A multi-state model for analyzing interval-censored semi-competing risks data

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Outline

- Introduction to motivating data
- Proposed model & parameter estimation
- Simulations
- Illustration with the PAQUID data
- Summary & concluding remarks

Motivating data

- Data from a prospective cohort study on the longevity of 248 dental veneered facets of conical crown-retained dentures placed in 48 patients (Frydman et al., 2013)
- The study unit is the dental veneered facet.

No. dental veneers	2	3	4	5	6	7	8	9	10	11	Total
No. patients	7	7	7	7	6	7	2	2	2	1	48

- The dental veneers were followed for fracture with the intervening event being discoloration

Motivating data

- Since the placement of the veneers, there were up to 5 scheduled yearly visits
- The times of discoloration and fracture before and after discoloration were interval censored
- Among the 248 dental veneers,
  - 99: right censored $\Longrightarrow$ Route 1
  - 30: fractured without prior discoloring event $\Longrightarrow$ Route 2
  - 103: discolored but not fractured $\Longrightarrow$ Route 3
  - 9: discolored & subsequently fractured $\Longrightarrow$ Route 4
  - 7: discolored & then fractured in the same interval $\Longrightarrow$ Route 5

Illness-death processes

- S_t : the state of a subject at time $t \geq 0$ under an illness-death process
  - $S_t \in \{0, 1, 2\}$
  - state 0: a healthy state
  - state 1: a non-fatal(NF) state (eg, discoloration, dementia)
  - state 2: a fatal(F) state (eg, fracture, death)
- $\mathcal{A} = \{(r, s) : (r, s) = (0, 1), (0, 2), (1, 2)\}$: the possible transitions from state r to state s
- Given covariates $\mathbf{x} = (x_1, x_2, \ldots, x_p)'$ and a frailty η, define the transition intensity from state r to state s at time t as

$$\lambda_{rs}(t|\mathbf{x}, \eta) = \lim_{dt \to 0} \frac{\Pr(S_{t+dt} = s | S_t = r, \mathbf{x}, \eta)}{dt}, \ (r, s) \in \mathcal{A}$$

  - $\lambda_{rs}(t|\mathbf{x}, \eta) = 0$ for $(r, s) \notin \mathcal{A}$

The proposed model

- Through the Cox regression model, the transition intensity $\lambda_{rs}(t|\mathbf{x},\eta)$ can be expressed as

$$\lambda_{rs}(t|\mathbf{x},\eta) = \theta_{rs}\gamma_{rs}t^{\gamma_{rs}-1}\exp(\boldsymbol{\beta}'_{rs}\mathbf{x}+\eta),\ (r,s)\in\mathcal{A}$$

  - $\boldsymbol{\beta}_{rs} = (\beta_{rs,1},\beta_{rs,2},\ldots,\beta_{rs,p})'$: the vector of the regression coefficients
  - $\theta_{rs}(\gamma_{rs})$: the scale (shape) parameter of the Weibull distribution
  - η : an unobservable normal frailty, $N(0,\sigma^2)$
- $\zeta = (\theta_{01},\theta_{02},\theta_{12},\gamma_{01},\gamma_{02},\gamma_{12},\boldsymbol{\beta}'_{01},\boldsymbol{\beta}'_{02},\boldsymbol{\beta}'_{12},\sigma^2)'$: the parameter vector in our model

Notations

- e_i $(i = 1, 2, \ldots, n)$: the entry time of study for the i-th subject
- a_i : the time of last visit at which an NF event is not observed
- b_i : the first time that an NF event is observed
- u_i : the time of last visit at which an F event is not observed
- v_i : the first time that an F event is observed
- s_i & t_i : unobservable exact NF & F event times
- c_i : censoring time

Notations

- Five possible routes
  - Route 1: $0 \to 0$
  - Route 2: $0 \to 2$
  - Route 3: $0 \to 1$
  - Route 4: $0 \to 1 \to 2$
  - Route 5: $0 \to$ 1 (hidden) $\to 2$
- $\mathcal{B}_h = \{i : I_{ih} = 1\}$: the set of subjects in Route h ($h = 1, 2, \ldots, 5$)
  - $I_{ih} = 1$ if the i-th subject follows Route h; 0 otherwise

Conditional likelihood for Route 1

- The likelihood function for a subject in $\mathcal{B}_1$ is

$$Q_{i1}(e_i, c_i|\mathbf{x}_i, \eta_i) = \exp\{-H_0(e_i, c_i|\mathbf{x}_i, \eta_i)\}, \ \ i \in \mathcal{B}_1$$

  - $H_0(t_1, t_2|\mathbf{x}, \eta) = \int_{t_1}^{t_2} \{\lambda_{01}(s|\mathbf{x}, \eta) + \lambda_{02}(s|\mathbf{x}, \eta)\} ds$

Possible mass time points

	Time →									
i	0	1	2	3	4	5	6	7	8	
1	u_1		v_1							
2		u_2			v_2					
3				u_3	v_3					
4						u_4		v_4		
5								u_5	v_5	
	$t_{(0)} = 0$		$t_{(1)} = 2$		$t_{(2)} = 4$			$t_{(3)} = 7$	$t_{(4)} = 8$	$t_{(5)} = \infty$

Possible mass time points of the F event

- Using the algorithm proposed by Collett (2015), define a subset of the endpoints of $(u_i, v_i]$ as

$$0 = t_{(0)} < t_{(1)} < t_{(2)} < \cdots < t_{(l)} < t_{(l+1)} = \infty$$

  - $t_{(1)}$: the smallest of the values of v_i
  - $t_{(k)}$ $(k = 2, 3, \ldots, l)$: the smallest of the values of v_i such that $u_i \geq t_{(k-1)}$

Weight allocations & conditional likelihood for Route 2

- For a subject in $\mathcal{B}_2$, define the weight at time $t_{(k)}$ as

$$\begin{aligned} w_{ik}^{(2)} &= P(t_i \in (t_{(k-1)}, t_{(k)}] | t_i \in (u_i, v_i], \mathbf{x}_i, \eta_i) \\ &= \frac{\phi_{ik} \exp\left\{-H_0(e_i, t_{(k)}|\mathbf{x}_i, \eta_i)\right\} \lambda_{02}(t_{(k)}|\mathbf{x}_i, \eta_i)}{\sum_{k=1}^{l} \phi_{ik} \exp\left\{-H_0(e_i, t_{(k)}|\mathbf{x}_i, \eta_i)\right\} \lambda_{02}(t_{(k)}|\mathbf{x}_i, \eta_i)}, \;\; i \in \mathcal{B}_2 \end{aligned}$$

  - $\phi_{ik} = I(t_{(k)} \in (u_i, v_i]), \;\; k = 1, 2, \ldots, l$
- The likelihood function for a subject in $\mathcal{B}_2$ is defined as a sum of weighted probabilities:

$$\begin{aligned} & Q_{i2}(e_i, u_i, v_i|\mathbf{x}_i, \eta_i) \\ & \quad = \sum_{k=1}^{l} w_{ik}^{(2)} \exp\{-H_0(e_i, t_{(k)}|\mathbf{x}_i, \eta_i)\}\lambda_{02}(t_{(k)}|\mathbf{x}_i, \eta_i), \;\; i \in \mathcal{B}_2 \end{aligned}$$

Possible mass time points of the NF event

- Similarly, define a subset of the endpoints of $(a_i, b_i]$ as

$$0 = s_{(0)} < s_{(1)} < s_{(2)} < \cdots < s_{(m)} < s_{(m+1)} = \infty$$

  - $s_{(1)}$: the smallest of the values of b_i
  - $s_{(j)}$ $(j = 2, 3, \ldots, m)$: the smallest of the values of b_i such that $a_i \geq s_{(j-1)}$

Weight allocations & conditional likelihood for Route 3

- For a subject in $\mathcal{B}_3$, define the weight at time $s_{(j)}$ as

$$w_{ij}^{(3)} = \frac{\phi_{ij}^* \exp\left\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\right\} \lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i)}{\sum_{j=1}^m \phi_{ij}^* \exp\left\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\right\} \lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i)}, \ i \in \mathcal{B}_3$$

  - $\phi_{ij}^* = I(s_{(j)} \in (a_i, b_i]), \ j = 1, 2, \ldots, m$
- The likelihood function for a subject in $\mathcal{B}_3$ is defined as a sum of weighted probabilities:

$$\begin{aligned} Q_{i3}(e_i, a_i, b_i, c_i|\mathbf{x}_i, \eta_i) &= \sum_{j=1}^m w_{ij}^{(3)} \exp\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\}\lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i) \\ &\quad \times \exp\{-H_1(s_{(j)}, c_i|\mathbf{x}_i, \eta_i)\}, \ i \in \mathcal{B}_3 \end{aligned}$$

  - $H_1(t_1, t_2|\mathbf{x}, \eta) = \int_{t_1}^{t_2} \lambda_{12}(s|\mathbf{x}, \eta) ds$

Weight allocations for Route 4

- For a subject in $\mathcal{B}_4$, define the weight corresponding to a pair of the NF & F event times $(s_{(j)}, t_{(k)})$ as

$$
\begin{aligned}
w_{ijk}^{(4)} = \phi_{ij}^{*}\phi_{ik} \exp\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\}\lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i) \\
\times \exp\left\{-H_1(s_{(j)}, t_{(k)}|\mathbf{x}_i, \eta_i)\right\} \lambda_{12}(t_{(k)}|\mathbf{x}_i, \eta_i) \\
\times \left[\sum_{j=1}^{m}\sum_{k=1}^{l} \phi_{ij}^{*}\phi_{ik} \exp\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\}\lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i)\right. \\
\left. \times \exp\{-H_1(s_{(j)}, t_{(k)}|\mathbf{x}_i, \eta_i)\}\lambda_{12}(t_{(k)}|\mathbf{x}_i, \eta_i)\right]^{-1}, \quad i \in \mathcal{B}_4
\end{aligned}
$$

Conditional likelihood for Route 4

- The likelihood function for a subject in $\mathcal{B}_4$ is defined as a sum of weighted probabilities:

$$
\begin{aligned}
&Q_{i4}(e_i, a_i, b_i, u_i, v_i|\mathbf{x}_i, \eta_i) \\
&\quad = \sum_{j=1}^{m}\sum_{k=1}^{l} w_{ijk}^{(4)} \exp\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\}\lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i) \\
&\qquad \times \exp\{-H_1(s_{(j)}, t_{(k)}|\mathbf{x}_i, \eta_i)\}\lambda_{12}(t_{(k)}|\mathbf{x}_i, \eta_i),\ \ i \in \mathcal{B}_4
\end{aligned}
$$

Weight allocations for Route 5

- For a subject in $\mathcal{B}_5$, define the weight corresponding to a pair of the NF & F event times $(s_{(j)}, t_{(k)})$ as

$$
\begin{aligned}
w_{ijk}^{(5)} = \phi_{ij}^{*}\phi_{ik}\varphi_{ijk} \exp\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\}\lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i) \\
\times \exp\left\{-H_1(s_{(j)}, t_{(k)}|\mathbf{x}_i, \eta_i)\right\} \lambda_{12}(t_{(k)}|\mathbf{x}_i, \eta_i) \\
\times \Bigg[\sum_{j=1}^{m}\sum_{k=1}^{l} \phi_{ij}^{*}\phi_{ik}\varphi_{ijk} \exp\{-H_0(e_i, s_{(j)}|\mathbf{x}_i, \eta_i)\}\lambda_{01}(s_{(j)}|\mathbf{x}_i, \eta_i) \\
\times \exp\{-H_1(s_{(j)}, t_{(k)}|\mathbf{x}_i, \eta_i)\}\lambda_{12}(t_{(k)}|\mathbf{x}_i, \eta_i)\Bigg]^{-1}, \quad i \in \mathcal{B}_5
\end{aligned}
$$

  - $\varphi_{ijk} = I(u_i < s_{(j)} \leq t_{(k)} \leq v_i)$

Conditional likelihood for Route 5

- The likelihood function for a subject in $\mathcal{B}_5$ is defined as a sum of weighted probabilities:

$$Q_{i5}(e_i, u_i = a_i, v_i = b_i | \mathbf{x}_i, \eta_i)$$
$$= \sum_{j=1}^{m} \sum_{k=1}^{l} w_{ijk}^{(5)} \exp\{-H_0(e_i, s_{(j)} | \mathbf{x}_i, \eta_i)\} \lambda_{01}(s_{(j)} | \mathbf{x}_i, \eta_i)$$
$$\times \exp\{-H_1(s_{(j)}, t_{(k)} | \mathbf{x}_i, \eta_i)\} \lambda_{12}(t_{(k)} | \mathbf{x}_i, \eta_i), \ \ i \in \mathcal{B}_5$$

Complete data-based likelihood

- Based on the complete data, the likelihood function is defined as

$$L(\zeta) = \prod_{i=1}^{n} \left\{ \prod_{h=1}^{5} Q_{ih}^{I_{ih}} \right\} \phi(0, \sigma^2; \eta_i),$$

  - $\phi(\cdot)$: *pdf* of $N(0, \sigma^2)$

Parameter estimation

- Use the NLMIXED procedure (SAS Institute Inc., 2015)
- Using the adaptive importance sampling proposed by Pinheiro & Bates (1995), compute the marginal likelihood,

$$m(\zeta) = \int \cdots \int L(\zeta) du_1 \cdots du_n$$

  - $\hat{\zeta}$: a minimizer of $f(\zeta) = -\log m(\zeta)$ using the iterative quasi-Newton algorithm
  - $\text{Var}(\hat{\zeta})$: the inverse of Hessian matrix evaluated at $\hat{\zeta}$

Simulation setup

- Baseline transition intensities: $Exp(\theta_{rs})$
  - $\theta_{01} = 0.006$, $\theta_{02} = 0.003$, $\theta_{12} = 0.004$
- Frailty: $\eta \sim N(0, \sigma^2)$
- Covariates($\mathbf{x} = (x_1, x_2)'$): $x_1 \sim Bernoulli(0.5)$, $x_2 \sim N(0, 1)$
- Censoring time(c): fixed at 365
- Designated visiting times: 15, 31, 45, 59, 74, 90, 105, 120, 135, 151, 166, 181, 196, 212, 227, 243, 258, 273, 288, 304, 319, 334, 349
- Actual visiting times: add random numbers from $N(0, 9)$ to each of designated time points,

$$0 = q_0 < q_{1i} < \cdots < q_{23,i} < q_{24} = 365, \;\; i = 1, 2, \ldots, n$$

- $n = 200$
- 500 iterations

Configurations

σ^2	Type	Regression parameter					
		$\beta_{01,1}$	$\beta_{02,1}$	$\beta_{12,1}$	$\beta_{01,2}$	$\beta_{02,2}$	$\beta_{12,2}$
0	even	0.5	0.5	0.5	1	1	1
	acc	0.5	0.5	0.7	1	1	1.4
	dec	0.5	0.7	0.5	1	1.4	1
0.1	even	0.5	0.5	0.5	1	1	1
	acc	0.5	0.5	0.7	1	1	1.4
	dec	0.5	0.7	0.5	1	1.4	1

Empirical results for the 'Proposed' and the 'Lee et al.'s models when $\sigma^2 = 0$

			Proposed				Lee et al.[1]			
Type	Parameter	True	r.Bias	SD	SEM	CP	r.Bias	SD	SEM	CP
even	$\beta_{01,1}$	0.5	-0.042	0.083	0.091	0.968	-0.111	0.097	0.098	0.918
	$\beta_{02,1}$	0.5	-0.044	0.126	0.129	0.956	0.203	0.184	0.187	0.922
	$\beta_{12,1}$	0.5	0.050	0.112	0.110	0.958	0.028	0.121	0.117	0.946
	$\beta_{01,2}$	1	-0.035	0.178	0.179	0.954	-0.107	0.195	0.193	0.912
	$\beta_{02,2}$	1	-0.013	0.248	0.255	0.950	0.175	0.406	0.387	0.948
	$\beta_{12,2}$	1	0.020	0.216	0.209	0.954	0.042	0.229	0.225	0.948
	σ^2					N/A				

[1] Results from the function `idm` in `SmoothHazards` R package

Empirical results for the ‘Proposed’ and the ‘Lee et al.’s models when $\sigma^2 = 0$

			Proposed				Lee et al.[2]			
Type	Parameter	True	r.Bias	SD	SEM	CP	r.Bias	SD	SEM	CP
acc	$\beta_{01,1}$	0.5	-0.039	0.089	0.091	0.950	-0.134	0.096	0.096	0.900
	$\beta_{02,1}$	0.5	-0.067	0.133	0.129	0.946	0.388	0.212	0.199	0.832
	$\beta_{12,1}$	0.7	0.065	0.127	0.113	0.920	0.041	0.129	0.123	0.940
	$\beta_{01,2}$	1	-0.023	0.182	0.180	0.944	-0.155	0.192	0.192	0.880
	$\beta_{02,2}$	1	-0.030	0.254	0.254	0.946	0.399	0.479	0.444	0.896
	$\beta_{12,2}$	1.4	0.032	0.214	0.212	0.938	0.039	0.238	0.235	0.926
	σ^2					N/A				

[2]Results from the function `idm` in `SmoothHazards` R package

Empirical results for the ‘Proposed’ and the ‘Lee et al.’s models when $\sigma^2 = 0$

Type	Parameter	True	Proposed r.Bias	Proposed SD	Proposed SEM	Proposed CP	Lee et al.[3] r.Bias	Lee et al.[3] SD	Lee et al.[3] SEM	Lee et al.[3] CP
dec	$\beta_{01,1}$	0.5	-0.051	0.092	0.095	0.946	-0.132	0.108	0.107	0.884
	$\beta_{02,1}$	0.7	-0.058	0.114	0.120	0.948	0.032	0.191	0.178	0.934
	$\beta_{12,1}$	0.5	0.043	0.123	0.117	0.950	0.043	0.129	0.124	0.938
	$\beta_{01,2}$	1	-0.036	0.182	0.187	0.968	-0.128	0.207	0.207	0.910
	$\beta_{02,2}$	1.4	-0.031	0.232	0.239	0.952	0.005	0.366	0.344	0.944
	$\beta_{12,2}$	1	0.032	0.228	0.219	0.932	0.041	0.252	0.237	0.932
	σ^2					N/A				

[3] Results from the function `idm` in `SmoothHazards` R package

Empirical results for the ‘Proposed’ and the ‘Touraine et al.’s models when $\sigma^2 = 0.1$

			Proposed				Touraine et al.[4]			
Type	Parameter	True	r.Bias	SD	SEM	CP	r.Bias	SD	SEM	CP
even	$\beta_{01,1}$	0.5	-0.051	0.091	0.096	0.950	-0.159	0.114	0.117	0.918
	$\beta_{02,1}$	0.5	-0.068	0.131	0.132	0.934	-0.168	0.157	0.153	0.916
	$\beta_{12,1}$	0.5	0.032	0.116	0.117	0.936	-0.193	0.148	0.429	0.934
	$\beta_{01,2}$	1	-0.038	0.189	0.189	0.942	-0.172	0.248	0.651	0.894
	$\beta_{02,2}$	1	-0.074	0.277	0.261	0.926	-0.163	0.338	0.582	0.894
	$\beta_{12,2}$	1	0.014	0.237	0.225	0.926	-0.163	0.299	0.570	0.916
	σ^2	0.1	-0.079	0.076	0.079	0.930	-1.696	0.159	0.161	0.556

[4] Results from the function `FreqID_HReg` in `SemiCompRisks` R package

Empirical results for the ‘Proposed’ and the ‘Touraine et al.’s models when $\sigma^2 = 0.1$

			Proposed				Touraine et al.[5]			
Type	Parameter	True	r.Bias	SD	SEM	CP	r.Bias	SD	SEM	CP
acc	$\beta_{01,1}$	0.5	-0.064	0.093	0.095	0.946	-0.079	0.122	0.117	0.898
	$\beta_{02,1}$	0.5	-0.071	0.129	0.131	0.954	-0.069	0.160	0.153	0.936
	$\beta_{12,1}$	0.7	0.054	0.122	0.121	0.942	-0.120	0.174	0.167	0.918
	$\beta_{01,2}$	1	-0.036	0.168	0.189	0.978	-0.160	0.231	0.232	0.920
	$\beta_{02,2}$	1	-0.071	0.244	0.261	0.946	-0.154	0.295	0.303	0.948
	$\beta_{12,2}$	1.4	0.031	0.231	0.229	0.944	-0.220	0.327	0.323	0.918
	σ^2	0.1	-0.019	0.079	0.079	0.936	-0.170	0.162	0.163	0.549

[5] Results from the function `FreqID_HReg` in `SemiCompRisks` R package

Empirical results for the 'Proposed' and the 'Touraine et al.'s models when $\sigma^2 = 0.1$

			Proposed				Touraine et al.[6]			
Type	Parameter	True	r.Bias	SD	SEM	CP	r.Bias	SD	SEM	CP
dec	$\beta_{01,1}$	0.5	-0.087	0.099	0.098	0.920	-0.193	0.133	0.125	0.896
	$\beta_{02,1}$	0.7	-0.067	0.119	0.122	0.942	-0.154	0.159	0.151	0.900
	$\beta_{12,1}$	0.5	0.031	0.132	0.123	0.940	-0.218	0.170	0.160	0.908
	$\beta_{01,2}$	1	-0.059	0.190	0.195	0.942	-0.223	0.258	0.250	0.858
	$\beta_{02,2}$	1.4	-0.048	0.234	0.247	0.930	-0.180	0.333	0.304	0.884
	$\beta_{12,2}$	1	0.021	0.221	0.233	0.972	-0.202	0.311	0.309	0.918
	σ^2	0.1	-0.192	0.071	0.077	0.936	-1.941	0.175	0.164	0.512

[6] Results from the function `FreqID_HReg` in `SemiCompRisks` R package

Sensitivity analysis for the type of even

Parameter	True	r.Bias	SD	SEM	CP	r.Bias	SD	SEM	CP
		$N(0, 0.1)$				$U(-0.548, 0.548)$			
$\beta_{01,1}$	0.5	-0.066	0.093	0.096	0.944	-0.064	0.092	0.094	0.950
$\beta_{02,1}$	0.5	-0.061	0.116	0.132	0.970	-0.051	0.137	0.131	0.932
$\beta_{12,1}$	0.5	0.021	0.128	0.117	0.922	0.050	0.119	0.116	0.954
$\beta_{01,2}$	1	-0.024	0.199	0.189	0.954	-0.044	0.184	0.188	0.958
$\beta_{02,2}$	1	-0.055	0.250	0.260	0.950	-0.043	0.263	0.262	0.952
$\beta_{12,2}$	1	0.010	0.232	0.225	0.938	0.035	0.217	0.224	0.962
σ^2	0.1	-0.075	0.077	0.078	0.920	-0.117	0.078	0.078	0.916
		$DE(0, 0.224)$				$G(10.5, 0.1)$			
$\beta_{01,1}$	0.5	-0.058	0.090	0.094	0.966	-0.071	0.091	0.095	0.946
$\beta_{02,1}$	0.5	-0.073	0.131	0.131	0.944	-0.057	0.125	0.131	0.960
$\beta_{12,1}$	0.5	0.055	0.122	0.116	0.938	0.044	0.124	0.116	0.940
$\beta_{01,2}$	1	-0.040	0.187	0.187	0.938	-0.044	0.182	0.188	0.954
$\beta_{02,2}$	1	-0.065	0.261	0.261	0.948	-0.026	0.258	0.261	0.948
$\beta_{12,2}$	1	0.034	0.219	0.220	0.950	0.029	0.225	0.224	0.948
σ^2	0.1	-0.197	0.067	0.075	0.918	-0.087	0.081	0.078	0.932

Dental veneers data (revisited)

- We could not directly use the data analyzed by Frydman et al. (2013) because there was no covariate available to us

Illustrative example: Paq1000 data

- Personnes Agées Quid (PAQUID): Helmer et al. (2001)
  - A prospective cohort study to investigate the impact of dementia on the risk of death
  - 3675 subjects aged 65 years or more, living in southwestern France, were recruited in 1988-90 and then screened for dementia every 2 or 3 years
- Instead analyze the `Paq1000` data included in the `SmoothHazard` R package
  - Ages: at the start of study (e_i), at the last dementia-free visit (a_i), at being diagnosed with dementia (b_i) & at death (t_i) or being right censored (c_i)
  - Covariates:
    - Sex: $0 =$ female, $1 =$ male
    - Primary school certificate: $0 =$ with certificate, $1 =$ without certificate

Illustrative example: Paq1000 data

- For an illustration of the proposed model,
  - When age-at-death of the i^{th} subject is exactly observed at t_i, set $u_i = t_i - \epsilon_{1i}$ & $v_i = t_i + \epsilon_{2i}$ for $\epsilon_{1i}, \epsilon_{2i} \sim U(0, 1)$
  - When the i^{th} subject is right censored at c_i, set $u_i = c_i$ & $v_i = \infty$

Paq1000 data: Parameter estimation

Transition	Parameter	Estimate	SE	t	P
$0 \rightarrow 1$	β_{01g}	-0.142	0.163	-0.869	0.385
	β_{01c}	-0.383	0.199	-1.925	0.054
	θ_{01}	0.010	0.000	83.126	$< .001$
	γ_{01}	8.935	1.062	8.410	$< .001$
$0 \rightarrow 2$	β_{02g}	0.505	0.095	5.333	$< .001$
	β_{02c}	0.009	0.106	0.083	0.934
	θ_{02}	0.011	0.000	179.083	$< .001$
	γ_{02}	12.014	0.780	15.401	$< .001$
$1 \rightarrow 2$	β_{12g}	0.705	0.225	3.130	0.002
	β_{12c}	-0.275	0.279	-0.989	0.323
	θ_{12}	0.012	0.000	28.201	$< .001$
	γ_{12}	9.152	1.908	4.796	$< .001$
	σ^2	0.198	0.094	2.103	0.035

Summary & concluding remarks

- Propose a parametric proportional hazards model with a normal frailty to analyze the semi-competing risks data when all three transition times are interval censored
- Partition the observed interval into several sub-intervals where either NF or F event can occur and then allocate the weight to each sub-interval in order to construct the likelihood functions
- The CPs of the regression parameters were close to a nominal level irrespective of types of the regression coefficients
- The parameter estimates were robust to the misspecification of the frailty distribution
- Extend the proposed model to a semiparametric model by employing a profile likelihood approach or a smoothing spline method

Thank you!