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Comparison between the marginal hazard and sub-distribution hazard with an assumed copula

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Competing risks

- Survival is determined by several different events of failures (Cox and Oakes 1984)

Example A:

Death due to breast cancer (Event 1)

Death due to other cancers (Event 2)

Example B:

Death (Event 1)

Dropout (Event 2)

Classical competing risks

- X : time to "Event 1"
- Y : time to "Event 2"
- $T = \min(X, Y)$: first occurring event time
- $\delta = \mathbf{I}(T = X)$: event type indicator

Marginal hazard functions

$$\begin{cases} \lambda_1(t) = \Pr(t \le X \le t + dt \mid X \ge t)/dt, \\ \lambda_2(t) = \Pr(t \le Y \le t + dt \mid Y \ge t)/dt, \end{cases}$$

***Marginal distributions are not identifiable from observed quantities** (T, δ)
:Nonidentifiability (Tsiatis 1975)

Three approaches to avoid nonidentifiability

- Cause-specific hazard (Kalbfleish & Prentice 2002)

$$\begin{cases} \lambda_1^{CS}(t) = \Pr(t \le T < t + dt, \delta = 1 \mid T \ge t) / dt, \\ \lambda_2^{CS}(t) = \Pr(t \le T < t + dt, \delta = 0 \mid T \ge t) / dt. \end{cases}$$

- Sub-distribution hazard (Fine & Gray 1999)

$$\begin{cases} \lambda_1^{Sub}(t) = \Pr(t \le T < t + dt, \delta = 1 \mid \{T \ge t\} \cup \{T < t, \delta = 0\}) / dt, \\ \lambda_2^{Sub}(t) = \Pr(t \le T < t + dt, \delta = 0 \mid \{T \ge t\} \cup \{T < t, \delta = 1\}) / dt. \end{cases}$$

- Assumed copula (Zheng & Klein 1995: Escarela & Carrière 2003)

$$\Pr(X > x, Y > y) = C_\theta\{S_1(x), S_2(y)\}$$

$$\begin{cases} S_1(t) = \exp[-\Lambda_1(t)] = \exp\left[-\int_0^t \lambda_1(s)ds\right], \\ S_2(t) = \exp[-\Lambda_2(t)] = \exp\left[-\int_0^t \lambda_2(s)ds\right]. \end{cases}$$

Copula

The Clayton copula:

$$C_\theta(u,v) = (u^{-\theta} + v^{-\theta} - 1)^{-1/\theta}, \qquad \theta > 0,$$

The Gumbel copula:

$$C_\theta(u,v) = \exp\left[-\{ (-\log u)^{\theta+1} + (-\log v)^{\theta+1} \}^{\frac{1}{\theta+1}} \right], \qquad \theta \geq 0,$$

The Farlie-Gumbel-Morgenstern (FGM) copula:

$$C_\theta(u,v) = uv\{1 + \theta(1-u)(1-v)\}, \qquad -1 \leq \theta \leq 1.$$

Independent risks assumption

$$X \perp Y$$

- Marginal hazard **<=>** Cause-specific hazard

$$\lambda_1(t) = \lambda_1^{CS}(t)$$

- Marginal hazard **<=>** Sub-hazard

$$\lambda_1^{Sub}(t) = \lambda_1(t)\frac{\exp\{-\Lambda_1(t)-\Lambda_2(t)\}}{1-\int_0^t \lambda_1(s)\exp\{-\Lambda_1(s)-\Lambda_2(s)\}dx}$$

Assumed copula

$$\Pr(X > x, Y > y) = C_\theta\{S_1(x), S_2(y)\}$$

***Theorem 1**: The marginal hazard and sub-hazard are connected through the equation*

$$\lambda_1^{Sub}(t) = \lambda_1(t)\frac{D_\theta^{[1,0]}\{\Lambda_1(t), \Lambda_2(t)\}}{1-\int_0^t \lambda_1(s) D_\theta^{[1,0]}\{\Lambda_1(s), \Lambda_2(s)\}ds},$$

$$\lambda_2^{Sub}(t) = \lambda_2(t)\frac{D_\theta^{[0,1]}\{\Lambda_1(t), \Lambda_2(t)\}}{1-\int_0^t \lambda_2(s) D_\theta^{[0,1]}\{\Lambda_1(s), \Lambda_2(s)\}ds}.$$

where $D_\theta(s,t) = C_\theta\{\exp(-s), \exp(-t)\}$,

$D_\theta^{[1,0]}(s,t) = -\frac{\partial}{\partial s} D_\theta(s,t)$, and $D_\theta^{[0,1]}(s,t) = -\frac{\partial}{\partial t} D_\theta(s,t)$

Example 1 (Clayton copula)

By Theorem 1,

$$\lambda_1^{Sub}(t) = \lambda(t)\frac{2\exp\{\theta\Lambda(t)\}[2\exp\{\theta\Lambda(t)\}-1]^{-1/\theta-1}}{1+[2\exp\{\theta\Lambda(t)\}-1]^{-1/\theta}}.$$

Under the Weibull model of $\Lambda(t)=\lambda t^{\nu}$,

$$\lambda_1^{Sub}(t) = \lambda\nu t^{\nu-1}\frac{2\exp(\lambda\theta t^{\nu})\{2\exp(\lambda\theta t^{\nu})-1\}^{-1/\theta-1}}{1+\{2\exp(\lambda\theta t^{\nu})-1\}^{-1/\theta}}.$$

Under the log-logistic (or Pareto type II) model of $\Lambda(t)=\gamma\log(1+\lambda t)$,

$$\lambda_1^{Sub}(t) = \frac{\gamma\lambda}{1+\lambda t}\frac{2(1+\lambda t)^{\theta\gamma}[2(1+\lambda t)^{\theta\gamma}-1\}^{-1/\theta-1}}{1+[2(1+\lambda t)^{\theta\gamma}-1\}^{-1/\theta}}.$$

Example: Clayton copula

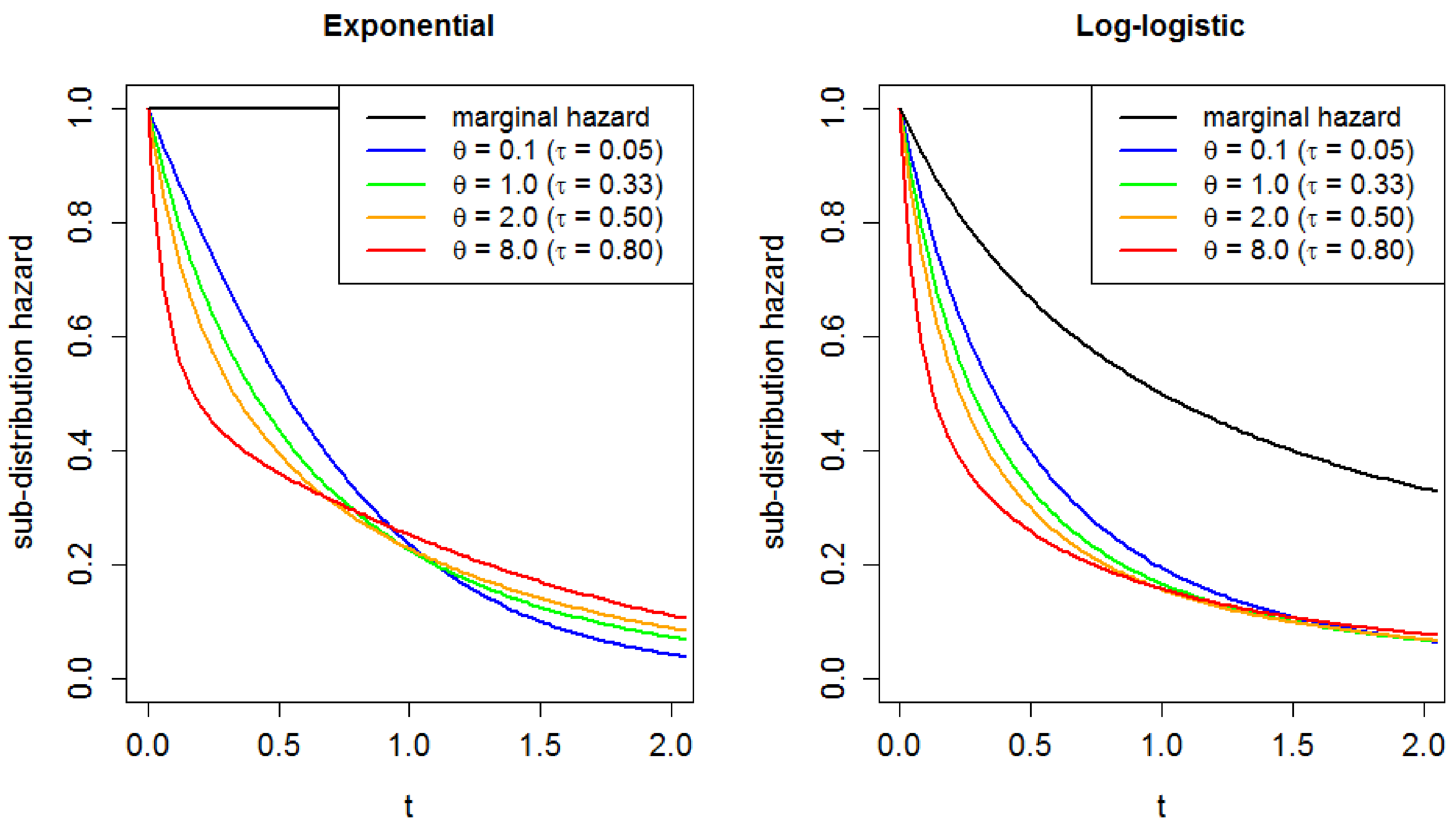


Figure 1. The marginal hazard and sub hazard under the Clayton copula.

The exponential model ($\nu = 1$) for the left, and log-logistic model ($\gamma = 1$) for the right.

How covariates affect hazards ?

Assume a marginal Cox model for Cause 1:

$$\lambda_1(t \mid \mathbf{Z}) = \lambda_{10}(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z})$$

By Theorem 1,

$$\lambda_1^{Sub}(t \mid \mathbf{Z}) = \lambda_{10}(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z})\frac{D_\theta^{[1,0]}\{\Lambda_{10}(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z}),\Lambda_2(t)\}}{1-\int_0^t \lambda_{10}(s)\exp(\boldsymbol{\beta}_1'\mathbf{Z})D_\theta^{[1,0]}\{\Lambda_{10}(s)\exp(\boldsymbol{\beta}_1'\mathbf{Z}),\Lambda_2(s)\}ds}$$

A non-proportional sub-distribution hazard in **Z**

⇨ The proportional sub-distribution model (Fine and Gray 1999)

$$\lambda_1^{Sub}(t \mid \mathbf{Z}) = \lambda_{10}^{Sub}(t)\exp(\boldsymbol{\beta}_1^{Sub}\mathbf{Z})$$ does not hold !.

Statistical Inference

- X_i : time to Event 1
- Y_j : time to Event 2
- C_j : independent censoring time
- $\mathbf{Z}_j$: covariates

Observed data: $(T_j, \delta_{1j}, \delta_{2j}, \mathbf{Z}_j)$, $j = 1, 2, ..., n$.

$$T_j = \min(X_j, Y_j, C_j), \quad \delta_{1j} = \mathbf{I}(T_j = X_j), \quad \delta_{2j} = \mathbf{I}(T_j = Y_j)$$

Inference

The Cox model on the sub hazards (Fine and Gray 1999)

$$\lambda_{1j}^{Sub}(t \mid \mathbf{Z}_j) = \lambda_{10}^{Sub}(t)\exp(\boldsymbol{\beta}_1^{Sub}\mathbf{Z}_j)$$

$\hat{\boldsymbol{\beta}}_1^{Sub}$ = the *cmprsk* R package (Gray 2014)

The Cox model on the marginal hazards (Chen 2010)

$$\lambda_{1j}(t \mid \mathbf{Z}_j) = \lambda_{10}(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z}_j), \qquad \lambda_{2j}(t \mid \mathbf{Z}_j) = \lambda_{20}(t)\exp(\boldsymbol{\beta}_2'\mathbf{Z}_j).$$

$$\Pr(X_j > x, Y_j > y \mid \mathbf{Z}_j) = C_\theta[\exp\{-\Lambda_{1j}(x \mid \mathbf{Z}_j)\}, \exp\{-\Lambda_{2j}(y \mid \mathbf{Z}_j)\}],$$

$(\hat{\boldsymbol{\beta}}_1, \hat{\boldsymbol{\beta}}_2, \hat{\Lambda}_{10}, \hat{\Lambda}_{20})$ = a semi-parametric MLE (Chen 2010).

θ must be pre-specified (assumed) to avoid nonidentifiability

Data: 125 lung cancer patients (Chen et al 2007)

- X_i = time-to-death (Cause 1)
- Y_j = time-to-dropout (Cause 2)
- Covariate = gene expression of *ZNF264*

The sub hazard model for Cause 1 (death)

$$\lambda_{1j}^{Sub}(t) = \lambda_{10}^{Sub}(t)\exp(\beta_1^{Sub} \times ZNF264_j),$$

The sub hazard model for Cause 2 (dropout)

$$\lambda_{2j}^{Sub}(t) = \lambda_{20}^{Sub}(t)\exp(\beta_2^{Sub} \times ZNF264_j).$$

The Cox model on the marginal hazards for Cause 1 and Cause 2 are specified as

$$\begin{cases} \lambda_{1j}(t) = \lambda_{10}(t)\exp(\beta_1 \times ZNF264_j) \\ \lambda_{2j}(t) = \lambda_{20}(t)\exp(\beta_2 \times ZNF264_j) \\ \Pr(X_j > x, Y_j > y) = [\exp\{\theta\Lambda_{1j}(x)\} + \exp\{\theta\Lambda_{2j}(y)\} - 1]^{-1/\theta} \end{cases}$$

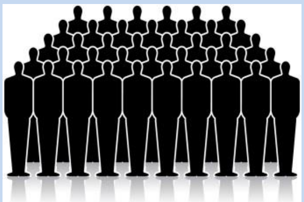
where we specified $\theta = 0$, 0.5, 2, or 8 ($\tau = 0$, 0.2, 0.5, or 0.8)

Table 1. Analysis of the lung cancer data usingthe sub hazard and the marginal hazard model[s]

		Cause 1 (death)	Cause 2 (censoring)
Sub hazard	$\hat{\beta}^{Sub}$	0.547	0.258
	(95%CI)	(0.200, 0.895)	(-0.179, 0.696)
Marginal (θ=0, τ=0)	$\hat{\beta}$	0.548	0.259
	(95%CI)	(0.144, 0.952)	(-0.176, 0.693)
Marginal (θ=0.5, τ=0.2)	$\hat{\beta}$	0.570	0.280
	(95%CI)	(0.162, 0.979)	(-0.143, 0.704)
Marginal (θ=2, τ=0.5)	$\hat{\beta}$	0.593	0.349
	(95%CI)	(0.198, 0.987)	(-0.051, 0.748)
Marginal (θ=8, τ=0.8)	$\hat{\beta}$	0.561	0.453
	(95%CI)	(0.251, 0.872)	(0.156, 0.751)

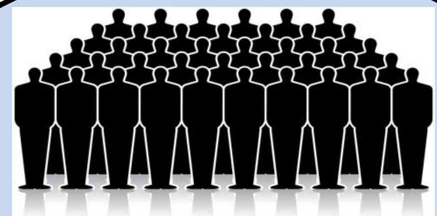
Extension to clustered data

Cluster 1 (Medium risk)



N_1=110

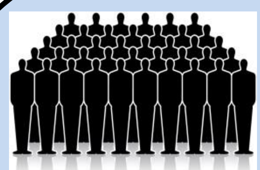
Cluster 3 (Medium risk)



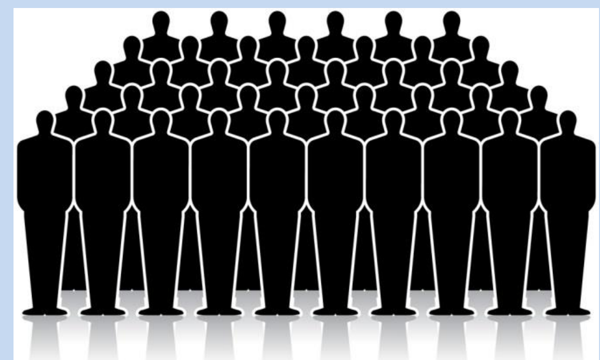
N_3=278

Cluster 4 (Low risk)

Cluster 2 (High risk)



N_2=58



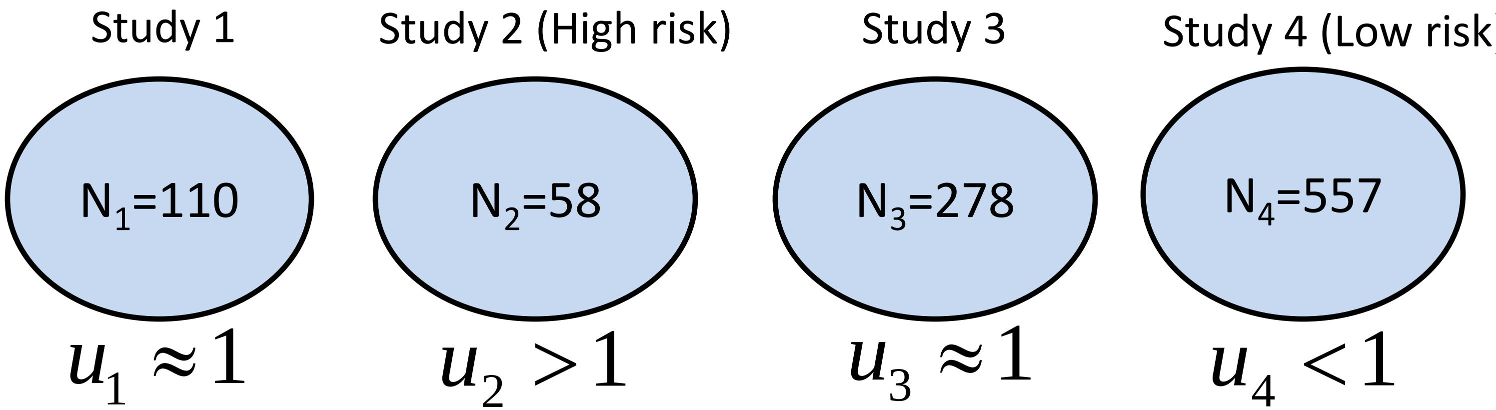
N_4=557

Combined sample size :

$$\sum_{i=1}^{4} N_i = 110 + 278 + 58 + 557$$

$$= 1003$$

- Shared frailty models



Gamma frailty :

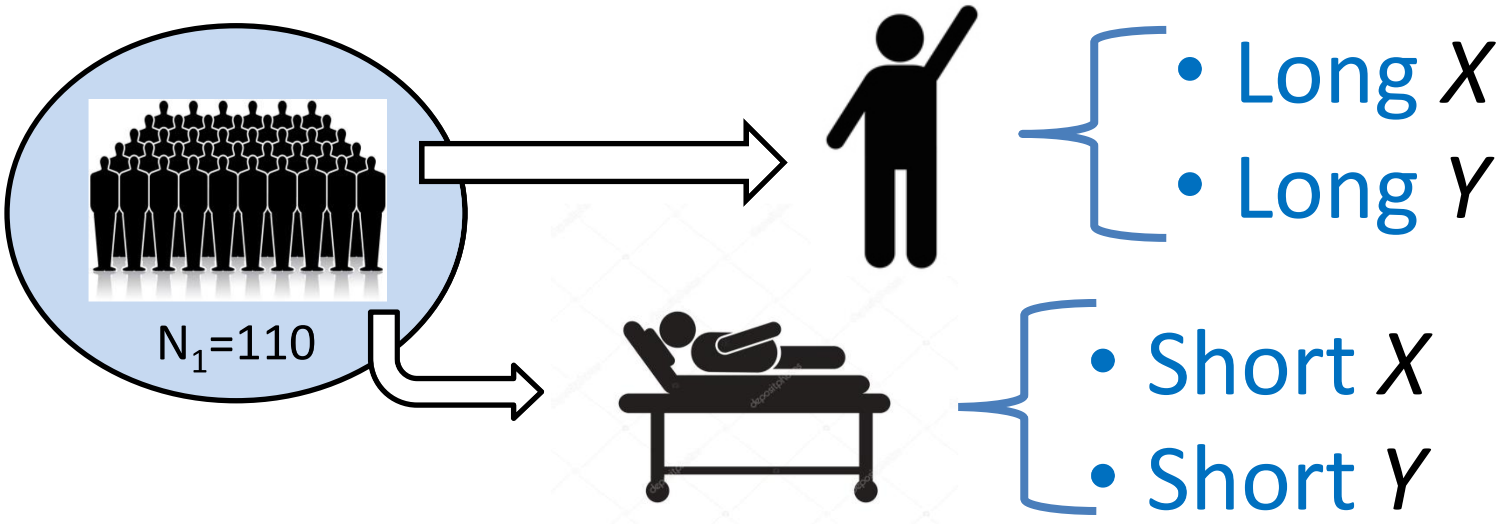
$$u_i \sim f_\eta(u) = \frac{1}{\Gamma(1/\eta)\eta^{1/\eta}} u^{\frac{1}{\eta}-1} \exp\left(-\frac{u}{\eta}\right),$$

$$\begin{cases} E[u_i] = 1 \\ Var[u_i] = \eta \end{cases}$$

Ref:(Burzykowski et al. 2001; Duchateau and Janssen 2007 Rondeau et al. 2011; Ha et al. 2018)

- X_{ij} : time to Event 1
- Y_{ij} : time to Event 2
- u_i : frailty for group i.

for $i = 1, 2, ..., G$ and $j = 1, 2, ..., N_i$.



Patient-level dependence between X and Y
(after accounting for cluster dependence)

- Sub-distribution hazards

$$\begin{cases} \lambda_1^{Sub}(t \mid u_i) = \Pr(t \le T < t + dt, \delta = 1 \mid \{T \ge t\} \cup \{T < t, \delta = 0\} \mid u_i) / dt, \\ \lambda_2^{Sub}(t \mid u_i) = \Pr(t \le T < t + dt, \delta = 0 \mid \{T \ge t\} \cup \{T < t, \delta = 1\} \mid u_i) / dt. \end{cases}$$

- Marginal hazards

$$\begin{cases} \lambda_{1ij}(t \mid u_i) = \Pr(t \le X_{ij} \le t + dt \mid X_{ij} \ge t, u_i) / dt \\ \lambda_{2ij}(t \mid u_i) = \Pr(t \le Y_{ij} \le t + dt \mid Y_{ij} \ge t, u_i) / dt \end{cases}$$

Assumed copula: $\Pr(X_{ij} > x, Y_{ij} > y \mid u_i) = C_\theta\{S_{1ij}(x \mid u_i), S_{2ij}(y \mid u_i)\}$

⇑Patient-level dependence

***Theorem 2**: Under the assumed copula moel,*

$$\Pr(X_{ij} > x, Y_{ij} > y \mid u_i) = C_\theta\{S_{1ij}(x \mid u_i), S_{2ij}(y \mid u_i)\},$$

the marginal hazard and sub hazard are connected through

$$\lambda_{1ij}^{Sub}(t \mid u_i) = \lambda_{1ij}(t \mid u_i) \frac{D_\theta^{[1,0]}\{\Lambda_{1ij}(t \mid u_i), \Lambda_{2ij}(t \mid u_i)\}}{1 - \int_0^t \lambda_{1ij}(x \mid u_i) D_\theta^{[1,0]}\{\Lambda_{1ij}(x \mid u_i), \Lambda_{2ij}(x \mid u_i)\} dx},$$

$$\lambda_{2ij}^{Sub}(t \mid u_i) = \lambda_{2ij}(t \mid u_i) \frac{D_\theta^{[0,1]}\{\Lambda_{1ij}(t \mid u_i), \Lambda_{2ij}(t \mid u_i)\}}{1 - \int_0^t \lambda_{2ij}(x \mid u_i) D_\theta^{[0,1]}\{\Lambda_{1ij}(x \mid u_i), \Lambda_{2ij}(x \mid u_i)\} dx}$$

Statistical Inference

- **Sub hazard Cox models (separate models)**

$$\lambda_{1ij}^{Sub}(t \mid u_i, \mathbf{Z}_{ij}) = u_i \lambda_{10}^{Sub}(t) \exp(\boldsymbol{\beta}_1^{Sub} \mathbf{Z}_{ij}), \quad \Longrightarrow \quad \hat{\boldsymbol{\beta}}_1^{Sub}$$

frailtyHL package

$$\lambda_{2ij}^{Sub}(t \mid u_i, \mathbf{Z}_{ij}) = u_i \lambda_{20}^{Sub}(t) \exp(\boldsymbol{\beta}_2^{Sub} \mathbf{Z}_{ij}). \quad \Longrightarrow \quad \hat{\boldsymbol{\beta}}_2^{Sub}$$

- **Marginal Cox models (joint model)**

cmrskCox.reg( ) in *joint.Cox* package

$$\begin{cases} \lambda_{1ij}(t \mid u_i, \mathbf{Z}_{ij}) = u_i \lambda_{10}(t) \exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij}) \\ \lambda_{2ij}(t \mid u_i, \mathbf{Z}_{ij}) = u_i^{\alpha} \lambda_{20}(t) \exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij}) \end{cases} \quad \Longrightarrow \quad (\hat{\boldsymbol{\beta}}_1, \hat{\boldsymbol{\beta}}_2)$$

$$\Pr(X_{ij} > x, Y_{ij} > y \mid u_i) = C_\theta\{ S_{1ij}(x \mid u_i), S_{2ij}(y \mid u_i) \}$$

θ must be pre-specified (assumed) to avoid nonidentifiability

Data example (bladder cancer Sylvester et al. 2006**)**

396 patients collected from G=21 centers

- X_{ij} : time to Event 1 (cancer recurrence)
- Y_{ij} : time to Event 2 (death prior to recurrence)
- u_i : frailty for a center i.

for $i = 1, 2, ..., G$ and $j = 1, 2, ..., N_i$.

Covariates:

- *Chemotherapy* (0 = No vs. 1 = Yes)
- *Age* (⩽65 years vs. >65 years).

- The sub hazard Cox models

$$\lambda_{1ij}^{Sub}(\, t \,|\, u_i \,) = u_i \lambda_{10}(t) \exp(\, \beta_{11}^{Sub} \times Chemo_{ij} + \beta_{12}^{Sub} \times Age_{ij} \,) \,,$$

$$\lambda_{2ij}^{Sub}(\, t \,|\, u_i \,) = u_i \lambda_{20}(t) \exp(\, \beta_{21}^{Sub} \times Chemo_{ij} + \beta_{22}^{Sub} \times Age_{ij} \,) \,.$$

The two sub hazard models are fitted separately.

- The marginal Cox model on Cause 1 and Cause 2 are specified as

$$\begin{cases} \lambda_{1ij}(\, t \,|\, u_i \,) = u_i \lambda_{10}(t) \exp(\, \beta_{11} \times Chemo_{ij} + \beta_{12} \times Age_{ij} \,) \\ \lambda_{2ij}(\, t \,|\, u_i \,) = u_i^{\alpha} \lambda_{20}(t) \exp(\, \beta_{21} \times Chemo_{ij} + \beta_{22} \times Age_{ij} \,) \\ \Pr(\, X_{ij} > x \,, Y_{ij} > y \,|\, u_i \,) = [\, \exp\{\, \theta \Lambda_{1j}(x \,|\, u_i) \,\} + \exp\{\, \theta \Lambda_{2j}(y \,|\, u_i) \,\} - 1 \,]^{-1/\theta} \end{cases}$$

We set $\theta = 0$, 0.5, 2, or 8, which correspond to $\tau = 0$, 0.2, 0.5, or 0.8

Table 2. Analysis of the bladder cancer data

			Cause 1 (recurrence)	Cause 2 (death)
Chemo	Sub-hazard	$\hat{\beta}^{Sub}$	-0.70 (-1.04, -0.36)	0.64 (-0.09, 1.37)
	Marginal (θ=0, τ=0)	$\hat{\beta}$	-0.55 (-0.91, -0.20)	0.34 (-0.38, 1.06)
	Marginal (θ=0.5, τ=0.2)	$\hat{\beta}$	-0.52 (-0.87, -0.17)	0.19 (-0.48, 0.86)
	Marginal (θ=2, τ=0.5)	$\hat{\beta}$	-0.51 (-0.86, -0.16)	-0.27 (-0.77, 0.23)
	Marginal (θ=8, τ=0.8)	$\hat{\beta}$	-0.30 (-0.63, 0.04)	-0.18 (-0.53, 0.18)
Age	Sub-hazard	$\hat{\beta}^{Sub}$	-0.22 (-0.50, 0.06)	0.93 (0.43, 1.43)
	Marginal (θ=0, τ=0)	$\hat{\beta}$	-0.10 (-0.39, 0.18)	0.73 (0.21, 1.26)
	Marginal (θ=0.5, τ=0.2)	$\hat{\beta}$	-0.07 (-0.36, 0.21)	0.66 (0.16, 1.17)
	Marginal (θ=2, τ=0.5)	$\hat{\beta}$	-0.04 (-0.31, 0.23)	0.37 (-0.02, 0.76)
	Marginal (θ=8, τ=0.8)	$\hat{\beta}$	-0.05 (-0.30, 0.20)	0.08 (-0.20, 0.36)

Conclusions

- **Establish a mathematical relationship between sub-hazard and marginal hazard**
  (key: an assumed copula)
- **Two Cox models (sub-hazard & marginal hazard)**
  - The fitted values of β's are numerically similar
  - The interpretation of β's are qualitatively different
- **Extend to clustered data**
  (via a frailty-copula model)
  - marginal semiparametric MLE
  cmrskCox.reg( ) in *joint.Cox* R package
- **Selection of θ is a concern in marginal hazard model**
  - adopt a sensitivity analysis