Supporting Information for (Penalized Survival Models for the Analysis of Alternating Recurrent Event Data) by (Lili Wang, Kevin He, and Douglas E. Schaubel)

1 Web Appendix A: Definition of $h(\cdot)$

Following the Appendix from Ripatti and Palmgren (2000):

$$h(\lambda_{01}(\cdot), \lambda_{02}(\cdot), \widehat{\boldsymbol{\theta}}) = \sum_{i=1}^{n} \sum_{j=1}^{(m_i+1)} \sum_{k=1}^{2} \delta_{ijk} \log(\lambda_{0k}(\widetilde{T}_{ijk})) + \sum_{i=1}^{n} \sum_{j=1}^{(m_i+1)} \sum_{k=1}^{2} \delta_{ijk} \log(\sum_{l=1}^{n} \sum_{p=1}^{(m_l+1)} Y_{lpk}(\widetilde{T}_{ijk}) \exp(\widehat{\eta}_{lpk}))$$
(1)
$$- \sum_{i=1}^{n} \sum_{j=1}^{(m_i+1)} \sum_{k=1}^{2} \Lambda_{0k}(\widetilde{T}_{ijk}) \exp(\widehat{\eta}_{ijk})$$

2 Web Appendix B: $\widehat{D}^{\#}$ is Positive-definite

Fixing D, a partial log-likelihood (PLL) is assumed to be concave with respect to γ , or in other words, $-(\partial^2 PLL)/(\partial \gamma \partial \gamma')$ is positive-definite. Variance matrix Σ and thus its inverse Σ^{-1} are positive-definite. $K_{PPL2}(\gamma) = -(\partial^2 PPLL)/(\partial \gamma \partial \gamma')$, sum of $-(\partial^2 PLL)/(\partial \gamma \partial \gamma')$ and Σ^{-1} , is positive-definite; so is its inverse $K_{PPL2}(\gamma)^{-1}$. In line of the *Remark* blow, $[K_{PPL2}(\hat{\gamma})^{-1}]_{blk_i}$ are positive-definite. As follows, the sum of quadratic terms $\hat{\gamma}_i \hat{\gamma}'_i$ and $[K_{PPL2}(\hat{\gamma})^{-1}]_{blk_i}$ would produce a positive-definite estimator $\hat{D}^{\#}$. The *remark* is claimed and proved as below.

Remark. If $\mathbf{K}_{PPL2}(\widehat{\boldsymbol{\gamma}})^{-1}$ is positive-definite, then $[\mathbf{K}_{PPL2}(\widehat{\boldsymbol{\gamma}})^{-1}]_{blk_i}$ are positive-definite.

Proof. Let $\mathbf{I}_i = [\mathbf{0}_{(1)}, \dots, \mathbf{1}_{(i)}, \dots, \mathbf{0}_{(n)}]'_{2 \times 2n}$, where $\mathbf{1}_i$ is a 2 × 2 identity matrix located at the i^{th} horizontal block or occupying columns 2i - 1 and 2i, leaving other components to be 0. Thus we have $[\mathbf{K}''_{PPL}(\widehat{\boldsymbol{\gamma}})^{-1}]_{blk_i} = \mathbf{I}'_i \mathbf{K}_{PPL2}(\widehat{\boldsymbol{\gamma}})^{-1} \mathbf{I}_i$. Since $\mathbf{K}_{PPL2}(\widehat{\boldsymbol{\gamma}})^{-1}$ is positive-definite, for $\forall \mathbf{x} \neq \mathbf{0}$, we shall have $\mathbf{x}' [\mathbf{K}_{PPL2}(\widehat{\boldsymbol{\gamma}})^{-1}]_{blk_i} \mathbf{x} = \mathbf{x}^{*T} \mathbf{K}_{PPL2}(\widehat{\boldsymbol{\gamma}})^{-1} \mathbf{x}^* > 0$, where $\mathbf{x}^* = [\mathbf{0}_1, \dots, \mathbf{x}, \dots, \mathbf{0}_n]' \neq \mathbf{0}$.

3 Web Appendix C: Comparison with Ripatti and Palmgren (2000) and Lee et al. (2018)

To the best of our knowledge, there is no literature that derived a direct estimator for the entire variance-covariance matrix within a hierarchical survival model. Recall that in hierarchical frailty model discussed by Ripatti and Palmgren (2000), the authors incorporated three independent frailties to ensure a positive correlation between two events in their model. Dharmarajan et al. (2018) built a correlated frailty model of competing risks with a negative correlation by flipping a sign for one of its random effects. They both predefined the correlation directions between two events, which can be summarized as

$$\lambda_{1ij}(t \mid \boldsymbol{Z}_1, \boldsymbol{\gamma}_i^*) = \lambda_{01}(t) \exp(\boldsymbol{\beta}_1' \boldsymbol{Z}_{1ij} + \boldsymbol{\gamma}_{1i}^* + \boldsymbol{\gamma}_{0i}^*) \lambda_{2ij}(t \mid \boldsymbol{Z}_1, \boldsymbol{\gamma}_i^*) = \lambda_{02}(t) \exp(\boldsymbol{\beta}_2' \boldsymbol{Z}_{2ij} + \boldsymbol{\gamma}_{2i}^* \pm \boldsymbol{\gamma}_{0i}^*),$$
(2)

where $\boldsymbol{\gamma}_i^* = [\gamma_{0i}^*, \gamma_{1i}^*, \gamma_{2i}^*]'$ are independent and identically distributed draws from a normal distribution $N(0, \boldsymbol{D}^*)$ and $\boldsymbol{D}^* = \text{diag}[\phi_0, \phi_1, \phi_2]$, and the plus-minus sign \pm controls the the correlation sign between two events. Note that we use a superscript * to distinguish the analogs in Ripatti and Palmgren (2000) from ours.

In the outer loop, the estimating equations for ϕ_d with d = 0, 1, 2 are

$$\frac{\partial \mathrm{MPLL}}{\partial \phi_d} = -\frac{1}{2} \left\{ tr\left(\boldsymbol{\Sigma}^{*-1} \frac{\partial \boldsymbol{\Sigma}^*}{\partial \phi_d}\right) + tr\left(\boldsymbol{K}_2^*(\widehat{\boldsymbol{\gamma}^*})^{-1} \frac{\partial \boldsymbol{\Sigma}^{*-1}}{\partial \phi_d}\right) - \widehat{\boldsymbol{\gamma}^*}' \boldsymbol{\Sigma}^{-1} \frac{\partial \boldsymbol{\Sigma}^*}{\partial \phi_d} \boldsymbol{\Sigma}^{*-1} \widehat{\boldsymbol{\gamma}^*} \right\} = 0.$$
(3)

Ripatti and Palmgren (2000) also suggested using the second derivative of the penalized partial log likelihood $K_{PPL2}^*(\boldsymbol{\gamma}) = \partial^2 PPLL/\partial \boldsymbol{\gamma}^* \partial \boldsymbol{\gamma}^{*\prime}$ in place of $K_2^*(\boldsymbol{\gamma}) = \partial^2 \boldsymbol{K}(\boldsymbol{\gamma}^*)/\partial \boldsymbol{\gamma}^* \partial \boldsymbol{\gamma}^{*\prime}$ to achieve a better estimating performance. In practice, due to the difficulty to obtain $\partial \boldsymbol{\Sigma}^{*-1}/\partial \phi_d$ and that its Newton-Raphson estimating procedure in the outer loop cannot ensure it to be positive-definite (though re-parametrization of the variance-covariance matrix might save this point), practitioners assume the independent frailty model with the sign of the covariance of \boldsymbol{D} pre-specified as in (2) for convenience. Under such assumption as in models (2), the estimators for variance-covariance components are

$$\widehat{\phi}_d = \frac{[\widehat{\gamma}^{*d}]'[\widehat{\gamma}^{*d}] + tr\left[\{K_{PPL2}^*(\widehat{\gamma}^*)^{-1}\}_d\right]}{n} \quad d \in \{0, 1, 2\},\tag{4}$$

where we define $\widehat{\gamma}^{*d} = [\widehat{\gamma}_{d1}^*, \dots, \widehat{\gamma}_{dn}^*]'$, and $\{K_{PPL2}^*(\widehat{\gamma}^*)^{-1}\}_d$ is the d^{th} sub-matrix of $K_{PPL2}^*(\widehat{\gamma}^*)^{-1}$ corresponding to $\widehat{\gamma}^{*d}$. In other words, $tr[\{K_{PPL2}^*(\widehat{\gamma}^*)^{-1}\}_d]$ is summing up every d^{th} elements on the diagonal of $K_{PPL}^*(\widehat{\gamma}^*)^{-1}$. Note that $K_2^*(\gamma^*)$ is diagonal while $K_{PPL}^*(\gamma^*)$ is not, taking the trace $tr[\{K_{PPL2}^*(\widehat{\gamma}^*)^{-1}\}_d]$ is comparable to taking the sum of the diagonal blocks in our proposed method. Consequently, the entire variance matrix \widehat{D}^* can be assembled as

$$\widehat{\boldsymbol{D}}^* = \begin{bmatrix} \widehat{\phi}_1 + \widehat{\phi}_0 & \pm \widehat{\phi}_0 \\ \pm \widehat{\phi}_0 & \widehat{\phi}_2 + \widehat{\phi}_0 \end{bmatrix}.$$
(5)

Since the main difference between the two methods lie in the outer loop procedure, the regression parameter estimation would not be affected much (Table 3 and Web Table 3). Moreover, compared to coxme, the proposed approach reduces the computation burden by estimating fewer parameters in the inner loop: 2n + p vs 3n + p. Meanwhile in Web Table 4, we compared the outputs from our method with an accelerated failure time (AFT) method designed for alternating recurrent episodes (Lee et al, 2018). The AFT method has been implemented in an R package BivRec (version 1.0.0), which was quite fast and accurate, but it did not provide variance component estimates, and efficiency of the regression parameter estimates was lower than the PPL methods (Web Tables 3-4). Coxme and the proposed method provides similar estimations, the accuracy from coxme is slightly better, but requires much longer computation time.

4 Web Appendix D: Additional simulation studies

4.1 Larger cluster size

We increased the cluster size (m_i) in Web Table 1 to show that it will largely reduce the estimation bias for the variance components, and provide a better estimation on the regression parameters. The sample size is fixed at n = 100, and other settings are consistent with the simulation settings in the manuscript.

4.2 High censoring, large sample size, and many covariates

In order to test whether our proposed method works well for datasets with large proportion of censoring rate and many regression variables. We let 95% of the samples with censoring time C = 0.4, and the other 5% with censoring time C = 10, the baselines intensities are $\lambda_{0k} = 1.5$. The frailty is following a bivariate normal distribution $\gamma \sim BVN(\mathbf{0}_2, \mathbf{D})$ where $\mathbf{D}[1, 1] = \mathbf{D}[2, 2] = 0.25$ and $\mathbf{D}[1, 2] = \pm 0.125$. The gap times were generated from exponential distribution with intensity $\lambda_{0k} \exp(\beta' \mathbf{Z}_{ijk}) \gamma_{ik}$, where the covariates were simulated from a standard normal distribution. For each event type, there are 30 regression as an arithmetic sequence with constant increments ranging from -1 to +1 (p = 60). For each of the 500 replicates, we generated n = 6,000 subjects, 75 - 80% censoring rate, and around 8,000 event pairs in total. For $\mathbf{D}[1, 2] = 0.125$, the average estimated random effect variance-covariance matrix is quite accurate with bias of the estimates for D[1, 1] to be -0.007 (ESE: 0.035), D[2, 2] to be -0.008 (ESE: 0.046), and D[1, 2] to be -0.005 (ESE: 0.025); for D[1, 2] = -0.125, the respective estimation biases were -0.008 (ESE: 0.036), -0.005 (ESE: 0.051), and -0.001 (ESE: 0.026). The estimation of the regression parameters were also quite accurate according to the plots in Web Figures 1-4.

	True		Strong	g D		True		Weak	D	
	Value	Bias	ESD	ASE	CP	Value	Mean	ESD	ASE	CP
λ_{0k}	6	$\widetilde{m_i} = 16$					$\widetilde{m_i} = 18$			
β_1	1	-0.001	0.029	0.028	0.948	1	-0.002	0.030	0.030	0.940
β_2	-1	-0.001	0.028	0.029	0.944	-1	0.001	0.030	0.030	0.944
D[1, 1]	0.7	-0.031	0.105	0.107	0.900	0.25	-0.006	0.046	0.043	0.894
D[2, 2]	1.2	-0.047	0.193	0.179	0.874	0.25	-0.001	0.044	0.044	0.926
D[1, 2]	0.2	-0.038	0.101	0.099	0.916	0.125	-0.006	0.033	0.033	0.938
λ_{0k}	15	$\widetilde{m_i} = 40$					$\widetilde{m_i} = 45$			
β_1	1	-0.001	0.018	0.018	0.952	1	-0.001	0.019	0.019	0.954
β_2	-1	-0.000	0.018	0.018	0.958	-1	-0.000	0.018	0.019	0.964
D[1, 1]	0.7	-0.014	0.104	0.102	0.908	0.25	-0.005	0.041	0.038	0.902
D[2, 2]	1.2	-0.016	0.163	0.171	0.920	0.25	-0.005	0.040	0.038	0.930
D[1, 2]	0.2	-0.018	0.099	0.095	0.932	0.125	-0.005	0.031	0.029	0.922

Web Table 1: Estimating regression coefficients and variance components for varying cluster sizes, based on 500 replicates, with n = 100 and $\lambda_{01} = \lambda_{02}$.

 $\widetilde{m_i}$: median of m_i .

	A	dmissio	1	D	ischarge	2
	Estimate	$\widehat{\mathrm{SE}}$	P-value	Estimate	$\widehat{\operatorname{SE}}$	P-value
Age (per 5 years)	-0.025	0.010	0.016	-0.050	0.010	< 0.001
Height (per 5 cm)	-0.027	0.019	0.149	-0.003	0.018	0.875
Female	0.020	0.075	0.786	-0.049	0.072	0.494
Vascular access						
Arteriovenous graft	0.547	0.171	0.001	0.003	0.147	0.986
Central venous catheter	0.810	0.064	< 0.001	0.085	0.059	0.149
Comorbid conditions						
CAD	0.465	0.074	< 0.001	-0.100	0.067	0.136
Cancer	0.215	0.089	0.016	-0.208	0.081	0.010
CVD	0.195	0.083	0.019	-0.048	0.074	0.518
Stroke	0.203	0.098	0.038	0.019	0.087	0.832
CHF	0.074	0.074	0.319	0.020	0.069	0.770
Diabetes	0.054	0.061	0.377	-0.076	0.059	0.200
Hypertension	0.020	0.073	0.788	0.123	0.075	0.099
COPD	0.275	0.098	0.005	-0.038	0.086	0.660
Neurological disorder	0.378	0.110	0.001	-0.319	0.094	0.001
Psychological disorder	0.298	0.099	0.003	-0.065	0.087	0.456
PVD	0.117	0.085	0.171	0.130	0.078	0.095
Cellulitis	0.175	0.144	0.222	-0.408	0.124	0.001
Countries						
Belgium	0.401	0.138	0.004	0.138	0.123	0.263
Canada	0.250	0.135	0.065	-0.657	0.123	< 0.001
China	-0.583	0.241	0.015	-1.004	0.251	< 0.001
Gulf	-0.051	0.141	0.715	0.218	0.138	0.113
Germany	1.021	0.109	< 0.001	-0.284	0.095	0.003
Italy	0.381	0.137	0.006	-0.536	0.129	< 0.001
Japan	0.867	0.109	< 0.001	-0.431	0.106	< 0.001
Spain	-0.122	0.136	0.366	-0.331	0.133	0.013
Sweden	0.514	0.141	< 0.001	0.107	0.130	0.411
UK	0.573	0.146	< 0.001	-0.315	0.138	0.023
USA: Asian	-0.125	0.322	0.697	-0.107	0.350	0.759
USA: African-American	-0.034	0.095	0.720	0.011	0.100	0.910
USA: Caucasian	0	-	-	0	-	-
Variance	1.105	-	-	0.339	-	-

Web Table 2: Estimation on the DOPPS data by fitting two frailty models separately (using coxme)



Web Figure 1: D[1,2] = 0.125: for event type 1, we have 30 parameters ranging from -1 to +1. The sub-figure on the left has shown that entries of β_1 were plotted against the average value of their estimates, which is quite close to the red reference line y = x; On the right, we show the CPs for all the regression parameters form event 1, and the red line denotes the nominal value 0.95.



Web Figure 2: D[1, 2] = 0.125: for event type 2, we have 30 parameters ranging from -1 to +1. The sub-figure on the left has shown that entries of β_1 were plotted against the average value their estimates, which is quite close to the red reference line y = x; On the right, we show the CPs for all the regression parameters form event 2, and the red line denotes the nominal value 0.95.



Web Figure 3: D[1,2] = -0.125: for event type 1, we have 30 parameters ranging from -1 to +1. The sub-figure on the left has shown that entries of β_1 were plotted against the average value of their estimates, which is quite close to the red reference line y = x; On the right, we show the CPs for all the regression parameters form event 1, and the red line denotes the nominal value 0.95.



Web Figure 4: D[1,2] = -0.125: for event type 2, we have 30 parameters ranging from -1 to +1. The sub-figure on the left has shown that entries of β_1 were plotted against the average value their estimates, which is quite close to the red reference line y = x; On the right, we show the CPs for all the regression parameters form event 2, and the red line denotes the nominal value 0.95.

	True		Proposed me	ethod			coxme	e	
	Value	Bias	ESE	ASE	CP	Bias	ESE	ASE	CP
	cr = 6.24%	$\tilde{m}_i = 12$							
			time cost:	162s			time cost:	1929s	
$eta_1[1]$	-1	0.018	0.069	0.066	0.934	0.017	0.069	0.067	0.938
$\beta_1[2]$	-0.5	0.006	0.060	0.061	0.946	0.005	0.060	0.062	0.946
$\beta_1[3]$	0	-0.002	0.063	0.060	0.924	-0.002	0.063	0.060	0.928
$\beta_1[4]$	0.5	-0.008	0.062	0.062	0.944	-0.008	0.062	0.062	0.944
$\beta_1[5]$	1	-0.019	0.069	0.066	0.914	-0.018	0.069	0.067	0.916
$eta_2[1]$	-1	0.017	0.070	0.068	0.952	0.016	0.070	0.069	0.950
$\beta_2[2]$	-0.5	0.005	0.065	0.063	0.934	0.004	0.065	0.063	0.936
$\beta_2[3]$	0	0.000	0.062	0.061	0.934	0.000	0.062	0.061	0.938
$\beta_2[4]$	0.5	-0.005	0.067	0.063	0.932	-0.005	0.067	0.064	0.934
$eta_2[5]$	1	-0.024	0.070	0.068	0.918	-0.023	0.070	0.069	0.926
D[1,1]	0.25	-0.026	0.050	I	ı	-0.022	0.052	ı	ı
$oldsymbol{D}[2,2]$	0.25	-0.021	0.051	I	ı	-0.017	0.054	ı	ı
$oldsymbol{D}[1,2]$	0.125	-0.015	0.037	ı	ı	-0.009	0.039	ı	ı
	cr=6.29%	$\tilde{m}_i = 11$							
			time cost:	142s			time cost:	1908s	
$eta_1[1]$	-1	0.012	0.073	0.068	0.934	0.012	0.073	0.068	0.934
$\beta_1[2]$	-0.5	0.005	0.065	0.063	0.952	0.005	0.066	0.063	0.954
$\beta_1[3]$	0	0.002	0.066	0.061	0.918	-0.002	0.066	0.061	0.918
$\beta_1[4]$	0.5	-0.005	0.067	0.063	0.924	-0.005	0.067	0.063	0.926
$eta_1[5]$	1	-0.012	0.069	0.068	0.942	-0.012	0.068	0.068	0.942
$eta_2[1]$	-1	0.011	0.076	0.070	0.938	0.011	0.076	0.070	0.938
$\beta_2[2]$	-0.5	0.009	0.068	0.064	0.916	0.009	0.068	0.064	0.916
$\beta_2[3]$	0	-0.001	0.063	0.062	0.934	-0.001	0.063	0.062	0.934
$\beta_2[4]$	0.5	-0.009	0.065	0.064	0.944	-0.009	0.065	0.064	0.944
$\beta_2[5]$	1	-0.013	0.074	0.070	0.946	-0.013	0.074	0.070	0.948
$\boldsymbol{D}[1,1]$	0.25	-0.018	0.054	ı	ı	-0.018	0.055	ı	ı
$\boldsymbol{D}[2,2]$	0.25	-0.018	0.050	ı	ı	-0.017	0.051	ı	ı
$\boldsymbol{D}[1,2]$	-0.125	0.003	0.038	I	ı	0.005	0.039	ı	I

Web Table 3: Comparing the Proposed method with coxme

	True		Proposed me	ethod			BivRe	0	
	Value	Bias	ESE	ASE	CP	Bias	ESE	ASE	CP
	cr = 6.24%	$\tilde{m}_i = 12$							
			time cost:	162s			time cost:	79.1s	
$eta_1[1]$	-1	0.018	0.069	0.066	0.934	0.005	0.087	0.084	0.950
$\beta_1[2]$	-0.5	0.006	0.060	0.061	0.946	0.004	0.083	0.079	0.934
$eta_1[3]$	0	-0.002	0.063	0.060	0.924	-0.000	0.083	0.079	0.938
$\beta_1[4]$	0.5	-0.008	0.062	0.062	0.944	-0.004	0.082	0.079	0.948
$\beta_1[5]$	1	-0.019	0.069	0.066	0.914	-0.007	0.087	0.084	0.944
$eta_2[1]$	-1	0.017	0.070	0.068	0.952	-0.011	0.094	0.091	0.948
$eta_2[2]$	-0.5	0.005	0.065	0.063	0.934	0.003	0.085	0.084	0.952
$\beta_2[3]$	0	0.000	0.062	0.061	0.934	0.002	0.084	0.083	0.940
$\beta_2[4]$	0.5	-0.005	0.067	0.063	0.932	0.004	0.082	0.084	0.962
$\beta_2[5]$	1	-0.024	0.070	0.068	0.918	0.022	0.086	0.091	0.958
$\boldsymbol{D}[1,1]$	0.25	-0.026	0.050	ı	ı	ı	I	I	ı
$\boldsymbol{D}[2,2]$	0.25	-0.021	0.051	ı	ı	ı	I	ı	ı
$oldsymbol{D}[1,2]$	0.125	-0.015	0.037	ı	I	ı	I	ı	ı
	cr=6.29%	$\tilde{m}_i=11$							
			time cost:	142s			time cost:	73.8s	
$eta_1[1]$	-1	0.012	0.073	0.068	0.934	0.006	0.094	0.085	0.926
$eta_1[2]$	-0.5	0.005	0.065	0.063	0.952	-0.003	0.086	0.081	0.944
$\beta_1[3]$	0	0.002	0.066	0.061	0.918	-0.006	0.091	0.079	0.902
$\beta_1[4]$	0.5	-0.005	0.067	0.063	0.924	-0.006	0.089	0.081	0.922
$\beta_1[5]$	1	-0.012	0.069	0.068	0.942	-0.006	0.089	0.087	0.936
$\beta_2[1]$	-1	0.011	0.076	0.070	0.938	-0.002	0.094	0.097	0.970
$\beta_2[2]$	-0.5	0.009	0.068	0.064	0.916	-0.004	0.090	0.090	0.966
$\beta_2[3]$	0	-0.001	0.063	0.062	0.934	0.003	0.089	0.087	0.974
$\beta_2[4]$	0.5	-0.009	0.065	0.064	0.944	0.005	0.087	0.088	0.960
$eta_2[5]$	1	-0.013	0.074	0.070	0.946	0.007	0.104	0.096	0.944
$\boldsymbol{D}[1,1]$	0.25	-0.018	0.054	ı	ı	ı	I	I	ı
$oldsymbol{D}[2,2]$	0.25	-0.018	0.050	ı	ı	ı	I	ı	ı
$\boldsymbol{D}[1,2]$	-0.125	0.003	0.038	ı	ı	I	I	ı	ı

Web Table 4: Comparing the proposed method with BivRec