Causal-inference framework for time-to-event surrogate and true endpoints

Florian Stijven

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Introduction

- Further exploration gaussian copula model
- 3 cases with unidentifiable correlations fixed, and identifiable correlations varied
  - to see effect on association between ΔS and ΔT
- Association assessed by
  - regression line $E[\Delta T|\Delta S]$
  - individual causal association
- Two measures for quantifying ICA:
  - First one based on information theory: R_h
  - Second one directly follows from copula model: ρ_Δ

Joint model

- Joint distribution of potential outcomes:

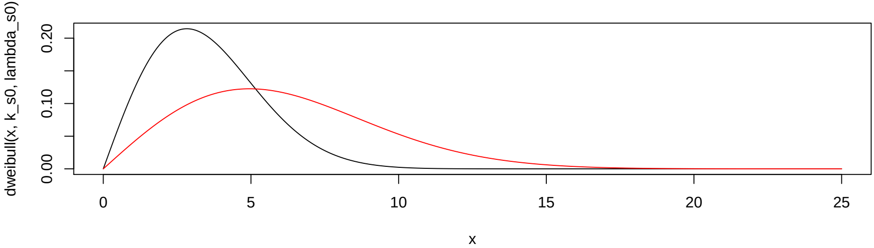
$$f(S_0, S_1, T_0, T_1) = c(\mathbf{u}, \Sigma) \cdot f_{S_0}(S_0) \cdot f_{S_1}(S_1) \cdot f_{T_0}(T_0) \cdot f_{T_1}(T_1)$$

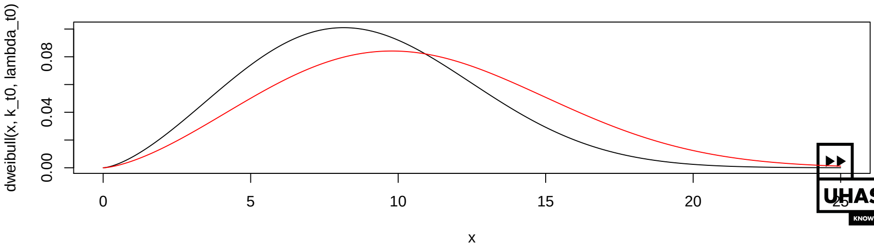
  where $c(\mathbf{u}, \Sigma)$ is a gaussian copula
- Marginal distributions for S_0, S_1, T_0 and T_1
  - $f_{S_0}(S_0)$, $f_{S_1}(S_1)$, $f_{T_0}(T_0)$ and $f_{T_1}(T_1)$
  - e.g. log-normal, log-logistic, Weibull...
  - are identifiable

Marginal Distributions

- $S_0 \sim Weibull(\lambda = 4, k = 2)$
  - $E[S_0] = 3.54$
- $S_1 \sim Weibull(\lambda = 7, k = 2)$
  - $E[S_1] = 6.20$
- $T_0 \sim Weibull(\lambda = 10, k = 2.5)$
  - $E[T_0] = 8.87$
- $T_1 \sim Weibull(\lambda = 12, k = 2.5)$
  - $E[T_1] = 10.65$

Marginal Distributions (ctd.)

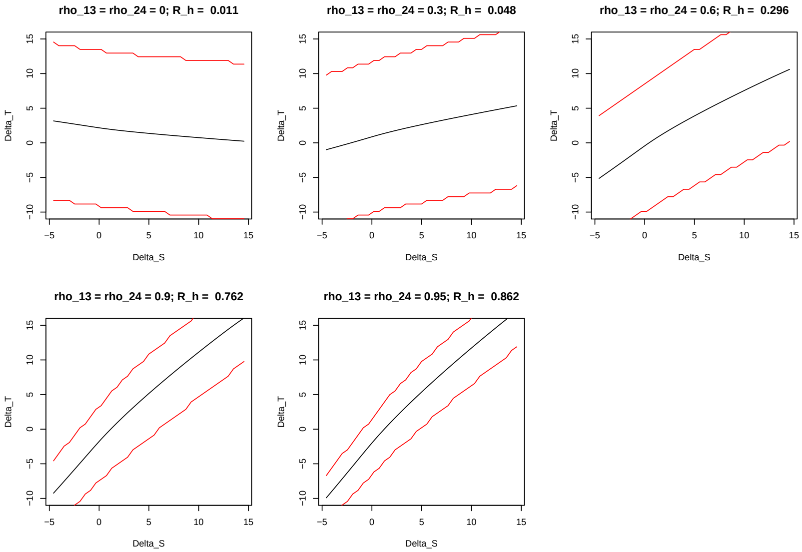




Case 1

- small positive unobservable correlations
- $$\Sigma = \begin{pmatrix} 1 & 0.1 & \rho_{S_0,T_0} & 0.1 \\ 0.1 & 1 & 0.1 & \rho_{S_1,T_1} \\ \rho_{S_0,T_0} & 0.1 & 1 & 0.1 \\ 0.1 & \rho_{S_1,T_1} & 0.1 & 1 \end{pmatrix}$$
- ρ_{S_0,T_0} and $\rho_{S_1,T_1} \in \{0, 0.3, 0.6, 0.9, 0.95\}$

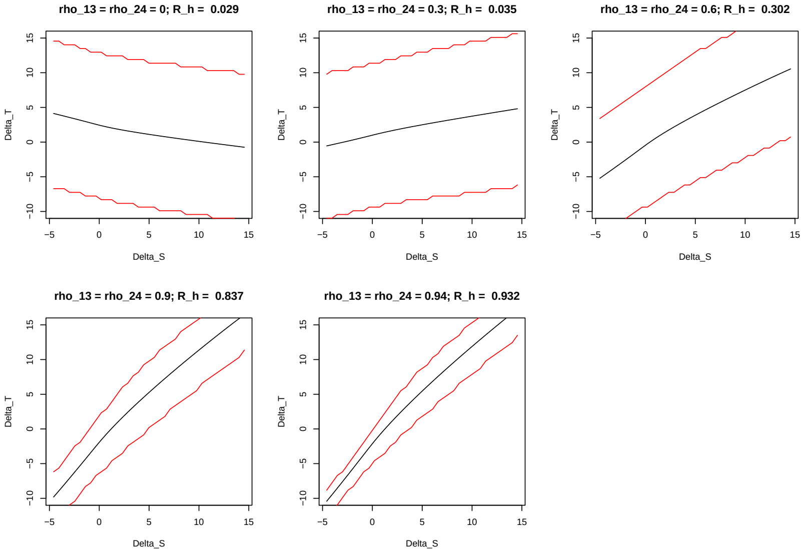
Case 1 (ctd.)


rho_13 = rho_24 = 0; R_h = 0.011
rho_13 = rho_24 = 0.3; R_h = 0.048
rho_13 = rho_24 = 0.6; R_h = 0.296
rho_13 = rho_24 = 0.9; R_h = 0.762
rho_13 = rho_24 = 0.95; R_h = 0.862
Delta_T
Delta_S
−10
−5
0
5
10
15

Case 2

- larger positive unobservable correlations
- $$\Sigma = \begin{pmatrix} 1 & 0.2 & \rho_{S_0,T_0} & 0.15 \\ 0.2 & 1 & 0.15 & \rho_{S_1,T_1} \\ \rho_{S_0,T_0} & 0.15 & 1 & 0.2 \\ 0.15 & \rho_{S_1,T_1} & 0.2 & 1 \end{pmatrix}$$
- ρ_{S_0,T_0} and $\rho_{S_1,T_1} \in \{0, 0.3, 0.6, 0.9, 0.94\}$

Case 2 (ctd.)

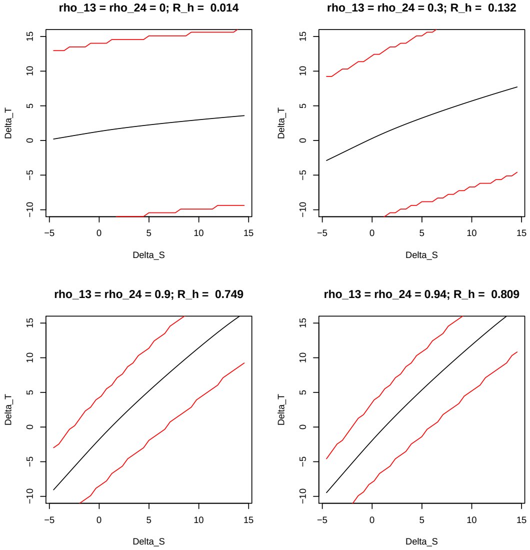

rho_13 = rho_24 = 0; R_h = 0.029
rho_13 = rho_24 = 0.3; R_h = 0.035
rho_13 = rho_24 = 0.6; R_h = 0.302
rho_13 = rho_24 = 0.9; R_h = 0.837
rho_13 = rho_24 = 0.94; R_h = 0.932
Delta_T
Delta_S
−10
−5
0
5
10
15

Case 3

- negative unobservable correlations
  - might be less plausible
- $$\Sigma = \begin{pmatrix} 1 & -0.2 & \rho_{S_0,T_0} & -0.15 \\ -0.2 & 1 & -0.15 & \rho_{S_1,T_1} \\ \rho_{S_0,T_0} & -0.15 & 1 & -0.2 \\ -0.15 & \rho_{S_1,T_1} & -0.2 & 1 \end{pmatrix}$$
- ρ_{S_0,T_0} and $\rho_{S_1,T_1} \in \{0, 0.3, 0.6, 0.9, 0.94\}$

UHASSELT KNOWLEDGE IN ACTION

Case 3 (ctd.)



rho_13 = rho_24 = 0; R_h = 0.014
rho_13 = rho_24 = 0.3; R_h = 0.132
rho_13 = rho_24 = 0.6; R_h = 0.375
rho_13 = rho_24 = 0.9; R_h = 0.749
rho_13 = rho_24 = 0.94; R_h = 0.809
Delta_T
Delta_S
−5
0
5
10
15
−10

Measures for ICA: R_h

- defined as follows: $R_h = 1 - \exp(-2 \cdot I(\Delta S, \Delta T))$
  - where $I(\Delta S, \Delta T) = \int f(\Delta S, \Delta T) \log\left(\frac{f(\Delta S) \cdot f(\Delta T)}{f(\Delta S, \Delta T)}\right) d\Delta S d\Delta T$
- $I(\Delta S, \Delta T)$, $f(\Delta S, \Delta T)$, $f(\Delta S)$ and $f(\Delta T)$ computed by numerical integration
  - Error due to numerical approximation
  - Very computer intensive

$\rho_{S_0,T_0} = \rho_{S_1,T_1}$	0	0.30	0.60	0.90	0.95 (0.94)
case 1	0.011	0.048	0.296	0.762	0.862
case 2	0.029	0.035	0.302	0.837	0.932
case 3	0.014	0.132	0.375	0.749	0.809

UHASSELT KNOWLEDGE IN ACTION

Measures for ICA: ρ_Δ

- Consider normal transformed variables
- e.g. $q_{S_0} = \Phi^{-1}(F_{S_0}(S_0)) \sim N(0,1)$
- Gaussian copula: $(q_{S_0}, q_{S_1}, q_{T_0}, q_{T_1})' \sim N_4(\mathbf{0}, \Sigma)$
- $\rho_\Delta = cor(q_{S_1} - q_{S_0}, q_{T_1} - q_{T_0})$
  - follows directly from Σ
  - thus requires no numerical integration

$$\rho_\Delta = \frac{\rho_{S_0,T_0} + \rho_{S_1,T_1} - \rho_{S_0,T_1} - \rho_{S_1,T_0}}{2\sqrt{(1-\rho_{T_0,T_1})(1-\rho_{S_0,S_1})}}$$

where

$$\rho_{S_0,T_0} = cor(q_{S_0}, q_{T_0})$$

Measures for ICA: ρ_Δ (ctd.)

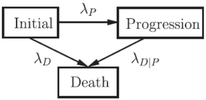
- same ranking (except for $\rho_{S_0,T_0} = \rho_{S_1,T_1} = 0$)
  - relation between ρ_Δ and R_h should be explored further
- BUT: interpretation not clear
  - e.g. $S_0 < S_1$ does not necessarily imply $q_{S_0} < q_{S_1}$
  - $\Rightarrow \Delta S = S_1 - S_0 > 0$ does not necessarily imply $\Delta q_S = q_{S_1} - q_{S_0} > 0$

$\rho_{S_0,T_0} = \rho_{S_1,T_1}$	0	0.30	0.60	0.90	0.95 (0.94)
case 1	-0.011	0.222	0.555	0.889	0.944
case 2	-0.188	0.188	0.563	0.934	0.988
case 3	0.125	0.375	0.625	0.875	0.908

To do

- implement sensitivity analysis (as for normal-normal case etc.)
- Then apply on real data set?
- Issue of time orderings
    - Approach $\pm$ suitable if S is (almost) never censored by T (OS)
    - So $S << T$: e.g. time-to-response (S) and death (T)

Explicit consideration of time orderings (Proposal)



- illness-death type of model:
- induce association (within treatment group) by frailties $Z_{0,i}$ and $Z_{1,i}$ (e.g. for control group)
  - $\lambda_{S_0,i}(t|Z_{0,i}) = \lambda_{0,S}(t) \cdot Z_{0,i} \cdot (A_i)$
  - $\lambda_{T_0,i}(t|Z_{0,i}) = \lambda_{0,T}(t) \cdot Z_{0,i} \cdot (A_i)$
  - $\lambda_{T_0|S_0,i}(t|Z_{0,i}) = \lambda_{0,S|T}(t) \cdot Z_{0,i} \cdot I(T_0 > S_0) \cdot (A_i)$
- Induce association across treatment groups by frailty (A_i) with fixed distribution
  - Parameters of this distribution fixed at different values in sensitivity analysis
  - e.g. $A_i \sim \Gamma(\theta, \theta)$ and fix θ at each iteration of sensitivity analysis
- Very complex, difficult to fit $\rightarrow$ Bayesian estimation?

Appendix: Relative ranking

- ranking from large to small association

$\rho_{S_0,T_0} = \rho_{S_1,T_1}$	0	0.30	0.60	0.90	0.95 (0.94)
case 1	0.011 (15)	0.048 (11)	0.296 (9)	0.762 (5)	0.862 (2)
case 2	0.029 (13)	0.035 (12)	0.302 (8)	0.837 (3)	0.932 (1)
case 3	0.014 (14)	0.132 (10)	0.375 (7)	0.749 (6)	0.809 (4)

$\rho_{S_0,T_0} = \rho_{S_1,T_1}$	0	0.30	0.60	0.90	0.95 (0.94)
case 1	-0.011 (14)	0.222 (11)	0.555 (9)	0.889 (5)	0.944 (2)
case 2	-0.188 (15)	0.188 (12)	0.563 (8)	0.934 (3)	0.988 (1)
case 3	0.125 (13)	0.375 (10)	0.625 (7)	0.875 (6)	0.908 (4)