Joint Models in R

Day 6

- Use R software to fit a joint model

Joint Modeling Framework

- The standard joint model

$$h_i(t|\mathcal{M}_i(t)) = h_0(t)\exp\{\gamma' w_i + \alpha m_i(t)\}$$
$$y_i(t) = m_i(t) + \epsilon_i(t)$$
$$= x_i'(t)\beta + z_i'(t)b_i + \epsilon_i(t)$$

where $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$

Example: PBC Study

- **Research question:** What is the association between the time-varying serum bilirubin that is measured with error and the risk of death?
- We are going to fit a joint model that explicitly accounts for the endogeneity of the serum bilirubin marker

Example: PBC Study

- We are going to fit the following joint model to the PBC Study data

$$
\begin{aligned}
h_i(t) &= h_0(t)\exp\{\gamma_1 \text{D-penecil}_i + \alpha m_i(t)\} \\
y_i(t) &= m_i(t) + \epsilon_i(t), \qquad \epsilon_i(t) \sim N(0, \sigma^2) \\
&= \beta_0 + \beta_1 t + \beta_2\{t \times \text{D-penecil}_i\} + b_{i0} + b_{i1}t + \epsilon_i(t) \\
b_i &\sim N(0, D)
\end{aligned}
$$

Simple Joint Model

- Use the R software package "JM"
- Fit the joint model using the function "jointModel" from JM
- Takes as main arguments:
  - A linear mixed model built using "lme" from the package "nlme"
    - Using longitudinal data set
  - A Cox PH model built using "coxph" from the package "survival"
    - Using the "unique" data set (one row per subject)
- In the Cox PH model set x = TRUE to include the design matrix in the returned object

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

survFit <- coxph(Surv(years, status2) ~ drug, data = pbc2.id, x = TRUE)
```

Simple Joint Model

- Fit the joint model using jointModel assuming a piece-wise constant baseline hazard
- "timevar": specifies the name of the time variable in the linear mixed-effects model
- "method": specifies the type of baseline risk function, and the numerical integration approach

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

survFit <- coxph(Surv(years, status2) ~ drug, data = pbc2.id, x = TRUE)

jointFit <- jointModel(lmeFit, survFit, timeVar="year", method = "piecewise-PH-aGH")
```

Simple Joint Model

```
summary(jointFit)
```

```
##
## Call:
## jointModel(lmeObject = lmeFit, survObject = survFit, timeVar = "year",
##     method = "piecewise-PH-aGH")
##
## 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
##  -1916.363 3864.727 3924.615
##
## Variance Components:
##             StdDev    Corr
## (Intercept)  1.0024  (Intr)
## year         0.1808  0.4274
## Residual     0.3471
##
## Coefficients:
## Longitudinal Process
##                     Value Std.Err z-value p-value
## (Intercept)        0.4923  0.0583  8.4449 <0.0001
## year               0.1830  0.0184  9.9592 <0.0001
## year:drugD-penicil 0.0035  0.0245  0.1419  0.8871
##
## Event Process
##                 Value Std.Err  z-value p-value
## drugD-penicil  0.0668  0.1810   0.3688  0.7122
## Assoct         1.2417  0.0941  13.1974 <0.0001
## log(xi.1)     -4.4381  0.2595 -17.1018
## log(xi.2)     -4.2957  0.2784 -15.4277
## log(xi.3)     -4.5924  0.3260 -14.0880
## log(xi.4)     -4.5557  0.3776 -12.0649
## log(xi.5)     -4.2348  0.3436 -12.3239
## log(xi.6)     -3.8468  0.3605 -10.6697
## log(xi.7)     -4.7075  0.5027  -9.3643
##
## Integration:
## method: (pseudo) adaptive Gauss-Hermite
## quadrature points: 5
##
## Optimization:
## Convergence: 0
```

- Estimation is conducted using a hybrid optimization procedure to locate the MLEs:
  - Starts with EM algorithm for a fixed number of iterations
  - If convergence is not achieved then switches to a quasi-Newton algorithm
- The summary function returns for both the longitudinal and survival submodels:
  - Parameter estimates
  - Standard errors
  - Asymptotic Wald tests

Simple Joint Model: Longitudinal Submodel

```
## Call:
## jointModel(lmeObject = lmeFit, survObject = survFit, timeVar = "year",
##     method = "piecewise-PH-aGH")
##
## 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
##  -1916.363 3864.727 3924.615
##
## Variance Components:
##              StdDev    Corr
## (Intercept)  1.0024  (Intr)
## year         0.1808  0.4274
## Residual     0.3471
##
## Coefficients:
## Longitudinal Process
##                     Value Std.Err z-value p-value
## (Intercept)        0.4923  0.0583  8.4449 <0.0001
## year               0.1830  0.0184  9.9592 <0.0001
## year:drugD-penicil 0.0035  0.0245  0.1419  0.8871
```

Simple Joint Model: Survival Submodel

```
## Event Process
##                  Value Std.Err  z-value p-value
## drugD-penicil   0.0668  0.1810   0.3688  0.7122
## Assoct          1.2417  0.0941  13.1974 <0.0001
## log(xi.1)      -4.4381  0.2595 -17.1018
## log(xi.2)      -4.2957  0.2784 -15.4277
## log(xi.3)      -4.5924  0.3260 -14.0880
## log(xi.4)      -4.5557  0.3776 -12.0649
## log(xi.5)      -4.2348  0.3436 -12.3239
## log(xi.6)      -3.8468  0.3605 -10.6697
## log(xi.7)      -4.7075  0.5027  -9.3643
##
## Integration:
## method: (pseudo) adaptive Gauss-Hermite
## quadrature points: 5
##
## Optimization:
## Convergence: 0
```

- The xi.1,…, xi.7 are the ξ_q $(q = 1, \ldots, 7)$ parameters in our piecewise-constant baseline risk function (default is knots placed at percentiles of the observed event times)

$$h_0(t) = \sum_{q=1}^{Q} \xi_q I(v_{q-1} < t \leq v_q)$$

Simple Joint Model: Survival Submodel

```
## Event Process
##                  Value Std.Err  z-value p-value
## drugD-penicil   0.0668  0.1810   0.3688  0.7122
## Assoct          1.2417  0.0941  13.1974 <0.0001
## log(xi.1)      -4.4381  0.2595 -17.1018
## log(xi.2)      -4.2957  0.2784 -15.4277
## log(xi.3)      -4.5924  0.3260 -14.0880
## log(xi.4)      -4.5557  0.3776 -12.0649
## log(xi.5)      -4.2348  0.3436 -12.3239
## log(xi.6)      -3.8468  0.3605 -10.6697
## log(xi.7)      -4.7075  0.5027  -9.3643
##
## Integration:
## method: (pseudo) adaptive Gauss-Hermite
## quadrature points: 5
##
## Optimization:
## Convergence: 0
```

- The "Assoct" parameter is our α parameter and represents the association between $m_i(t)$ (true log-bilirubin) and the risk of death
- Strong association between log-bilirubin and risk of death, with a unit increase in the marker corresponding to a exp(1.24)= 3.46-fold increase in the risk of death (95% CI: 2.88, 4.16)

Simple Joint Model: Method

- "method" argument specifies the type of relative risk model and the type of numerical integration algorithm

  [baseline hazard]-[parameterization]-[numerical integration]

- "piecewise-PH-GH": PH model with piecewise-constant baseline hazard
- "spline-PH-GH": PH model with B-spline-approximated log baseline hazard
- "weibull-PH-GH": PH model with Weibull baseline hazard
- "Cox-PH-GH": AFT model with Weibull baseline hazard
- "weibull-AFT-GH": AFT model with Weibull baseline hazard
- GH: Gauss-Hermite
- aGH: pseudo-adaptive Gauss-Hermite rule

Comparison of baseline hazard functions

	Cox Log HR (SE)	Weibull Log HR (SE)	Piecewise Log HR (SE)
D-penecil	0.066 (0.159)	0.038 (0.179)	0.067 (0.180)
Association (α)	1.213 (0.050)	1.247 (0.094)	1.242 (0.094)

- Unspecified baseline hazard severely underestimates the standard error of the parameters
- Consider using a flexible, but specified form for the baseline hazard

Simple Joint Model

- Methods are available for the majority of the standard generic functions
  - summary(), anova(), vcov(), logLik(), AIC()
  - coef(), fixef(), ranef()
  - fitted(), residuals()
  - plot()

Confidence intervals

```
confint(jointFit, parm="all")
```

```
##                             2.5 %        est.     97.5 %
## Y.(Intercept)          0.37802532 0.492277792 0.60653026
## Y.year                 0.14699822 0.183015754 0.21903329
## Y.year:drugD-penicil -0.04458294 0.003480921 0.05154479
## T.drugD-penicil      -0.28795533 0.066750603 0.42145653
## T.Assoct              1.05730695 1.241716332 1.42612572
```

```
confint(jointFit, parm="Longitudinal")
```

```
##                            2.5 %        est.     97.5 %
## (Intercept)          0.37802532 0.492277792 0.60653026
## year                 0.14699822 0.183015754 0.21903329
## year:drugD-penicil -0.04458294 0.003480921 0.05154479
```

```
exp(confint(jointFit, parm="Event"))
```

```
##                    2.5 %     est.   97.5 %
## drugD-penicil 0.7497951 1.069029 1.524180
## Assoct        2.8786083 3.461550 4.162541
```

Inference for Joint Models

- For testing the null hypothesis $H_0: \theta = \theta_0$ vs. $H_a: \theta \neq \theta_0$
- For nested models:
  - Likelihood ratio test
  - Score test
  - Wald test
- For non-nested models
  - AIC, BIC, …

Comparison of nested models

- Compare our original model, with a nested model in which there is no treatment effect in the survival submodel
- Testing $H_0: \gamma_1 = 0$
- Likelihood ratio test: p=0.71 (same p-value for Wald test)

```
survFit.2 <- coxph(Surv(years, status2) ~ 1, data = pbc2.id, x = TRUE)
jointFit.2 <- jointModel(lmeFit, survFit.2, timeVar="year", method = "piecewise-PH-aGH")
anova(jointFit.2, jointFit)
```

```
##
##                AIC     BIC  log.Lik  LRT df p.value
## jointFit.2 3862.87 3919.01 -1916.43
## jointFit   3864.73 3924.61 -1916.36 0.14  1  0.7078
```

Comparison of nested models

- Compare our original model, with a nested model in which there is no treatment x time effect in the longitudinal submodel
- Testing $H_0: \beta_2 = 0$
- Likelihood ratio test: p=0.90 (similar p-value for Wald test)

```
lmeFit.3 <- lme(log(serBilir) ~ year, data = pbc2, random = ~ year | id)
survFit.3 <- coxph(Surv(years, status2) ~ drug, data = pbc2.id, x = TRUE)
jointFit.3 <- jointModel(lmeFit.3, survFit.3, timeVar="year", method = "piecewise-PH-aGH")
anova(jointFit.3, jointFit)
```

```
##
##                AIC     BIC  log.Lik  LRT df p.value
## jointFit.3 3862.74 3918.89 -1916.37
## jointFit   3864.73 3924.61 -1916.36 0.01  1   0.903
```

Comparison of nested models

- Compare our original model, with a nested model in which there is no treatment x time effect in the longitudinal submodel AND no treatment effect in the survival submodel
- Testing $H_0: \beta_2 = \gamma_1 = 0$
- Likelihood ratio test: p=0.93

```
lmeFit.4 <- lme(log(serBilir) ~ year, data = pbc2, random = ~ year | id)
survFit.4 <- coxph(Surv(years, status2) ~ 1, data = pbc2.id, x = TRUE)
jointFit.4 <- jointModel(lmeFit.4, survFit.4, timeVar="year", method = "piecewise-PH-aGH")
anova(jointFit.4, jointFit)
```

```
##
##                AIC     BIC  log.Lik  LRT df p.value
## jointFit.4 3860.89 3913.30 -1916.45
## jointFit   3864.73 3924.61 -1916.36 0.17  2  0.9202
```

Estimating Treatment Effects

- Let's take a closer look at how the treatment effects enter into a particular joint model

$$
\begin{aligned}
h_i(t) &= h_0(t)\exp\{\gamma_1 \mathrm{Tmt}_i + \alpha m_i(t)\} \\
y_i(t) &= m_i(t) + \epsilon_i(t), \qquad \epsilon_i(t) \sim N(0, \sigma^2) \\
&= \beta_0 + \beta_1 t + \beta_2 \mathrm{Tmt}_i + b_{i0} + b_{i1} t + \epsilon_i(t)
\end{aligned}
$$

- Because the models are linked, we have direct and indirect treatment effects on survival
- β_2: the direct effect of the treatment on the longitudinal outcome
- γ_1: the direct effect of the treatment on survival
- $\alpha\beta_2 + \gamma_1$: the overall treatment effect on survival

Comparison with Extended Cox

- Extended Cox model tends to underestimate the true treatment effect on survival, both direct and overall
- Extended Cox model tends to underestimate the association estimates when measurement error is present
- Major source of bias in the Extended Cox model is due to measurement error compared to the LOCF assumption

Breakout Session #6

- A randomized clinical trial in which longitudinal and survival data was collected to compare the efficacy and safety of two antiretroviral drugs in treating patients who had failed/were intolerant of AZT therapy
- Longitudinal marker: CD4 cell counts
- Survival outcome: time to death
- Research goal: **How is CD4 cell counts associated with a person's risk of death?**
- Lower CD4 cell counts are associated with increased risk of death

Breakout Session #6

1. Load the R package "JM" and the data set aids

```
> library(JM)
> data(aids)
```

2. Read the help page on the "aids" data set (?aids)

- patient: patient identifier
- Time: time to death or censoring (survival time)
- death: event indicator
- CD4: longitudinal CD4 cell count variable
- obstime: time points at which CD4 cell counts was recorded
- drug: levels ddC (zalcitabine) and ddI (didanosine)

Breakout Session #6

We want to fit the following joint model

$$
\begin{aligned}
y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= \beta_0 + \beta_1 t + \beta_2\{\mathrm{ddI} \times t\} + b_{i0} + b_{i1} + \epsilon_i(t), \epsilon_i(t) \sim N(0, \sigma^2) \\
h_i(t) &= h_0(t) \exp\{\gamma \mathrm{ddI}_i + \alpha m_i(t)\}
\end{aligned}
$$

3. Fit the linear mixed effects model for CD4 counts using lme()

4. Fit the Cox PH model using coxph() (remember to set x=TRUE)

Breakout Session #6

5. Fit the joint model based on the fitted linear mixed and Cox models using the function jointModel()
   - Specify the baseline hazard as a piecewise-constant baseline hazard and the (pseudo) adaptive GH rule

6. Use summary() to obtain output of the fitted joint model.

7. **Interpret the association between CD4 counts and the risk of death.**

Breakout Session #6

8. Use the “start”, “stop”, “event” columns to fit the time-dependent (Extended) Cox model, with CD4 as the time-dependent variable.

9. **Compare the estimated association between CD4 counts and survival from this model with your joint model.**

Breakout Session #6

10. From the joint model, test for treatment effects in the joint process. Fit the appropriate models and perform the appropriate statistical tests.

11. Interpret your results.

Breakout Session #6

12. Consider a more flexible function of time in the longitudinal marker submodel. Instead of a linear effect for time, use a polynomial/spline instead.

- Fit the new joint model based on this updated longitudinal submodel, compare this model with your original joint model.

13. Interpret your results.