Biostatistics (2020), **0**, 0, *pp.* 1–6
doi:10.1093/biostatistics/output

Joint frailty modelling of time-to-event data to elicit the evolution pathway of events: A generalised linear mixed model approach

Supplementary Materials

SHU-KAY NG*

School of Medicine and Menzies Health Institute Queensland, Griffith University, Australia

s.ng@griffith.edu.au

RICHARD TAWIAH

School of Psychology, University of New South Wales, Australia

GEOFFREY J. MCLACHLAN

Department of Mathematics, University of Queensland, Australia

VINOD GOPALAN

School of Medicine and Menzies Health Institute Queensland, Griffith University, Australia

S1. Estimation of variance components and asymptotic variances

The proposed joint modelling method adopts a GLMM approach within a frailty modelling framework to account for correlation among individual times to (recurrent) events and death. As illustrated in the Methods section, the GLMM method involves the computations of the first deriva-

*To whom correspondence should be addressed.

tives of l_1 with respect to η and ζ within the Newton-Raphson iterative procedure in Equation (2.6) in the main text. Let $Q_1 = \mathrm{diag}(\varpi_1^R, ..., \varpi_N^R)$, $E_1 = \mathrm{diag}(e_1^R, ..., e_N^R)$, and $S_1 = (s_1^R, ..., S_N^R)$, where $\varpi_l^R = \exp(\eta_l)$, $e_l^R = \delta_l^R / \sum_{j=1}^N \varpi_j^R$, and $s_l^R = \sum_{j=1}^N e_j^R$ $(l = 1, \ldots, N)$. It can be shown that

$$\frac{\partial l_1}{\partial \eta} = \Delta^R - Q_1 F_1 E_1 \mathbf{1}_N$$

and

$$-\frac{\partial^2 l_1}{\partial \eta \partial \eta^T} = Q_1 S_1 - Q_1 F_1 E_1^2 F_1^T Q_1,$$

where Δ^R is the vector of censoring indicators for the gap times between recurrent events, F_1 is a $N \times N$ lower-triangular matrix with non-zero elements of one, and $\mathbf{1}_N$ is a vector of ones with dimension being specified by the subscript. Similarly, we have

$$\frac{\partial l_1}{\partial \zeta} = \Delta^D - Q_2 F_2 E_2 \mathbf{1}_M$$

and

$$-\frac{\partial^2 l_1}{\partial \zeta \partial \zeta^T} = Q_2 S_2 - Q_2 F_2 E_2^2 F_2^T Q_2,$$

where Δ^D is the vector of censoring indicators for the death time; E_2, F_2, Q_2, and S_2 have the same form as E_1, F_1, Q_1, and S_1, respectively, with a dimension of M instead of N. The information matrix $\boldsymbol{G}$ in Section 2.2 of the main text is a simplification of $-\partial^2 l_\Omega / \partial \Omega \partial \Omega^T$, given by

$$\boldsymbol{G} = \begin{bmatrix} X_1^T & 0 \\ 0 & X_2^T \\ Z_1^T & 0 \\ 0 & Z_2^T \end{bmatrix} \begin{bmatrix} D_{\eta\eta} & D_{\eta\zeta} \\ D_{\zeta\eta} & D_{\zeta\zeta} \end{bmatrix} \quad \begin{bmatrix} X_1 & 0 & Z_1 & 0 \\ 0 & X_2 & 0 & Z_2 \end{bmatrix} +$$

$$\frac{1}{\theta_u^2 \theta_v^2 (1-\rho^2)} \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \theta_v^2 I_M & -\rho\theta_u\theta_v I_M \\ 0 & 0 & -\rho\theta_u\theta_v I_M & \theta_u^2 \end{bmatrix},$$

where $D_{\eta\eta} = -\partial^2 l_2 / \partial\eta\partial\eta^T$, $D_{\zeta\zeta} = -\partial^2 l_2 / \partial\zeta\partial\zeta^T$ and $D_{\eta\zeta} = D_{\zeta\eta} = -\partial^2 l_2 / \partial\eta\partial\zeta^T = -\partial^2 l_2 / \partial\zeta\partial\eta^T = 0$. It follows that the inverse matrix of $\boldsymbol{G}$ can be written in a block form as:

$$\boldsymbol{G}^{-1} = \begin{bmatrix} \boldsymbol{B}_{\beta,\beta} & \boldsymbol{B}_{\beta,\gamma} & \boldsymbol{B}_{\beta,q} \\ \boldsymbol{B}_{\gamma,\beta} & \boldsymbol{B}_{\gamma,\gamma} & \boldsymbol{B}_{\gamma,q} \\ \boldsymbol{B}_{q,\beta} & \boldsymbol{B}_{q,\gamma} & \boldsymbol{B}_{q,q} \end{bmatrix},$$

where the asymptotic standard errors of $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are given by

$$\text{var}\begin{bmatrix}\hat{\boldsymbol{\beta}}\\ \hat{\boldsymbol{\gamma}}\end{bmatrix} = \begin{bmatrix}\boldsymbol{B}_{\beta,\beta} & \boldsymbol{B}_{\beta,\gamma}\\ \boldsymbol{B}_{\gamma,\beta} & \boldsymbol{B}_{\gamma,\gamma}\end{bmatrix}. \tag{S1.1}$$

For the variance component parameters $\boldsymbol{\Phi} = (\theta_u^2, \theta_v^2, \rho)^T$, the equation of the first order derivative of the REML log likelihood is

$$\text{tr}\boldsymbol{\Sigma}^{-1}\frac{\partial\boldsymbol{\Sigma}}{\partial\boldsymbol{\Phi}} + \text{tr}\left(\boldsymbol{B}_{q,q} + \boldsymbol{q}\boldsymbol{q}^T\right)\frac{\partial\boldsymbol{\Sigma}^{-1}}{\partial\boldsymbol{\Phi}} = 0, \tag{S1.2}$$

where, tr denotes the trace of a matrix. Solving (S1.2), we have

$$\text{tr}\boldsymbol{\Sigma}^{-1}\frac{\partial\boldsymbol{\Sigma}}{\partial\theta_u^2} = \frac{M}{\theta_u}, \quad \text{tr}\boldsymbol{\Sigma}^{-1}\frac{\partial\boldsymbol{\Sigma}}{\partial\theta_v^2} = \frac{M}{\theta_v}, \quad \text{tr}\boldsymbol{\Sigma}^{-1}\frac{\partial\boldsymbol{\Sigma}}{\partial\rho} = -\frac{2M\rho}{(1-\rho^2)}. \tag{S1.3}$$

and that

$$\begin{aligned}
\text{tr}(\boldsymbol{B}_{q,q} + \boldsymbol{q}\boldsymbol{q}^T)\frac{\partial\boldsymbol{\Sigma}^{-1}}{\partial\theta_u^2} &= \frac{1}{\theta_u^4\theta_v^2(1-\rho^2)}(-\theta_v^2\Im_1 + \rho\theta_u\theta_v\Im_2),\\
\text{tr}(\boldsymbol{B}_{q,q} + \boldsymbol{q}\boldsymbol{q}^T)\frac{\partial\boldsymbol{\Sigma}^{-1}}{\partial\theta_v^2} &= \frac{1}{\theta_u^2\theta_v^4(1-\rho^2)}(-\theta_u^2\Im_3 + \rho\theta_u\theta_v\Im_2),\\
\text{tr}(\boldsymbol{B}_{q,q} + \boldsymbol{q}\boldsymbol{q}^T)\frac{\partial\boldsymbol{\Sigma}^{-1}}{\partial\rho} &= \frac{1}{\theta_u^2\theta_v^2(1-\rho^2)^2}(-2\rho\theta_v^2\Im_1 - 2(1+\rho)\theta_u\theta_v\Im_2 + 2\rho\theta_u^2\Im_3),
\end{aligned} \tag{S1.4}$$

where $\Im_1 = \text{tr}\left\{K_1\left(\boldsymbol{B}_{q,q} + \boldsymbol{q}\boldsymbol{q}^T\right)\right\}$, $\Im_2 = \text{tr}\left\{K_2\left(\boldsymbol{B}_{q,q} + \boldsymbol{q}\boldsymbol{q}^T\right)\right\}/2$, $\Im_3 = \text{tr}\left\{K_3\left(\boldsymbol{B}_{q,q} + \boldsymbol{q}\boldsymbol{q}^T\right)\right\}$ and

$$K_1 = \begin{bmatrix}I_M & 0\\ 0 & 0\end{bmatrix}, \quad K_2 = \begin{bmatrix}0 & I_M\\ I_M & 0\end{bmatrix}, \quad \text{and} \quad K_3 = \begin{bmatrix}0 & 0\\ 0 & I_M\end{bmatrix}.$$

Further simplifying the resulting equations by substituting Equations (S1.3) and (S1.4) into (S1.2), we obtain the REML estimators for θ_u^2, θ_v^2 and ρ given in Equation (2.7) in the main text.

The asymptotic standard errors of θ_u^2, θ_v^2, and ρ are given by:

$$\text{var}\begin{bmatrix}\hat{\theta}_u^2\\ \hat{\theta}_v^2\\ \hat{\rho}\end{bmatrix} = 2\begin{bmatrix}a_{11} & a_{12} & a_{13}\\ a_{12}{}^T & a_{22} & a_{23}\\ a_{13}{}^T & a_{23}{}^T & a_{33}\end{bmatrix}^{-1}, \tag{S1.5}$$

where

$$a_{11} = \text{tr}(J_1 - J_2)^2, \quad a_{12} = \text{tr}(J_1J_3 + J_2J_4 - 2J_1J_4),$$

$$a_{13} = \text{tr}(J_1J_5 + J_2J_6 - 2J_1J_6), \quad a_{22} = \text{tr}(J_3 - J_4)^4,$$

$$a_{23} = \mathrm{tr}(J_3J_5 + J_4J_6 - 2J_3J_6), \quad a_{33} = \mathrm{tr}(J_5 - J_6)^2,$$

and where

$$J_1 = \boldsymbol{B}_{q,q}\frac{\partial \boldsymbol{\Sigma}^{-1}}{\partial \theta_u^2}, J_2 = \boldsymbol{\Sigma}\frac{\partial \boldsymbol{\Sigma}^{-1}}{\partial \theta_u^2}, J_3 = \boldsymbol{B}_{q,q}\frac{\partial \boldsymbol{\Sigma}^{-1}}{\partial \theta_v^2},$$
$$J_4 = \boldsymbol{\Sigma}\frac{\partial \boldsymbol{\Sigma}^{-1}}{\partial \theta_v^2}, J_5 = \boldsymbol{B}_{q,q}\frac{\partial \boldsymbol{\Sigma}^{-1}}{\partial \rho}, J_6 = \boldsymbol{\Sigma}\frac{\partial \boldsymbol{\Sigma}^{-1}}{\partial \rho}.$$

S2. Additional simulation data sets

As described in the Results section of the main text, two additional simulated data sets were generated. In Set 7, we assess the performance under a different setting of covariate effects (here, both X_{j1} and X_{j2} increase the risk of multimorbidity, whereas X_{j1} increases but X_{j2} reduces the risk of death). In Set 8, we examine the robustness of the model to mis-specification of the normality assumption of the random effects by generating $\boldsymbol{q}$ from mixtures of two normal distributions. All other parameters were kept the same as those in the base model in Set 1.

We compare the proposed joint frailty model with informative censoring to the classical frailty model. Assessment is based on 500 replicated simulations for each set. The corresponding averaged censoring proportions for δ_j^D in Sets 7 and 8 are 71.3% and 84.0%, respectively. Table S1 presents the comparison for Sets 7 and 8, in terms of the average bias, the average of the standard error estimates (SEE), the sample standard error of the estimates over 500 replications (SE), and the coverage probability (CP) of 95% confidence interval based on the normal approximation. From Table S1, no appreciable bias is observed, confirming the applicability of the proposed joint frailty model in both settings. In general, there is good agreement between SEE and SE for all the fixed-effect parameters, indicating that the standard errors of these parameters are well estimated. The SEE and SE are also comparable for the variance components, except θ_u for multimorbidity when the variance component parameters are small ($\leqslant 0.8$). This is also reflected in the CP, which is lower than the nominal level. This finding implies that the standard error of θ_u^2 may be underestimated in some situations and thus caution should be exercised in interpreting the significance level to this variance component parameter; see the main text for discussion on formal tests of heterogeneity when prediction of subject-specific frailties is relevant. Comparatively, the estimates obtained from the standard frailty model have generally a larger bias. In both settings, the standard errors of θ_u^2 are overestimated.

[*Received August 1, 2010; revised October 1, 2010; accepted for publication November 1, 2010*]

Table S1. *Results of simulated data (Sets 7 and 8)*

	Parameter (True value)	Joint frailty model				Frailty model			
		Bias	SEE	SE	CP	Bias	SEE	SE	CP
Set 7	β_1 (0.3)	-0.019	0.33	0.32	0.95	-0.062	0.32	0.32	0.95
	β_2 (0.5)	-0.009	0.16	0.16	0.96	0.009	0.16	0.16	0.96
	γ_1 (0.8)	-0.021	0.20	0.18	0.97		n.a.		
	γ_2 (-0.3)	0.038	0.10	0.10	0.94		n.a.		
	θ_u (0.8)	0.042	0.07	0.16	0.85	-0.140	0.65	0.21	1.00
	θ_v (0.8)	0.015	0.07	0.09	0.91		n.a.		
	ρ (0.8)	0.007	0.02	0.03	0.87		n.a.		
Set 8	β_1 (-0.6)	0.030	0.37	0.38	0.96	0.060	0.37	0.38	0.96
	β_2 (0.8)	-0.035	0.19	0.19	0.96	-0.052	0.18	0.19	0.95
	γ_1 (-0.8)	-0.003	0.26	0.25	0.96		n.a.		
	γ_2 (0.5)	0.009	0.13	0.12	0.96		n.a.		
	θ_u (0.8)	0.038	0.06	0.14	0.88	-0.190	0.74	0.25	1.00
	θ_v (0.8)	0.025	0.06	0.10	0.91		n.a.		
	ρ (0.8)	0.007	0.01	0.02	0.88		n.a.		