Software Implementation for Joint Modelling of Repeated Measurements and Survival Data

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Newcastle, 16th June 2008

Outline

- Repeated measurements data
- Survival data
- Latent processes and joint modelling

Software

- implementation in R
- simulation study
- worked examples

Summary

Repeated observations made on units over time:

General model $Y_{ij} = X_{1i}(t_{ij})^{\mathcal{T}}eta_1 + R_{1i}(t_{ij}) + Z_{ij}$

- β_1 are population-level parameters
- *R*₁ is a latent process incorporating random effects and/or a stationary Gaussian process (SGP)
- independent measurement errors

$$Z_{ij} \sim N(0, \tau^2)$$

Example: random slope and intercept model

Laird-Ware (1982) model

$$Y_{ij} = X_{1i}(t_{ij})\beta_1 + U_{0i} + U_{1i}t_{ij} + Z_{ij}$$

where

$$\begin{pmatrix} U_{0i} \\ U_{1i} \end{pmatrix} \sim \begin{pmatrix} N \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \nu_{00} & \nu_{01} \\ \nu_{10} & \nu_{11} \end{pmatrix} \end{pmatrix},$$

or, alternatively,

$$U_i \sim N(\mathbf{0}, V).$$

Measurement process density

$$(2\pi\tau^2)^{-1/2} \exp\{-(y_{ij} - X_{1i}(t_{ij})\beta_1 - U_{0i} - U_{1i}t_{ij})^2/2\tau^2\}$$

• Standard software readily available to fit such models

eg. library(nlme) in R

→

Survival data

Collection of times observed on individuals when an event of interest is recorded. Focus on single event - survival data:

Cox proportional hazards model

$$h_i(t) = h_0(t) \exp\{X_{2i}(t)\beta_2 + R_{2i}(t)\}$$

- R₂ is a latent process
- Observe time *F_i* with associated failure indicator

$$\delta_i = \begin{cases} 0 & \text{censored,} \\ 1 & \text{failure.} \end{cases}$$

Survival data density

$$h_i(F_i)^{\delta_i} \exp\left[-\int_0^{F_i} h_i(v) dv\right]$$

Dominates survival analysis. Readily available in statistical packages

• eg. library(survival) in R

Generally we have

$$R_k(t) = D_k(t)U_k + W_k(t)$$

Software focus is on models of form

 $R_k(t)=D_k(t)U_k$

only

- Accommodating SGP is computationally intensive
- Random effects model may take several forms, eg.



- 2 intercept and slope: $U_0 + U_1 t$
- Quadratic: $U_0 + U_1t + U_2t^2$

Choice of latent association

 Association is via the respective latent processes, ie. for the Laird-Ware model



(1) proportional association: $R_2(t) = \gamma R_1(t)$

$$h_i(t) = h_0(t) \exp\{X_{2i}(t)\beta_2 + \gamma(U_{0i} + U_{1i}t)\}$$



$$h_i(t) = h_0(t) \exp\{X_{2i}(t)\beta_2 + \gamma U_{0i}\}$$

separate effects association:

$$h_i(t) = h_0(t) \exp\{X_{2i}(t)\beta_2 + \gamma_0 U_{0i} + \gamma_1 U_{1i}t\}$$

frailty:

$$h_{i}(t) = h_{0}(t) \exp\{X_{2i}(t)\beta_{2} + \gamma_{0}U_{0i} + \gamma_{1}U_{1i}t + U_{2i}\}$$

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Interpreting the latent association: γ

- Positive values of γ suggest that positive values for the associated random effects increase the hazard of 'failure'. The hazard will increase with the magnitude of U
- Similarly, negative values of γ imply that sub-zero values for the random effects alleviate the chances of experiencing the event of interest
- Example: Laird-Ware model



The joint model...

Observed data likelihood

$$\prod_{i=1}^{m} \left[\int_{-\infty}^{\infty} \left\{ \prod_{j=1}^{n_i} f(\boldsymbol{y}_{ij} \mid \boldsymbol{u}_i) \right\} f(\boldsymbol{F}_i, \delta_i \mid \boldsymbol{u}_i) f(\boldsymbol{u}_i) \ d\boldsymbol{u}_i \right]$$

- Complete data likelihood
- EM algorithm



- solve score equations
- maximum likelihood estimates
- Newton-Raphson iterative algorithm
- Is there a way to visually gauge any relationship?

Longitudinal profiles prior to drop-out: random intercept model

- > library(joineR)
- > jointplot(intlong,intsurv,lag=4)



Longitudinal profiles prior to drop-out: random intercept-and-slope model





Longitudinal profiles prior to drop-out: quadratic model

> jointplot(quadlong,quadsurv,lag=11)



Longitudinal profiles prior to drop-out: change-point model

> jointplot(changelong,changesurv,lag=4)



Longitudinal profiles prior to drop-out: liver cirrhosis data

- > library(joineR)
- > jointplot(liverlong,liversurv,lag=10)



Why R?

- + free, easy-to-use
- user sees only R syntax
- + use built-in libraries to provide starting values
- not as quick as 'compile-and-run' languages such as C/Fortran
- Does it work?
 - Simulate from a range of models
 - Vary parameter choices
 - Test in simulations

- Simulate data from Laird-Ware joint model with m = 500 and 1000 patients, measured at 5 time-points, t = (0, 1, 2, 3, 4)
- Continuous, binary and time covariates in longitudinal sub-model
- Continuous and binary covariates also appear in survival sub-model
- Consider intercept-and-slope model for latent association
- Plot and fit using R software
- > library(joineR)
- > jointplot(simlong,simsurv,lag=4)
- > fit=joint(simlong,simsurv)

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Joint plot of simulated data



Parameter	True Estimate (se)				
β_{10}	0.00	-0.02 (0.06)			
β_{11}	0.00	0.00 (0.05)			
β_{12}	0.00	0.00 (0.06)			
β_{13}	0.00	-0.04 (0.05)			
τ^2	1.00	0.99 (0.04)			
ν_0^2	1.00	1.02 (0.10)			
ν_1^2	1.00	0.99 (0.08)			
ρ	0.50	0.50 (0.06)			
β_{21}	0.00	0.01 (0.09)			
β_{22}	0.00	0.01 (0.07)			
γ	0.50	0.47 (0.04)			

Table: Simulation study: m = 500, 100 sims

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Parameter	Irue	Estimate (se)		
β_{10}	0.00	-0.01 (0.04)		
β_{11}	0.00	0.00 (0.04)		
β_{12}	0.00	0.00 (0.04		
β_{13}	0.00	-0.01 (0.03)		
τ^2	1.00	1.00 (0.03)		
ν_0^2	1.00	1.00 (0.07)		
ν_1^2	1.00	0.99 (0.05)		
ρ	0.50	0.50 (0.04)		
β_{21}	0.00	0.00 (0.05)		
β_{22}	0.00	0.01 (0.06)		
γ	0.50	0.49 (0.02)		

Table: Simulation study: m = 1000, 100 sims

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- All of the functions for the workshop are available in the R package joineR
- This workshop uses only a subset of the functions that will be available in the future
- We load the library and can see what functions are contained using
 - > library(joineR)
 - > help(package=joineR)

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Application: Schizophrenia data

Load the data into R using data(pansslong, pansssurv)

- 517 subjects, 2-year study
- 173 events of interest, covariate info
- Fit variety of models using software

A
$$R_1(t) = U_0; R_2(t) = \gamma_1 R_1(t)$$

B
$$R_1(t) = U_0 + U_1 t$$
; $R_2(t) = \gamma_1 R_1(t)$

C
$$R_1(t) = U_0 + U_1 t$$
; $R_2(t) = \gamma_1 U_0 + \gamma_2 U_1 t$

- > jointplot(pansslong,pansssurv,lag=8)
- > fit1=joint(pansslong,pansssurv,model="int")
- > fit2=joint(pansslong,pansssurv)
- > fit3=jointsep(pansslong,pansssurv)

Viewing the data in R

[4,] 4 0.212

[5,] 5 0.488

```
> pansslong[1:5,]
          id
                   Υ
                      t X1 1 X1 2 X1 3 X1 4 ...
[1,]
           1
                 78
                      0
                           1
                                0
                                      0
                                           0 . . .
[2,]
           2
                  84
                      0
                           1
                                      0
                                           0 ...
                                 0
           3
                           1
[3,]
                 101 0
                                0
                                      0
                                           0 ...
[4,]
           4
                 104 0
                           1
                                           0 ...
                                 0
                                      0
           5
                           1
[5,]
                96
                      0
                                 0
                                      0
                                           0
                                             . . .
> pansssurv[1:5,]
     id
            F cens X2_1 X2_2
[1,]
      1 0.068
                  0
                       0
                            1
[2,] 2 0.079
                  0
                       0
                            1
[3,] 3 0.099
                  0
                       0
                            0
```

Viewing help pages in R

> ?joint

joint

package:joineR

R Documentation

Fit joint model for survival and longitudinal data measured with error

Description:

This generic function fits a joint model with random latent association, building on the formulation described in Wulfsohn and Tsiatis (1997) while allowing for the presence of longitudinal and survival covariates, and three choices for the latent process. The link between the longitudinal and survival processes is assumed to be proportional.

Usage:

joint(longdat, survdat, longsep = FALSE, survsep = FALSE, gpt = 3, max.it = 200, tol = 0.001, lgpt = 10, model=c("intslope","int","quad"))

Joint plot of schizophrenia data



Viewing the fitted model object

```
> fit2=joint(pansslong,pansssurv,survsep=T)
> names(fit2)
[1] "ldaests" "survests" "sep.ll" "jointests"
   "joint.ll"
> fit2$ldaests
[1] "No separate results requested"
> names(fit2$survests)
[1] "b2"
       "haz"
                                  "sf"
                        "rs"
                                              "nev" ...
> names(fit2$jointests)
[1] "b1" "b2" "gamma" "varz"
                                       "V" "conv" "iters"
> fit2$jointests$gamma
[1] 0.05237285
```

Viewing the fitted model object (ctd.)

```
> fit2$jointests$b2
[1] 0.6144488 -0.7615617
```

```
> fit2$survests$b2
[1] 0.4794350 -0.4968896
```

```
> fit2$joint.ll
[1] -11273.75
```

```
> fit2$sep.ll
[1] -11364.43
```

```
> fit2$joint.ll-fit2$sep.ll
[1] 90.67833
```

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Parameter	Model A		Model B		Model C	
	Est	Se	Est	Se	Est	Se
$ au^2$	151.88	(5.09)	101.51	(3.96)	101.05	(3.94)
ν_0^2	302.04	(20.11)	275.40	(23.08)	274.45	(22.45)
ν_1^2	-	-	9.84	(1.86)	11.52	(2.03)
ρ	-	-	0.04	(0.08)	0.07	(0.09)
β_{21}	0.51	(0.21)	0.61	(0.24)	0.66	(0.25)
β_{22}	-0.69	(0.22)	-0.76	(0.27)	-0.77	(0.28)
γ_1	0.05	(0.01)	0.05	(0.01)	0.04	(0.01)
γ_2	-	-	-	-	0.12	(0.02)
$\log L_J$	-11435.68		-11273.75		-11251.06	
logL _S	-11488.97		-11364.43		-11364.43	

 Table:
 Parameter estimates from joint analysis of PANSS data using three different association models

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Summary and future work

- Accommodation of 'any' random effects structure
- Adopted simple form for the latent association
 - flexibility of user-chosen association
- Could, theoretically, incorporate an SGP/spline models
 - trade-off of model complexity versus computational workload. SGP models would take considerable time to fit
 - intercept and slope is popular and often suffices
 - from humble beginnings...
- Software for transformation models also available
- Variety of other functions also in 'joineR' package
- Deposit on CRAN website (http://www.r-project.org/)...
- Extension to competing risks set-up

- Laird, B. M. and Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics* 38, 963–974.
- Wulfsohn, M. S. and Tsiatis A. A. (1997). A joint model for survival and longitudinal data measured with error. *Biometrics 53*, 330–339.
- Henderson R, Diggle P, and Dobson, A. (2000). Joint modelling of longitudinal measurements and event time data. *Biostatistics* 1, 465–480.

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