dependence $\eta = 0.5$ and still a significant dependence between recurrent event and terminal event $\theta = 0.5$. This setting just allows to compare the regression coefficient estimates between the proposed model and the model by Rondeau *et al.*

4.3. *Results of the simulation study*

We fitted the new joint frailty model with two independent gamma frailties and the joint frailty model with one random effect presented by Rondeau *et al.* [15] to compare the estimation of parameters when a significant inter-recurrences dependence is introduced or not. We present the results in Table I.

The death rate ranges from 35.1% to 53.3%. The average number of observed recurrent events per subject ranges from 1.07 to 1.26 in the conducted simulation studies, with a maximum fixed of 8. Between 45.2% and 56.3% of the subjects did not have any recurrent event.

In the first setting, the regression coefficients are well estimated, and their coverage probabilities are close to the nominal level of 95% for all the models. The estimate mean value of the parameter η is overestimated in particular considering a sample of $N = 100$ subjects and tend to be unbiased when we increase the sample size. This may be due to the positivity constraint (square transformation) imposed for the variance parameters. Regarding the proposed model with baseline hazard functions approximated by splines, the variance parameter θ is underestimated with a coverage probability inferior to the nominal level. For the model with Weibull baseline hazard functions, θ is well estimated with a coverage probability close to 95% for $N = 1000$. The variance parameters $\tilde{\theta}$ of the model by Rondeau *et al.* is also biased, and this bias is reduced with the sample size. In this setting, the proposed model and the model by Rondeau *et al.* are equivalent.

In the second setting, the regression coefficients are well estimated except for β_1^* in the model by Rondeau *et al.* For the proposed model, the variance parameters are well estimated with better results for η. The mean estimates for η with the sample size at $N = 500$ is 0.500 and with $N = 1000$ is 0.505, which is very close to the true value of $\eta = 0.5$. The 95% confidence interval of η covers the true value of $\eta = 0.5$ in 96.4% of the simulations.

However, as expected, the new joint frailty model with two independent gamma random effects and the joint frailty model with only one random effect [15] are both valid and equivalent when data have no

Table I. Summary of simulation results.

	Proposed model (splines) $[u_i v_i, u_i]$				Proposed model (Weibull) $[u_i v_i, u_i]$				Model by Rondeau *et al.* (splines) $[\omega_i, \omega_i^{\alpha}]$			
	Est.	SE emp.	SE $(\sqrt{\widehat{H^{-1}}})$	CP	Est.	SE emp.	SE $(\sqrt{\widehat{H^{-1}}})$	CP	Est.	SE emp.	SE $(\sqrt{\widehat{H^{-1}}})$	CP
Setting I: $\theta = 0.5$, $\eta = 0.01$												
$N = 100$												
$\beta_1 = 1$	1.051	0.295	0.266	92.9	1.001	0.257	0.269	96.8	1.018	0.267	0.259	92.7
$\beta_2 = -0.5$	−0.518	0.253	0.243	94.8	−0.535	0.231	0.245	96.4	−0.531	0.243	0.230	92.7
$\beta_1^* = 0.7$	0.759	0.310	0.296	92.9	0.715	0.302	0.296	95.5	0.794	0.402	0.330	92.7
$\theta = 0.5$	0.429	0.194	0.166	85.9	0.460	0.169	0.173	91.9	—	—	—	—
$\eta = 0.01$	0.128	0.143	0.168	84.8	0.133	0.139	0.183	85.4	—	—	—	—
$\tilde{\theta} \sim 0.5$	—	—	—	—	—	—	—	—	0.535	0.192	0.176	87.1
$\alpha \sim 1$	—	—	—	—	—	—	—	—	1.180	0.744	0.478	83.9
$N = 500$												
$\beta_1 = 1$	1.016	0.110	0.116	95.4	1.005	0.118	0.118	96.1	1.013	0.114	0.116	95.4
$\beta_2 = -0.5$	−0.497	0.098	0.104	96.9	−0.517	0.104	0.106	94.4	−0.508	0.105	0.102	94.8
$\beta_1^* = 0.7$	0.733	0.123	0.132	95.4	0.698	0.129	0.132	94.1	0.710	0.129	0.134	94.8
$\theta = 0.5$	0.457	0.092	0.082	84.3	0.486	0.087	0.079	87.9	—	—	—	—
$\eta = 0.01$	0.054	0.058	0.063	78.0	0.057	0.058	0.070	80.3	—	—	—	—
$\tilde{\theta} \sim 0.5$	—	—	—	—	—	—	—	—	0.533	0.110	0.097	85.8
$\alpha \sim 1$	—	—	—	—	—	—	—	—	0.929	0.214	0.204	86.6
$N = 1000$												
$\beta_1 = 1$	1.017	0.081	0.082	93.8	1.008	0.083	0.081	94.6	1.022	0.085	0.082	94.0
$\beta_2 = -0.5$	−0.499	0.070	0.073	96.7	−0.506	0.071	0.072	95.5	−0.507	0.073	0.073	93.6
$\beta_1^* = 0.7$	0.729	0.089	0.093	95.9	0.700	0.099	0.092	93.0	0.708	0.097	0.094	93.6
$\theta = 0.5$	0.449	0.061	0.059	79.2	0.496	0.057	0.057	94.2	—	—	—	—
$\eta = 0.01$	0.042	0.041	0.044	78.1	0.035	0.037	0.046	78.6	—	—	—	—
$\tilde{\theta} \sim 0.5$	—	—	—	—	—	—	—	—	0.529	0.087	0.071	82.6
$\alpha \sim 1$	—	—	—	—	—	—	—	—	0.906	0.155	0.142	80.6

Table I. Continued

	Proposed model (splines) $[u_i v_i, u_i]$				Proposed model (Weibull) $[u_i v_i, u_i]$				Model by Rondeau *et al.* (splines) $[\omega_i, \omega_i^{\alpha}]$			
	Est.	SE emp.	SE $(\sqrt{\widehat{H^{-1}}})$	CP	Est.	SE emp.	SE $(\sqrt{\widehat{H^{-1}}})$	CP	Est.	SE emp.	SE $(\sqrt{\widehat{H^{-1}}})$	CP
Setting II: $\theta = 0.5$, $\eta = 0.5$												
$N = 100$												
$\beta_1 = 1$	1.013	0.315	0.309	95.0	0.999	0.317	0.311	94.6	1.000	0.314	0.283	91.2
$\beta_2 = -0.5$	−0.493	0.303	0.285	92.5	−0.497	0.299	0.287	93.1	−0.490	0.300	0.264	90.6
$\beta_1^* = 0.7$	0.736	0.320	0.305	94.2	0.703	0.318	0.306	93.9	0.678	0.336	0.235	86.8
$\theta = 0.5$	0.491	0.217	0.203	88.1	0.523	0.200	0.202	94.1	0.533	0.110	0.097	85.8
$\eta = 0.5$	0.487	0.325	0.317	91.6	0.467	0.318	0.314	93.5	—	—	—	—
$\tilde{\theta} = ?$	—	—	—	—	—	—	—	—	0.825	0.168	0.106	—
$\alpha = ?$	—	—	—	—	—	—	—	—	0.632	0.463	0.223	—
$N = 500$												
$\beta_1 = 1$	1.014	0.148	0.137	93.4	1.006	0.147	0.138	93.0	1.009	0.148	0.130	91.8
$\beta_2 = -0.5$	−0.500	0.128	0.127	95.2	0.502	0.127	0.127	94.8	−0.497	0.128	0.121	94.0
$\beta_1^* = 0.7$	0.717	0.136	0.134	94.6	0.700	0.135	0.134	94.4	0.635	0.124	0.112	87.8
$\theta = 0.5$	0.482	0.114	0.102	87.6	0.520	0.104	0.097	90.4	—	—	—	—
$\eta = 0.5$	0.500	0.158	0.148	92.2	0.483	0.156	0.145	92.2	—	—	—	—
$\tilde{\theta} = ?$	—	—	—	—	—	—	—	—	0.860	0.062	0.088	—
$\alpha = ?$	—	—	—	—	—	—	—	—	0.494	0.101	0.090	—
$N = 1000$												
$\beta_1 = 1$	1.014	0.100	0.097	94.6	1.006	0.099	0.097	94.8	1.012	0.099	0.092	93.4
$\beta_2 = -0.5$	−0.502	0.093	0.090	95.2	−0.504	0.093	0.090	94.6	−0.498	0.093	0.086	94.2
$\beta_1^* = 0.7$	0.727	0.090	0.095	96.2	0.713	0.091	0.095	96.6	0.649	0.080	0.084	90.6
$\theta = 0.5$	0.472	0.082	0.074	87.0	0.517	0.076	0.070	91.0	—	—	—	—
$\eta = 0.5$	0.505	0.105	0.106	96.4	0.485	0.103	0.103	93.6	—	—	—	—
$\tilde{\theta} = ?$	—	—	—	—	—	—	—	—	0.862	0.042	0.063	—
$\alpha = ?$	—	—	—	—	—	—	—	—	0.442	0.064	0.066	—

CP, coverage probability; SE, standard error.

inter-recurrence dependence. In the case of two sources of heterogeneity, for example, inter-recurrence dependence and dependence between the two hazard functions, we noticed a slight advantage for the proposed model regarding the regression coefficients. Moreover, the proposed model can distinguish these two dependencies.

4.4. Sensitivity analysis

We conducted a sensitivity analysis to demonstrate the robustness of the joint frailty model with two independent random effects against misspecification of the frailty distribution. We generated log-normal frailty distributions with a mean set at 1 and variance frailties at 0.492 and 0.822. We generated 500 replicate data sets with such log-normal frailty terms while keeping other settings unchanged ($\beta_1 = 1.0$, $\beta_2 = -0.5$, $\beta_3 = 0.7$). We then fitted the data sets by the joint frailty model, still assuming a gamma distribution for the frailty. From Table II, we observe that, apart from the variance of the frailty estimates $\hat{\theta}$ and $\hat{\eta}$, other parameter estimates have only very small biases, and the coverage probabilities are close to the nominal level 0.95. Under this model misspecification, regression parameter estimates have very small biases, and the coverage probabilities are close to the nominal level 0.95. The standard errors are very well estimated for the regression coefficients, the variance terms, so the model shows robustness against misspecification of the frailty distribution.

5. Application to follicular lymphoma patients

This study aimed to estimate the influence of prognostic factors (hazard ratios) associated with occurrences of follicular lymphoma relapses and death. If death is considered as a dependent terminating event for relapses, it becomes necessary to use a joint frailty model to make valid inferences. Another important point is to study whether the subjects who are at higher risk of relapses tend to have a higher or a lower risk of death. This approach allows us to assess firstly the association between follicular lymphoma relapses and death and secondly the dependence of the relapses within subjects.

5.1. Rationale

Eleven thousand new cases of follicular lymphoma occur every year in France, with an increasing incidence. The incidence of non-Hodgkin's lymphoma has doubled over the past two decades in most westernized countries [27]. The elucidation of prognostic factors and their influence are critical for making progress in disease prevention and treatment. Age and stage at first diagnosis are some of the prognostic factors that should be considered. Many other prognostic factors could be added to explain

Table II. Simulation results under misspecification of random effect distribution.

		Proposed model (splines)		
	Est.	SE emp.	SE $(\sqrt{\widehat{H^{-1}}})$	CP
$N = 500$				
$\beta_1 = 1$	1.015	0.141	0.136	93.6
$\beta_2 = -0.5$	−0.502	0.142	0.130	93.6
$\beta_1^* = 0.7$	0.726	0.127	0.127	94.8
$\theta = 0.492$	0.337	0.085	0.087	38.6
$\eta = 0.822$	0.646	0.154	0.153	65.8
$N = 1000$				
$\beta_1 = 1$	1.017	0.096	0.096	95.4
$\beta_2 = -0.5$	−0.495	0.094	0.091	95.2
$\beta_1^* = 0.7$	0.716	0.089	0.089	94.4
$\theta = 0.492$	0.328	0.056	0.061	15.0
$\eta = 0.822$	0.646	0.103	0.109	49.0

CP, coverage probability; SE, standard error.

the evolution of the disease, but we do not have measurements in our database. A model that can deal with non-observed prognostic factors (heterogeneity of data), recurrent event times, and terminal event times is needed. This leads us to the joint frailty models.

5.2. *Data*

We wanted to model relapses in follicular lymphoma patients in the presence of a dependent terminating event (death). We analyzed the influence of prognostic factors, such as gender, stage at first diagnosis (tumor burden with the Ann Arbor stages III–IV versus I–II), and age of the patient at diagnosis, on the occurrences of relapse and death. We did not consider serum lactate dehydrogenate levels (for tumor aggressiveness) or hemoglobin levels (consequences of the lymphoma on the host) even though they are also incorporated in the Follicular Lymphoma International Prognostic Index [28] because there were too many missing data.

We applied the different joint frailty models to analyze relapses and survival among patients with follicular lymphoma. The Bergonié Institute provided our data. A total of 409 patients were followed from 1965 to 2000 after a first diagnosis, and 198 (48%) patients did not have a relapse. The follow-up period thus varied between 11 days and 30 years. The number of patients having one, two, three, or four relapses was 150 (37%), 44 (11%), 11 (2.5%), and 6 (1.5%), respectively, with an average of 0.71 relapse per patient. During the follow-up, 249 (61%) patients had died, and the remaining patients were alive (censored) at the end of follow-up. We assumed that this censoring was independent of relapses and death. The covariates of interest were stage of the disease at diagnosis, age (older or younger than 60 years), and gender. There were 190 men (47%); 208 patients had their first diagnosis when they were younger than 60 years (51%), and 204 (50%) patients were originally diagnosed at stages I and II.

5.3. *Results with joint frailty models*

To compare the parameter estimates described in Table III and the conclusions deduced, we fitted the new joint frailty model with two independent random effects and the joint frailty model with one random effect proposed by Rondeau *et al.* [15].

We found that patient age had a significant effect on the hazards of recurrent event gap times and on survival. Older patients had a shorter gap time to each next relapses and died earlier. Therefore, older patients could die before experiencing a relapse. The effect of the stage at the first diagnosis is also significantly associated with the hazards of recurrent events and survival. Patients diagnosed with a stage III or IV of follicular lymphoma have a higher risk of relapses and death than patients diagnosed at earlier

Table III. Analysis of recurrences and death for follicular lymphoma patients.

Covariate	Proposed model (splines) $[u_i v_i, u_i]$ RR (95% CI)	Proposed model (Weibull) $[u_i v_i, u_i]$ RR (95% CI)	Model by Rondeau *et al.* $[\omega_i, \omega_i^{\alpha}]$ RR (95% CI)
For Relapses			
Stage: III–IV vs. I–II	1.45 (1.03–2.03)	1.50 (1.06–2.13)	1.47 (1.08–1.99)
Age (years): ⩾60 vs. <60	1.80 (1.28–2.53)	1.91 (1.34–2.71)	1.73 (1.27–2.35)
Gender: women vs. men	1.02 (0.75–1.40)	0.95 (0.67–1.34)	1.08 (0.80–1.46)
For Death			
Stage: III–IV vs. I–II	2.23 (1.57–3.17)	2.19 (1.53–3.13)	2.66 (1.74–4.05)
Age (years): ⩾60 vs. <60	3.95 (2.72–5.74)	3.61 (2.50–5.23)	4.43 (2.91–6.72)
Gender: women vs. men	0.77 (0.55–1.09)	0.76 (0.53–1.09)	0.84 (0.50–1.44)
$\theta = \text{var}(u_i)$ (SE)	0.90 (0.17)	1.00 (0.17)	—
$\tilde{\theta} = \text{var}(\omega_i)$ (SE)	—	—	0.70 (0.13)
$\eta = \text{var}(v_i)$ (SE)	0.12 (0.04)	0.12 (0.04)	—
α (SE)	—	—	1.63 (0.34)
LCV	7.156	7.173	6.634

LCV, likelihood cross-validation; SE, standard error.
RR, Relative Risk.

stages of the disease, that is, stage I or II. This finding underlines the importance of an early diagnosis of follicular lymphoma. For survival and relapses, the gender did not have any significant effect. In comparing the proposed model with the model by Rondeau *et al.*, we obtained similar hazard ratios. The likelihood cross-validation criterion [29] was here not better for the proposed model.

Regarding the results from the joint frailty models with one random effect [15], the variance of the frailty $\tilde{\theta}$ and the coefficient α are significantly different from 0. This shows that relapse and death times are dependent. Moreover, the coefficient α estimated value ($\alpha > 0$) obtained by this model illustrate a positive association between recurrent and terminal events. This means that the effect of non-observed prognostic factors produces a biological weakening or a strengthening of both events (relapses and death). At this point, with only the model by Rondeau *et al.*, we cannot conclude whether there is an inter-recurrences dependence hidden inside this observed dependence.

The proposed model also detects a small but significant inter-recurrences dependence, the variance η being significantly different from 0. We can deduce that there is indeed a significant dependence between the relapse gap times, which means that the duration between two consecutive relapses depends slightly on the previous duration intervals. Note that the joint frailty model with one random effect cannot provide us this information; it only informs about the dependence between the two rates.

6. Conclusion and discussion

We presented a joint frailty model with two independent random effects to model simultaneously recurrent event data with a dependent terminal event. The proposed joint frailty model for possibly right-censored model was able not only to express the dependence among different of recurrent events, but also to deal with the association between recurrent and terminal events. This joint modeling approach can be seen as an extension of the methods proposed by Rondeau *et al.* [15] or by Liu *et al.* [13]. The simulation study indicated that the approach works well for practical situations. One advantage of the aforementioned approach is that several covariate effects may be assessed for recurrence or death rates and that these covariates may be time dependent or time independent. In total, there are many reasons to use joint frailty models for two survival endpoints, including giving a general description of the data, correcting for bias in survival analysis due to dependent terminal event, and improving efficiency of survival analysis thanks to the use of supplementary information. Furthermore, they also provide information on whether recurrences times can be used as surrogate endpoints for overall survival. We suggest a more complex feature of dependence between the two event rates. This joint frailty model distinguishes the inter-recurrences dependence and the dependence between terminal and recurrent events by using independent gamma frailties. We did a simulation study and generated data where these two dependencies are present. We deduced that the joint gamma frailty model with two independent random effects gives unbiased regression coefficients (i.e., hazard ratios) and better coverage probabilities than the previous joint frailty model with one random effect. Furthermore, our proposed model provides more information and indicates the origin of the dependencies between the observed times, assessed through the variances of the random effects θ, η. Hence, this model yields useful indications for further programs to prevent relapses and death from disease in events such as breast cancer.

We proposed to use the penalized likelihood maximization method, which needs the choice of smoothing parameters and the number of knots to approximate the hazard functions. These parameters may be important for the convergence, the inversion of the Hessian matrix, and for providing interpretable estimates. We also proposed to use the maximum of likelihood estimation method when the baseline hazard functions are parametrized as Weibull functions. In several articles, the estimation method used is a variant of the Expectation–Maximization algorithm [13, 14], which does not provide a direct variance estimator of random effects nor a smoothed estimation of the hazard functions. This work gives smoothed estimates of hazard functions that represent incidence and mortality rates in epidemiology, which are meaningful for clinicians. It is natural in epidemiology to impose a continuous hazard function with small local variations.

Through the proposed model (1), there is an underlying assumption; that is, that recurrent events and terminal event are positively associated through a shared random effect. Even if, in oncology and in many other diseases, relapses and death are rarely negatively associated, we worked also on a more flexible approach with a power coefficient in the terminal event hazard function such as that in Liu *et al.* [13] and Rondeau *et al.* [18] to avoid this positivity constraint and to allow a possibly negative association between the two hazard functions. However, this model could have, in some cases, identifiability issues.

A solution would be to consider a joint frailty model with two correlated random effects, one for each hazard function; this would be another extension of the work of Liu *et al.* [13] and Rondeau *et al.* [18].

In frailty models, we consider that frailties are constant across time, but it should be acknowledged that non-observed prognostic factors (environmental, food habits, salary, etc.) may change during the follow-up, especially in the long term. Hence, another interesting perspective is to develop new models in which frailties may change across time, by using the Lévy stochastic process [30]. In this article, we focus on one type of recurrent event, and for many other diseases, we can observe different types of recurrent events, such as locoregional and metastatic relapses for breast cancer. It could be useful to develop joint frailty models that can deal with different types of dependent recurrent events with a dependent terminal event.

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APPENDIX A. Log-likelihood of the proposed model for time-to-event time scale

Firstly, we calculate the conditional contribution of individual i to the likelihood. Let us note also that $\delta_{i(n_i+1)} = 0$.

$$V_i(\Phi|u_i, v_i) = \lambda_i(T_i^*)^{\delta_i^*} \prod_{j=1}^{n_i} r_i(T_{ij})^{\delta_{ij}} u_i^{n_i+\delta_i^*} v_i^{n_i} \exp\left(-u_i v_i \sum_{j=1}^{n_i+1} \int_{T_{i(j-1)}}^{T_{ij}} Y_i(t) r_i(t) \mathrm{d}t\right) \times \exp\left(-u_i \int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right) \tag{6}$$

We deduce the expression of the marginal likelihood by integrating the conditional likelihood:

$$V_i(\Phi) = \int_0^\infty \int_0^\infty V_i(\Phi|u_i, v_i) f(u_i, v_i) \mathrm{d}u_i \mathrm{d}v_i.$$

The random effects $u_i \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$ and $v_i \sim \Gamma\left(\frac{1}{\eta}, \frac{1}{\eta}\right)$ are mutually independent and identically distributed, which means that the joint probability density function is the product of the two margins:

$$f(u_i, v_i) = f(u_i) f(v_i), \quad f(u_i) = \frac{u_i^{\frac{1}{\theta}-1} \exp\left(-\frac{u_i}{\theta}\right)}{\theta^{\frac{1}{\theta}} \Gamma\left(\frac{1}{\theta}\right)}, \quad f(v_i) = \frac{v_i^{\frac{1}{\eta}-1} \exp\left(-\frac{v_i}{\eta}\right)}{\eta^{\frac{1}{\eta}} \Gamma\left(\frac{1}{\eta}\right)}.$$

The marginal contribution of i to the likelihood is

$$\begin{aligned} V_i(\Phi) &= \lambda_i(T_i^*)^{\delta_i^*} \prod_{j=1}^{n_i} r_i(T_{ij})^{\delta_{ij}} \int_0^\infty \int_0^\infty u_i^{n_i+\delta_i^*} v_i^{n_i} \exp\left(-u_i v_i \sum_{j=1}^{n_i+1} \int_{T_{i(j-1)}}^{T_{ij}} Y_i(t) r_i(t) \mathrm{d}t\right) \\ &\quad \times \exp\left(-u_i \int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right) f(u_i) f(v_i) \mathrm{d}u_i \mathrm{d}v_i \\ &= \lambda_i(T_i^*)^{\delta_i^*} \prod_{j=1}^{n_i} r_i(T_{ij})^{\delta_{ij}} \times \int_0^\infty u_i^{n_i+\delta_i^*} f(u_i) \exp\left(-u_i \int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right) \\ &\quad \times \int_0^\infty \frac{v_i^{n_i+\frac{1}{\eta}-1}}{\Gamma\left(\frac{1}{\eta}\right)} \exp\left(-v_i\left(\frac{1}{\eta} + u_i \sum_{j=1}^{n_i+1} \int_{T_{i(j-1)}}^{T_{ij}} Y_i(t) r_i(t) \mathrm{d}t\right)\right) \mathrm{d}v_i \mathrm{d}u_i \end{aligned}$$

$$
\begin{aligned}
&= \lambda_i(T_i^*)^{\delta_i^*} \prod_{j=1}^{n_i} r_i(T_{ij})^{\delta_{ij}} \int_0^{\infty} u_i^{n_i+\delta_i^*} f(u_i) \\
&\quad \times \exp\left(-u_i \int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right) \frac{\Gamma(n_i+\frac{1}{\eta})}{\eta^{\frac{1}{\eta}}\Gamma\left(\frac{1}{\eta}\right)\left(\frac{1}{\eta}+u_i\sum_{j=1}^{n_i+1}\int_{T_{i(j-1)}}^{T_{ij}} Y_i(t)r_i(t)\mathrm{d}t\right)^{n_i+\frac{1}{\eta}}} \mathrm{d}u_i \\
&= \lambda_i(T_i^*)^{\delta_i^*} \prod_{j=1}^{n_i} r_i(T_{ij})^{\delta_{ij}} \frac{\Gamma\left(n_i+\frac{1}{\eta}\right)\eta^{n_i}}{\Gamma(\frac{1}{\eta})} \\
&\quad \times \int_0^{\infty} \frac{u_i^{n_i+\delta_i^*} f(u_i)\exp\left(-u_i\int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right)}{\left(1+u_i\eta\sum_{j=1}^{n_i+1}\int_{T_{i(j-1)}}^{T_{ij}} Y_i(t)r_i(t)\mathrm{d}t\right)^{n_i+\frac{1}{\eta}}} \mathrm{d}u_i .
\end{aligned}
\tag{7}
$$

The contribution of i to the marginal log-likelihood for time-to-event time scale is

$$
\begin{aligned}
l_i(\Phi) &= \delta_i^* \log\left(\lambda_i(T_i^*)\right) + \sum_{j=1}^{n_i} \delta_{ij} \log\left(r_i(T_{ij})\right) + \log\left(\Gamma\left(n_i+\frac{1}{\eta}\right)\right) + n_i\log(\eta) - \log\left(\Gamma\left(\frac{1}{\eta}\right)\right) \\
&\quad + \log\left(\int_0^{\infty} \frac{u_i^{n_i+\delta_i^*+\frac{1}{\theta}-1}\exp\left(-u_i\left(\frac{1}{\theta}+\int_0^{T_i^*} Y_i(t)\lambda_i(t)\mathrm{d}t\right)\right)}{\left(1+u_i\eta\sum_{j=1}^{n_i+1}\int_{T_{i(j-1)}}^{T_{ij}} Y_i(t)r_i(t)\mathrm{d}t\right)^{n_i+\frac{1}{\eta}} \theta^{\frac{1}{\theta}}\Gamma\left(\frac{1}{\theta}\right)} \mathrm{d}u_i\right).
\end{aligned}
\tag{8}
$$

The overall log-likelihood for time-to-event time scale is

$$
l(\Phi) = \sum_i l_i(\Phi).
$$

We just have to replace T_{ij} by S_{ij} and $\int_{T_{i(j-1)}}^{T_{ij}}$ by $\int_0^{S_{ij}}$ in the expression of the log-likelihood for time-to-event time scale to obtain the log-likelihood for gap times presented in the Section 3.1.

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