Estimating parameters of a frailty semi-competing model with measurement errors in covariates

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Risks data and models

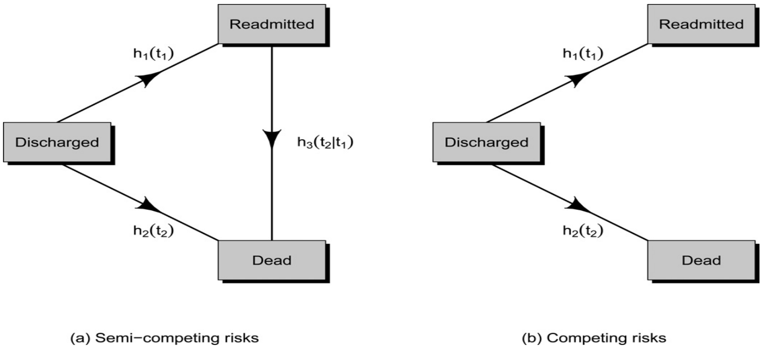

Figure 1: Semi-competing and competing risks data, Source: Haneuse and Lee (2016)

Three states:
initial=discharged, non-terminal=illness and terminal=death

Risks data and models

- Single endpoint risk: Cox PH model (Cox, 1972)
- Multiple competing risks: Martin J. Crowder (2001). *Classical competing risks*
  - Examples: recurrence, cancer cell metastasis and death occur after surgery
  - Shortcoming: only the first onset or terminal endpoint is considered as an event, and any subsequent observed events are combined as the same event or unobserved competing risks are censored.
- Semi-competing risks data
  - Coupla approach (Fine et al. 2001) and Regression approach et al. (2007)
  - Semi-competing risks model (Shu et al. (2007), Lee et al. (2015,2016))

Illness-death model

Let T_1 and T_2 be the two survival times to the non-terminal event and terminal event, respectively. The shared frailty illness-death model by Shu et al. (2007) is defined as below:

$$\lambda_1(t_1) = \gamma\lambda_{01}(t_1)e^{Z^T\beta_1}, \quad t_1 > 0,$$

$$\lambda_2(t_2) = \gamma\lambda_{02}(t_2)e^{Z^T\beta_2}, \quad t_2 > 0,$$

$$\lambda_3(t_2|t_1) = \gamma\lambda_{03}(t_2)e^{Z^T\beta_3}, \quad t_2 > t_1 > 0,$$

where γ is the shared frailty.

Goal: To estimate the transition intensities

Measurement error and cluster feature

- Measurement error
  - Carroll et al. (2006)
  - Buonaccorsi (2010)
- Cluster feature (shared frailty)
  subjects may come from different locations or have some different features
- Measurement errors have not been studied for shared frailty semi-competing risks model

Semi-competing risks cluster data with measurement errors

- m: the number of independent clusters
- n_i: the number of subjects within ith cluster.
- T_{ij1}: the time to the nonterminal event for jth subject in ith cluster
- T_{ij2}: the time to the terminal event for jth subject in ith cluster.
- Z_{ij}: p-dimensional covariate vector, mutually independent both within and among clusters. $\widehat{Z}_{ij}$ is the observed Z_{ij} with meansurement errors
- C_{ij}: noninformative right censoring time
  - $s_{ij1} = min(T_{ij1}, T_{ij2}, C_{ij})$, $\delta_{ij1} = I(s_{ij1} = T_{ij1})$,
  - $s_{ij2} = min(T_{ij2}, C_{ij})$, $\delta_{ij2} = I(s_{ij2} = T_{ij2})$.
- Observed data with measurement error:

$$\{(s_{ij1}, s_{ij2}, \delta_{ij1}, \delta_{ij2}, \widehat{Z}_{ij}), j = 1, ..., n_i; i = 1, ...m\}$$

Frailty semi-competing model for cluster data

- Three states: initial, non-terminal and terminal, corresponding to $k = 1, 2, 3$.

$$\lambda_1(t_{ij1}; Z_{ij}, \omega_{i1}) = \omega_{i1}\lambda_{01}(t_{ij1})e^{Z_{ij}^T\beta_1}, \quad t_{ij1} > 0, \tag{1}$$

$$\lambda_2(t_{ij2}; Z_{ij}, \omega_{i2}) = \omega_{i2}\lambda_{01}(t_{ij2})e^{Z_{ij}^T\beta_2}, \quad t_{ij2} > 0, \tag{2}$$

$$\lambda_3(t_{ij2}|t_{ij1}; Z_{ij}, \omega_{i3}) = \omega_{i3}\lambda_{03}(t_{ij2}|t_{ij1})e^{Z_{ij}^T\beta_3}, \quad t_{ij2} > t_{ij1} \tag{3}$$

- Shared frailty in ith cluster at state k: $\omega_{ik} \sim \Gamma(1/\theta_k, 1/\theta_k)$
- Markov transition $\lambda_{03}(t_{ij2}|t_{ij1}) = \lambda_{03}(t_{ij2})$
- Baseline transition times: Weibull distributions

$$\lambda_{0k}(t) = \alpha_k\gamma_k t^{\alpha_k-1}, \quad \Lambda_{0k}(t) = \gamma_k t^{\alpha_k}, \quad k = 1, 2, 3.$$

Notations

Let $\omega_k^T = (\omega_{1k}, \cdots, \omega_{mk})$, $k = 1, 2, 3$, $\boldsymbol{\omega}^T = \left(\omega_1^T, \omega_2^T, \omega_3^T\right)$ and

$$\boldsymbol{\phi}^T = \left(\alpha_1, \alpha_2, \alpha_3, \gamma_1, \gamma_2, \gamma_3, \beta_1^T, \beta_2^T, \beta_3^T\right) \text{ and } \boldsymbol{\theta}^T = (\theta_1, \theta_2, \theta_3).$$

For $i = 1, ..., m$, denote

$$D_{i1} = \sum_{j=1}^{n_i} \delta_{ij1}, \quad D_{i2} = \sum_{j=1}^{n_i} (1 - \delta_{ij1})\delta_{ij2}, \quad D_{i3} = \sum_{j=1}^{n_i} \delta_{ij1}\delta_{ij2}.$$

Log-likelihood function without measurement error

The log-likelihood for the whole sample is

$$\begin{aligned} l(\phi, \boldsymbol{\theta}, \boldsymbol{\omega}) &= \sum_{i=1}^{m} \ln L_i\left(\phi, \boldsymbol{\theta}, \omega_{i1}, \omega_{i2}, \omega_{i3}\right) \\ &= l_1(\theta_1, \omega_1) + l_1(\theta_2, \omega_2) + l_1(\theta_3, \omega_3) + l_2(\phi, \boldsymbol{\omega}), \end{aligned}$$

where

$$l_1(\theta_k, \omega_k) = \sum_{i=1}^{m} \left[\left(\frac{1}{\theta_k} + D_{ik} - 1 \right) \ln \omega_{ik} - \frac{\omega_{ik}}{\theta_k} - \ln \Gamma(\frac{1}{\theta_k}) - \frac{1}{\theta_k} \ln \theta_k \right],$$

where

$$l_2(\phi, \omega) = \sum_{i=1}^{m} \sum_{j=1}^{n_i} \Big\{ \delta_{ij1}(1-\delta_{ij2}) \left[\ln(\lambda_{01}(s_{ij1})) + Z_{ij}^T \beta_1 \right]$$
$$+ \delta_{ij1}\delta_{ij2} \left[\ln(\lambda_{01}(s_{ij1})) + \ln(\lambda_{03}(s_{ij2})) + Z_{ij}^T (\beta_1 + \beta_3) \right]$$
$$+ (1-\delta_{ij1})\delta_{ij2} \left[\ln(\lambda_{02}(s_{ij2})) + Z_{ij}^T \beta_2 \right] - r(s_{ij1}, s_{ij2}, Z_{ij}) \Big\}.$$

where

$$r(s_{ij1}, s_{ij2}, Z_{ij}) = \omega_{i1}\Lambda_{01}(s_{ij1}) e^{Z_{ij}^T \beta_1} + \omega_{i2}\Lambda_{02}(s_{ij2}) e^{Z_{ij}^T \beta_2} + \omega_{i3} \left[\Lambda_{03}(s_{ij2}) - \Lambda_{03}(s_{ij1}) \right] e^{Z_{ij}^T \beta_3}.$$

Measurement error model

- Denote
  - $Z_{ij}^T = (X_{ij}^T, V_{ij}^T)$,
    X_{ij} is a subvector of error-prone covariates, W_{ij} be the surrogate measurement of X_{ij}
  - $\hat{Z}_{ij}^T = (W_{ij}^T, V_{ij}^T)$, $\beta_k^T = (\beta_{kx}^T, \beta_{kv}^T)$.
- Additive measurement error (Carroll et al. 2006): For simplicity, let X_{ij} be univariate variable,

$$W_{ij} = X_{ij} + \varepsilon_{ij}, \quad j = 1, \cdots, n_i, \quad i = 1, \cdots, m,$$

where the errors $\{\varepsilon_{ij}\}$ is a simple random sample from $N(0, \sigma_0^2)$ and σ_0^2 is assumed a known positive constant.

Corrected log-likelihood function

Let $\eta_0(t) = Ee^{t\varepsilon_{ij}} = e^{\sigma_0^2 t^2}$. The $l_2(\phi, \omega)$ is corrected as

$$
\begin{aligned}
l_{c2}(\phi, \omega) &= \sum_{i=1}^{m} \sum_{j=1}^{n_i} \Big\{ \delta_{ij1}(1-\delta_{ij2})[\ln(\lambda_{01}(s_{ij1})) + \hat{Z}_{ij}^T \beta_1] \\
&\quad + \delta_{ij1}\delta_{ij2}[\ln(\lambda_{01}(s_{ij1})) + \ln(\lambda_{03}(s_{ij2})) + \hat{Z}_{ij}^T(\beta_1 + \beta_3)] \\
&\quad + (1-\delta_{ij1})\delta_{ij2}[\ln(\lambda_{02}(s_{ij2})) + \hat{Z}_{ij}^T \beta_2] - \hat{r}(s_{ij1}, s_{ij2}, \hat{Z}_{ij}) \Big\},
\end{aligned}
$$

where

$$
\begin{aligned}
&\hat{r}(s_{ij1}, s_{ij2}, \hat{Z}_{ij}) \\
&= \eta_0^{-1}(\beta_{1x})\omega_{i1}\Lambda_{01}(s_{ij1})e^{\hat{Z}_{ij}^T\beta_1} + \eta_0^{-1}(\beta_{2x})\omega_{i2}\Lambda_{02}(s_{ij2})e^{\hat{Z}_{ij}^T\beta_2} \\
&+ \eta_0^{-1}(\beta_{3x})\omega_{i3}\left[\Lambda_{03}(s_{ij2}) - \Lambda_{03}(s_{ij1})\right] e^{\hat{Z}_{ij}^T\beta_3}.
\end{aligned}
$$

Corrected maximum likelihood estimators (CMLE)

The corrected log-likelihood

$$l_c(\boldsymbol{\phi}, \boldsymbol{\theta}, \boldsymbol{\omega}) = l_1(\theta_1, \omega_1) + l_1(\theta_2, \omega_2) + l_1(\theta_3, \omega_3) + l_{c2}(\boldsymbol{\phi}, \boldsymbol{\omega}). \quad (4)$$

Given the shared frailties $\{\omega_{ik}, i = 1, \cdots, m; k = 1, 2, 3\}$, find the corrected MLE of θ_k and ϕ

MLE of θ_k given ω_k

$$\widehat{\theta}_k = \underset{\theta_k}{\operatorname{argmax}}\, l_1(\theta_k, \omega_k), k = 1, 2, 3, \quad (5)$$

CMLE of ϕ given ω

$$\widehat{\phi} = \underset{\phi}{\operatorname{argmax}}\, l_{c2}(\phi, \omega). \quad (6)$$

Corrected maximum likelihood estimators (CMLE)

The corrected log-likelihood

$$l_c(\boldsymbol{\phi}, \boldsymbol{\theta}, \boldsymbol{\omega}) = l_1(\theta_1, \omega_1) + l_1(\theta_2, \omega_2) + l_1(\theta_3, \omega_3) + l_{c2}(\boldsymbol{\phi}, \boldsymbol{\omega}). \quad (4)$$

Given the shared frailties $\{\omega_{ik}, i = 1, \cdots, m; k = 1, 2, 3\}$, find the corrected MLE of θ_k and ϕ

MLE of θ_k given ω_k

$$\widehat{\theta}_k = \underset{\theta_k}{\operatorname{argmax}}\, l_1(\theta_k, \omega_k), k = 1, 2, 3, \quad (5)$$

CMLE of ϕ given ω

$$\widehat{\boldsymbol{\phi}} = \underset{\boldsymbol{\phi}}{\operatorname{argmax}}\, l_{c2}(\boldsymbol{\phi}, \boldsymbol{\omega}). \quad (6)$$

Bayes estimators

The posterior distribution of ω_{ik} is

$$\pi(\omega_{ik}|\alpha_k, \gamma_k, \beta_k, \theta_k) \propto \omega_{ik}{}^{A_{ik}-1} e^{-\omega_{ik} B_{ik}}, \tag{7}$$

where

$$A_{ik} = \frac{1}{\theta_k} + D_{ik}, \quad B_{ik} = \frac{1}{\theta_k} + \frac{1}{\eta_0(\beta_{kx})} \sum_{j=1}^{n_i} \gamma_k s_{ijk}^{\alpha_k} e^{\hat{Z}_{ij}^T \beta_k}.$$

Bayes estimators of the shared frailties

$$\widehat{\omega}_{ik} = E(\omega_{ik}|\alpha_k, \gamma_k, \beta_k, \theta_k) = \frac{A_{ik}}{B_{ik}}, \quad i = 1, \cdots, m, k = 1, 2, 3. \tag{8}$$

EM algorithm: E-step

$$E_{\omega_k} l_1(\theta_k, \omega_k) = \sum_{i=1}^{m} \Bigg\{ \left(\frac{1}{\theta_k} + D_{ik} - 1 \right) (\psi(A_{ik}) - \ln(B_{ik})) - \frac{A_{ik}}{B_{ik}\theta_k} - \ln\Gamma\left(\frac{1}{\theta_k}\right) - \frac{1}{\theta_k}\ln\theta_k \Bigg\}, \quad (9)$$

where $\psi(x) = \frac{d}{dx}\ln(\Gamma(x)) = \frac{\Gamma'(x)}{\Gamma(x)}$.

$$E_{\omega} l_{c2}(\boldsymbol{\phi}, \boldsymbol{\omega}) = \sum_{i=1}^{m}\sum_{j=1}^{n_i} \Big\{ \delta_{ij1}(1-\delta_{ij2}) \left[\ln(\lambda_{01}(s_{ij1})) + \hat{Z}_{ij}^T \beta_1\right] + \delta_{ij1}\delta_{ij2}\left[\ln(\lambda_{01}(s_{ij1})) + \ln(\lambda_{03}(s_{ij2})) + \hat{Z}_{ij}^T(\beta_1 + \beta_3)\right] + (1-\delta_{ij1})\delta_{ij2}\left[\ln(\lambda_{02}(s_{ij2})) + \hat{Z}_{ij}^T\beta_2\right] - r^*(s_{ij1}, s_{ij2}, \hat{Z}_{ij}) \Big\}, \quad (10)$$

where $r^*(s_{ij1}, s_{ij2}, \hat{Z}_{ij}) = E_{\omega}\hat{r}(s_{ij1}, s_{ij2}, \hat{Z}_{ij})$.

EM algorithm: M-step

Step 1. Given initial values of $\{\omega_{ik}\}$, obtain the initial estimates of $\boldsymbol{\theta}$ and ϕ by (5) and (6).

Step 2. Calculate A_{ik} and B_{ik}, renew the estimate $\hat{\omega}_{ik}$ by (8).

Step 3. Renew the estimates $\boldsymbol{\theta}$ and ϕ by maximizing (9) and (10).

Step 4. Repeat Steps 2-3 till the distance between consecutive iterative estimates is smaller than 10^{-4}.

Simulation Setting

- true parameter values: $(\theta_1, \theta_2, \theta_3) = (0.5, 0.5, 1)$, $(\alpha_1, \alpha_2, \alpha_3) = (0.8, 1.1, 0.9)$, $(\gamma_1, \gamma_2, \gamma_3) = (0.05, 0.01, 0.01)$, $\beta_1 = (1, 1)^T$, $\beta_2 = (1, 1)^T$ and $\beta_3 = (1, -1)^T$.
- $\{x_{ij}\}$ and $\{v_{ij}\}$ are independent simple random samples from $N(0, 1)$
- Messure errors $\{\epsilon_{ij}\}$ is a simple random sample from $N(0,\ \sigma_0^2)$
- $\sigma_0^2 = 0, 0.1, 0.25, 0.5$
- $m = 10$
- $n_1 = n_2 = \cdots = n_m = 50,\ 100$
- 500 replicates

Sample data generation

- Generate a sample $\{\omega_{ik}, i = 1, \cdots, m,\}$ from $\Gamma(1/\theta_k, 1/\theta_k)$ for each $k = 1, 2, 3$.
- Generate covariate samples $\{x_{ij}\}$ and $\{v_{ij}\}$ from $N(0, 1)$, and denote $Z_{ij}^T = (x_{ij}, v_{ij})$, $j = 1, \cdots, n_1$, $i = 1, \cdots, m$. If measurement error is present, we further generate a sample of ε_{ij} from $N(0, \sigma_0^2)$ and calculate $w_{ij} = x_{ij} + \varepsilon_{ij}$ to obtain $\widehat{Z}_{ij} = (w_{ij}, v_{ij})^T$.
- Generate the non-terminal event time T_{ij1} satisfying (1)and the terminal event time T_{ij2} satisfying (2).
- Consider two fixed censoring times: $C_{ij} = 365$ and $C_{ij} = \infty$.

Sample data generation

Table 1: Four combinations

Relation	s_{ij1}	s_{ij2}	δ_{ij1}	δ_{ij2}
$T_{ij1} < T_{ij2} \leq C_{ij}$	T_{ij1}	T_{ij2}	1	1
$T_{ij1} \leq C_{ij} < T_{ij2}$	T_{ij1}	C_{ij}	1	0
$T_{ij2} \leq min(C_{ij}, T_{ij1})$	T_{ij2}	T_{ij2}	0	1
$C_{ij} < T_{ij2} \leq T_{ij1}$	C_{ij}	C_{ij}	0	0

Three estimation procedures

- MBEM: maximum likelihood and Bayes estimation with EM algorithm
- CMBEM: corrected maximum likelihood and Bayes estimation with EM algorithm
- BMCMC: Bayes estimation with MCMC algorithm (Lee et al. (2016))

Simulation results

Table 1: Results for data with no measurement error

Method		$\hat{\beta}_{1x}$	$\hat{\beta}_{1v}$	$\hat{\beta}_{2x}$	$\hat{\beta}_{2v}$	$\hat{\beta}_{3x}$	$\hat{\beta}_{3v}$
Noncensored and $n = 500$							
MBEM	BIAS	0.013	0.008	0.018	0.011	0.025	-0.059
	MSE	0.006	0.005	0.010	0.009	0.007	0.009
BMCMC	BIAS	-0.049	-0.052	0.021	0.033	-0.033	-0.034
	MSE	0.019	0.020	0.031	0.029	0.027	0.021
Noncensored and $n = 1000$							
MBEM	BIAS	0.010	0.008	0.004	0.003	0.003	-0.046
	MSE	0.003	0.003	0.004	0.004	0.004	0.005
BMCMC	BIAS	-0.047	-0.048	0.037	0.032	-0.018	-0.043
	MSE	0.016	0.015	0.021	0.021	0.018	0.015
censored and $n = 500$							
MBEM	BIAS	0.015	0.016	0.021	0.026	0.016	-0.066
	MSE	0.006	0.006	0.011	0.010	0.012	0.014
BMCMC	BIAS	-0.082	-0.065	0.001	0.014	-0.076	0.066
	MSE	0.022	0.020	0.024	0.025	0.039	0.029
censored and $n = 1000$							
MBEM	BIAS	0.008	0.008	0.015	0.012	0.008	-0.059
	MSE	0.003	0.003	0.005	0.006	0.007	0.008
BMCMC	BIAS	-0.071	-0.067	0.013	0.017	-0.089	0.071
	MSE	0.016	0.016	0.019	0.017	0.033	0.023

Simulation results

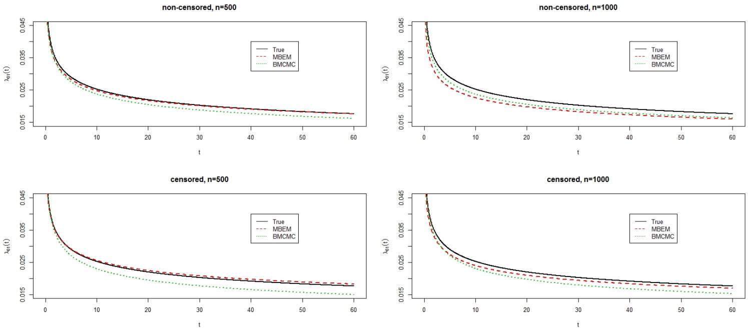

Figure 2: $\lambda_{01}(t)$ for data with no measurement error

Simulation results

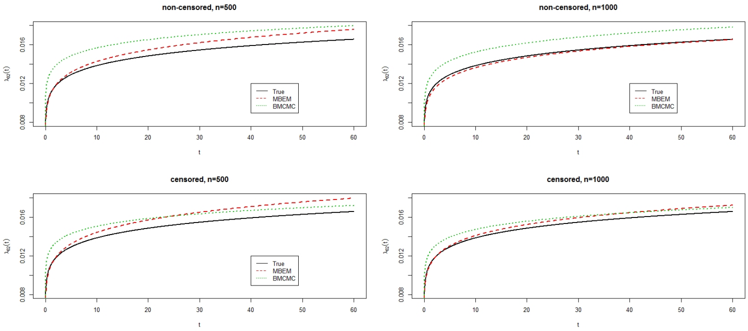

Figure 3: $\lambda_{02}(t)$ for data with no measurement error

Simulation results

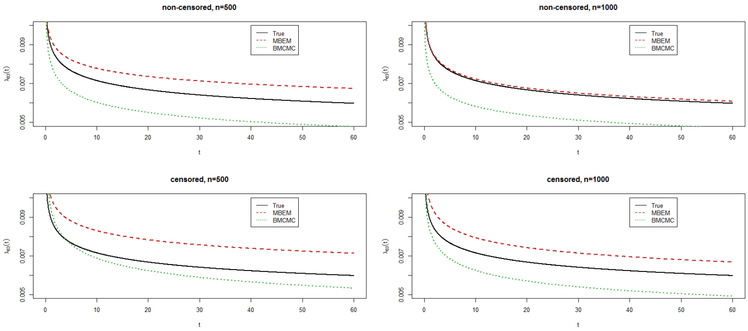

Figure 4: $\lambda_{03}(t)$ for data with no measurement error

Simulation results

Table 2: Estimation for noncensored data with measurement error (n=500)

Method		$\hat{\beta}_{1x}$	$\hat{\beta}_{1v}$	$\hat{\beta}_{2x}$	$\hat{\beta}_{2v}$	$\hat{\beta}_{3x}$	$\hat{\beta}_{3v}$
$\sigma_0 = 0.1$							
CMBEM	BIAS	0.026	0.021	0.017	0.016	0.022	-0.058
	MSE	0.007	0.007	0.010	0.011	0.008	0.009
MBEM	BIAS	-0.003	0.005	0.004	0.005	0.009	-0.055
	MSE	0.006	0.005	0.010	0.008	0.007	0.008
BMCMC	BIAS	-0.052	-0.041	0.044	0.051	-0.048	-0.028
	MSE	0.018	0.020	0.029	0.032	0.028	0.021
$\sigma_0 = 0.25$							
CMBEM	BIAS	0.019	0.019	0.031	0.025	0.038	-0.063
	MSE	0.008	0.007	0.013	0.011	0.012	0.010
MBEM	BIAS	-0.072	-0.017	-0.086	-0.014	-0.076	-0.037
	MSE	0.010	0.006	0.018	0.010	0.013	0.007
BMCMC	BIAS	-0.054	-0.048	0.042	0.048	-0.039	-0.020
	MSE	0.021	0.021	0.029	0.033	0.028	0.021
$\sigma_0 = 0.5$							
CMBEM	BIAS	0.044	0.031	0.068	0.042	0.084	-0.075
	MSE	0.015	0.009	0.032	0.018	0.030	0.014
MBEM	BIAS	-0.257	-0.072	-0.284	-0.100	-0.287	0.013
	MSE	0.071	0.011	0.087	0.020	0.088	0.006
BMCMC	BIAS	-0.051	-0.052	0.025	0.023	-0.038	-0.036
	MSE	0.019	0.022	0.024	0.026	0.029	0.025

Simulation results

Table 3: Estimation for noncensored data with measurement error (n=1000)

Method		$\hat{\beta}_{1x}$	$\hat{\beta}_{1v}$	$\hat{\beta}_{2x}$	$\hat{\beta}_{2v}$	$\hat{\beta}_{3x}$	$\hat{\beta}_{3v}$
				$\sigma_0 = 0.1$			
CMBEM	BIAS	0.007	0.007	0.008	0.008	0.005	-0.043
	MSE	0.003	0.003	0.005	0.005	0.003	0.004
MBEM	BIAS	-0.009	-0.001	-0.015	-0.001	-0.013	-0.042
	MSE	0.003	0.003	0.005	0.004	0.003	0.005
BMCMC	BIAS	-0.035	-0.037	0.033	0.023	-0.013	-0.046
	MSE	0.013	0.012	0.019	0.018	0.017	0.014
				$\sigma_0 = 0.25$			
CMBEM	BIAS	0.012	0.007	0.011	0.012	0.017	-0.055
	MSE	0.004	0.003	0.006	0.006	0.004	0.006
MBEM	BIAS	-0.077	-0.023	-0.090	-0.033	-0.093	-0.026
	MSE	0.008	0.003	0.012	0.006	0.012	0.004
BMCMC	BIAS	-0.048	-0.043	0.021	0.023	-0.031	-0.027
	MSE	0.015	0.016	0.018	0.020	0.020	0.015
				$\sigma_0 = 0.5$			
CMBEM	BIAS	0.024	0.013	0.033	0.022	0.034	-0.056
	MSE	0.007	0.004	0.013	0.008	0.010	0.007
MBEM	BIAS	-0.263	-0.084	-0.294	-0.114	-0.301	0.021
	MSE	0.071	0.010	0.090	0.017	0.093	0.004
BMCMC	BIAS	-0.055	-0.053	0.018	0.016	-0.016	-0.048
	MSE	0.014	0.015	0.018	0.021	0.014	0.016

Simulation results

Table 4: Estimation for censored data with measurement error (n=500)

Method		$\hat{\beta}_{1x}$	$\hat{\beta}_{1v}$	$\hat{\beta}_{2x}$	$\hat{\beta}_{2v}$	$\hat{\beta}_{3x}$	$\hat{\beta}_{3v}$
$\sigma_0 = 0.1$							
CMBEM	BIAS	0.016	0.018	0.023	0.027	0.024	-0.070
	MSE	0.006	0.007	0.011	0.011	0.013	0.015
MBEM	BIAS	0.002	0.016	-0.006	0.012	0.000	-0.068
	MSE	0.006	0.006	0.010	0.011	0.012	0.015
BMCMC	BIAS	-0.069	-0.060	0.007	0.021	-0.106	0.062
	MSE	0.021	0.019	0.025	0.027	0.052	0.031
$\sigma_0 = 0.25$							
CMBEM	BIAS	0.018	0.022	0.028	0.030	0.036	-0.068
	MSE	0.007	0.006	0.013	0.012	0.018	0.015
MBEM	BIAS	-0.071	-0.009	-0.076	-0.030	-0.077	-0.055
	MSE	0.010	0.006	0.015	0.011	0.018	0.013
BMCMC	BIAS	-0.082	-0.074	0.018	0.030	-0.092	0.070
	MSE	0.022	0.021	0.027	0.025	0.042	0.031
$\sigma_0 = 0.5$							
CMBEM	BIAS	0.047	0.029	0.080	0.050	0.125	-0.096
	MSE	0.017	0.010	0.038	0.021	0.065	0.022
MBEM	BIAS	-0.256	-0.074	-0.281	-0.095	-0.287	-0.038
	MSE	0.070	0.011	0.087	0.019	0.091	0.011
BMCMC	BIAS	-0.074	-0.073	0.012	0.026	-0.109	0.080
	MSE	0.021	0.020	0.024	0.027	0.043	0.031

Simulation results

Table 5: Results for censored data with measurement error (n=1000)

Method		$\hat{\beta}_{1x}$	$\hat{\beta}_{1v}$	$\hat{\beta}_{2x}$	$\hat{\beta}_{2v}$	$\hat{\beta}_{3x}$	$\hat{\beta}_{3v}$
$\sigma_0 = 0.1$							
CMBEM	BIAS	0.007	0.006	0.011	0.008	0.013	-0.057
	MSE	0.003	0.003	0.005	0.005	0.007	0.008
MBEM	BIAS	-0.008	0.003	-0.005	0.006	-0.009	-0.052
	MSE	0.003	0.003	0.004	0.005	0.006	0.008
BMCMC	BIAS	-0.077	-0.065	0.005	0.022	-0.093	0.070
	MSE	0.016	0.014	0.018	0.018	0.035	0.023
$\sigma_0 = 0.25$							
CMBEM	BIAS	0.010	0.007	0.022	0.017	0.016	-0.060
	MSE	0.004	0.003	0.006	0.005	0.008	0.009
MBEM	BIAS	-0.077	-0.021	-0.087	-0.030	-0.089	-0.046
	MSE	0.009	0.003	0.012	0.006	0.013	0.006
BMCMC	BIAS	-0.072	-0.063	0.001	0.017	-0.090	0.064
	MSE	0.015	0.014	0.016	0.016	0.030	0.020
$\sigma_0 = 0.5$							
CMBEM	BIAS	0.023	0.017	0.022	0.016	0.062	-0.071
	MSE	0.006	0.004	0.010	0.007	0.021	0.011
MBEM	BIAS	-0.267	-0.074	-0.286	-0.104	-0.295	-0.025
	MSE	0.073	0.008	0.085	0.015	0.091	0.005
BMCMC	BIAS	-0.080	-0.072	0.011	0.021	-0.096	0.079
	MSE	0.017	0.017	0.018	0.016	0.034	0.024

Simulation results

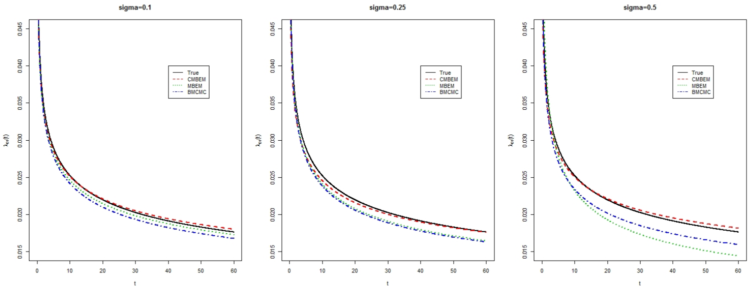

Figure 5: $\lambda_{01}(t)$ for noncensored data with measurement error and $n = 500$

Simulation results

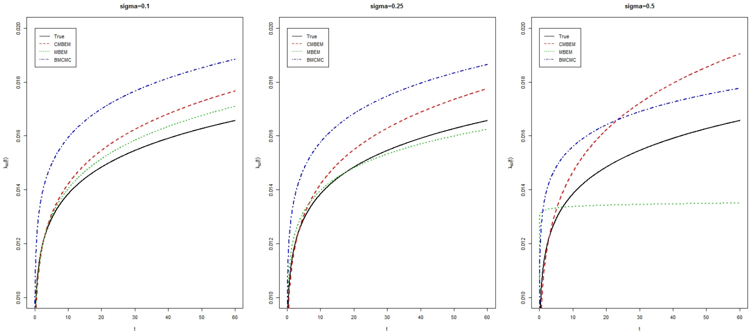

Figure 6: $\lambda_{02}(t)$ for noncensored data with measurement error and $n = 500$

Simulation results

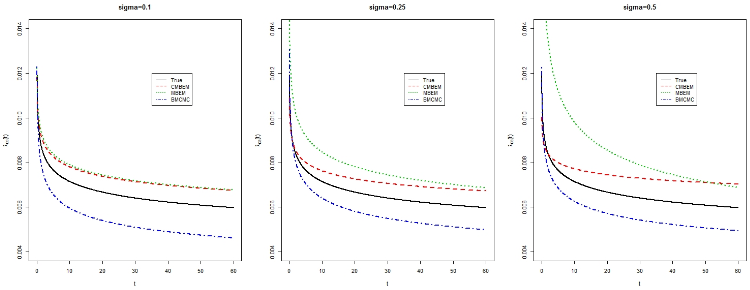

Figure 7: $\lambda_{03}(t)$ for noncensored data with measurement error and $n = 500$

Simulation results

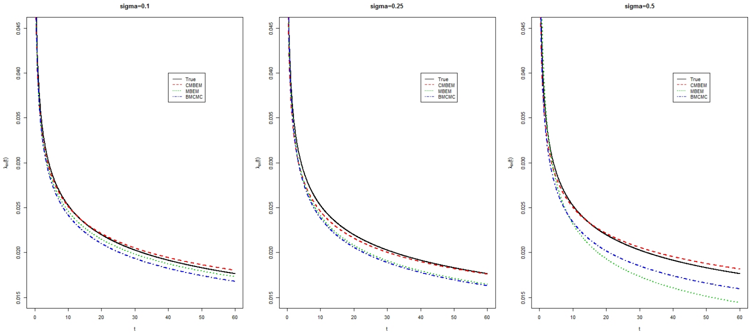

Figure 8: $\lambda_{01}(t)$ for noncensored data with measurement error and $n = 1000$

Simulation results

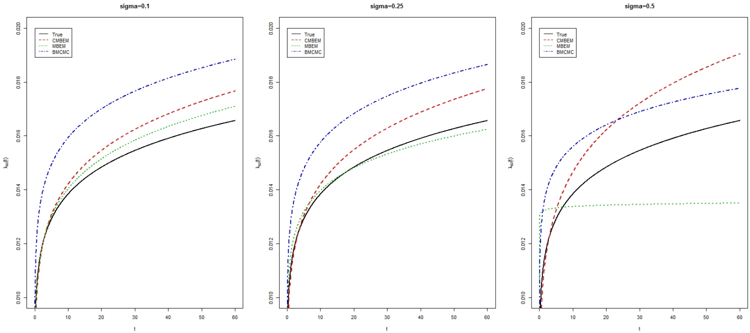

Figure 9: $\lambda_{02}(t)$ for noncensored data with measurement error and $n = 1000$

Simulation results

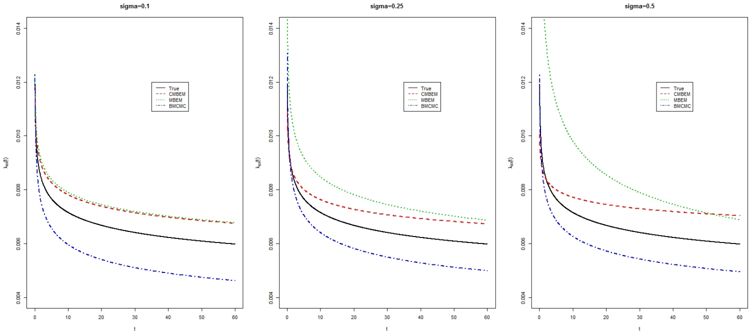

Figure 10: $\lambda_{03}(t)$ for noncensored data with measurement error and $n = 1000$

Simulation results

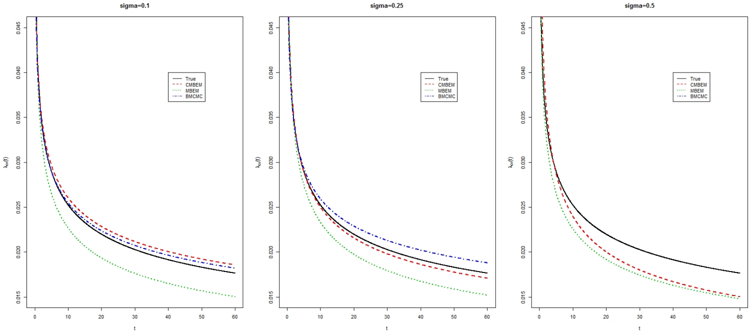

Figure 11: $\lambda_{01}(t)$ for censored data with measurement error and $n = 500$

Simulation results

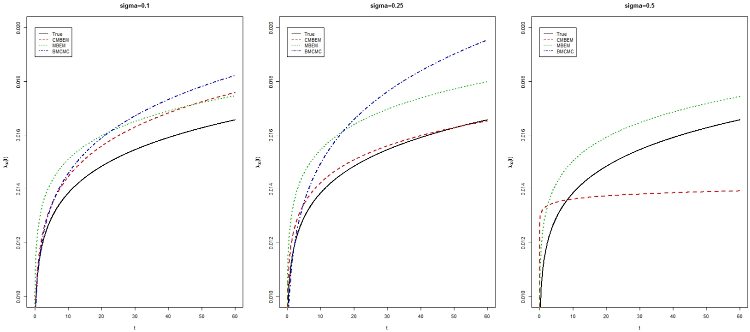

Figure 12: $\lambda_{02}(t)$ for censored data with measurement error and $n = 500$

Simulation results

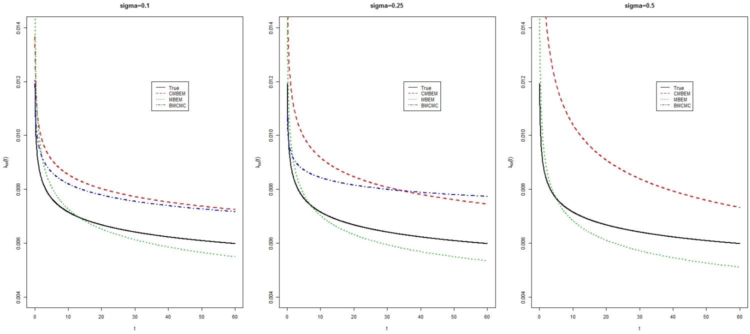

Figure 13: $\lambda_{03}(t)$ for censored data with measurement error and $n = 500$

Simulation results

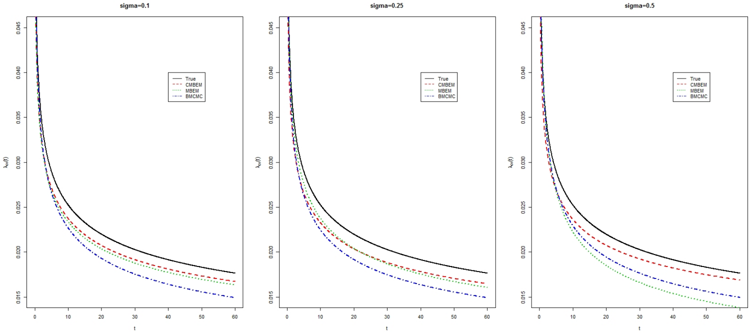

Figure 14: $\lambda_{01}(t)$ for censored data with measurement error and $n = 1000$

Simulation results

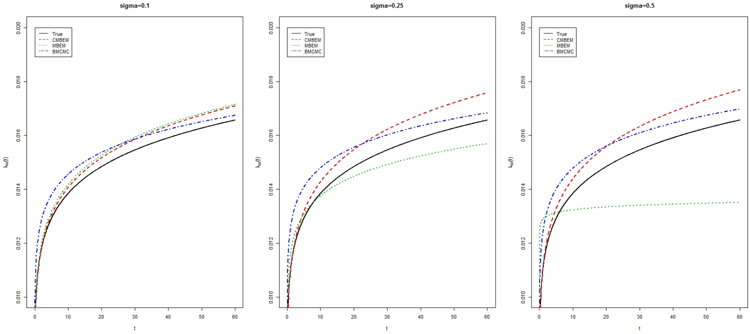

Figure 15: $\lambda_{02}(t)$ for censored data with measurement error and $n = 1000$

Simulation results

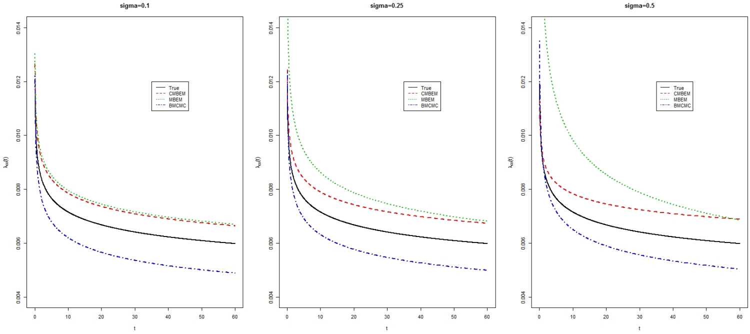

Figure 16: $\lambda_{03}(t)$ for censored data with measurement error and $n = 1000$

Simulation results

- For small variation in measurement error (e.g. $\sigma_0 = 0.1$), both CMBEM and MBEM perform very well with very small absolute biases and MSEs no matter the data is censored or not, while BMCMC is relatively worse. For example, from Table 3, the relative efficiencies of BMCMC to CMBEM and BMCMC to MBEM for $\hat{\beta}_{2x}$ are both 3.8, and for $\hat{\beta}_{2v}$ are 3.6 and 4.5.
- As the error variance increases, CMBEM becomes more efficient in estimating $\beta_{kx}, k = 1, 2, 3$. However, MBEM gradually shows the lost of efficiency. For example, from Table 2, the relative efficiencies of MBEM to CMBEM are 4.73, 2.72 and 2.93. Furthermore, the absolute biases of the estimators $\hat{\beta}_{kx}$ by MBEM are much larger than those by CMBEM. Regarding to the performance of the estimators for β_{kv}, Tables 2-5 show that CMBEM still remain small absolute biases and MSEs, sometimes even smaller than MBEM.

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Simulation results

- BMCMC seems not very sensitive to the increase of the error variance. Notice that no matter the error variance is small or large, most of the results by CMBEM are better than those by BMCMC.
- With the increase of sample size, the estimators by CMBEM becomes more effective, but those by MBEM and BMCMC do not improve as much.
- Figures 4-7 show that CMBEM performs more competitively than MBEM and BMCMC in most simulation settings. Among the three estimated baseline hazard functions, all three procedures perform the best for $\widehat{\lambda}_{01}(t)$, followed by $\widehat{\lambda}_{02}(t)$ and $\widehat{\lambda}_{03}(t)$. It is also notice that, as the sample size increases, both $\widehat{\lambda}_{02}(t)$ and $\widehat{\lambda}_{03}(t)$ are significantly improved by CMBEM and comparable to BMCMC, while MBEM is not robust, typically when $\sigma_0 = 0.5$.

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MGUS Data

- MGUS: monoclonal gammopathy of undertermined significance data (Kyle et al. 2018), available in R survival package
- 1384 observations with 10 variables
- Three clusters: homoglobin low, normal, high
- Covariate with measurement error: the size of the monoclonal serum spike (*mspike*)
- Accurately observed covariate: *age*
- Non-terminal event: plasma cell malignancy (*PCM)*
- *Terminal event: death*

Results for MGUS Data

Table 2: The covariate effects estimated for MGUS

Method		$\hat{\beta}_{1x}$	$\hat{\beta}_{1v}$	$\hat{\beta}_{2x}$	$\hat{\beta}_{2v}$	$\hat{\beta}_{3x}$	$\hat{\beta}_{3v}$
CMBEM	Estimate	0.8921	0.0139	0.0321	0.0544	0.0323	0.0541
	SE	0.1716	0.0066	0.0545	0.0042	0.0546	0.0043

Results for MGUS Data

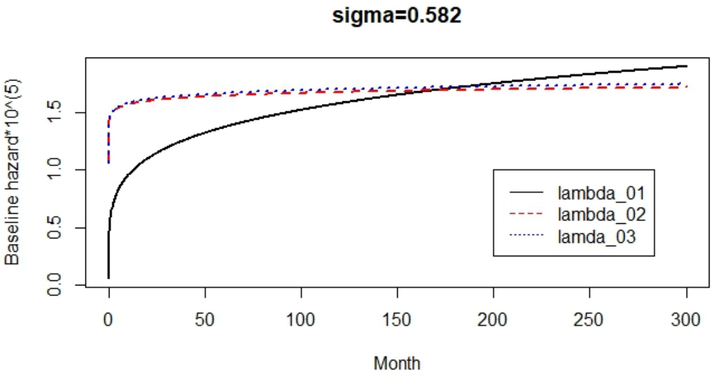

Figure 17: The baseline hazard estimated for MGUS

Results for MGUS Data

- *age* is significant for all three baseline hazards, while *mspike* is significant only for the hazard from healthy to *PCM*
- the risks from PCM to death and direct to death are about the same, while the PCM risk is much smaller than the previous two transitions within 15 years.

Conclusion

- a shared frailty semi-competing model with measurement errors in covariates for cluster data
- propose a corrected maximum likelihood estimation for the covariate effects and Bayes estimation for the shared frailties
- EM algorithm is utilized for numerical optimization.
- simulation study shows that the proposed method works better than the Bayes estimation with MCMC algorithm in Lee et al. (2016).

Discussion

- Interval censored semi-competing risks data?
- Different baseline hazard functions or frailty distributions?
- Theoretically properties?

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Thank you !