Biometrical Journal **00** (2012) 00, zzz–zzz / DOI: 10.1002/bimj.200100000

Supplementary material for the paper entitled: Multivariate frailty models for two types of recurrent events with a dependent terminal event: Application to breast cancer data

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Received zzz, revised zzz, accepted zzz

Key words: Breast cancer; Frailty models; Penalized likelihood; Recurrent events

1 Likelihood construction and gap ($S_{ij}^{(l)}$) timescales

1.1 For calendar timescales ($T_{ij}^{(l)}$)

Firstly, we calculate the conditional contribution of the individual i to the likelihood. Let us remind also that $\delta_{i(n_i^{(l)})}^{(l)} = 0, l \in \{1, 2\}$.

$$
\begin{aligned}
L_i(\Phi|u_i, v_i) &= \prod_{j=1}^{n_i^{(1)}} P(X_{ij}^{(1)} = T_{ij}^{(1)} | X_{ij}^{(1)} > T_{i(j-1)}^{(1)}, u_i, v_i)^{\delta_{ij}^{(1)}} P(X_{ij}^{(1)} > T_{ij}^{(1)} | X_{ij}^{(1)} > T_{i(j-1)}^{(1)}, u_i, v_i)^{1-\delta_{ij}^{(1)}} \\
&\times \prod_{j=1}^{n_i^{(2)}} P(X_{ij}^{(2)} = T_{ij}^{(2)} | X_{ij}^{(2)} > T_{i(j-1)}^{(2)}, u_i, v_i)^{\delta_{ij}^{(2)}} P(X_{ij}^{(2)} > T_{ij}^{(2)} | X_{ij}^{(2)} > T_{i(j-1)}^{(2)}, u_i, v_i)^{1-\delta_{ij}^{(2)}} \\
&\times P(D_i = T_i^* | u_i, v_i)^{\delta_i^*} P(D_i > T_i^* | u_i, v_i)^{1-\delta_i^*} \\
&= \prod_{j=1}^{n_i^{(1)}} r_i^{(1)}(T_{ij}^{(1)} | u_i, v_i)^{\delta_{ij}^{(1)}} \frac{P(X_{ij}^{(1)} > T_{ij}^{(1)} | u_i, v_i)}{P(X_{ij}^{(1)} > T_{i(j-1)}^{(1)} | u_i, v_i)} \\
&\times \prod_{j=1}^{n_i^{(2)}} r_i^{(2)}(T_{ij}^{(2)} | u_i, v_i)^{\delta_{ij}^{(2)}} \frac{P(X_{ij}^{(2)} > T_{ij}^{(2)} | u_i, v_i)}{P(X_{ij}^{(2)} > T_{i(j-1)}^{(2)} | u_i, v_i)} \times \lambda(T_i^* | u_i, v_i)^{\delta_i^*} P(D_i > T_i^* | u_i, v_i)
\end{aligned}
$$

The random effects (u_i, v_i) are Gaussian and correlated with $var(u_i) = \theta$, $var(v_i) = \eta$, $corr(u_i, v_i) = \rho$, and $f(u_i, v_i) = \dfrac{1}{2\pi\sqrt{\theta\eta}\sqrt{(1-\rho^2)}} \exp\left(\dfrac{-u_i^2/\theta + 2\rho u_i v_i/\sqrt{\theta\eta} - v_i^2/\eta}{2(1-\rho^2)}\right)$.

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We integrate the conditional contribution of the individual i:

$$L_i(\Phi) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} L_i(\Phi|u_i, v_i) \times f(u_i, v_i) du_i dv_i.$$

We then obtain the individual marginal contribution to the likelihood :

$$\begin{aligned}
L_i(\Phi) &= \frac{\prod_{j=1}^{n_i^{(1)}} r_i^{(1)}(T_{ij}^{(1)})^{\delta_{ij}^{(1)}} \prod_{j=1}^{n_i^{(2)}} r_i^{(2)}(T_{ij}^{(2)})^{\delta_{ij}^{(2)}} \lambda(T_i^*)^{\delta_i^*}}{2\pi\sqrt{\theta\eta}\sqrt{(1-\rho^2)}} \\
&\times \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \exp\left(-\exp(u_i)\sum_{j=1}^{n_i^{(1)}+1}\int_{T_{i(j-1)}^{(1)}}^{T_{ij}^{(1)}} r_i^{(1)}(t)dt\right)\exp\left(-\exp(v_i)\sum_{j=1}^{n_i^{(2)}+1}\int_{T_{i(j-1)}^{(2)}}^{T_{ij}^{(2)}} r_i^{(2)}(t)dt\right) \\
&\times \exp\left(-\exp(\alpha_1 u_i + \alpha_2 v_i)\int_0^{T_i^*}\lambda_i(t)dt\right) \\
&\times \exp\left(n_i^{(1)}u_i + n_i^{(2)}v_i + \delta_i^*(\alpha_1 u_i + \alpha_2 v_i)\right)\exp\left(\frac{-u_i^2/\theta + 2\rho u_i v_i/\sqrt{\theta\eta} - v_i^2/\eta}{2(1-\rho^2)}\right) du_i dv_i
\end{aligned}$$

$$\begin{aligned}
L_i(\Phi) &= \frac{\prod_{j=1}^{n_i^{(1)}} r_i^{(1)}(T_{ij}^{(1)})^{\delta_{ij}^{(1)}} \prod_{j=1}^{n_i^{(2)}} r_i^{(2)}(T_{ij}^{(2)})^{\delta_{ij}^{(2)}} \lambda(T_i^*)^{\delta_i^*}}{2\pi\sqrt{\theta\eta}\sqrt{(1-\rho^2)}} \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \exp\Bigg[\\
&\times \Bigg(-\exp(u_i)\sum_{j=1}^{n_i^{(1)}+1}\int_{T_{i(j-1)}^{(1)}}^{T_{ij}^{(1)}} r_i^{(1)}(t)dt - \exp(v_i)\sum_{j=1}^{n_i^{(2)}+1}\int_{T_{i(j-1)}^{(2)}}^{T_{ij}^{(2)}} r_i^{(2)}(t)dt \\
&- \exp(\alpha_1 u_i + \alpha_2 v_i)\int_0^{T_i^*}\lambda_i(t)dt\Bigg) \\
&+ \left(\frac{-u_i^2/\theta + 2\rho u_i v_i/\sqrt{\theta\eta} - v_i^2/\eta}{2(1-\rho^2)} + (n_i^{(1)} + \delta_i^*\alpha_1)u_i + (n_i^{(2)} + \delta_i^*\alpha_2)v_i\right)\Bigg] du_i dv_i
\end{aligned}$$

1.2 For gap timescales ($S_{ij}^{(l)}$)

In the gap timescale formulation, the likelihood expression is the same except that $T_{ij}^{(l)}$, $l \in 1, 2$, is replaced by $S_{ij}^{(l)}$ and $\int_{T_{i(j-1)}^{(l)}}^{T_{ij}^{(l)}}$ by $\int_0^{S_{ij}^{(l)}}$. The full marginal likelihood for the gap timescale is written as follow:

$$\begin{aligned}
L_i(\Phi) &= \frac{\prod_{j=1}^{n_i^{(1)}} r_i^{(1)}(S_{ij}^{(1)})^{\delta_{ij}^{(1)}} \prod_{j=1}^{n_i^{(2)}} r_i^{(2)}(S_{ij}^{(2)})^{\delta_{ij}^{(2)}} \lambda(T_i^*)^{\delta_i^*}}{2\pi\sqrt{\theta\eta}\sqrt{(1-\rho^2)}} \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \exp\Bigg[\\
&\Bigg(-\exp(u_i)\sum_{j=1}^{n_i^{(1)}+1}\int_0^{S_{ij}^{(1)}} r_i^{(1)}(t)dt - \exp(v_i)\sum_{j=1}^{n_i^{(2)}+1}\int_0^{S_{ij}^{(2)}} r_i^{(2)}(t)dt - \exp(\alpha_1 u_i + \alpha_2 v_i)\int_0^{T_i^*}\lambda_i(t)dt\Bigg) \\
&+ \left(\frac{-u_i^2/\theta + 2\rho u_i v_i/\sqrt{\theta\eta} - v_i^2/\eta}{2(1-\rho^2)} + (n_i^{(1)} + \delta_i^*\alpha_1)u_i + (n_i^{(2)} + \delta_i^*\alpha_2)v_i\right)\Bigg] du_i dv_i
\end{aligned}$$

1.3 Estimation of the individual random effects u_i, v_i for the martingale residuals

Let $T_i = \{T_{ij}^{(l)}, j^{(l)} = 1, ..., n_i^{(l)} + 1\}$. The posterior probability density function is $f(u_i, v_i|T_i, \widehat{\Phi}) = \dfrac{f(T_i|u_i, v_i, \widehat{\Phi}) * f(u_i, v_i|\widehat{\Phi})}{f(T_i|\widehat{\Phi})}$ and $f(u_i, v_i|T_i, \widehat{\Phi}) \propto f(T_i|u_i, v_i, \widehat{\Phi}) * f(u_i, v_i|\widehat{\Phi})$. Here $f(T_i|u_i, v_i, \widehat{\Phi})$ corresponds to likelihood of the individual i given $\widehat{\Phi}$ and given the random effects u_i, v_i.

The mode of the posterior probability density function is obtained by maximizing it using Marquardt algorithm:

$$
\begin{aligned}
f(u_i, v_i|T_i, \widehat{\Phi}) \quad \propto \quad & \exp\Bigg[\Bigg(- \exp(u_i) \int_0^{T_i^*} \widehat{r_i^{(1)}}(u)du - \exp(v_i) \int_0^{T_i^*} \widehat{r_i^{(2)}}(u)du \\
& - \exp(\widehat{\alpha_1} u_i + \widehat{\alpha_2} v_i) \int_0^{T_i^*} \widehat{\lambda}_i(u)du \Bigg) \\
& + \Bigg(\frac{-u_i^2/\widehat{\theta} + 2\widehat{\rho} u_i v_i / \sqrt{\widehat{\theta}\widehat{\eta}} - v_i^2/\widehat{\eta}}{2(1-\widehat{\rho}^2)} (n_i^{(1)} + \delta_i^* \widehat{\alpha_1}) u_i + (n_i^{(2)} + \delta_i^* \widehat{\alpha_2}) v_i \Bigg) \Bigg]
\end{aligned}
$$

2 Description of the data

Table 1 provides a brief description of the data.

3 Simulation study

We consider different settings for the parameters α_1, α_2 and ρ. We present three illustrative and interesting settings. These objective is to compare the parameter estimates between the proposed models and the reduced models when these three different events are dependent or not totally dependent. Note that the reduced models for recurrent events are shared frailty models and a Cox model for the terminal event. In the first setting, we have generated data with a significant and positive dependency between recurrent events and terminal event ($\rho = 0.5$, $\alpha_1 = 1, \alpha_2 = 1$). In the second setting, we generated independent random effects ($\rho = 0$). The two types of recurrent events are independent but are positively linked to the terminal event ($\alpha_1 = 1, \alpha_2 = 1$). In the third setting, the two recurrent events are negatively dependent ($\rho = -0.5$). The first one is negatively associated to the terminal event hazard function ($\alpha_1 = -1$), whereas the second one is positively linked to the terminal event hazard function ($\alpha_2 = 0.5$).

3.1 Results of the simulation study

The results for sample size of N=1000 are presented in the main document, the results for the sample size of N=250 and N=500 are reported in Tables 2 and 4. The death rate is around two thirds. The average number of observed recurrent events (the first and the second types) per subject ranges from 1.62 to 2.08 in the conducted simulation studies. Around a third of the subjects did not have any recurrent events. The simulation results for the three setting and the three sample sizes of N=250 and N=500 are presented the the Tables 2, 4.

Such as for the sample size N=1000 presented in the main document, the results of the simulation study for N=250 and N=500 are satisfying. Regression coefficients are well estimated, standard errors are also well estimated. The flexibility parameters α_1, α_2 are overestimated and θ is underestimated. The parameter η is well estimated.

Table 1 Description of the data (N=1070)

Variables	Modalities	Number of patients (frequencies)
Age	age $\leq$ 40	82 (7.7%)
	40 $<$ age $\leq$55	393 (36.7%)
	age $>$ 55	595 (55.6%)
Grade	I	316 (29.5%)
	II	488 (45.6%)
	III	266 (24.9%)
Lymph node	N+	452 (42.2%)
	N-	618 (57.8%)
Tumor size	$\geq$20mm	243 (22.7%)
	$<$20mm	827 (77.3%)
HR+ (positive status of hormone receptors)	Yes	889 (83.1%)
	No	181 (16.9%)
Pro-mib1 (proliferation index using Mib1)	mib1$>$15% or high proliferation	404 (37.8%)
	mib1$\leq$15% and low proliferation	666 (62.2%)
HER 2+ (human epidermal growth factor receptor-2+)	Yes	121 (11.3%)
	No	949 (88.7%)
PVI (peritumoral vascular invasion)	Yes	287 (26.8%)
	No	783 (73.2%)

Table 2 Results of simulation study (N=250)

	Proposed model (Piecewise constant) $[u_i, v_i, \alpha_1 u_i + \alpha_2 v_i]$				Proposed model (M-splines) $[u_i, v_i, \alpha_1 u_i + \alpha_2 v_i]$				Reduced (M-splines) $[u_i, v_i, -]$			
	Mean	S.E. emp.	E.S.E. $(\sqrt{\widehat{H^{-1}}})$	C.P.	Mean	S.E. emp.	E.S.E. $(\sqrt{\widehat{H^{-1}}})$	C.P.	Mean	S.E. emp.	E.S.E. $(\sqrt{\widehat{H^{-1}}})$	C.P.
Setting I: $\rho = 0.5, \alpha_1 = \alpha_2 = 1$												
1^{st} type of recurrent events												
β_1 = 0.5	0.511	0.137	0.133	93.4	0.519	0.136	0.133	94.0	0.478	0.135	0.129	92.8
β_2 = 0.7	0.696	0.121	0.122	95.2	0.701	0.124	0.122	95.8	0.712	0.135	0.132	94.6
2^{nd} type of recurrent events												
β_3 = 0.6	0.598	0.137	0.140	96.4	0.606	0.138	0.141	96.6	0.561	0.133	0.134	94.2
β_4 = -0.5	-0.500	0.122	0.126	95.2	-0.497	0.123	0.126	95.2	-0.503	0.131	0.134	95.4
β_5 = 0.3	0.317	0.132	0.125	93.2	0.321	0.131	0.125	93.2	0.325	0.137	0.132	94.2
Terminal event (Death)												
β_6 = 0.4	0.430	0.238	0.239	95.8	0.462	0.253	0.253	95.8	0.161	0.179	0.163	24.2
θ = 0.5	0.470	0.105	0.111	93.2	0.461	0.109	0.116	90.7	0.342	0.105	0.098	57.6
η = 0.5	0.482	0.130	0.122	91.6	0.486	0.137	0.131	91.8	0.330	0.118	0.105	58.6
ρ = 0.5	0.497	0.138	0.136	94.2	0.495	0.137	0.137	95.0	-	-	-	-
α_1 = 1	1.098	0.394	0.378	96.2	1.149	0.513	0.447	97.6	-	-	-	-
α_2 = 1	0.076	0.395	0.388	97.0	1.114	0.502	0.447	96.0	-	-	-	-
Setting II: $\rho = 0, \alpha_1 = 1, \alpha_2 = 1$												
β_1 = 0.5	0.500	0.137	0.132	94.2	0.507	0.137	0.132	95.0	0.482	0.138	0.131	94.4
β_2 = 0.7	0.699	0.123	0.126	95.6	0.702	0.123	0.127	95.4	0.723	0.138	0.134	94.8
2^{nd} type of recurrent events												
β_3 = 0.6	0.604	0.141	0.140	95.6	0.608	0.143	0.140	95.2	0.584	0.143	0.137	94.2
β_4 = -0.5	-0.507	0.133	0.131	94.0	-0.505	0.134	0.131	94.4	-0.511	0.145	0.136	93.0
β_5 = 0.3	0.309	0.129	0.129	94.8	0.311	0.128	0.129	94.2	0.323	0.140	0.135	93.8
Terminal event (Death)												
β_6 = 0.4	0.417	0.228	0.217	96.0	0.441	0.244	0.230	96.4	0.170	0.186	0.174	23.2
θ = 0.5	0.471	0.104	0.103	90.0	0.465	0.110	0.108	89.2	0.423	0.113	0.101	78.2
η = 0.5	0.491	0.122	0.113	91.4	0.487	0.125	0.120	91.0	0.418	0.119	0.109	79.4
ρ = 0	-0.012	0.154	0.152	93.8	-0.019	0.157	0.154	94.0	-	-	-	-
α_1 = 1	1.126	0.328	0.314	97.2	1.170	0.453	0.393	96.4	-	-	-	-
α_2 = 1	1.094	0.322	0.316	95.4	1.156	0.437	0.401	95.8	-	-	-	-
Setting III: $\rho = -0.5, \alpha_1 = -1, \alpha_2 = 0.5$												
1^{st} type of recurrent events												
β_1 = 0.5	0.508	0.133	0.125	93.2	0.508	0.132	0.125	93.4	0.532	0.142	0.132	91.2
β_2 = 0.7	0.695	0.123	0.115	92.2	0.697	0.126	0.116	93.8	0.687	0.153	0.120	91.0
2^{nd} type of recurrent events												
β_3 = 0.6	0.603	0.136	0.138	95.4	0.607	0.138	0.139	95.8	0.585	0.137	0.136	94.8
β_4 = -0.5	-0.507	0.130	0.129	94.4	-0.505	0.131	0.130	94.2	-0.513	0.141	0.135	94.0
β_5 = 0.3	0.300	0.123	0.127	95.0	0.303	0.124	0.127	95.0	0.310	0.135	0.134	94.2
Terminal event (Death)												
β_6 = 0.4	0.420	0.208	0.207	95.2	0.431	0.214	0.213	95.6	0.161	0.192	0.182	29.4
θ = 0.5	0.480	0.097	0.093	91.8	0.482	0.100	0.095	91.2	0.420	0.102	0.103	80.8
η = 0.5	0.486	0.114	0.112	92.6	0.488	0.125	0.120	92.4	0.412	0.119	0.109	79.6
ρ = -0.5	-0.517	0.117	0.118	93.8	-0.520	0.116	0.118	93.2	-	-	-	-
α_1 = -1	-1.045	0.372	0.339	95.4	-1.101	0.420	0.393	96.4	-	-	-	-
α_2 = 0.5	0.547	0.327	0.306	96.6	0.545	0.351	0.325	98.0	-	-	-	-

Table 3 Results of simulation study (N=500)

	Proposed model (Piecewise constant) $[u_i, v_i, \alpha_1 u_i + \alpha_2 v_i]$				Proposed model (M-splines) $[u_i, v_i, \alpha_1 u_i + \alpha_2 v_i]$				Reduced (M-splines) $[u_i, v_i, -]$			
	Mean	S.E. emp.	E.S.E. ($\sqrt{\widehat{H^{-1}}}$)	C.P.	Mean	S.E. emp.	E.S.E. ($\sqrt{\widehat{H^{-1}}}$)	C.P.	Mean	S.E. emp.	E.S.E. ($\sqrt{\widehat{H^{-1}}}$)	C.P.
Setting I: $\rho = 0.5, \alpha_1 = \alpha_2 = 1$												
1^{st} type of recurrent events												
β_1 = 0.5	0.504	0.098	0.094	94.6	0.514	0.099	0.094	95.2	0.473	0.097	0.091	92.8
β_2 = 0.7	0.699	0.083	0.086	96.2	0.695	0.085	0.087	96.0	0.717	0.093	0.094	94.6
2^{nd} type of recurrent events												
β_3 = 0.6	0.603	0.101	0.099	93.8	0.613	0.100	0.100	95.2	0.564	0.098	0.095	91.0
β_4 = -0.5	-0.498	0.087	0.089	95.6	-0.480	0.090	0.090	92.8	-0.504	0.096	0.094	95.2
β_5 = 0.3	0.308	0.085	0.088	96.4	0.298	0.088	0.088	95.4	0.313	0.090	0.093	95.4
Terminal event (Death)												
β_6 = 0.4	0.412	0.168	0.166	94.4	0.419	0.164	0.166	94.6	0.149	0.154	0.131	23.8
θ = 0.5	0.478	0.079	0.079	92.8	0.463	0.083	0.082	89.6	0.353	0.077	0.070	45.6
η = 0.5	0.487	0.088	0.086	92.8	0.492	0.094	0.093	93.8	0.335	0.080	0.075	40.2
ρ = 0.5	0.496	0.092	0.094	96.2	0.530	0.092	0.095	95.2	-	-	-	-
α_1 = 1	1.064	0.252	0.241	94.8	0.998	0.312	0.277	94.6	-	-	-	-
α_2 = 1	1.046	0.241	0.247	97.2	1.031	0.313	0.287	94.0	-	-	-	-
Setting II: $\rho = 0, \alpha_1 = 1, \alpha_2 = 1$												
1^{st} type of recurrent events												
β_1 = 0.5	0.503	0.096	0.094	94.0	0.506	0.097	0.094	93.6	0.485	0.098	0.093	93.2
β_2 = 0.7	0.700	0.088	0.089	96.2	0.702	0.089	0.090	95.8	0.721	0.097	0.095	94.8
2^{nd} type of recurrent events												
β_3 = 0.6	0.604	0.098	0.098	95.2	0.605	0.099	0.098	95.4	0.583	0.100	0.096	93.0
β_4 = -0.5	-0.503	0.090	0.092	95.4	-0.501	0.089	0.093	95.6	-0.509	0.097	0.096	94.0
β_5 = 0.3	0.302	0.091	0.091	94.8	0.303	0.091	0.091	94.8	0.309	0.098	0.095	94.8
Terminal event (Death)												
β_6 = 0.4	0.415	0.154	0.151	93.8	0.425	0.158	0.155	95.8	0.156	0.164	0.149	27.8
θ = 0.5	0.480	0.074	0.073	91.6	0.476	0.078	0.077	90.2	0.434	0.080	0.072	78.2
η = 0.5	0.492	0.083	0.079	91.6	0.490	0.087	0.085	91.4	0.424	0.086	0.077	77.8
ρ = 0	-0.012	0.106	0.106	94.0	-0.016	0.108	0.107	93.2	-	-	-	-
α_1 = 1	1.088	0.229	0.209	95.0	1.111	0.260	0.249	98.2	-	-	-	-
α_2 = 1	1.061	0.232	0.212	94.8	1.086	0.269	0.253	96.8	-	-	-	-
Setting III: $\rho = -0.5, \alpha_1 = -1, \alpha_2 = 0.5$												
1^{st} type of recurrent events												
β_1 = 0.5	0.496	0.090	0.091	93.8	0.494	0.094	0.090	93.2	0.523	0.112	0.102	90.6
β_2 = 0.7	0.697	0.080	0.081	94.8	0.693	0.085	0.083	94.4	0.683	0.123	0.085	91.4
2^{nd} type of recurrent events												
β_3 = 0.6	0.602	0.102	0.098	95.7	0.603	0.104	0.099	95.4	0.578	0.099	0.096	92.6
β_4 = -0.5	-0.504	0.093	0.091	94.8	-0.505	0.098	0.092	92.8	-0.516	0.102	0.096	93.0
β_5 = 0.3	0.304	0.093	0.091	95.4	0.305	0.092	0.090	94.4	0.312	0.099	0.095	93.6
Terminal event (Death)												
β_6 = 0.4	0.408	0.134	0.137	95.6	0.418	0.154	0.147	95.2	0.154	0.167	0.153	28.2
θ = 0.5	0.486	0.061	0.059	91.8	0.486	0.071	0.069	91.2	0.438	0.094	0.096	78.2
η = 0.5	0.498	0.080	0.081	94.6	0.496	0.090	0.085	94.4	0.423	0.086	0.078	77.0
ρ = -0.5	-0.504	0.071	0.072	94.8	-0.508	0.081	0.082	94.6	-	-	-	-
α_1 = -1	-1.020	0.256	0.248	96.4	-1.060	0.256	0.248	95.4	-	-	-	-
α_2 = 0.5	0.524	0.206	0.198	96.6	0.529	0.206	0.198	95.6	-	-	-	-

4 Supplementary scenarios

We also tried to generate data close to the application in order to validate the parameter estimates obtained by using the proposed model. We then generated few recurrent events per subject, between 0.25 and 0.5 recurrent event per individual and 50% of censored data. We generated M=500 replicate datasets with N=1000 individuals. We tried also two scenarios including an extreme scenario with a high correlation coefficient

- Scenario IV: $\theta = 1$, $\eta = 5$, $\alpha_1 = 1$, $\alpha_2 = 1$, $\rho = 0.5$
- Scenario V (extreme scenario): $\theta = 1$, $\eta = 5$, $\alpha_1 = 1$, $\alpha_2 = 1$, $\rho = 0.9$

We fitted multivariate frailty models with piecewise hazard functions.

Table 4 Results of simulation study (N=1000)

	Proposed model (Piecewise) $[u_i, v_i, \alpha_1 u_i + \alpha_2 v_i]$			
	Est.	S.E. emp.	E.S.E. ($\sqrt{\widehat{H^{-1}}}$)	C.P.
Setting IV: $\theta = \mathbf{1}, \eta = \mathbf{5}, \rho = \mathbf{0.5}, \alpha_\mathbf{1} = \alpha_\mathbf{2} = \mathbf{1}$				
1^{st} type of recurrent events				
β_1 = 0.5	0.493	0.102	0.102	94.4
β_2 = 0.7	0.699	0.083	0.086	96.2
2^{nd} type of recurrent events				
β_3 = 0.6	0.603	0.101	0.099	93.8
β_4 = -0.5	-0.498	0.087	0.089	95.6
β_5 = 0.3	0.308	0.085	0.088	96.4
Terminal event (Death)				
β_6 = 0.4	0.412	0.168	0.166	94.4
θ = 0.5	0.398	0.099	0.100	78.8
η = 5	4.686	0.433	0.467	91.4
ρ = 0.5	0.503	0.139	0.134	93.6
α_1 = 1	1.117	0.425	0.414	96.8
α_2 = 1	1.030	0.101	0.105	94.4
Setting V : $\theta = \mathbf{1}, \eta = \mathbf{5}, \rho = \mathbf{0.9}, \alpha_\mathbf{1} = \alpha_\mathbf{2} = \mathbf{1}$				
1^{st} type of recurrent events				
β_1 = 0.5	0.510	0.070	0.076	93.2
β_2 = 0.7	0.707	0.064	0.076	98.3
2^{nd} type of recurrent events				
β_3 = 0.6	0.643	0.207	0.203	96.6
β_4 = -0.5	-0.505	0.187	0.182	94.9
β_5 = 0.3	0.325	0.186	0.179	94.9
Terminal event (Death)				
β_6 = 0.4	0.414	0.208	0.203	96.6
θ = 0.5	0.458	0.081	0.075	86.4
η = 5	4.847	0.439	0.402	89.8
ρ = 0.9	0.881	0.139	0.134	93.6
α_1 = 1	0.751	0.748	0.691	89.8
α_2 = 1	1.087	0.224	0.236	96.6

For the scenario IV, conclusions are similar to the three previous scenarios. This shows that even if the number of events is small, the proposed model gives satisfactory results. No convergence issues were observed in this scenario.

Concerning the scenario V (with few number of recurrent events and a high correlation coefficient $\rho = 0.9$), we noticed some convergence issues. Nevertheless, we can see that results are quite satisfactory for the cases of convergence. This shows that the estimates obtained after the convergence with this model are robust even for some limit cases such as the application.