Additive Regression Model with Frailty on Semi-competing Risks Data

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Outline

- Introduction to semi-competing risks data
- Proposed models and parameter estimation
- Simulations
- Application to the colon cancer data
- Summary & discussion

Semi-competing risks data

- Bivariate survival data with non-terminal event(eg, tumor recurrence) and terminal event(eg, death)
- Terminal event censors non-terminal event but not vice versa
  - With competing risks data, two events censor each other
- Two event times are possibly correlated

Illustration of semi-competing risks data(Jiang et al.,2003)

- (X, Y) : a pair of event times, X : time to non-terminal event; Y : time to terminal event

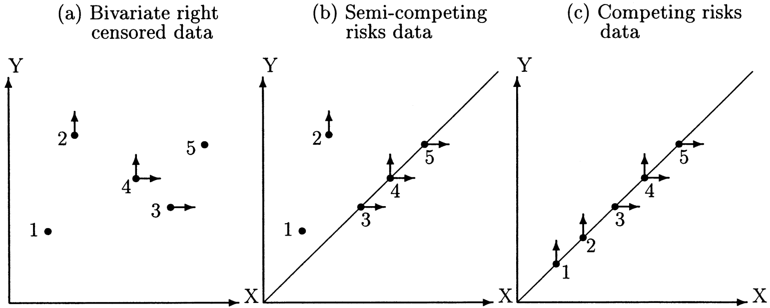


Fig. 1. Illustration of semicompeting risks data; a dot means both X and Y are observed for that subject; an arrow in the direction of X means X is censored for that subject; an arrow in the direction of Y means Y is censored for that subject.

Colon Cancer Study(CCS) data

- This trial was a national intergroup trial in the 1980's to study the drugs levamisole and fluorouracil for adjuvant therapy for resected colon carcinoma
- 929 patients with stage III disease were randomly assigned to observation care only(315), levamisole alone(310), or levamisole combined with fluorouracil(Lev+5-FU, 304)
- The time to cancer recurrence and the survival time were both considered important outcome measures
- Lin(1994) treated cancer recurrence as the first failure type and death as the second because cancer recurrence occurs before death $\Rightarrow$ bivariate survival data
  - Moertel et al.(1995), Shen &Thall(1998), He & Lawless(2003)
- Instead, in this talk, we treat cancer recurrence as the non-terminal event and death as the terminal event $\Rightarrow$ semi-competing risks data

Previous work

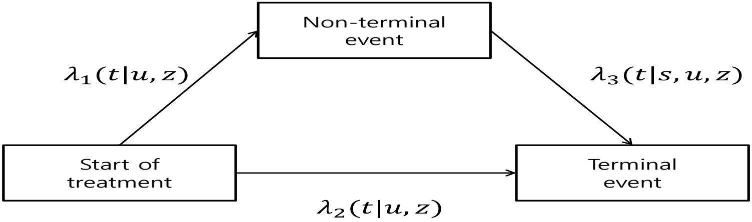
- Two aims: to examine dependence structure of the two events via joint survival function and to model marginal distribution of non-terminal event
- Without covariates
  - Use parametric copula model $S(s,t) = C\{S_1(s), S_2(t), \alpha\},\ 0 < s \le t < \infty$, a kind of model formulation using latent times, where C : copula function(eg, $C(u,v,w) = \{u^{1-w} + v^{1-w} - 1\}^{-1/(1-w)}$, $\alpha(\ge 0)$: parameter measuring the correlation
  - Fine et al.(2001), Wang(2003), Jiang et al.(2005), Lakhal et al.(2008)
- With covariates
  - Peng & Fine(2007): Use time-dependent copula model $S(s,t|z) = C\{S_1(s|z), S_2(t|z), \alpha(s,t)\}$, where $\alpha(s,t)$: time-dependent association parameter
  - Xu et al.(2010): Use an illness-death compartment model with a shared frailty

Observed data

- $O = \{O_i = (Y_{i1} = T_{i1} \wedge T_{i2} \wedge C_i, Y_{i2} = T_{i2} \wedge C_i, \delta_{i1} = I(T_{i1} \leq Y_{i2}), \delta_{i2} = I(T_{i2} \leq C_i), z_i')',\ i = 1, \ldots, n\}$
  - T_{i1} : time to relapse
  - T_{i2} : time to death
  - C_i : censoring time
  - $z_i = (z_{i1}, \ldots, z_{ip})'$: covariate vector
- Remark
  - $(\delta_1, \delta_2) = (1, 1)$: death with relapse $\Rightarrow Y_1 < Y_2;\ T_1 = Y_1\ \&\ T_2 = Y_2$
  - $(\delta_1, \delta_2) = (1, 0)$: still alive with relapse $\Rightarrow$ $Y_1 < Y_2;\ T_1 = Y_1\ \&\ T_2 > Y_2$
  - $(\delta_1, \delta_2) = (0, 1)$: deth without relapse $\Rightarrow$ $Y_1 = Y_2;\ T_1 > Y_1\ \&\ T_2 = Y_1$
  - $(\delta_1, \delta_2) = (0, 0)$: still alive without relapse $\Rightarrow$ $Y_1 = Y_2;\ T_1 > Y_1\ \&\ T_2 > Y_1$
- Our goal: to estimate covariate effects on the rates of terminal and non-terminal events, and also to evaluate the dependence of terminal event on non-terminal event

Illness-death model

- Three conditional transition functions: (1) for time to relapse, (2) for time to death without relapse, and (3) for time to death with relapse
  - $\lambda_1(t|u,z) = \lim_{\Delta\to 0} \frac{P\{T_1 \in (t, t+\Delta) | T_1 \geq t, T_2 \geq t, u, z\}}{\Delta} = \lambda_{01}(t) + u + \beta_1' z$
  - $\lambda_2(t|u,z) = \lim_{\Delta\to 0} \frac{P\{T_2 \in (t, t+\Delta) | T_1 \geq t, T_2 \geq t, u, z\}}{\Delta} = \lambda_{02}(t) + u + \beta_2' z$
  - $\lambda_3(t|s,u,z) = \lim_{\Delta\to 0} \frac{P\{T_2 \in (t, t+\Delta) | T_1 = s, T_2 \geq t, u, z\}}{\Delta} =$ $\lambda_{03}(t) + u + \beta_3' z,\ 0 < s \leq t$
    - u : frailty(eg, gamma frailty with mean 1 and variance θ)



Illness-death model: remark

- excess(additive) risk model with time-fixed covariates (Lin & Ying, 1994)
- shared frailty model with the additive effect
- Markov model for (3): depend only on t
- dependency of T_2 on T_1 is described both by the baseline hazard difference $\lambda_{02}(t) - \lambda_{03}(t)$ and by the frailty u

Likelihood construction

- Conditional likelihood for the i-th individual

$$L_{c,i} = \{\lambda_{01}(Y_{i1})+u_i+\beta_1' z_i\}^{\delta_{i1}}\{\lambda_{02}(Y_{i1})+u_i+\beta_2' z_i\}^{(1-\delta_{i1})\delta_{i2}}\{\lambda_{03}(Y_{i2})+u_i+\beta_3' z_i\}^{\delta_{i1}\delta_{i2}}$$
$$\times \exp[-\{\Lambda_{01}(Y_{i1}) + \Lambda_{02}(Y_{i1}) + \delta_{i1}\Lambda_{03}(Y_{i1}, Y_{i2})\}]$$
$$\times \exp[-\{(\beta_1' z)Y_{i1} + (\beta_2' z_i)Y_{i1} + \delta_{i1}(\beta_3' z_i)(Y_{i2} - Y_{i1}) + u_i(Y_{i1} + Y_{i2})\}],$$

where $\Lambda_{03}(s, t) = \Lambda_{03}(t) - \Lambda_{03}(s),\ \ s \leq t$

Piecewise exponential models for baseline hazards

- $s_{10} = s_{20} = s_{30} = 0$ and $s_{1K_1} = s_{2K_2} = s_{3K_3} = \infty$
- $\lambda_{1k_1} = d\Lambda_{01}(s_{1k_1}),\ \lambda_{2k_2} = d\Lambda_{02}(s_{2k_2}),\ \lambda_{3k_3} = d\Lambda_{03}(s_{3k_3}),\ k_m = 1, \dots, K_m,\ m = 1, 2, 3$
- For $\lambda_{01}(t)$, $\lambda_{01} = (\lambda_{11}, \lambda_{12}, \dots, \lambda_{1K_1})'$ on $I_{11} = (s_{10}, s_{11}], I_{12} = (s_{11}, s_{12}], \dots, I_{1K_1} = (s_{1K_1-1}, s_{1K_1})$
- For $\lambda_{02}(t)$, $\lambda_{02} = (\lambda_{21}, \lambda_{22}, \dots, \lambda_{2K_2})'$ on $I_{21} = (s_{20}, s_{21}], I_{22} = (s_{21}, s_{22}], \dots, I_{2K_2} = (s_{2K_2-1}, s_{2K_2})$
- For $\lambda_{03}(t)$, $\lambda_{03} = (\lambda_{31}, \lambda_{32}, \dots, \lambda_{3K_3})'$ on $I_{31} = (s_{30}, s_{31}], I_{32} = (s_{31}, s_{32}], \dots, I_{3K_3} = (s_{3K_3-1}, s_{3K_3})$

Representation of baseline hazards & cumulative baseline hazards

- $\lambda_{01}(Y_{i1}) = \sum_{k_1=1}^{K_1} \lambda_{1k_1} d_{11,ik_1}$, where $d_{11,ik_1} = I(Y_{i1} \in I_{1k_1})$
- $\lambda_{02}(Y_{i1}) = \sum_{k_2=1}^{K_2} \lambda_{2k_2} d_{12,ik_2}$, where $d_{12,ik_2} = I(Y_{i1} \in I_{2k_2})$
- $\lambda_{03}(Y_{i2}) = \sum_{k_3=1}^{K_3} \lambda_{3k_3} d_{23,ik_3}$, where $d_{23,ik_3} = I(Y_{i2} \in I_{3k_3})$

Representation of baseline hazards & cumulative baseline hazards

- $\Lambda_{01}(Y_{i1}) = \sum_{k_1=1}^{K_1} \left\{ (Y_{i1} - s_{1k_1-1}) d_{11,ik_1} + (s_{1k_1} - s_{1k_1-1})(1 - \sum_{l_1=1}^{k_1} d_{11,il_1}) \right\} \lambda_{1k_1}$
- $\Lambda_{02}(Y_{i1}) = \sum_{k_2=1}^{K_2} \left\{ (Y_{i1} - s_{2k_2-1}) d_{12,ik_2} + (s_{2k_2} - s_{2k_2-1})(1 - \sum_{l_2=1}^{k_2} d_{12,il_2}) \right\} \lambda_{2k_2}$
- $\Lambda_{03}(Y_{i1}, Y_{i2}) = \{(Y_{i2} - Y_{i1}) d_{13,i1} d_{23,i1} + (s_{31} - Y_{i1}) d_{13,i1}(1 - d_{23,i1})\}\lambda_{31}$

$$+ \sum_{k_3=2}^{K_3} \left\{ (Y_{i2} - Y_{i1}) d_{13,ik} d_{23,ik} + (s_{3k_3} - Y_{i1}) d_{13,ik} \left(1 - \sum_{l_3=1}^{k_3} d_{23,il_3} \right) \right.$$

$$+ (s_{3k_3} - s_{3k_3-1}) \left(\sum_{l_3=1}^{k_3-1} d_{13,il_3} \right) \left(1 - \sum_{l_3=1}^{k_3} d_{23,il_3} \right)$$

$$\left. + (Y_{i2} - s_{3k_3-1}) \left(\sum_{l_3=1}^{k_3-1} d_{13,il_3} \right) d_{23,ik_3} \right\} \lambda_{3k_3},$$

where $d_{13,ik_3} = I(Y_{i1} \in I_{3k_3})$

Full likelihood

- Full likelihood for the ith individual

$$L_{f,i} = L_{c,i} \times g(u_i|\theta)$$

where $g(u|\theta)$: pdf of $\Gamma(\theta, 1/\theta)$

- Log full likelihood

$$l_f = \sum_{i=1}^{n} l_{f,i},$$

where $l_{f,i} = \log L_{f,i} = -\{A_{i1}(Y_{i1}) + A_{i2}(Y_{i1}) + \delta_{i1} A_{i3}(Y_{i1}, Y_{i2}) + (Y_{i1} + Y_{i2})u_i\}$

$$+\delta_{i1}\log(a_{i1} + u_i) + (1 - \delta_{i1})\delta_{i2}\log(a_{i2} + u_i) + \delta_{i1}\delta_{i2}\log(a_{i3} + u_i)$$

$$+(\theta^{-1} - 1)\log(u_i) - \theta^{-1}u_i - \log\{\Gamma(\theta^{-1})\} - \theta^{-1}\log(\theta)$$

  - $a_{im}(t) = \lambda_{0m}(t) + \beta'_m z_i$: function of $\lambda_{0m} = (\lambda_{m1}, \ldots, \lambda_{mK_m})'$ and β_m, $m = 1, 2, 3$
  - $A_{im}(t) = \Lambda_{0m}(t) + (\beta'_m z_i)t, \;\; m = 1, 2;$
    $A_{i3}(s,t) = \Lambda_{03}(s,t) + (\beta'_3 z_i)(t - s)$

Estimation

- In E-step, calculate the expectation of the function of frailty such as $E(u_i|O_i)$, $E\{\log(u_i)|O_i, \hat{\eta}\}$, and $E\{\log(\mathrm{const} + u_i)|O_i, \hat{\eta}\}$, from the density of $f(u_i|O_i, \hat{\eta})$ using the Gauss-Laguerre quadrature technique
- In M-step, estimate parameters by maximizing the log full likelihood wrt $\eta = (\theta, \beta_1', \beta_2', \beta_3', \lambda_{01}', \lambda_{02}', \lambda_{03}')'$
- Iterate both E-step and M-step until the estimates converge
- Remark
  - Use the Louis' method for variance estimation, i.e., $\hat{I}^{-1} = -\hat{E}\left\{\frac{\partial^2 l_f}{\partial\eta\partial\eta'}|O, \hat{\eta}\right\} - \hat{E}\left\{\frac{\partial l_f}{\partial\eta}\frac{\partial l_f}{\partial\eta'}|O, \hat{\eta}\right\} + \hat{E}\left\{\frac{\partial l_f}{\partial\eta}|O, \hat{\eta}\right\}\hat{E}\left\{\frac{\partial l}{\partial\eta'}|O, \hat{\eta}\right\}$

Simulation setup

- Three intervals of piecewise hazards: I_{m1} =(0, 0.15], I_{m2} =(0.15, 0.77], I_{m3}=(0.77,∞), $m = 1, 2, 3$
- Baseline hazards: $\lambda_{01} = (0.2, 0.3, 0.4)'$, $\lambda_{02} = (0.2, 0.3, 0.4)'$, $\lambda_{03} = (0.3, 0.4, 0.5)'$
- Single 0-1 binary covariate
- Covariate effects: $\beta_1 = \beta_2 = \beta_3 = 1$
- Censoring: no censoring or 15% censoring from $U(0, 5)$
- Gamma frailty(G): θ =0.3 or 0.8(Kendall's tau τ=0.13 or 0.28)
- Sample size(n)=300
- Simulation replication=1,000

Simulation results: param. estimates for $\beta_1, \beta_2, \beta_3$, and θ

CR%	Parm	True	Est	Bias	(Bias%)[1]	SD	MSE	CP
0	β_1	1	1.023	0.023	(2.3)	0.297	0.288	0.952
	β_2	1	1.012	0.012	(1.2)	0.287	0.289	0.955
	β_3	1	1.030	0.030	(3.0)	0.336	0.328	0.947
	θ	0.3	0.315	0.015	(4.9)	0.168	0.124	
	β_1	1	1.013	0.013	(1.3)	0.263	0.263	0.958
	β_2	1	1.011	0.011	(1.1)	0.273	0.265	0.938
	β_3	1	1.028	0.028	(2.8)	0.318	0.308	0.949
	θ	0.8	0.780	-0.020	(2.5)	0.031	0.130	
15	β_1	1	1.031	0.031	(3.1)	0.314	0.296	0.952
	β_2	1	1.020	0.020	(2.0)	0.302	0.297	0.947
	β_3	1	1.034	0.034	(3.4)	0.373	0.358	0.943
	θ	0.3	0.316	0.016	(5.5)	0.161	0.142	
	β_1	1	1.013	0.013	(1.3)	0.269	0.272	0.954
	β_2	1	1.016	0.016	(1.6)	0.291	0.273	0.939
	β_3	1	1.029	0.029	(2.9)	0.355	0.345	0.939
	θ	0.8	0.779	-0.021	(2.6)	0.024	0.134	

[1] $|\text{Bias}|/\text{True} \times 100$

Simulation result: misspecification of frailty distribution

				Bias%			MSE			CP		
CR%	τ	Parm	True	G	IG	PS[2]	G	IG	PS	G	IG	PS
0	0.13	β_1	1	0.0	0.6	0.3	0.29	0.31	0.28	0.945	0.959	0.952
		β_2	1	1.2	2.5	1.3	0.29	0.31	0.29	0.958	0.953	0.947
		β_3	1	4.6	1.9	3.6	0.33	0.35	0.33	0.948	0.958	0.950
		θ	0.3	7.4			0.12					
	0.28	β_1	1	0.1	2.4	4.9	0.26	0.32	0.26	0.954	0.947	0.935
		β_2	1	0.5	2.7	4.4	0.26	0.32	0.26	0.950	0.937	0.933
		β_3	1	1.3	3.6	1.1	0.30	0.36	0.29	0.939	0.947	0.952
		θ	0.8	2.4			0.13					
15	0.13	β_1	1	0.2	0.7	4.1	0.29	0.32	0.30	0.947	0.960	0.946
		β_2	1	1.9	2.6	3.5	0.30	0.32	0.30	0.958	0.953	0.947
		β_3	1	4.1	0.7	3.6	0.36	0.38	0.36	0.939	0.952	0.954
		θ	0.3	9.5			0.14					
	0.28	β_1	1	1.2	2.5	6.1	0.27	0.33	0.27	0.949	0.949	0.938
		β_2	1	1.0	3.1	3.2	0.27	0.33	0.26	0.949	0.945	0.939
		β_3	1	0.9	4.8	1.4	0.34	0.39	0.33	0.952	0.951	0.958
		θ	0.8	2.6			0.13					

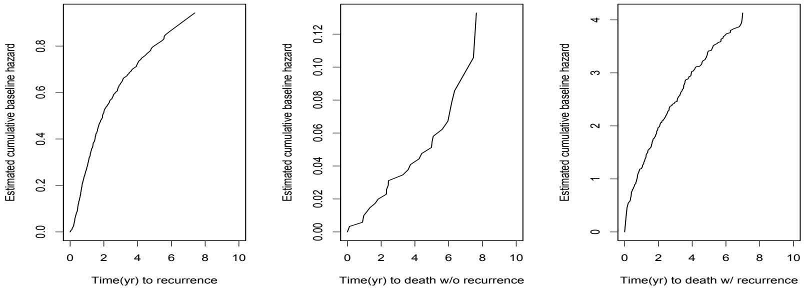
[2] IG: inverse gamma with η =0.79 or 3.37, PS: positive stable with α =0.87 or 0.72

CCS data: summary statistics

		Observation only	Lev+5-FU
Total patients		315 (100)[3]	304 (100)
	Censored with no event	125 (40)	170 (56)
	Dead w/o relapse	13 (4)	15 (5)
	Relapsed	177 (56)	119 (39)
Patients w/ relapse		177 (100)	119 (100)
	Censored w/ relapse	22 (12)	11 (9)
	Dead w/ relapse	155 (88)	108 (91)

[3] Percent%

CCS data: estimated cumulative baseline hazards[4]



- Set intervals as
  - $I_{11} = (0, 1], I_{12} = (1, 2], I_{13} = (2, 4], I_{14} = (4, 5], I_{15} = (5, \infty)$
  - $I_{21} = (0, 5], I_{22} = (5, \infty)$
  - $I_{31} = (0, 1], I_{32} = (1, 2], I_{33} = (2, 4], I_{34} = (4, 5], I_{35} = (5, \infty)$

[4] Ling & Ying(1994)'s model ignoring frailty

CCS data: parameter estimates[5]

	Interval	Est	SE	95% CI		p-value
				Parameter		
Relapse		-38.2	11.9	(-61.6,	-14.8)	0.001
Death w/o relapse		-0.9	4.2	(-9.1,	7.3)	0.835
Death w/ relapse		143.9	82.6	(-18.0,	305.9)	0.082
Frailty		0.79	0.04	(0.71,	0.87)	0.000
				Baseline hazard		
Relapse	(0,1]	259.6	21.6	(217.3,	302.0)	0.000
	(1,2]	223.0	22.8	(178.3,	267.7)	0.000
	(2,4]	89.6	12.4	(65.4,	113.9)	0.000
	(4,5]	65.5	14.4	(37.3,	93.7)	0.000
	$(5,\infty)$	49.1	12.4	(24.8,	73.4)	0.000
Death w/o relapse	(0,5]	9.3	3.2	(3.0,	15.5)	0.004
	$(5,\infty)$	21.9	8.8	(4.6,	39.1)	0.013
Death w/ relapse	(0,1]	871.3	143.6	(589.8,	1152.8)	0.000
	(1,2]	768.1	95.1	(581.7,	954.6)	0.000
	(2,4]	546.0	65.7	(417.2,	674.7)	0.000
	(4,5]	375.4	95.4	(188.4,	562.4)	0.000
	$(5,\infty)$	300.8	70.7	(162.1,	439.4)	0.000

[5] unit: per a one-thousand-person year

Summary & discussion

- Propose the additive risk frailty approach for the modeling of semi-competing risks data
- For the fitting of the baseline hazards, employ a piecewise exponential model with the different number of cut-points according to the baseline hazard
- Estimate parameters via EM algorithm and obtain their variance estimates using the Louis' method
- Simulations showed that our proposed method has good performance in terms of bias and coverage probability and is robust to the misspecification of the frailty distribution
- Future work
    - How to assess the goodness-of-fit of the proposed model?
    - How to incorporate time-varying covariate effects into the proposed model like the Aalen's additive risk model?

Thank you!