Frailty model approach for the clustered interval-censored data with informative censoring

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August 9, 2015

Outline

- Introduction: interval-censored data, informative censoring
- Model specification
- Likelihood construction
- Parameter estimation procedure
- Simulations
- Illustrative real example
- Concluding remarks

What is interval-censored survival data?

- In clinical trials with periodic follow-up, each subject is observed through several examinations. However, a subject may skip one or more pre-appointed visits and then return with the failure already occurred. In these situations, the true event time of interest lies in an interval of the form
$$(L, R],$$
where L is the last time seen without disease, and R is the first time the subject appeared with disease
- So, a subject with $R = \infty$ is right-censored at L. On the contrary, a subject with $L = 0$ is left-censored at R

In what situations may informative censorung occur?

- Most existing methodologies with regression analysis were developed under the assumption of 'non-informative censoring' mechanism (Zhang et al., 2005). The failure time and visiting times of subjects are frequently assumed to be independent
- However, in some situations, this assumption does not hold. For instance, when failure occurs, a patient could experience some symptoms prior to or together with failure. This makes the patient tend to visit the doctor earlier than scheduled (Zhang et al., 2007; Wang et al., 2010)

How do we deal with informative censorung?

- However, it is virtually impossible to observe both the failure time and the censoring times simultaneously. Subsequently, it is not possible to test the dependence or independence assumption of the censoring mechanism
- One remedy to circumvent these difficulties is to impose extra assumptions or modelling

Review on related works

- Huang & Wolfe (2002) have dealt with the clustered right-censored data assuming the dependence between the failure time and the censoring time
- Zhang et al. (2005, 2007) and Wang et al. (2010) have utilized frailty models to explain a dependence structure between the failure time and the censoring times for the interval-censored data with informative censoring
- Kim & Kim (2012) proposed an estimating procedure using the Cox PH model with a shared frailty for the clustered interval-censored data under the non-informative censoring assumption
- In this talk, we extend the arguments of Huang & Wolfe (2002) and Kim & KIm (2014) to the clustered interval-censored data in the presence of informative censoring

Notation

- T_{ij} : the failure time for the j^{th} subject within the i^{th} cluster $(i = 1, \ldots, n;\ j = 1, \ldots, n_i)$
- U_{ij}, V_{ij} : two observation times with $U_{ij} \leq V_{ij}$
  - Although we cannot observe the exact failure time T_{ij}, it is only less than or equal to U_{ij}, between U_{ij} and V_{ij}, or greater than V_{ij}
  - W_{ij} : the gap time defined as $W_{ij} = V_{ij} - U_{ij}$ if V_{ij} is available; otherwise $W_{ij} = \infty$
- $\delta_{1ij} = I(T_{ij} \leq U_{ij})$ and $\delta_{2ij} = I(U_{ij} < T_{ij} \leq V_{ij})$
- $\mathbf{x}_{ij}$: a $p \times 1$ vector of covariates
- So, the observed data for the j^{th} subject within the i^{th} cluster have the form of

$$\mathbf{o}_{ij} = (U_{ij}, V_{ij}, \delta_{1ij}, \delta_{2ij}, \mathbf{x}'_{ij})'.$$

Subsequently, $\mathbf{o} = (\mathbf{o}'_1, \ldots, \mathbf{o}'_n)'$, where $\mathbf{o}_i = (\mathbf{o}'_{i1}, \ldots, \mathbf{o}'_{in_i})'$

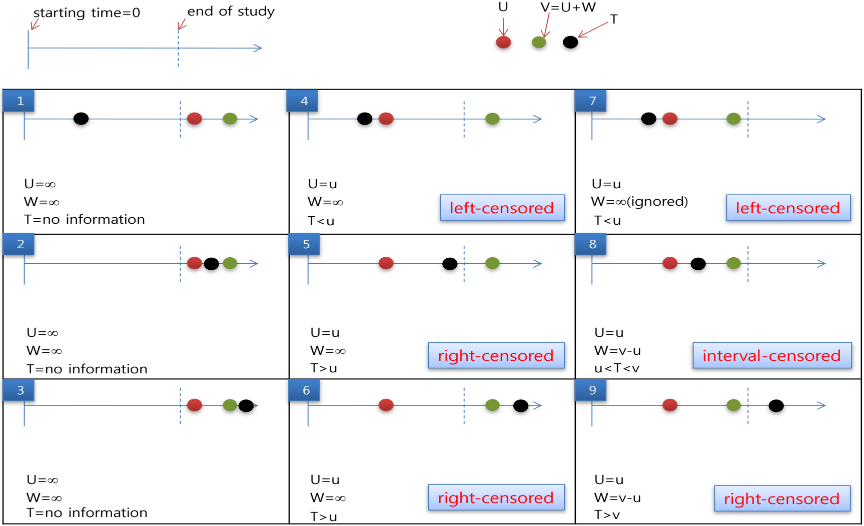
Proposed models

- Assume that T_{ij}'s within the ith cluster share an unobservable frailty r_i and conditional on $\mathbf{x}_{ij}$ and r_i, they are independent
  - r_i : a normal frailty with a mean of 0 and variance θ
- To incorporate the informative censoring, consider Cox PH models with a shared frailty for T_{ij}, U_{ij}, and W_{ij}, respectively:

$$\begin{aligned} \lambda_t(t|\mathbf{x}_{ij}, r_i) &= \lambda_{0t}(t)\exp\{\boldsymbol{\beta}_t'\mathbf{x}_{ij} + r_i\}, & (1) \\ \lambda_u(t|\mathbf{x}_{ij}, r_i) &= \lambda_{0u}(t)\exp\{\boldsymbol{\beta}_u'\mathbf{x}_{ij} + \alpha_u r_i\}, & (2) \\ \lambda_w(t|\mathbf{x}_{ij}, r_i) &= \lambda_{0w}(t)\exp\{\boldsymbol{\beta}_w'\mathbf{x}_{ij} + \alpha_w r_i\}, & (3) \end{aligned}$$

  where $\boldsymbol{\beta}_t$, $\boldsymbol{\beta}_u$, and $\boldsymbol{\beta}_w$ are the regression coefficients, $\lambda_{0t}(\cdot)$, $\lambda_{0u}(\cdot)$, and $\lambda_{0w}(\cdot)$ are the baseline hazard functions for T_{ij}, U_{ij}, and W_{ij}, respectively, and α_u and α_w are unknown parameters representing the degree of dependency between T_{ij} and U_{ij} and between T_{ij} and W_{ij}, respectively
- Assume that T_{ij}, U_{ij}, and W_{ij} are conditionally independent given $\mathbf{x}_{ij}$ and r_i

Schematic diagram



Likelihood construction

- Given $\mathbf{x}_{ij}$ and r_i, the likelihood function L_{ij} for the j^{th} subject within the i^{th} cluster can be expressed as follows:
  - when T_{ij} is left-censored at u_{ij} and W_{ij} is right-censored at 0,

$$L_{ij} = P(U_{ij} = u_{ij}|\mathbf{x}_{ij}, r_i)P(T_{ij} \in (0, u_{ij}]|\mathbf{x}_{ij}, r_i);$$

  - when T_{ij} is interval-censored in $(u_{ij}, v_{ij}]$ but W_{ij} is exactly observed as $(v_{ij} - u_{ij})$,

$$L_{ij} = P(U_{ij} = u_{ij}|\mathbf{x}_{ij}, r_i)P(T_{ij} \in (u_{ij}, v_{ij}]|\mathbf{x}_{ij}, r_i)P(W_{ij} = v_{ij} - u_{ij}|\mathbf{x}_{ij}, r_i);$$

  - when both T_{ij} and W_{ij} are right-censored at u_{ij} and 0, respectively,

$$L_{ij} = P(U_{ij} = u_{ij}|\mathbf{x}_{ij}, r_i)P(T_{ij} \in (u_{ij}, \infty)|\mathbf{x}_{ij}, r_i),$$

  - when T_{ij} is right-censored at v_{ij} but W_{ij} is exactly observed as $(v_{ij} - u_{ij})$,

$$L_{ij} = P(U_{ij} = u_{ij}|\mathbf{x}_{ij}, r_i)P(T_{ij} \in (v_{ij}, \infty)|\mathbf{x}_{ij}, r_i)P(W_{ij} = v_{ij} - u_{ij}|\mathbf{x}_{ij}, r_i)$$

Likelihood construction

- Thus, given $\mathbf{x}_{ij}$ and r_i, the conditional likelihood for the j^{th} subject within the i^{th} cluster can be written as

$$\begin{aligned} L_{ij} &= P(T_{ij} \in (0, u_{ij}]|\mathbf{x}_{ij}, r_i)^{\delta_{1ij}} P(T_{ij} \in (u_{ij}, v_{ij}]|\mathbf{x}_{ij}, r_i)^{\delta_{2ij}} \\ &\times P(T_{ij} \in (u_{ij}, \infty)|\mathbf{x}_{ij}, r_i)^{\delta_{3ij}(1-\psi_{ij})} P(T_{ij} \in (v_{ij}, \infty)|\mathbf{x}_{ij}, r_i)^{\delta_{3ij}\psi_{ij}} \\ &\times P(U_{ij} = u_{ij}|\mathbf{x}_{ij}, r_i) P(W_{ij} = v_{ij} - u_{ij}|\mathbf{x}_{ij}, r_i)^{\psi_{ij}}, \end{aligned} \tag{4}$$

where $\delta_{1i} = 1 - \delta_{1i} - \delta_{2i}$ and $\psi_{ij} = I(W_{ij} < \infty)$;

Equivalence class

- Define $(l_{ij}, r_{ij}]$ as

$$(l_{ij}, r_{ij}] = \begin{cases} (0, u_{ij}], & \delta_{1ij} = 1, \\ (u_{ij}, v_{ij}], & \delta_{2ij} = 1, \\ (u_{ij}, \infty), & \delta_{3ij} = 1 \text{ and } \psi_{ij} = 0, \\ (v_{ij}, \infty), & \delta_{3ij} = 1 \text{ and } \psi_{ij} = 1 \end{cases}$$

- Consider an equivalence class of points,

$$0 = s_0 < s_1 < \cdots < s_m < s_{m+1} = \infty,$$

of the set $\mathcal{S} = \{(l_{ij}, r_{ij}]; i = 1, \ldots, n; j = 1, \ldots, n_i\}$

Parameterization

- Define

$$\Lambda_{0t}(s_k) = \sum_{q=0}^{k} \exp\{\gamma_q\} \text{ for } k = 0, \ldots, m+1,$$

where $\gamma_0 = -\infty$ and $\gamma_{m+1} = \infty$, and also for $k = 1, \ldots, m+1$,

$$\begin{aligned} \phi_{ijk} &= I((s_{k-1}, s_k] \in (l_{ij}, r_{ij}]), \\ S_t(s_k|\mathbf{x}_{ij}, r_i) &= \exp\{-\Lambda_{0t}(s_k)\exp(\beta_t'\mathbf{x}_{ij} + r_i)\}, \end{aligned}$$

and

$$g_{ijk} = S_t(s_{k-1}|\mathbf{x}_{ij}, r_i) - S_t(s_k|\mathbf{x}_{ij}, r_i)$$

- So,

$$P(T_{ij} \in (l_{ij}, r_{ij}]|\mathbf{x}_{ij}, r_i) = \sum_{k=1}^{m+1} \phi_{ijk} g_{ijk}$$

Parameterization

- Let $0 < \xi_1 < \cdots < \xi_a < \infty$ and $0 < \zeta_1 < \cdots < \zeta_b < \infty$ be distinct realizations of u_{ij} and w_{ij}, respectively
- Let $\boldsymbol{\lambda}_{0u} = (\lambda_{0u}(\xi_1), \ldots, \lambda_{0u}(\xi_a))'$ and $\boldsymbol{\lambda}_{0w} = (\lambda_{0w}(\zeta_1), \ldots, \lambda_{0w}(\zeta_b))'$ be the vectors of discrete baseline hazard functions of U_{ij}'s and W_{ij}'s, respectively.
- Let $\boldsymbol{\eta} = (\boldsymbol{\beta}'_t, \boldsymbol{\beta}'_u, \boldsymbol{\beta}'_w, \alpha_u, \alpha_w, \boldsymbol{\gamma}', \boldsymbol{\lambda}'_{0u}, \boldsymbol{\lambda}'_{0w})'$ denote the vector of the parameters, where $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_m)'$

Full likelihood

- Then the conditional likelihood in (4) can be expressed as

$$
\begin{aligned}
L_{ij}(\boldsymbol{\eta}) &= \left\{ \sum_{k=1}^{m+1} \phi_{ijk} g_{ijk} \right\} \\
&\times \lambda_{0u}(u_{ij}) \exp\{\boldsymbol{\beta}_u' \mathbf{x}_{ij} + \alpha_u r_i\} \exp\{-\Lambda_{0u}(u_{ij}) \exp(\boldsymbol{\beta}_u' \mathbf{x}_{ij} + \alpha_u r_i)\} \\
&\times [\lambda_{0w}(w_{ij}) \exp\{\boldsymbol{\beta}_w' \mathbf{x}_{ij} + \alpha_w r_i\} \exp\{-\Lambda_{0w}(w_{ij}) \exp(\boldsymbol{\beta}_w' \mathbf{x}_{ij} + \alpha_w r_i)\}]^{\psi_{ij}}
\end{aligned}
$$

- The full likelihood of the i^{th} cluster based on complete data is defined by

$$
L_i^c(\boldsymbol{\eta}, \theta) = \left\{ \prod_{j=1}^{n_i} L_{ij}(\boldsymbol{\eta}) \right\} f(r_i; \theta),
$$

where $f(r_i; \theta)$ is *pdf* of the normal frailty with mean 0 and variance θ

Complete-data-based likelihood

- Therefore, the log-likelihood based on complete data can be written as

$$
\begin{aligned}
l^c(\boldsymbol{\eta}, \theta) &= \sum_{i=1}^{n}\sum_{j=1}^{n_i}\log\left\{\sum_{k=1}^{m+1}\phi_{ijk}g_{ijk}\right\} \\
&+ \sum_{i=1}^{n}\sum_{j=1}^{n_i}\sum_{p=1}^{a} I(U_{ij}=\xi_p)\{\log\lambda_{0u}(\xi_p)+\boldsymbol{\beta}_u'\mathbf{x}_{ij}+\alpha_u r_i \\
&\quad -\Lambda_{0u}(\xi_p)\exp(\boldsymbol{\beta}_u'\mathbf{x}_{ij}+\alpha_u r_i)\} \\
&+ \sum_{i=1}^{n}\sum_{j=1}^{n_i}\sum_{q=1}^{b} I(W_{ij}=\zeta_q)\psi_{ij}\{\log\lambda_{0w}(\zeta_q)+\boldsymbol{\beta}_w'\mathbf{x}_{ij}+\alpha_w r_i \\
&\quad -\Lambda_{0w}(\zeta_q)\exp(\boldsymbol{\beta}_w'\mathbf{x}_{ij}+\alpha_w r_i)\} \\
&- \frac{1}{2}\sum_{i=1}^{n}\left\{\log(2\pi\theta)+\frac{r_i^2}{\theta}\right\} \qquad (5)
\end{aligned}
$$

Parameter estimation

- Since r_i is not observable, we employ the EM algorithm for parameter estimation
- We need to replace the terms involving r_i by the conditional expectations
  - For any frailty function $g(r_i)$, the conditional expectation can be written as

$$E[g(r_i)|\mathbf{o}_i, \boldsymbol{\eta}, \theta] = \frac{\int_{-\infty}^{\infty} g(r_i) L_i^c(\boldsymbol{\eta}, \theta) dr_i}{\int_{-\infty}^{\infty} L_i^c(\boldsymbol{\eta}, \theta) dr_i}$$

- Using Gauss-Hermite method (Abramowitz and Stegun, 1970), the conditional expectation can be approximated as

$$\hat{E}[g(r_i)|\mathbf{o}_i, \boldsymbol{\eta}, \theta] = \frac{\sum_{s=1}^{M} g(r_i(x_s)) L_i^c(\boldsymbol{\eta}, \theta; \mathbf{o}_i, r_i(x_s)) w_s}{\sum_{s=1}^{M} L_i^c(\boldsymbol{\eta}, \theta; \mathbf{o}_i, r_i(x_s)) w_s}$$

  - x_s : a horizontal abscissa with weight w_s for $s = 1, \ldots, M$, where M is a pre-specified value

Parameter estimation

- Since the expectation of (5) is decomposed into four terms, the M-step is proceeded by estimating term by term
- For estimating $(\beta_t', \gamma')'$, we employed one-step Newton-Raphson algorithm
  - $(\beta_t^{(l)'}, \gamma^{(l)'})'$: the $l^{th}(l = 0, \dots)$ iterative solution of $(\beta_t', \gamma')'$
  - The $(l+1)^{th}$ solution can be derived from the following equation:

$$\begin{pmatrix} \beta_t^{(l+1)} \\ \gamma^{(l+1)} \end{pmatrix} = \begin{pmatrix} \beta_t^{(l)} \\ \gamma^{(l)} \end{pmatrix} - \hat{E}[H_t|\mathbf{o}, \beta_t^{(l)}, \gamma^{(l)}]^{-1} \hat{E}[U_t|\mathbf{o}, \beta_t^{(l)}, \gamma^{(l)}],$$

where

$$U_t(\boldsymbol{\beta}_t, \gamma) = \begin{pmatrix} \frac{\partial l^c(\boldsymbol{\eta},\theta)}{\partial \boldsymbol{\gamma}'} \\ \frac{\partial l^c(\boldsymbol{\eta},\theta)}{\partial \boldsymbol{\beta}_t'} \end{pmatrix} \text{ and } H_t(\boldsymbol{\beta}_t, \gamma) = \begin{bmatrix} \frac{\partial^2 l^c(\boldsymbol{\eta},\theta)}{\partial \boldsymbol{\gamma} \partial \boldsymbol{\gamma}'} & \frac{\partial^2 l^c(\boldsymbol{\eta},\theta)}{\partial \boldsymbol{\gamma} \partial \boldsymbol{\beta}_t'} \\ \frac{\partial^2 l^c(\boldsymbol{\eta},\theta)}{\partial \boldsymbol{\beta}_t \partial \boldsymbol{\gamma}'} & \frac{\partial^2 l^c(\boldsymbol{\eta},\theta)}{\partial \boldsymbol{\beta}_t \partial \boldsymbol{\beta}_t'} \end{bmatrix}$$

Parameter estimation

- For estimating $(\boldsymbol{\beta}'_u, \alpha_u)'$, we first determine the Breslow-type estimate for $\boldsymbol{\lambda}_{0u}$ (Klein & Moeschberger, 2003). Then we use this estimate to derive one-step estimate of $(\boldsymbol{\beta}'_u, \alpha_u)'$
- Similarly, we obtain one-step estimates of $(\boldsymbol{\beta}'_w, \alpha_w)'$ after obtaining the Breslow-type estimate for $\boldsymbol{\lambda}_{0w}$
- Now let $\hat{\boldsymbol{\eta}}$ denote the maximum likelihood estimate of $\boldsymbol{\eta}$

Variance estimation

- By the method of Louis (1982) the estimated variance-covariance matrix of $\hat{\boldsymbol{\eta}}$ can be defined as the inverse of the observed matrix $I(\hat{\boldsymbol{\eta}})$, where

$$I(\hat{\boldsymbol{\eta}}) = E\left[-\frac{\partial^2 l^c(\boldsymbol{\eta},\theta)}{\partial\boldsymbol{\eta}\partial\boldsymbol{\eta}'}\middle|\mathbf{o},\hat{\boldsymbol{\eta}},\hat{\theta}\right] - E\left[\frac{\partial l^c(\boldsymbol{\eta},\theta)}{\partial\boldsymbol{\eta}}\frac{\partial l^c(\boldsymbol{\eta},\theta)}{\partial\boldsymbol{\eta}'}\middle|\mathbf{o},\hat{\boldsymbol{\eta}},\hat{\theta}\right]$$

- Thus, the inference regarding $\boldsymbol{\beta}_t$, $\boldsymbol{\beta}_u$, and $\boldsymbol{\beta}_w$ can be done using the sub-matrix of $I(\hat{\boldsymbol{\eta}})^{-1}$ in conjunction with these parameters. Similarly, we use the elements of $I(\hat{\boldsymbol{\eta}})^{-1}$ for the inference of α_u and α_w

Setup

- The frailty r_i is generated from a normal distribution with a mean of zero and variance θ
  - $\theta = 1$ and 2
- The values of t_{ij}, u_{ij}, and w_{ij} are generated from the models (1)-(3) accordingly
  - A binary covariate z_{ij} is generated from a Bernoulli trial with a success probability of 0.5
  - Set $\beta_u = \beta_w = \beta_t = \alpha_u = \alpha_w = 0.5$, and $\lambda_u(t) = 4$, $\lambda_w(t) = 8$, and $\lambda_t(t) = 16$ f $t > 0$
  - We control the last observation to be 10 so that the values of t_{ij}, u_{ij}, and v_{ij} cannot be observed
- We use different number of clusters ($n = 25$, 100, and 200) with the same n_i being 2, 3, or 5 for each cluster and n_i being generated from the discrete uniform distribution $\{1, \ldots, 5\}$

Simulation results: when n_i's are equal for each cluster

Table 1: Simulation results of the mean of bias (Bias), the standard deviation (SE), the mean of standard error (SEM) of parameter estimates, and the coverage probability (CP) based on 1,000 replications when n_i's are equal for each cluster

		n_i											
		2				3				5			
n	Parameter	Bias	SE	SEM	CP	Bias	SE	SEM	CP	Bias	SE	SEM	CP
						$\theta = 1$							
25	β_u	0.017	0.326	0.310	94.7	0.026	0.267	0.248	92.8	0.014	0.196	0.189	94.1
	α_u	0.014	0.185	0.174	93.3	0.016	0.142	0.139	94.9	0.011	0.111	0.106	94.7
	β_w	0.037	0.383	0.357	94.2	0.020	0.291	0.283	94.6	0.017	0.224	0.215	94.6
	α_w	0.032	0.221	0.205	94.4	0.014	0.169	0.162	93.8	0.015	0.129	0.123	93.4
	β_t	0.076	0.537	0.527	95.2	0.052	0.437	0.415	94.6	0.076	0.314	0.306	94.2
	θ	0.070	0.829	0.643	87.2	0.096	0.696	0.551	88.8	0.087	0.510	0.453	91.2
100	β_u	0.004	0.148	0.148	94.6	0.005	0.117	0.120	95.7	0.002	0.093	0.092	94.6
	α_u	0.008	0.080	0.080	95.7	0.003	0.067	0.065	95.1	0.003	0.052	0.050	94.3
	β_w	0.016	0.169	0.167	94.7	-0.006	0.141	0.135	94.1	0.012	0.101	0.104	96.0
	α_w	0.004	0.095	0.092	95.2	0.006	0.074	0.075	95.3	0.003	0.057	0.058	95.5
	β_t	0.021	0.254	0.253	95.1	0.046	0.199	0.202	94.0	0.055	0.152	0.151	94.0
	θ	-0.077	0.388	0.291	81.9	-0.005	0.313	0.250	87.7	0.041	0.241	0.213	92.1
200	β_u	0.004	0.105	0.104	95.7	0.001	0.084	0.084	96.0	-0.002	0.066	0.065	95.1
	α_u	0.003	0.057	0.056	94.0	0.003	0.045	0.046	95.1	0.000	0.035	0.035	95.6
	β_w	-0.001	0.119	0.117	94.7	-0.007	0.096	0.095	94.8	0.004	0.076	0.073	93.2
	α_w	0.004	0.066	0.064	95.2	0.001	0.052	0.052	94.5	0.003	0.041	0.040	94.7
	β_t	0.020	0.179	0.178	95.5	0.033	0.138	0.142	95.0	0.061	0.110	0.107	94.7
	θ	-0.102	0.263	0.201	80.5	-0.022	0.214	0.174	87.5	0.044	0.174	0.150	91.0
						$\theta = 2$							
25	β_u	0.013	0.327	0.311	94.9	0.026	0.266	0.249	93.3	0.013	0.196	0.189	94.6
	α_u	0.015	0.141	0.132	93.7	0.016	0.106	0.105	95.6	0.010	0.084	0.081	94.9
	β_w	0.036	0.385	0.361	94.4	0.014	0.293	0.285	95.0	0.016	0.224	0.216	94.5
	α_w	0.030	0.166	0.159	95.4	0.014	0.130	0.125	94.8	0.013	0.098	0.095	94.1
	β_t	0.022	0.541	0.548	95.5	0.041	0.450	0.431	94.2	0.070	0.328	0.312	94.1
	θ	-0.276	1.070	0.862	80.1	0.000	1.070	0.830	84.4	0.084	0.851	0.752	89.6
100	β_u	0.004	0.147	0.148	94.3	0.005	0.117	0.120	95.7	0.003	0.093	0.092	94.4
	α_u	0.007	0.061	0.061	95.1	0.003	0.050	0.049	94.7	0.003	0.039	0.038	94.8
	β_w	0.016	0.170	0.169	94.6	-0.007	0.141	0.136	94.2	0.012	0.101	0.105	96.4
	α_w	0.005	0.072	0.071	95.6	0.006	0.058	0.058	94.8	0.003	0.044	0.044	94.6
	β_t	-0.010	0.263	0.268	95.5	0.032	0.209	0.210	95.9	0.052	0.151	0.154	94.1
	θ	-0.347	0.527	0.402	72.0	-0.134	0.468	0.379	82.9	0.023	0.399	0.356	91.7
200	β_u	0.004	0.105	0.104	95.5	0.001	0.084	0.084	95.9	-0.002	0.066	0.065	95.1
	α_u	0.003	0.043	0.043	94.4	0.003	0.034	0.035	95.4	0.000	0.026	0.027	95.5
	β_w	-0.002	0.119	0.118	94.4	-0.007	0.097	0.096	94.7	0.004	0.076	0.074	93.6
	α_w	0.003	0.051	0.050	94.9	0.002	0.040	0.040	94.6	0.002	0.032	0.031	94.5
	β_t	-0.009	0.189	0.188	95.9	0.024	0.146	0.148	95.2	0.060	0.111	0.108	94.6
	θ	-0.381	0.364	0.278	61.4	-0.150	0.330	0.264	81.4	0.015	0.290	0.250	91.3

Simulation results: when n_i's are unequal

Table 2: Simulation results of the mean of bias (Bias), the standard deviation (SE), the mean of standard error (SEM) of parameter estimates, and the coverage probability (CP) based on 1,000 replications when n_i's are unequal

		θ							
		1				2			
n	Parameter	Bias	SE	SEM	CP	Bias	SE	SEM	CP
25	β_u	0.023	0.267	0.254	94.2	0.023	0.267	0.254	94.2
	α_u	0.020	0.149	0.146	94.5	0.018	0.113	0.110	94.3
	β_w	0.003	0.296	0.289	94.1	0.000	0.300	0.291	94.5
	α_w	0.018	0.181	0.170	95.1	0.019	0.139	0.131	95.2
	β_t	0.051	0.429	0.420	94.8	0.043	0.439	0.436	95.9
	θ	0.078	0.711	0.565	85.7	-0.020	1.079	0.856	84.5
100	β_u	0.007	0.123	0.122	95.6	0.007	0.123	0.122	95.2
	α_u	0.000	0.069	0.066	94.5	0.000	0.053	0.050	93.7
	β_w	0.010	0.141	0.138	94.5	0.009	0.142	0.139	94.3
	α_w	0.009	0.078	0.077	95.1	0.008	0.061	0.059	94.8
	β_t	0.039	0.210	0.205	94.9	0.024	0.214	0.212	95.8
	θ	-0.013	0.331	0.258	85.6	-0.137	0.507	0.393	82.5
200	β_u	0.002	0.087	0.086	94.9	0.002	0.087	0.086	94.5
	α_u	0.004	0.043	0.046	97.2	0.003	0.033	0.035	97.2
	β_w	0.005	0.097	0.097	94.4	0.004	0.099	0.097	94.0
	α_w	0.001	0.054	0.053	94.6	0.001	0.041	0.041	95.0
	β_t	0.036	0.146	0.144	93.2	0.023	0.149	0.150	95.4
	θ	-0.014	0.221	0.181	87.2	-0.123	0.339	0.277	84.5

Simulation results: four different frailty distributions when n is equal to 100 and n_i's are unequal

Table 3: Simulation results of the mean of bias (Bias), the standard deviation (SD), the mean of standard error (SEM) of parameter estimates, and the coverage probability (CP) based on 1,000 replications under four different frailty distributions when n is equal to 100 and n_i's are unequal

	Frailty distribution															
	$N(0,2.43)$				$U(-2.70,2.70)$				$t(3.40)$				$G(1.46,0.68)$			
Parameter	Bias	SD	SEM	CP	Bias	SD	SEM	CP	Bias	SD	SEM	CP	Bias	SD	SEM	CP
β_u	0.006	0.123	0.122	95.4	0.005	0.124	0.122	95.0	0.001	0.118	0.122	95.9	-0.005	0.123	0.122	95.1
α_u	0.000	0.049	0.047	93.6	0.002	0.045	0.047	95.4	0.005	0.053	0.051	94.2	0.002	0.049	0.048	94.1
β_w	0.010	0.142	0.139	94.7	-0.003	0.144	0.139	94.4	-0.001	0.142	0.139	95.1	0.008	0.137	0.134	94.1
α_w	0.008	0.057	0.056	94.9	0.004	0.057	0.054	94.2	0.004	0.062	0.062	95.4	0.001	0.050	0.052	96.9
β_t	0.025	0.216	0.215	95.1	0.009	0.221	0.215	95.0	0.027	0.215	0.213	94.2	-0.055	0.226	0.230	94.5
θ	-0.184	0.548	0.451	84.1	-0.181	0.506	0.451	87.0	-0.611	0.576	0.386	54.2	-0.836	0.418	0.380	39.7

Mastitis data

- A observation study was conducted to estimate the incidence of different organisms causing mastitis in the dairy cattle population in Flanders
- A total of 100 cows was monitored at the udder-quarter level for bacterial infections from the time of parturition, at which the cow was included in the cohort and observed infection-free, until the end of the lactation period
- The four udder quarters are obviously clustered within a cow and udder quarters that experience an event are interval-censored because of periodic follow-up
- We want to investigate the effect of the covariates that change within cow (e.g. front and rear udder quarters) and covariates that change between cows (e.g. number of calving).

Results

Table 3: Parameter estimates, their standard errors, and *p*-values of mastitis data

Parameter		Estimate	SE	*p*-value
β_u				
	location: rear	0.175	0.101	0.082
	calving: 2-4	-0.110	0.109	0.317
	calving: >4	0.640	0.168	<0.001
α_u		0.819	0.053	<0.001
β_w				
	location: rear	0.086	0.104	0.405
	calving: 2-4	-0.154	0.112	0.170
	calving: >4	0.122	0.169	0.469
α_w		0.200	0.047	<0.001
β_t				
	location: rear	0.162	0.119	0.172
	calving: 2-4	-0.011	0.334	0.975
	calving: >4	1.618	0.473	0.001
θ		2.001	0.341	<0.001

Summary

- We proposed the Cox PH models with a shared frailty effect incorporated with clustered interval-censored data for which there exits a dependence between the failure time and the censoring times
- After constructing the likelihood function based on complete data, we employed the EM algorithm for parameter estimation
- Simulation results showed that when a cluster size is fixed, both Bias and SEM of parameter estimates except for θ decrease as the number of the clusters increases, and the CPs are close to the nominal level of 0.95.
- The overall trends were similar regardless of whether the number of observations within the same cluster is equal or unequal
- Moreover, our proposed method was robust to misspecified frailty distribution such as the uniform, t, and gamma distributions

Thank you!