# Analysis of interval-censored semi-competing risks data with missing intermediate events

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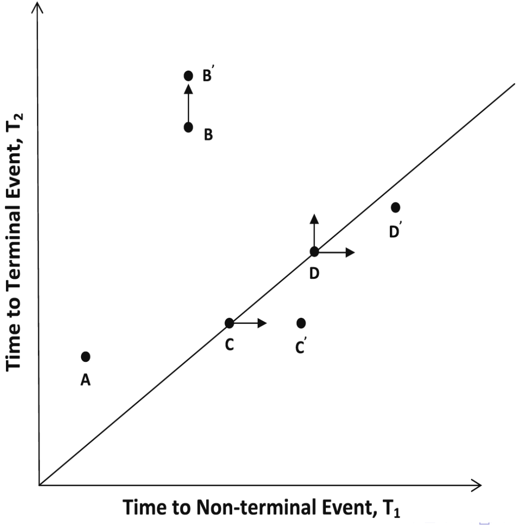
# Outline

- Semi-competing risks data? Interval censoring?
- Model specification
- Likelihood construction
- Simulation studies
- Illustrative example: PAQUID data
- Concluding remarks

# Representation on semi-competing risks data



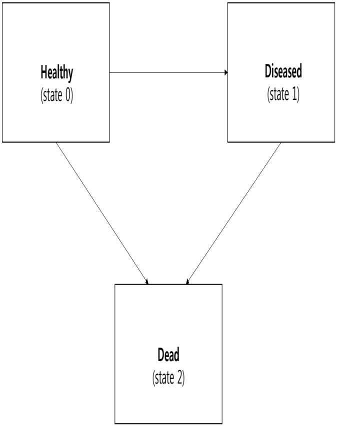
# PAQUID cohort: Interval censoring

**Table 1** Age in years at follow-up visits and diagnosis of dementia for four selected subjects of the PAQUID cohort, France, 1988–2010. Illustration of the possible configurations in the data with respect to the dementia and death status

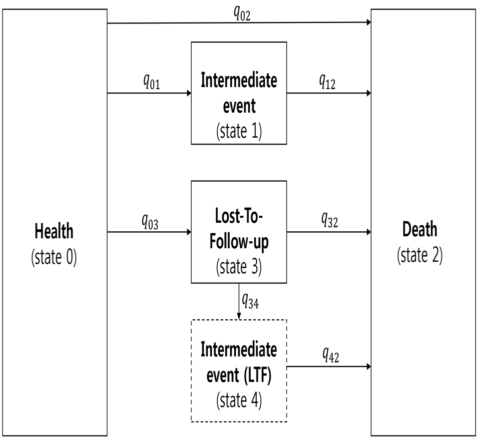
| | | | Follow-up visits | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Entry** | | 1 year | | 3 years | | 5 years | | 8 years | | 10 years | | 13 years | | 15 years | | 17 years | | 20 years | | **Latest follow-up** | |
| **Subject** | Age | Dem | Age | Dem | Age | Dem | Age | Dem | Age | Dem | Age | Dem | Age | Dem | Age | Dem | Age | Dem | Age | Dem | Age | Dead[a] |
| Never diagnosed with dementia and alive at the latest follow-up ($n = 545$, i.e. 15% of subjects in the PAQUID study) | | | | | | | | | | | | | | | | | | | | | | |
| A | 66.5 | 0 | N/A | N/A | 70.5 | 0 | N/A | N/A | 74.4 | 0 | 76.8 | 0 | 79.8 | 0 | 81.3 | 0 | N/A | N/A | N/A | N/A | 88.2 | 0 |
| Never diagnosed with dementia and died ($n = 2298$, i.e. 63% of subjects in the PAQUID study) | | | | | | | | | | | | | | | | | | | | | | |
| B | 70.4 | 0 | 71.5 | 0 | 73.6 | 0 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | 85.2 | 1 |
| Diagnosed with dementia and alive at the latest follow-up ($n = 193$, i.e. 5% of subjects in the PAQUID study) | | | | | | | | | | | | | | | | | | | | | | |
| C | 73.1 | 0 | N/A | N/A | 76.2 | 0 | 78.2 | 0 | 80.8 | 0 | 83.1 | 1 | 85.9 | 1 | 87.9 | 1 | 90.7 | 1 | 93.7 | 1 | 93.7 | 0 |
| Diagnosed with dementia and died ($n = 639$, i.e. 17% of subjects in the PAQUID study) | | | | | | | | | | | | | | | | | | | | | | |
| D | 78.3 | 0 | N/A | N/A | N/A | N/A | 83.4 | 0 | 86.9 | 0 | 88.5 | 0 | 91.2 | 1 | N/A | N/A | N/A | N/A | N/A | N/A | 99.0 | 1 |

Dem, indicator of dementia (1 for yes, 0 for no); N/A, missing data because the subject missed the follow-up visit, or not applicable because the subject died earlier.
[a]Indicator of vital status at the latest news (1 for dead, 0 for alive).

# Illness-death model *vs* multi-state model with LTF state




(a)




(b)

# Previous works

- Leffondré et al. (2013): a semi-parametric illness-death model
- Frydman & Szarek (2009): nonparametric ML estimation
- Siannis et al. (2007) & Barrett et al. (2011): a multi-sate model with an unobserved state

# Five-states model

- State 0: the health state
- State 1: a state to represent an intermediate event (IE)
- State 2: the terminal state (absorbing state)
- State 3: a state to represent loss to follow-up (LTF) for the intermediate process
- State 4: the unobservable state that represents an intermediate event experienced after the subject is LTF
- cf. Siannis et al. (2007)

# Transition intensities

- $S = \{S(t),\ t \geq 0\}$ : a multi-state process
  - $S(t) \in \{0, 1, 2, 3, 4\}$
- The intensity of a transition from state $r$ to state $s$ at time $t$ is defined as

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

  - $\mathcal{A} = \{(r,s) : (r,s) = (0,1), (0,2), (0,3), (1,2), (3,2), (3,4), (4,2)\}$
  - $\lambda_{rs}(t) = 0,\ (r,s) \notin \mathcal{A}$
  - $\lambda_{34}(t)$, $\lambda_{42}(t)$, and $\lambda_{32}(t)$ : NOT identifiable $\Rightarrow$ need assumptions on both $\lambda_{34}(t)$ and $\lambda_{42}(t)$

# Constraints on $\lambda_{34}(t)$ and $\lambda_{42}(t)$

- $\lambda_{02}(t) - \lambda_{01}(t) = r\{\lambda_{32}(t) - \lambda_{34}(t)\},\ t \geq 0, r > 0$
    - No information in the data concerning the value of $r$
- $\lambda_{42}(t) = \lambda_{12}(t)$
- cf. Siannis et al. (2007), Barrett et al. (2011)

# Model

- Given $\mathbf{x}$ and $u$, the transition intensity of $r \to s$ is assumed to be

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

  - $\alpha_{rs}(\theta_{rs})$ : the scale (shape) parameter of the weibull distribution
  - $\boldsymbol{\beta}_{rs}$ : the vector of regression coefficients
  - $\gamma = \exp(u)$ : an unobservable log-normal frailty, $u \sim N(0, \sigma^2)$
- $\boldsymbol{\zeta} = (\boldsymbol{\alpha}', \boldsymbol{\theta}', \boldsymbol{\beta}'_{01}, \boldsymbol{\beta}'_{02}, \boldsymbol{\beta}'_{03}, \boldsymbol{\beta}'_{12}, \boldsymbol{\beta}'_{32}, \sigma^2)'$ : the vector of parameters to be estimated
  - $\boldsymbol{\alpha} = (\alpha_{01}, \alpha_{02}, \alpha_{03}, \alpha_{12}, \alpha_{32})'$, $\boldsymbol{\theta} = (\theta_{01}, \theta_{02}, \theta_{03}, \theta_{12}, \theta_{32})'$
  - $\alpha_{34}, \alpha_{42}, \theta_{34}, \theta_{42}, \boldsymbol{\beta}_{34}, \boldsymbol{\beta}_{42}$ : deterministic from the two constraints

# Cumulative transition intensity functions

- The cumulative transition functions for leaving state 0, 1, 3, and 4 between $t_1$ and $t_2$ are given by, respectively,

$$\begin{aligned}
H_0(t_1, t_2|\mathbf{x}, u) &= \int_{t_1}^{t_2} \{\lambda_{01}(s|\mathbf{x}, u) + \lambda_{02}(s|\mathbf{x}, u) + \lambda_{03}(s|\mathbf{x}, u)\} ds \\
&= \sum_{r=1}^{3} \gamma \left\{ \alpha_{0r} \left( t_2^{\theta_{0r}} - t_1^{\theta_{0r}} \right) + (\boldsymbol{\beta}_{0r}' \mathbf{x})(t_2 - t_1) \right\}, \\
H_1(t_1, t_2|\mathbf{x}, u) &= \int_{t_1}^{t_2} \lambda_{12}(s|\mathbf{x}, u) ds = \gamma \left\{ \alpha_{12} \left( t_2^{\theta_{12}} - t_1^{\theta_{12}} \right) + (\boldsymbol{\beta}_{12}' \mathbf{x})(t_2 - t_1) \right\}, \\
H_3(t_1, t_2|\mathbf{x}, u) &= \int_{t_1}^{t_2} \{\lambda_{32}(s|\mathbf{x}, u) + \lambda_{34}(s|\mathbf{x}, u)\} ds \\
&= \gamma \left\{ \alpha_{32} \left( t_2^{\theta_{32}} - t_1^{\theta_{32}} \right) + (\boldsymbol{\beta}_{32}' \mathbf{x} + \boldsymbol{\beta}_{34}' \mathbf{x})(t_2 - t_1) + \alpha_{34} \left( t_2^{\theta_{34}} - t_1^{\theta_{34}} \right) \right\} \\
H_4(t_1, t_2|\mathbf{x}, u) &= \int_{t_1}^{t_2} \lambda_{42}(s|\mathbf{x}, u) ds = \gamma \left\{ \alpha_{42} \left( t_2^{\theta_{42}} - t_1^{\theta_{42}} \right) + (\boldsymbol{\beta}_{42}' \mathbf{x})(t_2 - t_1) \right\}.
\end{aligned}$$

# Notation

- $R$ : time to an IE
- $T$ : time to terminal event
- $L$ : time to LTF
- $C$ : censoring time
- $\mathcal{H}_0(s) = \{R \wedge L \wedge T > s\}$ : the corresponding history to a subject who is in state 0 at time $s$
- $\mathcal{H}_{3,f}(s) = \{L = f, R \wedge T > s, f \leq s\}$ : the corresponding history to a subject whose LTF have occurred at time $f$ and who is in state 3 at time $s$

# Six routes

- Route 1: 0→0; Route 2: 0→2; Route 3: 0→1; Route 4: 0→1→2; Route 5: 0→3; Route 6: 0→3→2
- $I_{ij}$ $(i = 1, 2, \dots, n;\ j = 1, 2, \dots, 6)$ : an indicator function for subject $i$ taking route $j$
- $\mathcal{B}_j = \{i : I_{ij} = 1\}$ : a set of subjects taking route $j$

# Observed data

- $a_i$ : time at the visit before the diagnostic visit for subject $i$
- $b_i$ : time at the diagnostic visit for subject $i$
- $t_i$ : time at death or censoring for subject $i$
- Note that
  - $i \in \mathcal{B}_1 \cup \mathcal{B}_2 \Rightarrow a_i, b_i \geq t_i$
  - $i \in \mathcal{B}_3 \cup \mathcal{B}_4 \Rightarrow a_i < b_i \leq t_i$
  - $i \in \mathcal{B}_5 \cup \mathcal{B}_6 \Rightarrow a_i < t_i$, but $b_i < t_i$ or $b_i \geq t_i$
  - $i \in \mathcal{B}_1 \cup \mathcal{B}_3 \cup \mathcal{B}_5 \Rightarrow t_i$ : time at censoring
  - $i \in \mathcal{B}_2 \cup \mathcal{B}_4 \cup \mathcal{B}_5 \Rightarrow t_i$ : time at death

# Likelihood

- For route 1 ($i \in \mathcal{B}_1$),

$$\begin{aligned} Q_{i1}(t_i|\mathbf{x}_i, u_i) &= \Pr(R_i \wedge L_i \wedge T_i > t_i|\mathcal{H}_0(0), \mathbf{x}_i, u_i) \\ &= \exp\{-H_0(0, t_i|\mathbf{x}_i, u_i)\} \end{aligned}$$

- For route 2 ($i \in \mathcal{B}_2$),

$$\begin{aligned} Q_{i2}(t_i|\mathbf{x}_i, u_i) &= \Pr(T = t_i, R \wedge L > t_i|\mathcal{H}_0(0), \mathbf{x}_i, u_i) \\ &= Q_{i1}(t_i|\mathbf{x}_i, u_i)\lambda_{02}(t_i|\mathbf{x}_i, u_i) \end{aligned}$$

# Likelihood

- Using the algorithm proposed by Collett (2015), define a subset of the endpoints of $(a_{i'}, b_{i'}]$, $i' \in \mathcal{B}_3 \cup \mathcal{B}_4$, as

$$0 = s_0 < s_1 < s_2 < \cdots < s_l < s_{l+1} = \infty$$

  - $s_1$ : the smallest of the values of $b_{i'}$
  - $s_m$ $(m = 2, \ldots, l)$ : the smallest of the values of $b_{i'}$ such that $a_{i'} \geq s_{m-1}$

- Define the weight at time $s_m$ for subject $i'$ as

$$w_{i'm} = \frac{d_{i'm} \exp\left\{-H_0(0, s_m | \mathbf{x}_{i'}, u_{i'})\right\} \lambda_{01}(s_m | \mathbf{x}_{i'}, u_{i'})}{\sum_{m'=1}^{l} d_{i'm'} \exp\left\{-H_0(0, s_{m'} | \mathbf{x}_{i'}, u_{i'})\right\} \lambda_{01}(s_{m'} | \mathbf{x}_{i'}, u_{i'})}$$

  - $d_{i'm} = I(s_m \in (a_{i'}, b_{i'}])$

# Likelihood

| $i$ | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $a_1$ | | $b_1$ | | | | | | | |
| 2 | | $a_2$ | | | $b_2$ | | | | | |
| 3 | | | | $a_3$ | | | $b_3$ | | | |
| 4 | | | | | | $a_4$ | | $b_4$ | | |
| 5 | | | | | | | | $a_5$ | $b_5$ | |
| | $s_0$ | | $s_1$ | | | | $s_2$ | | $s_3$ | $s_4(=\infty)$ |

# Likelihood

- For route 3 ($i \in \mathcal{B}_3$),

$$
\begin{aligned}
Q_{i3}(a_i, b_i, t_i|\mathbf{x}_i, u_i) &= \Pr(R_i \in (a_i, b_i], L_i > t_i, T_i > t_i|\mathcal{H}_0(0), \mathbf{x}_i, u_i) \\
&= \exp\{-H_0(0, a_i|\mathbf{x}_i, u_i)\} \\
&\quad \times \sum_{m=1}^{I} [d_{im} w_{im} \exp\{-H_0(a_i, s_m|\mathbf{x}_i, u_i)\}\lambda_{01}(s_m|\mathbf{x}_i, u_i) \\
&\qquad \times \exp\{-H_1(s_m, b_i|\mathbf{x}_i, u_i)\}] \exp\{-H_1(b_i, t_i|\mathbf{x}_i, u_i)\} \\
&= \sum_{m=1}^{I} [d_{im} w_{im} \exp\{-H_0(0, s_m|\mathbf{x}_i, u_i)\}\lambda_{01}(s_m|\mathbf{x}_i, u_i) \\
&\qquad \times \exp\{-H_1(s_m, t_i|\mathbf{x}_i, u_i)\}]
\end{aligned}
$$

- For route 4 ($i \in \mathcal{B}_4$),

$$
\begin{aligned}
Q_{i4}(a_i, b_i, t_i|\mathbf{x}_i, u_i) &= \Pr(R_i \in (a_i, b_i], L_i > t_i, R_i < T_i = t_i|\mathcal{H}_0(0), \mathbf{x}_i, u_i) \\
&= Q_3(a_i, b_i, t_i|\mathbf{x}_i, u_i)\lambda_{12}(t_i|\mathbf{x}_i, u_i)
\end{aligned}
$$

# Likelihood

- For route 5 ($i \in \mathcal{B}_5$),

$$\begin{aligned} Q_{i5}(a_i, b_i, t_i|\mathbf{x}_i, u_i) &= \Pr(R_i \wedge T_i > t_i|\mathcal{H}_{3,a_i}(a_i), \mathbf{x}_i, u_i) \\ &\quad + \Pr(R_i \in (a_i, t_i], T_i > t_i|\mathcal{H}_{3,a_i}(a_i), \mathbf{x}_i, u_i) \\ &= \exp\{-H_0(0, a_i|\mathbf{x}_i, u_i)\}\lambda_{03}(a_i|\mathbf{x}_i, u_i)\Big[\exp\{-H_3(a_i, t_i|\mathbf{x}_i, u_i)\} \\ &\quad + \int_{a_i}^{t_i} \exp\{-H_3(a_i, s|\mathbf{x}_i, u_i)\}\lambda_{34}(s|\mathbf{x}_i, u_i)\exp\{-H_4(s, t_i|\mathbf{x}_i, u_i)\}ds\Big] \end{aligned}$$

- For route 6 ($i \in \mathcal{B}_6$),

$$\begin{aligned} Q_{i6}(a_i, b_i, t_i|\mathbf{x}_i, u_i) &= \Pr(R_i > T_i, T_i = t_i|\mathcal{H}_{3,a_i}(a_i), \mathbf{x}_i, u_i) \\ &\quad + \Pr(R_i \in (a_i, t_i], R_i < T_i = t_i|\mathcal{H}_{3,a_i}(a_i), \mathbf{x}_i, u_i) \\ &= \exp\{-H_1(0, a_i|\mathbf{x}_i, u_i)\}\lambda_{03}(a_i|\mathbf{x}_i, u_i) \\ &\quad \Big[\exp\{-H_3(a_i, t_i|\mathbf{x}_i, u_i)\}\lambda_{32}(t_i|\mathbf{x}_i, u_i) \\ &\quad + \Big\{\int_{a_i}^{t_i} \exp\{-H_3(a_i, s|\mathbf{x}_i, u_i)\}\lambda_{34}(s|\mathbf{x}_i, u_i)\exp\{-H_4(s, t_i|\mathbf{x}_i, u_i)\}ds\Big\} \\ &\quad \times\lambda_{42}(t_i|\mathbf{x}_i, u_i)\Big] \end{aligned}$$

# Likelihood

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

$$L(\zeta) = \prod_{i=1}^{n} \left\{ \prod_{j=1}^{6} Q_{ij}^{I_{ij}} \right\} \phi(0, \sigma^2; u_i)$$

  - $\phi(\cdot)$ : *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 minimizder of $f(\zeta) = -\log m(\zeta)$ using the iterative quasi-Newton algorithm
  - $\mathrm{Var}(\hat{\zeta})$ : the inverse of Hessian matrix evaluated at $\hat{\zeta}$

# Simulation setup

- IE was assessed at 15, 31,. . ., 166, 181(days) with $\pm N(0, 5^2)$ days
- Exponential baseline hazards with $\theta_{rs} = 1$
- $x$ : 0-1 binary covariate with a success probability of 0.5
- $\gamma = \exp(u)$ : $u \sim N(0, 0.1)$ frailty
- Fixed censoring at 181(days)
- $r$ : 1 for the first constraint

# Simulation setup: Regression parameters

**Table 0.1** Regression parameters in the different scenarios of the simulation study

| Scenario | $\beta_{01}$ | $\beta_{02}$ | $\beta_{12}$ | $\beta_{03}$ | $\beta_{32}$ |
|---|---|---|---|---|---|
| 1 | 0.004 | 0.004 | 0.004 | 0.006 | 0.006 |
| 2 | 0.004 | 0.006 | 0.006 | 0.006 | 0.006 |
| 3 | 0.004 | 0.004 | 0.006 | 0.006 | 0.006 |
| 4 | 0.004 | 0.006 | 0.008 | 0.006 | 0.006 |
| 5 | 0.004 | 0.004 | 0.002 | 0.006 | 0.006 |
| 6 | 0.004 | 0.006 | 0.004 | 0.006 | 0.006 |

# Simulation setup: Scale parameters of the weibull distribution

**Table 0.2** Scale parameters of the weibull distribution in the different death rates of the simulation study

| Death rate | $\alpha_{01}$ | $\alpha_{02}$ | $\alpha_{12}$ | $\alpha_{03}$ | $\alpha_{32}$ |
|---|---|---|---|---|---|
| Low | 0.002 | 0.001 | 0.0005 | 0.004 | 0.001 |
| Modertae | 0.002 | 0.002 | 0.001 | 0.004 | 0.002 |
| High | 0.002 | 0.003 | 0.0015 | 0.004 | 0.003 |

# Simulated data generation

- Step 1: generate $R$, $T$, and $Lf$
  - $R$ : a solution to $\Lambda_{01}(t|x,u) + \ln(1-U_{01}) = 0$ *wrt* $t$, $U_{01} \sim U[0,1]$
  - $T$ : a solution to $\Lambda_{02}(t|x,u) + \ln(1-U_{02}) = 0$ *wrt* $t$, $U_{02} \sim U[0,1]$
  - $L$ : a solution to $\Lambda_{03}(t|x,u) + \ln(1-U_{03}) = 0$ *wrt* $t$, $U_{03} \sim U[0,1]$
  - If $C \leq R \wedge T \wedge L$, censored w/o being relapsed; stop $\Rightarrow$ Route 1
  - If $R = R \wedge T \wedge L$, relapsed; goto Step 2
  - If $T = R \wedge T \wedge L$, dead w/o being relapsed; stop $\Rightarrow$ Route 2
  - If $L = R \wedge T \wedge L$, LTF; goto Step 3
- Step 2: update $T$
  - $T$ : a solution to $\Lambda_{12}(t|x,u) + \ln(1-U_{12}) = 0$ *wrt* $t$, $U_{12} \sim U[1-\exp\{-\Lambda_{01}(R|x,u)\},1]$
  - If $C = T \wedge C$, censored w/ being relapsed; stop $\Rightarrow$ Route 3
  - If $T = T \wedge C$, dead w/ being relapsed; stop $\Rightarrow$ Route 4

# Simulated data generation

- Step 3: update $T$ and $R$
  - $T$ : a solution to $\Lambda_{32}(t|x,u) + \ln(1 - U_{32}) = 0$ *wrt* $t$, $U_{32} \sim U[1 - \exp\{-\Lambda_{32}(L|x,u)\}, 1]$
  - $R$ : a solution to $\Lambda_{34}(t|x,u) + \ln(1 - U_{34}) = 0$ *wrt* $t$, $U_{34} \sim U[1 - \exp\{-\Lambda_{34}(L|x,u)\}, 1]$
  - If $C \leq T \wedge R$, censored after LTF w/o being relapsed; stop $\Rightarrow$ Route 5
  - If $T = T \wedge R$, dead after LTF w/o being relapsed; stop $\Rightarrow$ Route 6
  - If $R = T \wedge R$, relapsed after LTF; goto Step 4
- Step 4: update $T$
  - $T$ : a solution to $\Lambda_{42}(t|x,u) + \ln(1 - U_{42}) = 0$ *wrt* $t$, $U_{42} \sim U[1 - \exp\{-\Lambda_{42}(R|x,u)\}, 1]$
  - If $C = T \wedge C$, censored after LTF w/ being relapsed; stop $\Rightarrow$ Route 5
  - If $T = T \wedge C$, dead after LTF w/ being relapsed; stop $\Rightarrow$ Route 6

# Simulation results: Average percentage of death event rates

**Table 0.3** Average percentage of death event rates in the different scenarios of the simulation study based on 500 data sets of 200 subjects each

| Scenario | Route | Low | Moderate | High |
|---|---|---|---|---|
| 1 | 2 | 22 | 28 | 31 |
| | 4 | 5 | 8 | 6 |
| | 6 | 17 | 19 | 19 |
| | **2 or 4 or 6** | **15** | **18** | **19** |
| 2 | 2 | 20 | 26 | 31 |
| | 4 | 7 | 8 | 7 |
| | 6 | 17 | 22 | 20 |
| | **2 or 4 or 6** | **15** | **18** | **19** |
| 3 | 2 | 18 | 24 | 29 |
| | 4 | 10 | 10 | 6 |
| | 6 | 15 | 18 | 20 |
| | **2 or 4 or 6** | **14** | **17** | **18** |
| 4 | 2 | 27 | 33 | 38 |
| | 4 | 8 | 8 | 7 |
| | 6 | 15 | 15 | 14 |
| | **2 or 4 or 6** | **16** | **18** | **19** |
| 5 | 2 | 13 | 20 | 25 |
| | 4 | 3 | 7 | 7 |
| | 6 | 11 | 15 | 15 |
| | **2 or 4 or 6** | **9** | **14** | **16** |
| 6 | 2 | 25 | 28 | 33 |
| | 4 | 8 | 8 | 8 |
| | 6 | 13 | 17 | 22 |
| | **2 or 4 or 6** | **15** | **18** | **21** |

# Simulation results: Empirical coverage rates

**Table 0.4** Empirical results of the proposed method in terms of the average of the relative bias(R.Bias) and the standard errors(SEM) and the coverage probability(CP) based on 500 data sets of 200 subjects each

| | | | Low | | | | Moderate | | | | High | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scenario | Param. | True | R.Bias (%) | SD ($\times 10^5$) | SEM ($\times 10^5$) | CP (%) | R.Bias (%) | SD ($\times 10^5$) | SEM ($\times 10^5$) | CP (%) | R.Bias (%) | SD ($\times 10^5$) | SEM ($\times 10^5$) | CP (%) |
| 1 | $\beta_{01}$ | 0.004 | -8.1 | 109 | 116 | 94.0 | -10.3 | 122 | 119 | 90.6 | -10.1 | 115 | 121 | 93.2 |
| | $\beta_{02}$ | 0.004 | 2.7 | 103 | 107 | 94.6 | 2.5 | 122 | 122 | 94.6 | 3.1 | 131 | 137 | 96.6 |
| | $\beta_{03}$ | 0.006 | -2.8 | 170 | 173 | 96.2 | -3.3 | 178 | 175 | 92.8 | -5.1 | 187 | 176 | 92.2 |
| | $\beta_{12}$ | 0.004 | -10.9 | 111 | 112 | 91.0 | -9.7 | 131 | 127 | 92.2 | -7.0 | 142 | 149 | 96.2 |
| | $\beta_{32}$ | 0.006 | 4.5 | 148 | 157 | 95.8 | 9.8 | 173 | 179 | 96.6 | 6.3 | 192 | 196 | 96.4 |
| | $\sigma^2$ | 0.1 | 102.0 | 16935 | 12758 | 90.0 | 84.9 | 14554 | 11999 | 91.8 | 65.5 | 13395 | 11531 | 92.6 |
| 2 | $\beta_{01}$ | 0.004 | -10.9 | 117 | 118 | 91.4 | -10.5 | 117 | 123 | 92.6 | -12.9 | 123 | 124 | 93.0 |
| | $\beta_{02}$ | 0.006 | -0.4 | 114 | 124 | 95.6 | -0.7 | 140 | 139 | 94.4 | 0.7 | 159 | 153 | 93.4 |
| | $\beta_{03}$ | 0.006 | -2.0 | 183 | 176 | 92.8 | -1.9 | 172 | 179 | 96.2 | -3.2 | 185 | 181 | 92.4 |
| | $\beta_{12}$ | 0.006 | -9.5 | 143 | 150 | 91.0 | -6.7 | 182 | 167 | 90.6 | -5.6 | 186 | 186 | 94.4 |
| | $\beta_{32}$ | 0.006 | 6.8 | 150 | 154 | 96.2 | 7.9 | 196 | 177 | 95.0 | 9.1 | 200 | 194 | 96.8 |
| | $\sigma^2$ | 0.1 | 82.2 | 16444 | 12239 | 89.6 | 75.5 | 17585 | 11683 | 86.4 | 62.0 | 16508 | 11178 | 87.2 |
| 3 | $\beta_{01}$ | 0.004 | -13.5 | 103 | 113 | 92.4 | -13.1 | 115 | 118 | 91.0 | -13.2 | 124 | 120 | 89.6 |
| | $\beta_{02}$ | 0.004 | 1.8 | 99 | 105 | 95.8 | 1.1 | 118 | 120 | 96.2 | 0.3 | 139 | 135 | 95.8 |
| | $\beta_{03}$ | 0.006 | -4.4 | 185 | 170 | 93.0 | -2.4 | 181 | 173 | 93.0 | -3.4 | 178 | 176 | 95.0 |
| | $\beta_{12}$ | 0.006 | -10.3 | 146 | 141 | 88.4 | -7.6 | 153 | 158 | 91.8 | -4.8 | 159 | 174 | 95.6 |
| | $\beta_{32}$ | 0.006 | 7.1 | 143 | 155 | 96.6 | 6.6 | 193 | 177 | 95.4 | 7.8 | 202 | 196 | 94.4 |
| | $\sigma^2$ | 0.1 | 112.8 | 19191 | 12698 | 88.6 | 90.9 | 17250 | 12046 | 87.6 | 62.9 | 15384 | 11143 | 86.8 |
| 4 | $\beta_{01}$ | 0.004 | -12.7 | 117 | 117 | 90.6 | -13.2 | 117 | 120 | 89.4 | -12.3 | 131 | 125 | 89.8 |
| | $\beta_{02}$ | 0.006 | 1.9 | 130 | 125 | 94.8 | 0.1 | 134 | 137 | 95.2 | 3.2 | 153 | 155 | 97.6 |
| | $\beta_{03}$ | 0.006 | -5.6 | 176 | 174 | 93.4 | -6.7 | 184 | 177 | 90.8 | -2.5 | 191 | 183 | 94.2 |
| | $\beta_{12}$ | 0.008 | -11.7 | 167 | 179 | 91.0 | -6.4 | 195 | 200 | 94.6 | -9.5 | 216 | 215 | 90.8 |
| | $\beta_{32}$ | 0.006 | 8.0 | 170 | 156 | 94.0 | 8.4 | 185 | 175 | 96.2 | 8.6 | 193 | 195 | 96.8 |
| | $\sigma^2$ | 0.1 | 81.2 | 15998 | 12026 | 92.4 | 88.7 | 16223 | 12005 | 89.2 | 80.3 | 15959 | 11828 | 92.8 |
| 5 | $\beta_{01}$ | 0.004 | -3.9 | 110 | 118 | 95.8 | -6.8 | 118 | 119 | 92.8 | -5.2 | 122 | 124 | 94.6 |
| | $\beta_{02}$ | 0.004 | 2.7 | 104 | 108 | 96.4 | -0.1 | 125 | 121 | 95.2 | 5.0 | 149 | 139 | 95.8 |
| | $\beta_{03}$ | 0.006 | 0.0 | 178 | 174 | 95.2 | -1.6 | 175 | 174 | 96.2 | -0.9 | 167 | 180 | 96.4 |
| | $\beta_{12}$ | 0.002 | -11.6 | 81 | 82 | 94.2 | -12.1 | 97 | 100 | 95.6 | -7.4 | 122 | 120 | 95.2 |
| | $\beta_{32}$ | 0.006 | 2.6 | 166 | 157 | 95.2 | 5.2 | 187 | 177 | 93.2 | 4.4 | 219 | 198 | 93.8 |
| | $\sigma^2$ | 0.1 | 100.3 | 21007 | 13223 | 89.4 | 100.3 | 21007 | 13223 | 89.4 | 72.1 | 15134 | 11907 | 90.2 |
| 6 | $\beta_{01}$ | 0.004 | -8.1 | 129 | 121 | 92.4 | -7.0 | 127 | 125 | 92.6 | -9.6 | 129 | 126 | 92.4 |
| | $\beta_{02}$ | 0.006 | -1.9 | 127 | 124 | 94.6 | -1.6 | 134 | 140 | 96.0 | -1.9 | 156 | 152 | 94.0 |
| | $\beta_{03}$ | 0.006 | -0.1 | 182 | 179 | 94.8 | 0.4 | 179 | 183 | 95.8 | -2.7 | 187 | 183 | 94.2 |
| | $\beta_{12}$ | 0.004 | -7.8 | 114 | 120 | 93.2 | -8.1 | 124 | 134 | 94.0 | -6.0 | 142 | 155 | 95.4 |
| | $\beta_{32}$ | 0.006 | 3.6 | 157 | 153 | 95.8 | 5.0 | 171 | 174 | 95.6 | 6.2 | 180 | 191 | 97.0 |
| | $\sigma^2$ | 0.1 | 77.4 | 17865 | 12317 | 90.4 | 97.5 | 19692 | 12513 | 86.8 | 69.4 | 15080 | 11906 | 93.0 |

# Sensitivity analysis: Choice of $r$

**Table 0.5** SENSITIVITY ANALYSIS OF THE PROPOSED METHOD DEPENDING ON THE DETERMINATION OF THE RATIO $r$ IN TERMS OF THE AVERAGE OF THE RELATIVE BIAS(R.BIAS) AND THE STANDARD ERRORS(SEM) AND THE COVERAGE PROBABILITY(CP) BASED ON 500 DATA SETS OF 200 SUBJECTS EACH

| | | $r$ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.5 | | | 0.75 | | | 1.5 | | | 2 | | |
| Param. | True | R.Bias (%) | SEM ($\times 10^5$) | CP (%) | R.Bias (%) | SEM ($\times 10^5$) | CP (%) | R.Bias (%) | SEM ($\times 10^5$) | CP (%) | R.Bias (%) | SEM ($\times 10^5$) | CP (%) |
| $\beta_{01}$ | 0.004 | -13.1 | 118 | 90.4 | -13.5 | 118 | 90.2 | -13.3 | 118 | 91.6 | -14.2 | 118 | 91.0 |
| $\beta_{02}$ | 0.004 | 1.4 | 121 | 97.2 | 0.0 | 120 | 95.8 | 1.4 | 121 | 96.2 | 3.5 | 121 | 95.4 |
| $\beta_{03}$ | 0.006 | -1.3 | 174 | 91.4 | -1.4 | 174 | 92.6 | -1.8 | 174 | 92.4 | -2.6 | 173 | 92.0 |
| $\beta_{12}$ | 0.006 | -8.2 | 158 | 90.8 | -9.0 | 157 | 91.4 | -8.5 | 158 | 91.4 | -9.6 | 157 | 90.6 |
| $\beta_{32}$ | 0.006 | 7.0 | 178 | 95.2 | 7.4 | 178 | 93.6 | 8.5 | 179 | 95.2 | 7.2 | 177 | 95.2 |
| $\sigma^2$ | 0.1 | 89.8 | 12307 | 92.4 | 100.8 | 12424 | 89.2 | 100.4 | 12472 | 86.4 | 91.7 | 12207 | 88.2 |

# Sensitivity analysis: Misspecification of frailty distribution

**Table 0.6** SENSITIVITY ANALYSIS OF THE PROPOSED METHOD DEPENDING ON THE UNDERLYING FRAILTY DISTRIBUTION IN TERMS OF THE AVERAGE OF THE RELATIVE BIAS(R.BIAS) AND THE STANDARD ERRORS(SEM) AND THE COVERAGE PROBABILITY(CP) BASED ON 500 DATA SETS OF 200 SUBJECTS EACH

| | | $N(0, 0.2)$ | | | $U(-0.775, 0.775)$ | | | $DE(0.316)$ | | | $G(5.483, 0.2)$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | R.Bias | SEM | CP | R.Bias | SEM | CP | R.Bias | SEM | CP | R.Bias | SEM | CP |
| Param. | True | (%) | ($\times 10^5$) | (%) | (%) | ($\times 10^5$) | (%) | (%) | ($\times 10^5$) | (%) | (%) | ($\times 10^5$) | (%) |
| $\beta_{01}$ | 0.004 | -14.3 | 119 | 86.0 | -14.3 | 119 | 90.4 | -13.5 | 118 | 89.4 | -15.3 | 119 | 88.2 |
| $\beta_{02}$ | 0.004 | 3.5 | 123 | 97.2 | 3.4 | 124 | 95.8 | 1.8 | 122 | 92.8 | 1.0 | 123 | 96.4 |
| $\beta_{03}$ | 0.006 | -7.2 | 175 | 91.2 | -4.3 | 176 | 95.0 | -6.4 | 174 | 92.0 | -7.4 | 174 | 90.0 |
| $\beta_{12}$ | 0.006 | -8.7 | 160 | 92.6 | -6.0 | 161 | 91.2 | -6.3 | 162 | 93.0 | -6.3 | 161 | 95.2 |
| $\beta_{32}$ | 0.006 | 6.8 | 182 | 95.2 | 9.7 | 184 | 95.8 | 6.9 | 181 | 96.4 | 9.6 | 183 | 96.6 |
| $\sigma^2$ | 0.2 | 29.8 | 13401 | 83.2 | 27.8 | 13288 | 86.0 | 21.2 | 13005 | 81.2 | 24.8 | 13142 | 83.4 |

# Illustrative example: PAQUID data set

- Personnes Ages 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 set included in the R package 'SmoothHazard'
- If time difference between the last visit and the latest follow-up of a subject is greater than 4 years, the subject is defined as being lost to follow-up since the last vist
  - 231 were LTF including 159 (68.8%) who died
  - Among 186 who were diagnosed with dementia, 127 (68.3%) died
  - Among 583 who were never diagnosed with dementia, 438 (75.1%) died
- Covariates: sex: 0=female, 1=male; primary school certificate: 0=w/ , 1=w/o certificate

# Analysis of Paq1000 data set

**Table 0.7** Regression parameter estimates(Est), their standard errors(SE), and p-values(P) according to a choice of $r$

| | | $r$ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.5 | | | 1 | | | 1.5 | | | 2 | | |
| Covariate | $\zeta$ | Est ($\times 10^4$) | SE ($\times 10^4$) | $P$ | Est ($\times 10^4$) | SE ($\times 10^4$) | $P$ | Est ($\times 10^4$) | SE ($\times 10^4$) | $P$ | Est $\times 10^4$ | SE ($\times 10^4$) | $P$ |
| Sex | $\beta_{011}$ | -7.7 | 3.3 | 0.028 | -7.7 | 3.3 | 0.028 | -7.6 | 3.3 | 0.028 | -7.6 | 3.3 | 0.028 |
| | $\beta_{021}$ | 19.5 | 5.4 | 0.001 | 19.5 | 5.4 | 0.001 | 19.5 | 5.4 | 0.001 | 19.6 | 5.4 | 0.001 |
| | $\beta_{031}$ | -5.4 | 3.7 | 0.151 | -5.4 | 3.7 | 0.152 | -5.4 | 3.7 | 0.151 | -5.4 | 3.7 | 0.152 |
| | $\beta_{121}$ | 466.2 | 301.5 | 0.132 | 470.6 | 301.4 | 0.128 | 470.8 | 301.1 | 0.128 | 472.0 | 301.2 | 0.127 |
| | $\beta_{321}$ | 41.9 | 89.8 | 0.644 | 30.6 | 90.2 | 0.737 | 26.5 | 90.2 | 0.771 | 24.7 | 90.4 | 0.787 |
| Certificate | $\beta_{012}$ | -6.3 | 3.6 | 0.088 | -6.3 | 3.6 | 0.089 | -6.3 | 3.6 | 0.089 | -6.3 | 3.6 | 0.089 |
| | $\beta_{022}$ | 1.4 | 6.0 | 0.819 | 1.4 | 6.0 | 0.818 | 1.4 | 6.0 | 0.821 | 1.4 | 6.0 | 0.819 |
| | $\beta_{032}$ | -0.6 | 4.3 | 0.887 | -0.6 | 4.3 | 0.890 | -0.6 | 4.3 | 0.888 | -0.6 | 4.3 | 0.890 |
| | $\beta_{122}$ | -351.2 | 304.9 | 0.258 | -346.8 | 305.1 | 0.264 | -345.9 | 305.0 | 0.265 | -344.9 | 305.1 | 0.267 |
| | $\beta_{322}$ | 94.5 | 119.3 | 0.434 | 93.4 | 119.9 | 0.442 | 92.9 | 120.1 | 0.445 | 92.7 | 120.2 | 0.446 |
| | $\sigma^2$ | 60.2 | 65.1 | 0.362 | 64.9 | 67.6 | 0.344 | 62.2 | 65.9 | 0.353 | 64.7 | 67.4 | 0.345 |
| $-2\log L$ | | 13157 | | | 13146 | | | 13141 | | | 13151 | | |
| AIC | | 13189 | | | 13178 | | | 13173 | | | 13183 | | |

# Concluding remarks

- Propose a Lin-Ying-type transition intensity model with a log-normal frailty to analyze the semi-competing risks data with missing intermediate events
- Based on the simulation results, the proposed method satisfied the nominal level of CP
- Moreover the proposed method was robust to the choice of $r$ and a misspecification of the underlying frailty distribution

Thank you!