A Model based on Mixture of Weibull Distributions for Depending Competing Risks Data in the Presence of Long-term Survivor

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Main Sections

Malignant Melanoma Cancer Data Set

- Melanoma : Skin cancer
- Collected at Odense University Hospital during 1962 to 1977
- Two hundred and five patients
- No of days after the operation
  - until they died
  - until they left the study
  - until the termination of the study in the year 1977

Malignant Melanoma Cancer Data Set

id	status	days	ulc	thick	sex
13	3	30	0	65	1
16	3	99	0	290	0
21	1	185	1	1208	1
97	2	35	0	134	1
469	1	204	1	484	1
789	3	10	1	676	1

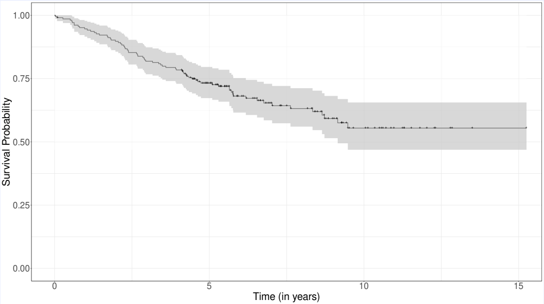
- id : Patient code
- status : Survival status (1: dead from melanoma, 2: alive, 3: dead from other cause)
- days : Survival time (in days)
- ulc : Ulceration (1: present, 0: absent)
- thick : Tumour thickness (in 1/100 mm)
- sex : Gender (0: female, 1: male)

Malignant Melanoma Cancer Data Set

- Available in `timereg` package
- Melanoma cancer: 28%
- Other causes: 7%
- Right censored: 65%
- Sex (Male 39%, Female 61%)
- Status of ulcer (Present 44%, Absent 56%)
- Thickness of tumor (Mean 2.92 mm, SD 2.92 mm)

Malignant Melanoma Cancer Data Set

- This data set was earlier analyzed by Rodrigues et al. 2011 and Pal and Balakrishnan 2016.
- Patients died due to other causes: Right censored
- The Kaplan-Meier estimate



- Levels off at a non-zero proportion
- Possibility of non-zero cure proportion

Proposed Model

Assumption

- The population consists of two groups
  - Susceptible
  - Cure
- There are K mutually exclusive and exhaustive causes for the event

Proposed Model

Mixture model for competing risks

- $\widetilde{T}$: Time-to-event
- $\widetilde{I}$: Cure indicator (0 : cured, 1 : susceptible)
- The conditional survival function (SF) of the time-to-event, given the subject belongs to susceptible group, is

$$S_{mix}(t) = P(\widetilde{T} > t|\widetilde{I} = 1) = \sum_{k=1}^{K} \pi_k S_k(t)$$

- K : Number of competing risks
- $\widetilde{N}$: Failure mode of a susceptible subject
- $\pi_k = P(\widetilde{N} = k|\widetilde{I} = 1)$: Probability of failure due to k-th cause
- $S_k(t) = P(\widetilde{T} > t|\widetilde{N} = k, \widetilde{I} = 1)$: Mode-specific conditional SF

Proposed Model

Mixture cure rate model

- The SF of $\widetilde{T}$ is

$$S_{pop}(t) = p_0 + (1 - p_0)S_{mix}(t) = p_0 + (1 - p_0)\sum_{k=1}^{K} \pi_k S_k(t)$$

- $p_0 = P(\widetilde{I} = 0)$: Cure probability

Proposed Model

Modelling $S_k(\cdot)$

- $k-$th mode-specific time-to-event follows Weibull distribution
- $S_k(t) = \exp\{-\lambda_k t^{\alpha_k}\}$ for $t > 0$
- $\lambda_k > 0$: Scale parameter
- $\alpha_k > 0$: Shape parameter

Proposed Model

Model with covariates

- Probability of a subject being cured depends on covariates
- Binary regression models
- Logistic link function

$$p_0(\boldsymbol{x};\, \boldsymbol{\beta}) = \frac{1}{1+\exp(\boldsymbol{x}^T\boldsymbol{\beta})}$$

- $\boldsymbol{x} = (1,\, x_1,\, \ldots,\, x_L)$: Vector of covariates
- $\boldsymbol{\beta} = (\beta_0,\, \beta_1,\, \ldots,\, \beta_L)$: Parameter vector

Likelihood Inference

Form of data

- Form of available data :

$$\{(t_\ell,\, \delta_\ell,\, \boldsymbol{x}_\ell) : \ell = 1,\, 2,\, \ldots,\, n\}$$

- t_ℓ : Observed value of $T_\ell = \min(\widetilde{T}_\ell, C_\ell)$
- δ_ℓ : Observed value of $\Delta_\ell = \widetilde{N} \times I(\widetilde{T}_\ell \leq C_\ell)$
- $\widetilde{T}$: Time-to-event
- C_ℓ : Censoring time
- $\boldsymbol{x}_\ell$: Covariate vector

Likelihood Inference

Likelihood function

- Likelihood function (non-informative censoring)

$$L(\boldsymbol{\gamma}) \propto \prod_{\ell=1}^{n} \left[\left\{ \prod_{k=1}^{K} \{(1 - p_0(\boldsymbol{x}_\ell;\, \boldsymbol{\beta}))\pi_k f_k(t_\ell; \boldsymbol{\theta}_k)\}^{I(\delta_\ell = k)} \right\} \{S_{pop}(t_\ell; \boldsymbol{\gamma})\}^{I(\delta_\ell = 0)} \right]$$

- $\boldsymbol{\gamma} = (\alpha_1, \ldots, \alpha_K, \lambda_1, \ldots, \lambda_K, \pi_1, \ldots, \pi_K, \beta_0, \beta_1, \ldots, \beta_L)$
- $\boldsymbol{\theta}_k = (\alpha_k,\, \beta_k)$

Likelihood Inference

Likelihood function

- MLEs can be found by maximizing likelihood function over

$$\boldsymbol{\Gamma} = \Big\{ \boldsymbol{\gamma} : \alpha_k > 0,\ \lambda_k > 0,\ k = 1, 2, \ldots, K, \\ 0 < \pi_k < 1,\ k = 1, 2, \ldots, K,\ \sum_{k=1}^{K} \pi_k = 1, \\ \beta_\ell \in \mathbb{R},\ \ell = 0, 1, 2, \ldots, L \Big\}$$

- $(3K + L + 1)$ dimensional constrained optimization problem

Likelihood Inference

EM based method – Complete data

- $\widetilde{I}$ is latent if $\delta = 0$
- $\widetilde{I} = 1$ if $\delta \neq 0$
- EM algorithm is a natural choice to obtain the MLEs
- The complete data :

$$\{(t_\ell,\, \delta_\ell,\, \boldsymbol{x}_\ell,\, i_\ell) : \ell = 1,\, 2,\, \ldots,\, n\}$$

- i_ℓ : Realized value of $\widetilde{I}$ for ℓ-th subject

Likelihood Inference

EM based method – Complete data likelihood

- Complete data likelihood function is

$$L_c(\boldsymbol{\theta}) \propto \left[\prod_{\ell \in J_1} \prod_{k=1}^{K} \{(1 - p_0(x_\ell;\, \boldsymbol{\beta}))\pi_k f_k(t_\ell; \boldsymbol{\theta}_k)\}^{I(\delta_\ell = k)}\right]$$

$$\times \left[\prod_{\ell \in J_0} \{p_0(x_\ell;\, \boldsymbol{\beta})\}^{1-i_\ell} \{(1 - p_0(x_\ell;\, \boldsymbol{\beta}))S_{mix}(t_\ell; \boldsymbol{\psi})\}^{i_\ell}\right]$$

- $J_1 = \{l : \delta_\ell \neq 0\}$ and $J_0 = \{l : \delta_\ell = 0\}$
- $\boldsymbol{\psi} = (\alpha_1, \ldots, \alpha_K, \lambda_1, \ldots, \lambda_K, \pi_1, \ldots, \pi_K)$

Likelihood Inference

EM based method – E and M step

- At the $(m+1)-$st step, the expectation of complete data log-likelihood function is

$$\widetilde{Q}^{(m+1)}(\boldsymbol{\gamma}) = \widetilde{Q}_1^{(m+1)}(\boldsymbol{\beta}) + \widetilde{Q}_2^{(m+1)}(\boldsymbol{\psi})$$

- $\widetilde{Q}_1^{(m+1)}(\cdot)$ is a (non-linear) function of $\boldsymbol{\beta}$ only
- $\widetilde{Q}_2^{(m+1)}(\cdot)$ is a (non-linear) function of $\boldsymbol{\psi}$ only
- Maximize $\widetilde{Q}_1^{(m+1)}(\cdot)$ and $\widetilde{Q}_2^{(m+1)}(\cdot)$ separately

Likelihood Inference

Confidence Interval

- Model parameters – Luis missing value principle
- Cure rate – δ-method

Analysis of Melanoma Data

Modelling

- Mode 1 – death due to malignant melanoma
- Mode 2 – death due to any other causes
- 3 covariates (ulcer status, tumour thickness and sex)
- Scale survival time dividing by 365
- Weibull model for cause specific distribution
- Logistic link function

Analysis of Melanoma Data

Model parameter estimates

Parameters	MLE	95% CI		
α_1 (shape, mode 1)	1.603	1.348	–	1.858
α_2 (shape, mode 2)	0.655	0.321	–	0.988
λ_1 (scale, mode 1)	0.085	0.051	–	0.119
λ_2 (scale, mode 2)	0.081	0.039	–	0.123
π_1 (mixture coefficient, mode 1)	0.564	0.418	–	0.710
π_2 (mixture coefficient, mode 2)	0.436	0.206	–	0.666
β_0 (intercept)	-2.238	-3.014	–	-1.461
β_1 (ulcer status)	1.654	0.796	–	2.512
β_2 (tumour thickness)	0.007	0.004	–	0.011
β_3 (sex)	1.432	0.608	–	2.256

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Thank You