Accommodating informative dropout and death: a joint modelling approach for longitudinal and semi-competing risks data

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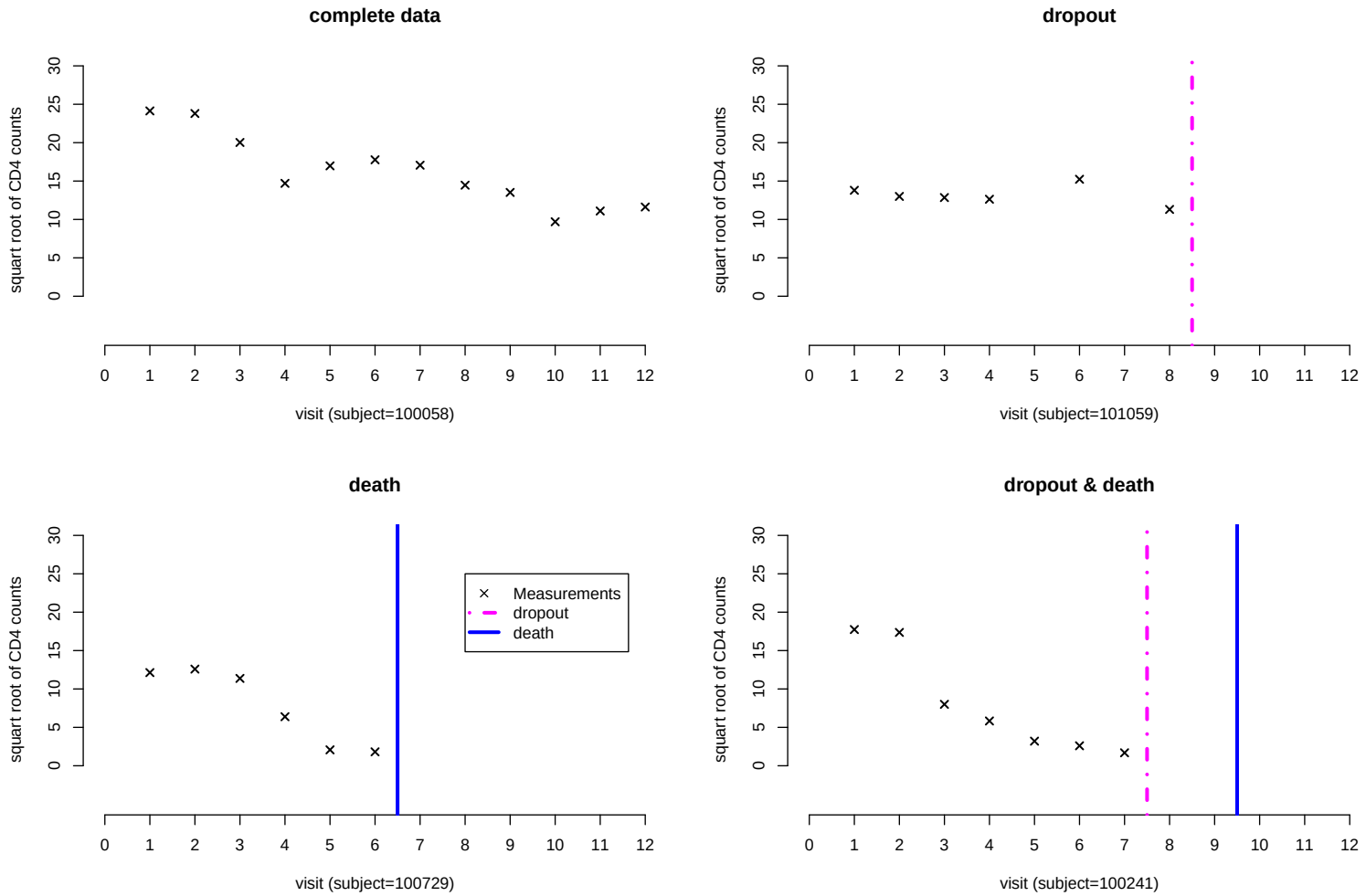
Outline

Introduction

- longitudinal and semi-competing risks data, e.g., CD4 counts, dropout and HIV-related death in the HIV epidemiology research study (HERS).



Some concepts

- mortal cohort;
- immortal cohort;
  (Aalen and Gunnes, 2010)

longitudinal profile models:

- unconditional models, e.g., random-effects models $f(Y_i(t))$;
- fully conditional models, e.g., $f(Y_i(t)|S_i = s)$, $s > t$;
- partly conditional models, e,g., $f(Y_i(t)|S_i > t)$ (Kurland and Heagerty, 2005; Kurland *et al.*, 2009);
  - GEE approaches;
  - a likelihood-based joint modelling approach proposed subsequently.

Notation

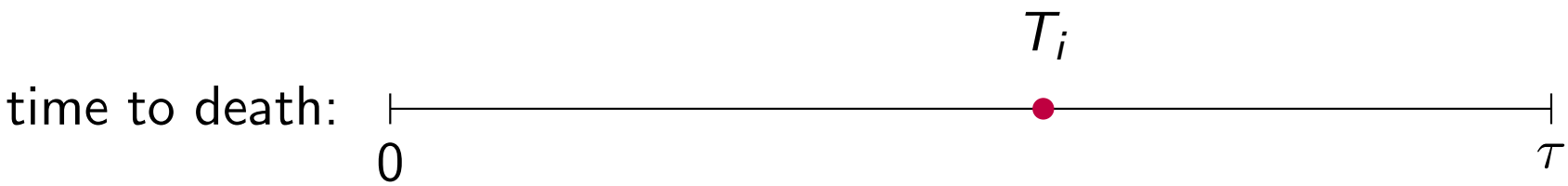
- scheduled repeated measurements of a longitudinal outcome $Y_i = (Y_{i1}, \ldots, Y_{iM})'$, taken at visits $1, \ldots, M$, e.g., $M = 12$ for the HERS data;
- informative dropout and death
  - dropout time denoted by D_i, observed data $D_i^* = min(D_i, S_i, C_i)$, $\delta_i^D = I(D_i \leq S_i, D_i \leq C_i)$;
  - death time denoted by S_i, observed data $S_i^* = min(S_i, C_i)$, $\delta_i^S = I(S_i \leq C_i)$;

  C_i denotes non-informative censoring, e.g., end of study;
- covariates X_i, e.g., sex, treatment arm;

Time-to-event processes

Time-to-event data,

- time to dropout: last visit of follow-up;
- time to death:

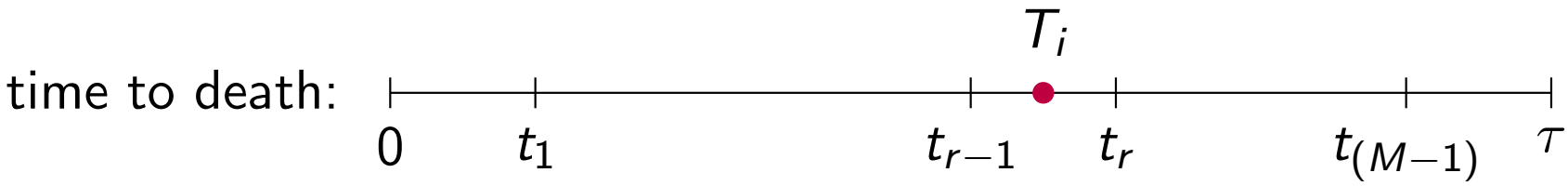


τ: the end of study.

Time-to-event processes

Discrete time-to-event data (*mathematical attractiveness*),

- time to dropout: last visit of follow-up;
- time to death:



τ: the end of study.

the discrete death time $S_i = r$ *(Barrett et al, 2015, JRSSB)*.

Joint models

Joint models for the longitudinal and semi-competing risks data,

$$\begin{cases} Y_{ij} = x_{ij}^T \beta + z_{ij}^T b_i + \epsilon_{ij} \\ Pr(D_i = r | D_i \geq r) = 1 - \Phi(x_{D,ir}^T \alpha_D + \gamma_{D,r}^T W_{D,ir} b_i) \\ Pr(S_i = r | S_i \geq r) = 1 - \Phi(x_{S,ir}^T \alpha_S + \gamma_{S,r}^T W_{S,ir} b_i) \end{cases},$$

- $\Phi(\cdot)$ standard normal cdf;
- β, α_D, α_S regression coefficients; $\gamma_{D,r}$, $\gamma_{S,r}$ association effects;
- random effects $b_i \sim N(0, \Sigma_b)$;
- $\epsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2)$;
- $W_{D,ir} b_i$, $W_{S,ir} b_i$ vectors of linear combinations of random effects, e.g., $W_{D,ir} b_i = (b_{i0}, b_{i1})^T$;
- conditional independence assumption given random effects b_i;

Likelihood function,

$$\prod_i L_i(\theta; y_i, D_i^*, \delta_i^D, S_i^*, \delta_i^S)$$

$$= \prod_i \int_{-\infty}^{\infty} f(\text{longitudinal data}|\theta, b_i) \times$$

$$Pr(\text{dropout data}|\theta, b_i) \times Pr(\text{death data}|\theta, b_i) \times f(b_i|\theta) db_i.$$

Semi-competing risks data

Four possible scenarios of the observed time-to-event data,

(1) neither dropout nor death:
$$D_i^* = d, S_i^* = s, (\delta_i^D, \delta_i^S) = (0, 0);$$

(2) dropout only:
$$D_i^* = d, S_i^* = s, (\delta_i^D, \delta_i^S) = (1, 0);$$

(3) death only:
$$D_i^* = d, S_i^* = s, (\delta_i^D, \delta_i^S) = (0, 1);$$

(4) both dropout and death:
$$D_i^* = d, S_i^* = s, (\delta_i^D, \delta_i^S) = (1, 1);$$

For the scenario (1), the likelihood function of observed data $\{y_i = (y_{i1}, \ldots, y_{in_i})', D_i^* = d, \delta_i^D = 0, S_i^* = s, \delta_i^S = 0\}$,

$$L_i(\theta; y_i, D_i^*, \delta_i^D, S_i^*, \delta_i^S)$$

$$= \int_{-\infty}^{\infty} \phi(y_i; x_i\beta + z_i b_i, \sigma^2 I_{n_i}) \prod_{k=1}^{d} \Phi(x_{D,ir}^T \alpha_D + \gamma_{D,r}^T W_{D,ir} b_i)$$

$$\prod_{\ell=1}^{s} \Phi(x_{S,ir}^T \alpha_S + \gamma_{S,r}^T W_{S,ir} b_i) \phi(b_i; 0, \Sigma_b) db_i$$

$$= L_{i1}(\cdot \backslash b_i) \Phi^{(d+s)}(A_{ds} + B_{ds} h_i; 0, I_{d+s} + B_{ds} H_i^{-1} B_{ds}^T)$$

- closed-form likelihood (skewed normal distribution, Arnold 2009);
- $L_{i1}(\cdot \backslash b_i)$, h_i, H_i, A_{ds}, B_{ds} function/vectors/matrices free of b_i;
- $\phi(\cdot; \mu, \Sigma)$ and $\Phi^{(d+s)}(\cdot; \mu, \Sigma)$ denote multivariate normal pdf/cdf.

Marginal mean profile conditional on being alive

- Unconditional population mean profile for an immortal cohort

$$E(Y_{ij}|x_{ij}) = x_{ij}^T \beta;$$

- Conditional mean profile given being alive for a mortal cohort, we can compute

$$E(Y_{ij}|x_{ij}, S_i \geq j) = x_{ij}^T \beta + z_{ij}^T E(b_i|S_i \geq j).$$

Analogously, $f(b_i|S_i \geq j)$ is a multivariate skew-normal distribution,

$$f(b_i|S_i \geq j) = f\big(b_i|S_i > (j-1)\big) = \frac{Pr\big(S_j > (j-1)|b_i\big) f(b_i)}{Pr(S_i > (j-1))},$$

closed form of its expectation can be obtained.

Statistical inference

1. Maximum likelihood-based approach (*exact likelihood*);
   - R software utilising *nlminb* or *optim*.
2. Bayesian approach;
   - implemented using WinBUGS.

HERS data description

HIV epidemiology research study (HERS) (Smith *et al.*, 1997)

# of subjects: 850 (HIV positive at baseline)	
CD4 counts	reviewed every 6 months up to 12 visits

time-to-event data	# of subjects
scenario (1): $(\delta_i^D, \delta_i^S) = (0,0)$	374
scenario (2): $(\delta_i^D, \delta_i^S) = (1,0)$	352
scenario (3): $(\delta_i^D, \delta_i^S) = (0,1)$	23
scenario (4): $(\delta_i^D, \delta_i^S) = (1,1)$	78

Objective: study the role of baseline patient characteristics (i.e., viral load, antiretroviral therapy (art), # of symptoms) on variation in longitudinal CD4 counts.

Models proposed for the HERS data

$$
\begin{cases}
Y_{ij} = \beta_0 + \beta_1 \mathit{visit} + \beta_{2\sim4}\text{viral load} + \beta_5 \mathit{symptoms} + \beta_6 \mathit{art} \\
+\beta_{7\sim9}\text{visit*viral load} + \beta_{10} \mathit{visit} * \mathit{symptoms} + \beta_{11} \mathit{visit} * \mathit{art} + b_{i0} + b_{i1} + \epsilon_{ij} \\
\\
Pr(D_i = r | D_i \geq r) = 1 - \Phi(\alpha_{D,i0} + \alpha_{D,i1\sim3}\text{viral load} + \alpha_{D,i4}\mathit{symptoms} \\
\qquad +\alpha_{D,i5}\mathit{art} + \alpha_{D,i6} r + \alpha_{D,i7} r^2 + \gamma_{D,0} b_{i0} + \gamma_{D,1} b_{i1}) \\
\\
Pr(S_i = r | S_i \geq r) = 1 - \Phi(\alpha_{S,i0} + \alpha_{S,i1\sim3}\text{viral load} + \alpha_{S,i4}\mathit{symptoms} \\
\qquad +\alpha_{S,i5}\mathit{art} + \alpha_{S,i6} r + \alpha_{S,i7} r^2 + \gamma_{S,0} b_{i0} + \gamma_{S,1} b_{i1})
\end{cases}
$$

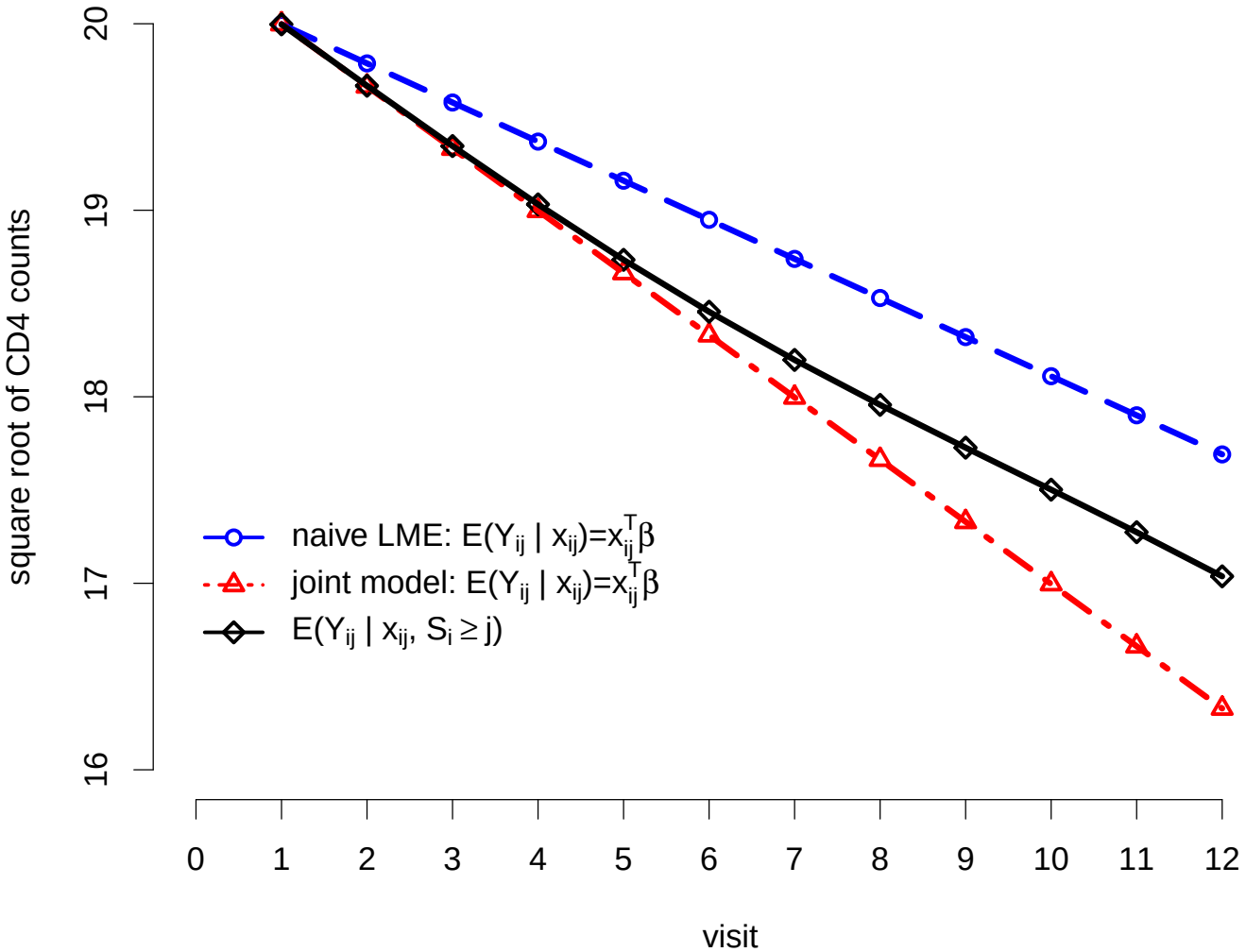
WinBUGS results

Longitudinal process (CD4 counts)

	Joint modelling (WinBUGS)				Linear mixed effects (LME)	
	mean	sd	2.5%	97.5%	estimate	sd
intercept	15.11	0.71	13.76	16.51	14.59	0.70
visit	-0.87	0.13	-1.11	-0.62	-0.57	0.12
viral load [1] (0-500)	10.00	0.79	8.42	11.56	10.52	0.79
viral load [2] (500-5k)	6.61	0.72	5.14	7.97	6.98	0.74
viral load [3] (5k-30k)	2.94	0.82	1.28	4.54	3.21	0.81
symptoms	-0.12	0.20	-0.51	0.28	-0.14	0.21
art at baseline	-4.66	0.43	-5.51	-3.83	-4.76	0.43
visit*viral load [1]	0.47	0.14	0.21	0.74	0.23	0.13
visit*viral load [2]	0.44	0.13	0.19	0.69	0.22	0.12
visit*viral load [3]	0.28	0.14	0.02	0.55	0.15	0.13
visit*symptoms	-0.05	0.03	-0.11	0.01	-0.03	0.03
visit*art	0.12	0.06	-0.01	0.23	0.16	0.06
$\gamma_{D,0}$	0.03	0.01	0.02	0.04	-	-
$\gamma_{D,1}$	0.44	0.05	0.35	0.54	-	-
$\gamma_{S,0}$	0.13	0.02	0.10	0.16	-	-
$\gamma_{S,1}$	1.23	0.17	0.93	1.58	-	-

Marginal mean profiles

Subjects: viral load [1], # of symptoms=1, antiretroviral therapy (art) at baseline;



Conclusions

1. a likelihood-based approach to capture the partly conditional mean profiles, accommodating both informative dropout and death;
2. offer inference for both mortal and immortal cohort;
3. a new model for semi-competing risks data in the joint modelling framework;
4. approach demonstrated by an analysis of the HERS data.

Key references

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4. Kurland, Brenda F., and Patrick J. Heagerty. "Directly parameterized regression conditioning on being alive: analysis of longitudinal data truncated by deaths." *Biostatistics* 6, no. 2 (2005): 241-258.

Thank You!

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