INSERM, Biostatistique
at Bordeaux, FRANCE
2014 / 11 / 5

A joint frailty-copula model between disease progression and death for meta-analysis

Takeshi Emura
Graduate Institute of Statistics
National Central University, TAIWAN

Part I (Review)

- Meta-analysis & survival analysis
- Joint model & motivating example
- Spline & Penalized likelihood

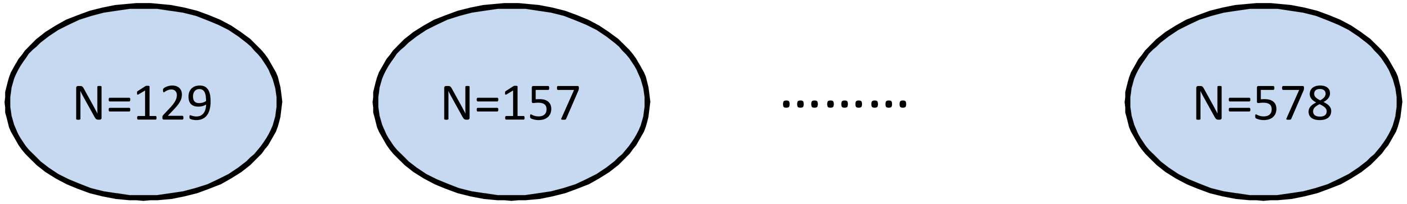
Part II (Proposed)

- Proposed method -- Copula approach
- Simulation
- Data analysis:

  -- Meta-analysis of ovarian cancer data

Meta-Analysis

- Synthesize multiple independent studies



- Useful to detect small (but consistent) effect
  - Treatment effect of chemotherapy on survival in head & neck cancer (Pignon et al. 2009)
  - The effect of CXCL12 gene on survival in ovarian cancer (Ganzfried et al. 2013)
  - The effect of ECRG 4 gene on survival in breast cancer (Sabatier et al. 2011)

Choice of endpoints

- Time-to-progression (TTP)
  (e.g., recurrence, metastasis)
- Death (OS)
  (Death from any cause)

Two endpoints of interest

- **Progression-free survival [PFS = min(TTP, OS)]**

1) Head & neck cancer data (Pignon et al., 2000; 2009)

→ *Separate* survival analysis on PSF and OS

2) Ovarian cancer data (Ganzfried et al. 2013)

→ Survival analysis on OS

3) Breast cancer data (Sabatier et al. 2011)

→ Separate survival analysis on PFS and OS

- Joint model = a bivariate model for TTP and OS

Time-to-progression (TTP)
Death (OS)

} Bivariate survival models (Large literature)

In meta-analysis:

➔ Study specific (random) effect to explain the heterogeneity

i) Bivariate survival analysis:
(TTP, OS) is jointly observed (Burzykowski et al. 2001)

ii) Competing risks analysis:
Only the first occurring event is observable:
min(TTP, OS, Censoring) (Rondeau et al. 2011)

- Meta analysis with frailty (Random effect)

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

- Data structure:

G independent clusters ($i = 1, 2, ..., G$)

each cluster contain N_i subjects ($j = 1, 2, ..., N_i$)

Share the same u_i

Data structure

X_{ij} = TTP (Recurrence, Relapse, etc.)

D_{ij} = OS (Death from any cause)

Dependence induced by u_i

C_{ij} = Administrative censoring (e.g., study end)

<u>Competing risks setting</u>:

Observe only the first occuring event time

$$T_{ij} = \min(X_{ij}, D_{ij}, C_{ij})$$

<u>Joint frailty model</u> (Rondeau et al., 2011)

$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t) \exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij}) & (\text{ time-to-progression } X_{ij} \text{ }) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha} \lambda_0(t) \exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij}) & (\text{ time-to-death } D_{ij} \text{ }) \end{cases}$$

Model Interpretation

Joint frailty model (Rondeau et al., 2011)

$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t) \exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij}) & (\text{ time-to-progression } X_{ij} \text{ }) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha} \lambda_0(t) \exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij}) & (\text{ time-to-death } D_{ij} \text{ }) \end{cases}$$

- Common effect across studies

All studies share common (true) effects

$\boldsymbol{\beta}_1'$ (on time-to-progression X_{ij})

$\boldsymbol{\beta}_1'$ (on time-to-death D_{ij})

- Heterogeneous effect across studies

u_i (on time-to-progression X_{ij})

u_i^{α} (on time-to-death D_{ij})

Patients backgrounds are different across studies

but they cannot be adjusted by observed covariates

Data structure

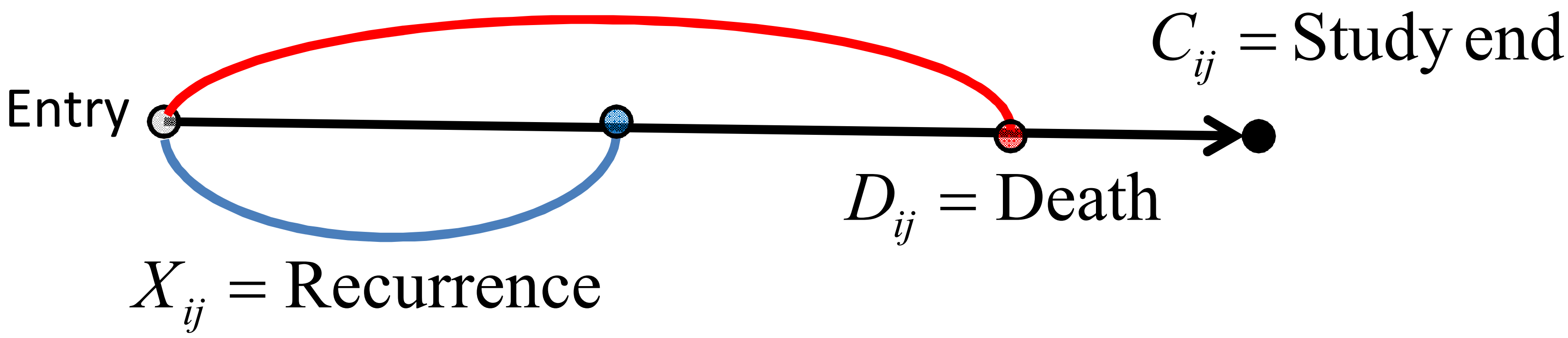


Fig. Case of $\delta_{ij} = 1$

<u>Observation</u> :

$$(T_{ij}, \delta_{ij}, \delta^{*}_{ij}, \mathbf{Z}_{ij}), \quad i = 1, 2, ..., G, \quad j = 1, 2, ..., N_i$$

$$T_{ij} = \min(X_{ij}, D_{ij}, C_{ij})$$

$$\delta_{ij} = \mathbf{I}\{ T_{ij} = X_{ij} \}, \quad \delta^{*}_{ij} = \mathbf{I}\{ T^{*}_{ij} = D_{ij} \}$$

Meta-analysis data for ovarian cancer (Ganzfried et al. 2013)

Data set (GEO accession number)	Sample size	The number of the first occurring events		
		Relapse $\delta_{ij} = 1$	Death $\delta_{ij}^{*} = 1$	Censoring $\delta_{ij} = \delta_{ij}^{*} = 0$
GSE17260	$N_1 = 110$	76	0	34
GSE30161	$N_2 = 58$	48	2	8
GSE9891	$N_3 = 278$	185	2	91
TCGA	$N_4 = 557$	266	110	181
Total	$\sum_{i=1}^{4} N_i = 1003$			

Compiled from R Bioconductor `curatedOvarianData` package (Ganzfried et al. 2013)

Competing risks data:

First occurring event	T_{ij}	δ_{ij}	δ_{ij}^*	Likelihood
Progression	X_{ij}	1	0	$\Pr(X_{ij} = t, D_{ij} > t \mid u_i)$
Death	D_{ij}	0	1	$\Pr(X_{ij} > t, D_{ij} = t \mid u_i)$
Censoring	C_{ij}	0	0	$\Pr(X_{ij} > t, D_{ij} > t \mid u_i)$

Log-likelihood of Rondeau et al. (2011):

$$\ell(\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0)$$

$$= \sum_{i=1}^{G} \left[\sum_{j=1}^{N_i} \{ \delta_{ij} \log r_{ij}(T_{ij}) + \delta_{ij}^* \log \lambda_{ij}(T_{ij}) \} \right.$$

$$\left. + \log \int_0^\infty \left\{ u_i^{m_i + \alpha m_i^*} \exp\left(-u_i \sum_{j=1}^{N_i} R_{ij}(T_{ij}) - u_i^{\alpha} \sum_{j=1}^{N_i} \Lambda_{ij}(T_{ij}) \right) \right\} f_\eta(u_i) du_i \right],$$

where $m_i = \sum_{j=1}^{N_i} \delta_{ij}$ and $m_i^* = \sum_{j=1}^{N_i} \delta_{ij}^*$.

- Baseline hazard approximation via spline (O’ Sullivan 1988; Joly, Commenges and Letenneur 1998)

$$\tilde{r}_0(t) = \sum_{\ell=1}^{L_r} g_\ell M_\ell(t), \qquad \tilde{\lambda}_0(t) = \sum_{\ell=1}^{L_\lambda} h_\ell M_\ell(t)$$

- Cubic M-spline bases (Ramsay 1988)

$$M_1(t) = -\frac{4I(\xi_1 \le t < \xi_2)}{\Delta} z_2(t)^3, \quad z_i(t) = \left(\frac{t-\xi_i}{\Delta}\right), \quad \xi_i = \text{knot}, \quad \Delta = \text{mesh}$$

$$M_2(t) = \frac{I(\xi_1 \le t < \xi_2)}{2\Delta}\{7z_1(t)^3 - 18z_1(t)^2 + 12z_1(t)\} + \frac{I(\xi_2 \le t < \xi_3)}{2\Delta} z_3(t)^3,$$

$$M_3(t) = \cdots$$

- Easy to integrate & differentiate, e.g., $\tilde{R}_0(t) = \int_0^t \tilde{r}_0(u)du$

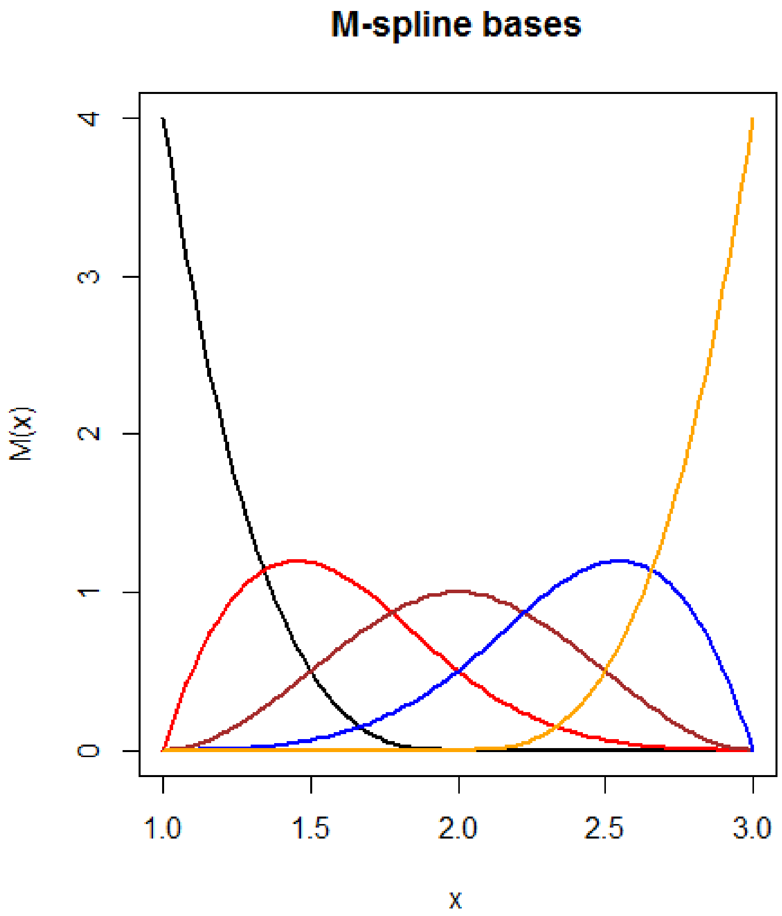
➔ Established strategy for hazard estimation

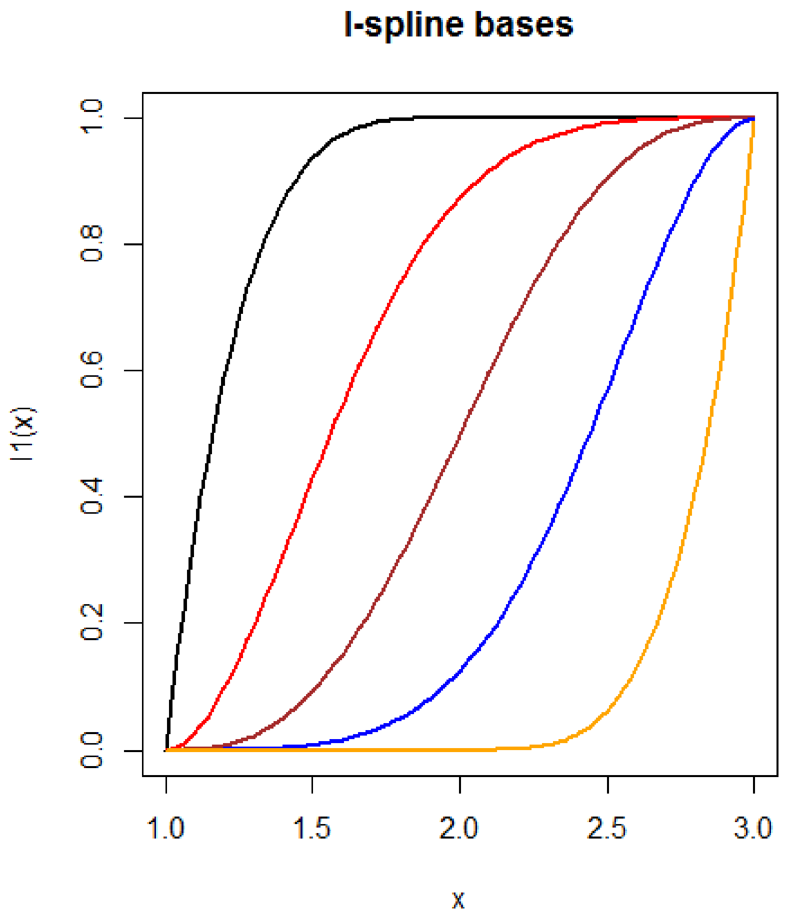
(see also Rondeau, Commenges and Joly 2003; Rondeau et al. 2011)

Cubic M-spline bases:

Equally spaced knots $\xi_1 = 1, \quad \xi_2 = 2, \quad \xi_3 = 3$

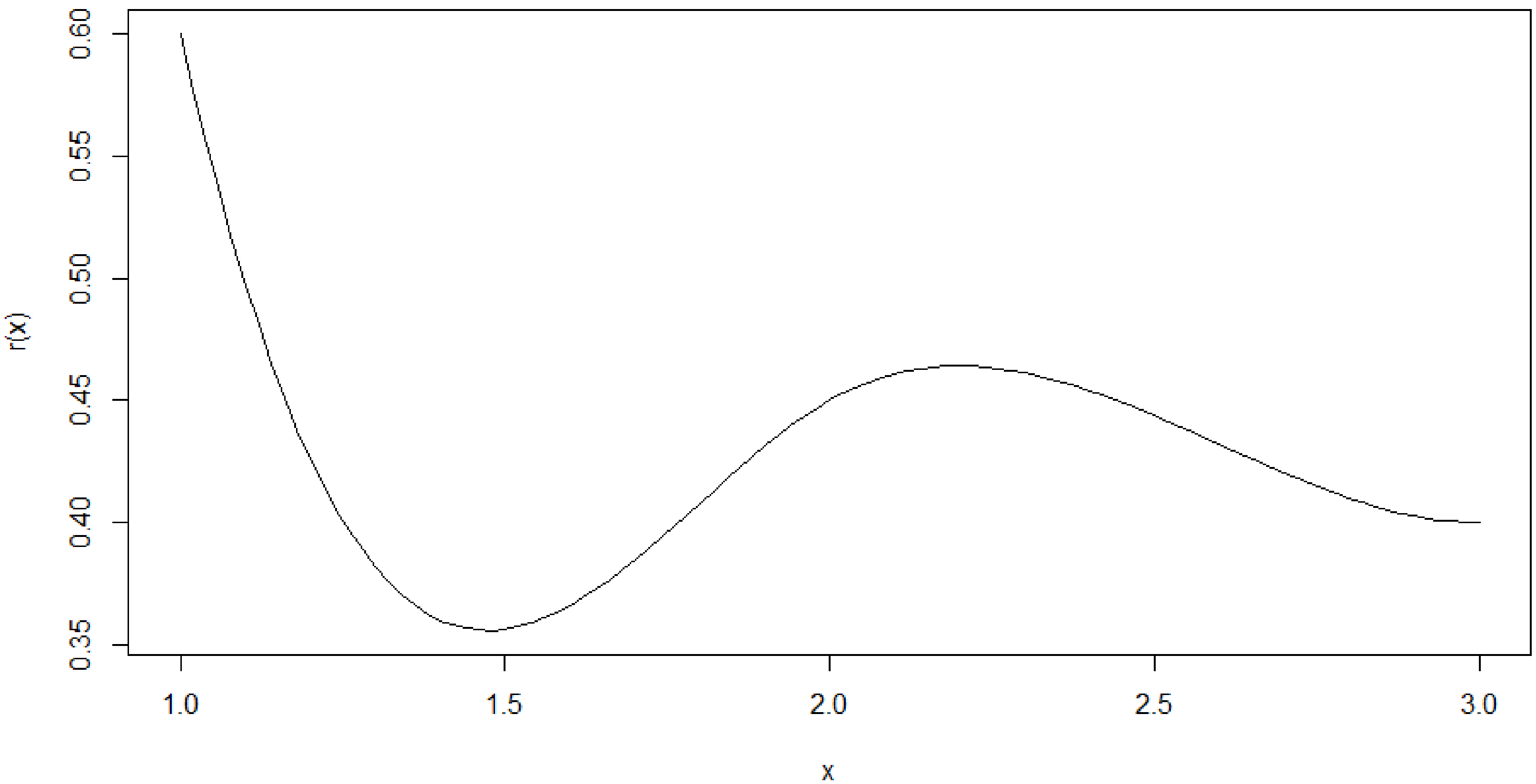
➔ **5 bases** : $M_1(t), M_2(t), M_3(t), M_4(t), M_5(t)$





Baseline hazard via cubic M-spline:

$$\widetilde{r}_0(x) = 0.15 \times M_1(t) + 1 \times M_2(t) + 0.3 \times M_3(t) + 0.2 \times M_4(t) + 0.1 \times M_5(t)$$



- Joint frailty model with penalized likelihood (Rondeau et al. 2011)

$$\ell(\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0) - \kappa_1 \int \ddot{\gamma}_0(t)^2 dt - \kappa_2 \int \ddot{\lambda}_0(t)^2 dt$$

$$\int \ddot{r}_0(t)^2 dt = \sum_{k=1}^{L_r} \sum_{\ell=1}^{L_r} g_k g_\ell \int \ddot{M}_k(t) \ddot{M}_\ell(t) dt, \quad \int \ddot{\lambda}_0(t)^2 dt = \sum_{k=1}^{L_\lambda} \sum_{\ell=1}^{L_\lambda} h_k h_\ell \int \ddot{M}_k(t) \ddot{M}_\ell(t) dt$$

- Optimal smoothing parameters

$$\mathrm{AIC}(\kappa_1, \kappa_2) = -2\hat{\ell}(\kappa_1, \kappa_2) + 2\mathrm{tr}\{\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)\hat{H}\},$$

$\hat{\ell}(\kappa_1, \kappa_2)$: the log-likelihood evaluated at the penalized MLE

$\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)$: converged Hessian matrix of the penalized MLE

$\hat{H}$: converged Hessian matrix of the un-penalized MLE (i.e., $\kappa_1 = \kappa_2 = 0$).

Part II: Proposed Methods

- We generalize the approach of Rondeau (2011) to account for the intra-subject dependence between TTP and OS

- Copula (Nelsen 2006) is used as a modeling tool (a flexible model for dependence)

Copula approach (Proposed)

- A Copula

$$C: [0,1]\times[0,1]\mapsto[0,1]$$

uniquely characterizes the dependence between two continuous random variables (Sklar's Theorem 1959):

Example 1: Independence copula: $C[v,w]=vw$

Example 2: Clayton copula (Clayton, 1978)

$$C_\theta(v,w)=(v^{-\theta}+w^{-\theta}-1)^{-1/\theta},\quad \begin{cases}\theta=0 & \text{independence}\\ \theta>0 & \text{positively dependece}\end{cases}$$

Proposed Idea

$X_{ij} = \text{TTP} \;(\text{Recurrence, Relapse, etc.})$

$D_{ij} = \text{OS} \;(\text{Death from any cause})$

Dependence induced by u_i

<u>Joint frailty model</u> (Rondeau et al., 2011)

$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z}_{ij}) & (\text{time-to-progression } X_{ij}) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha}\lambda_0(t)\exp(\boldsymbol{\beta}_2'\mathbf{Z}_{ij}) & (\text{time-to-death } D_{ij}) \end{cases}$$

- Still Independent censoring within a cluster

$$X_{ij} \perp D_{ij} \mid u_i$$

➔ **Our proposed idea:**
Relax this independence assumption via Copulas

Joint frailty-copula model (Proposed)

Frailty model (Rondeau et al., 2011)

$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z}_{ij}) & (\text{ time-to-progression } X_{ij} \text{ }) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha}\lambda_0(t)\exp(\boldsymbol{\beta}_2'\mathbf{Z}_{ij}) & (\text{ time-to-death } D_{ij} \text{ }) \end{cases}$$

$$+$$

Copula model:

$$\Pr(X_{ij} > x, D_{ij} > y \mid u_i) = C_\theta[\exp\{-R_{ij}(x \mid u_i)\}, \exp\{-\Lambda_{ij}(y \mid u_i)\}]$$

where C_θ is a copula (Nelsen, 2006), and

$$R_{ij}(x \mid u_i) = \int_0^x r_{ij}(v \mid u_i)dv, \qquad \Lambda_{ij}(y \mid u_i) = \int_0^y \lambda_{ij}(v \mid u_i)dv$$

3 dependence parameters

1. Copula parameter θ

   ➔ Related to conditional Kendall's tau $\tau_\theta(X_{ij}, D_{ij} \mid u_i)$

   e.g., Clayton copula: $\tau(X_{ij}, D_{ij} \mid u_i) = \theta/(\theta+2)$

   (Intra-subject dependence)

2. Frailty parameter $\eta = Var_\eta(u_i)$

   (Intra-cluster dependence due to the heterogeneity of studies)

3. Parameter α

   (Sign of the intra-cluster dependence)

   $\alpha > 0$ ➔ positively dependent

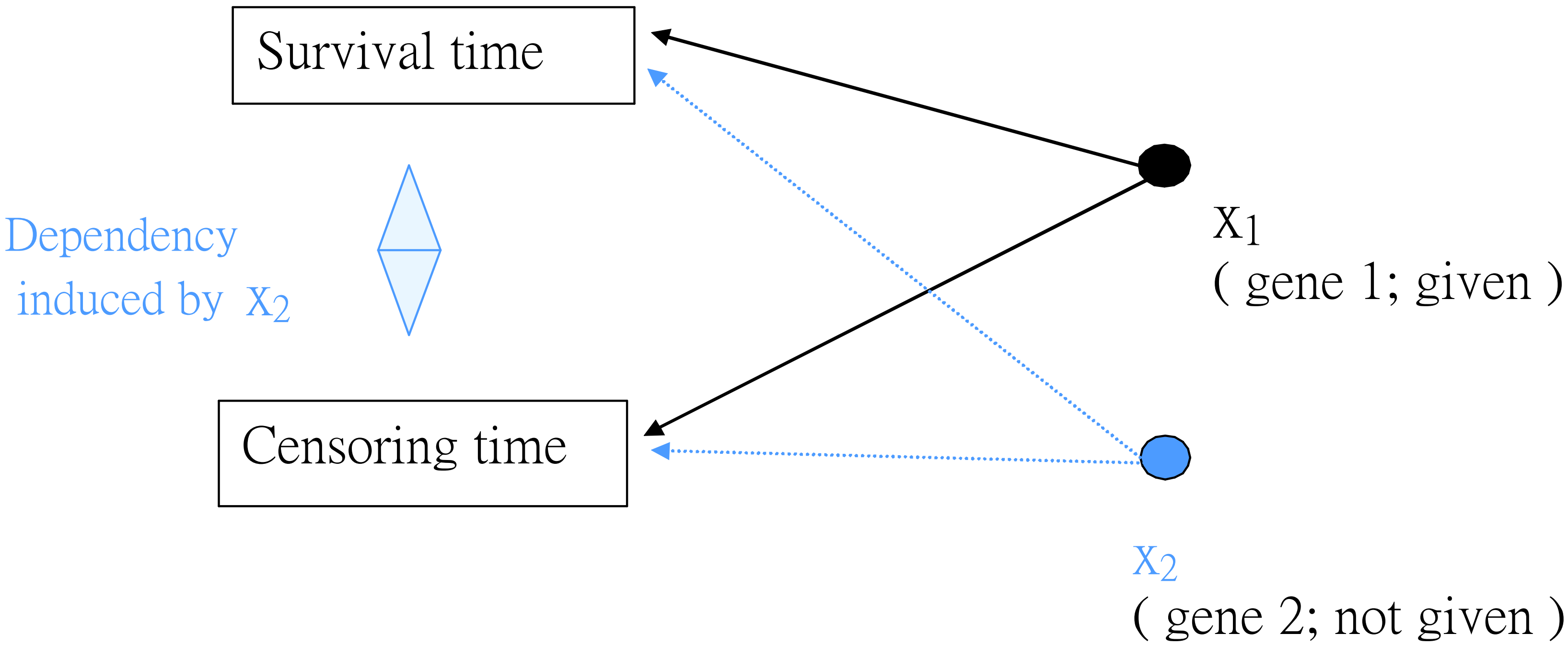
   $\alpha < 0$ ➔ negatively dependent

   $\alpha = 0$ ➔ independent.

Why such an elaborate model is necessary?

- Death immediately after progression.
  ➔ Strong dependence between TTP and OS
  (Kendall's tau > 0.5)
- Only a few covariates consistently measured across studies in meta-analysis
  ➔ Residual dependence between TTP and OS
  (unadjusted by covariates)

How independent censoring violate?



(Figure, Emura and Chen, 2014 SMMR)

- Survival (TTP) and censoring (OS) times usually cannot be conditionally independent given only x_1 regarding x_2 as unobserved covariate

Log-likelihood (proposed)

First occurring event	T_{ij}	δ_{ij}	δ^*_{ij}	Likelihood
Progression	X_{ij}	1	0	$\Pr(X_{ij} = t, D_{ij} > t \mid u_i)$
Death	D_{ij}	0	1	$\Pr(X_{ij} > t, D_{ij} = t \mid u_i)$
Censoring	C_{ij}	0	0	$\Pr(X_{ij} > t, D_{ij} > t \mid u_i)$

$$\ell(\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0 \mid \theta)$$

$$= \sum_{i=1}^{G} \Bigg[\sum_{j=1}^{N_i} \{ \delta_{ij} \log r_{ij}(T_{ij}) + \delta^*_{ij} \log \lambda_{ij}(T_{ij}) \}$$

$$+ \log \int_0^\infty \Bigg\{ \prod_{j=1}^{N_i} \eta_{\theta,\alpha}[\, R_{ij}(T_{ij}), \Lambda_{ij}(T_{ij}) \mid u_i \,]^{\delta_{ij}} \eta^*_{\theta,\alpha}[\, R_{ij}(T_{ij}), \Lambda_{ij}(T_{ij}) \mid u_i \,]^{\delta^*_{ij}}$$

$$\times \exp\left(- \sum_{i=1}^{N_i} \Psi_{\theta,\alpha}[\, R_{ij}(T_{ij}), \Lambda_{ij}(T_{ij}) \mid u_i \,] \right) \Bigg\} f_\eta(u_i) du_i \Bigg],$$

Dependence structure

(θ, η, α)

Log-likelihood (proposed)

Dependence structure characterized by

$$\Psi_{\theta,\alpha}(\, s, t \mid u\,) = -\log C_\theta[\, \exp(\,-us\,), \exp(\,-u^\alpha t\,)\,]$$

$$\eta_{\theta,\alpha} = \partial\Psi_{\theta,\alpha} / \partial s \,, \text{ and } \;\; \eta^*_{\theta,\alpha} = \partial\Psi_{\theta,\alpha} / \partial t$$

- Independent copula $C_\theta(\, v, w\,) = vw$

➔ $\Psi_{\theta,\alpha}(\, s, t \mid u\,) = us + u^\alpha t$

Reduces to the log-likelihood of Rondeau et al. (2011):

$$\ell(\,\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0\,)$$
$$= \sum_{i=1}^{G}\left[\sum_{j=1}^{N_i}\{\,\delta_{ij}\log r_{ij}(T_{ij}) + \delta^*_{ij}\log\lambda_{ij}(T_{ij})\,\}\right.$$
$$\left. + \log\int_0^\infty \left\{ u_i^{m_i+\alpha m_i^*} \exp\left(\,-u_i\sum_{j=1}^{N_i} R_{ij}(T_{ij}) - u_i^\alpha \sum_{j=1}^{N_i}\Lambda_{ij}(T_{ij})\,\right)\right\} f_\eta(u_i)du_i \right],$$

Extension to include left-truncation

Target lifetime : Age specific mortality

➔ Age at onset is subject to left-truncation

Let-truncation variable (L_{ij}) = Entry age

$$\ell(\alpha,\eta,\boldsymbol{\beta}_1,\boldsymbol{\beta}_2,r_0,\lambda_0\,|\,\theta)$$

$$=\sum_{i=1}^{G}\Bigg[\sum_{j=1}^{N_i}\{\,\delta_{ij}\log r_{ij}(T_{ij})+\delta_{ij}^{*}\log\lambda_{ij}(T_{ij})\,\}$$

$$+\log\int_0^{\infty}\Bigg\{\prod_{j=1}^{N_i}\eta_{\theta,\alpha}[\,R_{ij}(T_{ij}),\,\Lambda_{ij}(T_{ij})\,|\,u_i\,]^{\delta_{ij}}\,\eta_{\theta,\alpha}^{*}[\,R_{ij}(T_{ij}),\,\Lambda_{ij}(T_{ij})\,|\,u_i\,]^{\delta_{ij}^{*}}$$

$$\times\exp(-\sum_{i=1}^{N_i}\Psi_{\theta,\alpha}[\,R_{ij}(T_{ij}),\,\Lambda_{ij}(T_{ij})\,|\,u_i\,]\,)\Bigg\}f_{\eta}(u_i)du_i$$

$$-\log\int_0^{\infty}\exp\left(-\sum_{i=1}^{N_i}\Psi_{\theta,\alpha}[\,R_{ij}(L_{ij}),\,\Lambda_{ij}(L_{ij})\,|\,u_i\,]\right)f_{\eta}(u_i)du_i\Bigg]$$

- Penalized likelihood with cubic M-spline

➔ Directly follow Rondeau et al. (2011)

$$\ell(\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0 \mid \theta) - \kappa_1 \int \ddot{\gamma}_0(t)^2 dt - \kappa_2 \int \ddot{\lambda}_0(t)^2 dt$$

$$\int \ddot{r}_0(t)^2 dt = \sum_{k=1}^{L_r} \sum_{\ell=1}^{L_r} g_k g_\ell \int \ddot{M}_k(t) \ddot{M}_\ell(t) dt, \quad \int \ddot{\lambda}_0(t)^2 dt = \sum_{k=1}^{L_\lambda} \sum_{\ell=1}^{L_\lambda} h_k h_\ell \int \ddot{M}_k(t) \ddot{M}_\ell(t) dt$$

- Optimal smoothing parameters

$$\mathrm{AIC}(\kappa_1, \kappa_2) = -2\hat{\ell}(\kappa_1, \kappa_2) + 2\mathrm{tr}\{\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)\hat{H}\},$$

$\hat{\ell}(\kappa_1, \kappa_2)$: the log-likelihood evaluated at the penalized MLE

$\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)$: converged Hessian matrix of the penalized MLE

$\hat{H}$: converged Hessian matrix of the un-penalized MLE (i.e., $\kappa_1 = \kappa_2 = 0$).

Maximum of Penalized likelihood estimator

➔ Newton-type algorithms (e.g., R `nlm` routine)

$$(\hat{\alpha}, \hat{\eta}, \hat{\boldsymbol{\beta}}_1, \hat{\boldsymbol{\beta}}_2, \hat{r}_0, \hat{\lambda}_0)$$
$$= \arg\max\left[\ell(\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0 \mid \theta) - \kappa_1 \int \ddot{\gamma}_0(t)^2 dt - \kappa_2 \int \ddot{\lambda}_0(t)^2 dt\right]$$

given $(\theta, \hat{\kappa}_1, \hat{\kappa}_2)$

- Unidentifiability (Tsiatis, 1975) for the copula parameter θ

  ➔ Sensitivity analysis: try a few θ

$$\theta = 2 \;\; ➔ \;\; \tau(X_{ij}, D_{ij} \mid u_i) = 0.5$$
$$\theta = 8 \;\; ➔ \;\; \tau(X_{ij}, D_{ij} \mid u_i) = 0.8$$

Standard error (SE)

= the converged Hessian of the penalized log-likelihood (O' Sullivan 1988)

(Bayesian derivation: regard penalty as prior)

- 95% confidence interval for β_1

$$\hat{\beta}_1 \pm 1.96 \times \mathrm{SE}(\beta_1) = \hat{\beta}_1 \pm 1.96 \times \sqrt{-\{\, \hat{H}_{PL}^{-1}(\,\kappa_1, \kappa_2\,)\,\}_{\beta_1}}$$

- 95% confidence interval for the baseline hazard $r_0(t)$ is

$$\hat{r}_0(x) \pm 1.96 \times \mathrm{SE}\{\, \hat{r}_0(x)\,\} = \mathbf{M}'(x)\hat{\mathbf{g}} \pm 1.96 \times \sqrt{-\mathbf{M}'(x)\{\, \hat{H}_{PL}^{-1}(\,\kappa_1, \kappa_2\,)\,\}_{\mathbf{g}}\mathbf{M}(x)}\ ,$$

where $\mathbf{M}(t) = (\, M_1(x),\ \ldots,\ M_{L_r}(x)\,)'$.

Simulations: G=5, N=100 or 200

Simulation settings:

- Frailty: $u_i \sim$ Gamma $(1/\eta, \eta)$ where $\eta = 0.5$
- Covariate: $Z_{ij} \sim \text{Unif}(0,1)$
- Joint frailty-copula model

$$\Pr(X_{ij} > x, D_{ij} > y \mid u_i) = [\exp\{\theta R_{ij}(x \mid u_i)\} + \exp\{\theta \Lambda_{ij}(y \mid u_i)\} - 1]^{-1/\theta},$$

at $\theta = 2$ ➔ $\tau(X_{ij}, D_{ij} \mid u_i) = 0.5$.

- Marginals: $R_{ij}(x \mid u_i) = u_i r_0 x \exp(\beta_1 Z_{ij})$, $\Lambda_{ij}(y \mid u_i) = u_i^{\alpha} \lambda_0 y \exp(\beta_2 Z_{ij})$

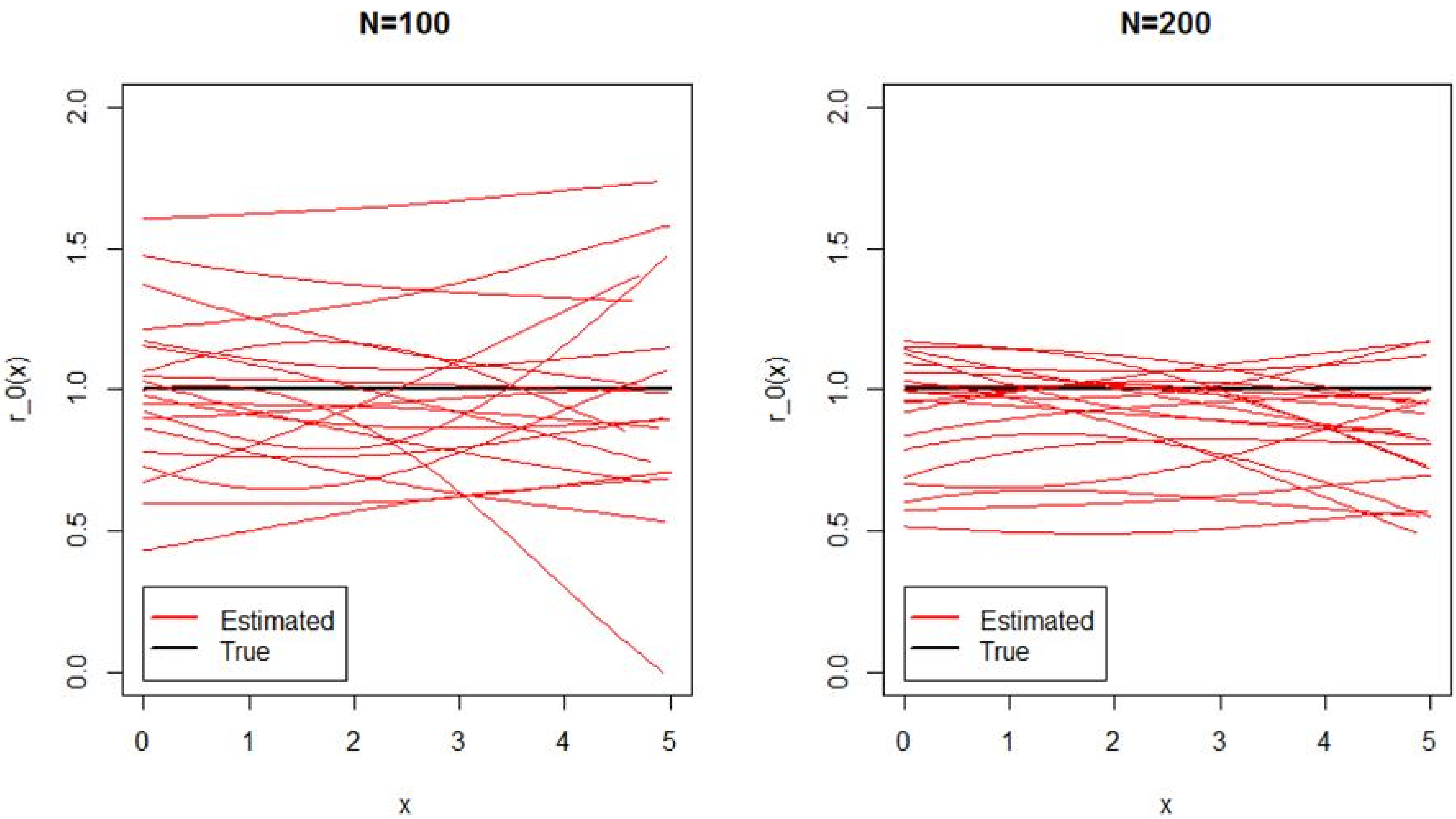
where $r_0 = 1$ and $\lambda_0 = 1$

- $C_{ij} \sim \text{Unif}(0,5)$ ➔ 15~31% censored subjects

Simulations: 500 runs, G=5

		$N_i = 100$				$N_i = 200$			
		Mean	SD	SE	CP%	Mean	SD	SE	CP%
CEN	β_1=1	1.014	0.173	0.163	0.93	1.017	0.127	0.114	0.94
=15%	β_2=1	1.030	0.170	0.164	0.95	1.007	0.122	0.114	0.95
	η=0.5	0.492	0.305	0.292	0.89	0.476	0.306	0.279	0.87
	α=1	1.008	0.109	0.096	0.94	0.995	0.097	0.065	0.90
	κ	30.850	13.886			22.310	15.495		
		Mean	SD	SDE	CP%	Mean	SD	SDE	CP%
CEN	β_1=0	-0.005	0.151	0.144	0.94	0.012	0.098	0.099	0.96
=23%	β_2=0	0.012	0.147	0.145	0.96	0.002	0.099	0.100	0.95
	η=0.5	0.474	0.312	0.282	0.87	0.485	0.300	0.284	0.91
	α=1	1.009	0.115	0.098	0.93	0.998	0.087	0.066	0.91
	κ	32.810	12.485			32.940	12.217		

Simulations: 20 runs, G=5



Setting (a): $\beta_1 = 1, \quad \beta_2 = 1, \quad r_0(x) = 1$ and $\lambda_0(y) = 1$

Meta-analysis data for ovarian cancer (Ganzfried et al. 2013)

Data set (GEO accession number)	Sample size	The number of the first occurring events		
		Relapse $\delta_{ij} = 1$	Death $\delta_{ij}^{*} = 1$	Censoring $\delta_{ij} = \delta_{ij}^{*} = 0$
GSE17260	$N_1 = 110$	76	0	34
GSE30161	$N_2 = 58$	48	2	8
GSE9891	$N_3 = 278$	185	2	91
TCGA	$N_4 = 557$	266	110	181
Total	$\sum_{i=1}^{4} N_i = 1003$			

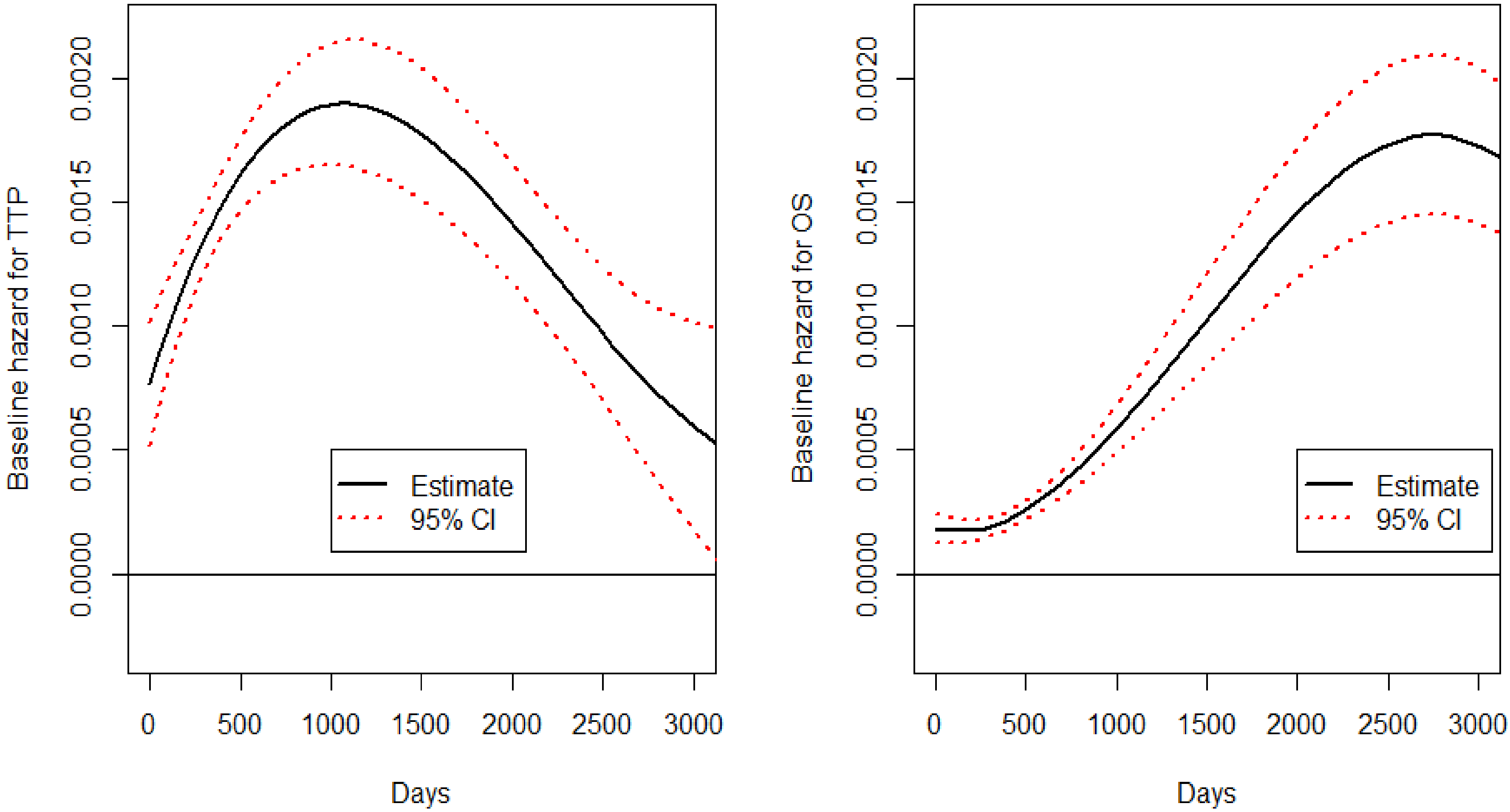
Complied from R Bioconductor curatedOvarianData package (Ganzfried et al. 2013)

Meta-analysis data for ovarian cancer (Ganzfried et al. 2013)

		$\theta = 2$	$\theta = 8$
		Kendall's $\tau = 0.5$	Kendall's $\tau = 0.8$
$\exp(\beta_1)$	RR for TTP (95%CI)	1.26 (1.16-1.36)	1.20 (1.11-1.29)
$\exp(\beta_2)$	RR for OS (95%CI)	1.17 (1.02-1.35)	1.19 (1.09-1.31)
	$\eta = Var_\eta(u_i)$ (SE)	0.099 (0.069)	0.106 (0.075)
	ML	-5654.184	-5643.798

* Ganzfried et al. (2013) reported RR=1.15 (1.09-1.23) for OS based on 14 studies

Meta-analysis data for ovarian cancer (Ganzfried et al. 2013)



Summary

We proposed a frailty-copula model for dependence between TTP and OS

- Extend the joint frailty model of Rondeau et al. (2011)
- More elaborate model for dependence

  ➔ allow intra-cluster dependence via copulas

Future work

- Unidentifiable problem of copula parameter θ

  ➔ Sensitivity analysis (try $\theta = 2, \quad \theta = 8$)
- We (with Dr. Nakatochi and Murotani) are searching the meta-analysis data of Sabatier et al. (2011 PLoS ONE)

Merci Beaucoup !