BIOS6643. L17 Joint Models of Longitudinal and Survival Data

In the JM package methods are available for the majority of the generic functions

- summary(), anova(), vcov(), logLik(), AIC()
- coef(),fixef(),ranef()
- fitted(), residuals()
- plot()

Primary Biliary Cirrhosis (PBC) study

- Primary biliary cirrhosis (PBC) is a chronic liver disease that leads to cirrhosis and eventually death
- 10-year study conducted by Mayo clinic (Murtagh et al., Hepatology, 1994)
- 158 randomized to treatment, 154 to placebo
- Longitudinal biomarker measurements of serum bilirubin at times 0, 6m, 1y, 2y, etc.

Outcomes:

1. Longitudinal biomarker: serum bilirubin
2. Time to death

Question of interest:

- What is the association between the time-varying serum bilirubin (that is measured with error) and the risk of death?

```
head(pbc2, 2)
```

```
##   id   years status      drug      age    sex      year ascites hepatomegaly
## 1  1 1.09517   dead D-penicil 58.76684 female 0.0000000     Yes          Yes
## 2  1 1.09517   dead D-penicil 58.76684 female 0.5256817     Yes          Yes
##   spiders                   edema serBilir serChol albumin alkaline  SGOT
## 1     Yes edema despite diuretics     14.5     261    2.60     1718 138.0
## 2     Yes edema despite diuretics     21.3      NA    2.94     1612   6.2
##   platelets prothrombin histologic status2
## 1       190        12.2          4       1
## 2       183        11.2          4       1
```

Joint model

```
lme.fit <- lme(log(serBilir) ~ year + year:drug,
               data=pbc2, random = ~year|id)

surv.fit <- coxph(Surv(years, status2) ~ drug,
```

```
             data=pbc2.id, x=TRUE)

## the knots of the piecewise constant are chosen based on the percentiles of events (5-6 internal knot
joint.fit <- jointModel(lme.fit, surv.fit,
             timeVar="year", method = "piecewise-PH-GH")
```

Summary

```
summary(joint.fit)
```

```
##
## Call:
## jointModel(lmeObject = lme.fit, survObject = surv.fit, timeVar = "year",
##     method = "piecewise-PH-GH")
##
## Data Descriptives:
## Longitudinal Process     Event Process
## Number of Observations: 1945 Number of Events: 140 (44.9%)
## Number of Groups: 312
##
## Joint Model Summary:
## Longitudinal Process: Linear mixed-effects model
## Event Process: Relative risk model with piecewise-constant
##      baseline risk function
## Parameterization: Time-dependent
##
##    log.Lik      AIC      BIC
##  -1979.492 3990.983 4050.871
##
## Variance Components:
##              StdDev    Corr
## (Intercept)  1.0121  (Intr)
## year         0.1725  0.4172
## Residual     0.3822
##
## Coefficients:
## Longitudinal Process
##                       Value Std.Err z-value p-value
## (Intercept)          0.5700  0.0243 23.4202 <0.0001
## year                 0.1830  0.0060 30.5971 <0.0001
## year:drugD-penicil -0.0086  0.0061 -1.4161  0.1567
##
## Event Process
##                  Value Std.Err  z-value p-value
## drugD-penicil  0.0705  0.1801   0.3912  0.6956
## Assoct         1.2569  0.0944  13.3188 <0.0001
## log(xi.1)     -4.4677  0.2607 -17.1380
## log(xi.2)     -4.3254  0.2794 -15.4785
## log(xi.3)     -4.6497  0.3303 -14.0765
## log(xi.4)     -4.6046  0.3824 -12.0416
## log(xi.5)     -4.2211  0.3430 -12.3067
## log(xi.6)     -3.7653  0.3490 -10.7891
```

```
## log(xi.7)     -4.6422  0.4902  -9.4706
##
## Integration:
## method: Gauss-Hermite
## quadrature points: 15
##
## Optimization:
## Convergence: 0
```

Confidence intervals

```
confint(joint.fit, parm='all')
```

```
##                            2.5 %         est.      97.5 %
## Y.(Intercept)         0.52231994  0.570023523 0.617727106
## Y.year                0.17126153  0.182982905 0.194704279
## Y.year:drugD-penicil -0.02048156 -0.008591143 0.003299269
## T.drugD-penicil      -0.28254449  0.070460690 0.423465870
## T.Assoct              1.07194950  1.256913478 1.441877457
```

Comparison of nested models

Conduct a test for whether there is a drug effect in the survival model.