PLSC 504 - Fall 2017
Frailty Models

October 12, 2017

"Frailty" Models

$$h_i(t) = \lambda_i(t)\nu_i$$

- $\nu_i = 1 \approx$ "baseline,"
- $\nu_i > 1 \rightarrow i$ has a greater-than-average hazard,
- $\nu_i < 1 \rightarrow$ the opposite.

More Frailty

Implies:

$$
\begin{aligned}
S(t|\nu_i) &= \exp\left[-\int_0^t h(t|\nu_i)dt\right] \\
&= \exp\left[-\int_0^t \nu_i h(t)dt\right] \\
&= \exp\left[-\int_0^t h(t)dt\right]^{\nu_i} \\
&= S(t)^{\nu_i}
\end{aligned}
$$

Typically:

- Assume $\nu_i \sim g(\nu)$, with
- $E(\nu) = 1$ and
- $\text{Var}(\nu) = \theta$

Example: Cox with Frailty

$$\begin{aligned} h_i(t) &= h_0(t)\nu_i \exp(\mathbf{X}_i\beta) \\ &= h_0(t)\exp(\mathbf{X}_i\beta + \alpha_i) \end{aligned}$$

where $\alpha_i = \ln(\nu_i)$.

(Also weibull, log-normal, etc.)

Frailty Distributions: Gamma

$$
\begin{aligned}
g(\nu) &= \mathcal{G}(\theta, 1/\theta) \\
&= \frac{\nu^{1/\theta-1}\exp\left(\frac{-\nu}{\theta}\right)}{\theta^{(1/\theta)}\Gamma(1/\theta)}
\end{aligned}
$$

with

$$
S_\theta(t) = \{1 - \theta \ln[S(t)]\}^{-1/\theta}
$$

Frailty Distributions: Inverse-Gaussian

$$
\begin{aligned}
g(\nu) &= \mathcal{IG}(\theta, 1/\theta) \\
&= (2\pi\theta\nu^3)^{-1/2} \exp\left[-\frac{1}{2\theta}\left(\alpha - 2 + \frac{1}{\nu}\right)\right]
\end{aligned}
$$

with

$$
S_\theta(t) = \exp\left\{\frac{1}{\theta}\left[1 - (1 - 2\theta \ln\{S(t)\})^{1/2}\right]\right\}
$$

An Important Distinction

Individual- (or *Unit*-) Specific Survival Function:

$$S(t|\nu_i) = S(t)^{\nu_i}$$

Population Average Survival Function:

$$\overline{S(t)} = \int_0^\infty S(t|\nu_i)g(\nu)d\nu$$

Estimation

- Originally: E-M algorithm (e.g. Klein 1992)
- Later: Penalized Likelihood
  - Two-level iterative procedure
  - Intuition: Iterate between fitting $\hat{\beta}|\theta$ for a range of θs, and searching over the (univariate) marginal likelihood for θ to obtain $\hat{\theta}$
  - Details: Therneau and Grambsch (2000, §9.6)

Practical Matters

- Computation...

> *"...if there are 300 families, each with their own frailty, and four other variables, then the full information matrix has* $304^2 = 92,416$ *elements. The Cholesky decomposition must be applied to this matrix with each Newton-Raphson iteration."*
>
> *– Therneau and Grambsch (2000, p. 258)*

- Fitting choices (fix θ vs. estimation, etc.)

- Predictions / interpretation (typically assume $\hat{\nu}_i = 1$).

Software

R

- `survival`: Fits a single `frailty` term via `frailty.gamma`, `frailty.gaussian`, or `frailty.t` to either Cox or parametric models.
- `coxme` (Cox w/Gaussian random effects; see below)
- `frailtypack` (parallel to `frailty` and `coxme`)
- Others (see the task view)

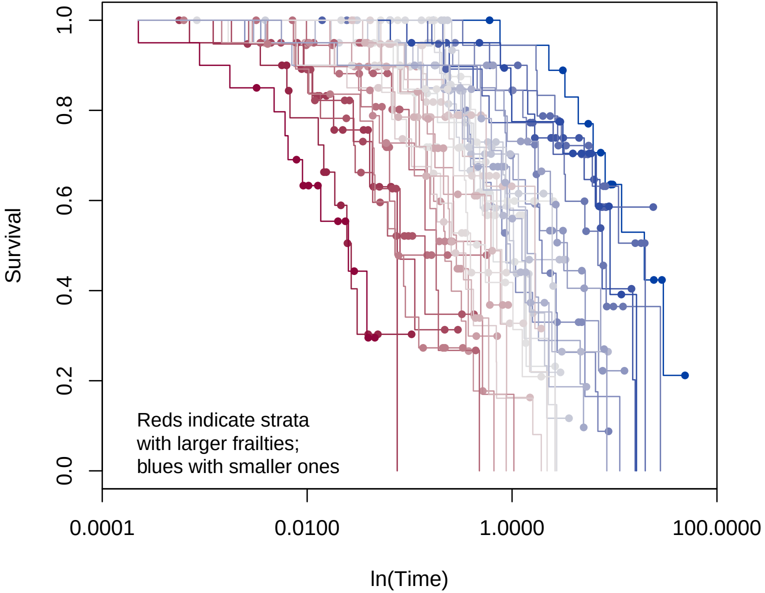
Stata

- The option `shared()` introduces one-level gamma-distributed frailties into `stcox`
- `streg` allows unshared or shared frailties (via `frailty()` and `shared()`, respectively) in both gamma and inverse-gaussian flavors in its parametric survival models; see Guiterrez (2002) for a good starting point.

Simulated Example

```
> set.seed(7222009)
> G<-1:40          # "groups"
> F<-rnorm(40)     # frailties
> data<-data.frame(cbind(G,F))
> data<-data[rep(1:nrow(data),each=20),]
> data$X<-rbinom(nrow(data),1,0.5)
> data$T<-rexp(nrow(data),rate=exp(0+1*data$X+(2*data$F)))
> data$C<-rbinom(nrow(data),1,0.5)
> data<-data[order(data$F),]

> S<-Surv(data$T,data$C)
```

K-M Plots By Strata



Cox Fit (No Frailty)

```
> cox.noF<-coxph(S~X,data=data)
> summary(cox.noF)
Call:
coxph(formula = S ~ X, data = data)

  n= 800, number of events= 381

   coef exp(coef) se(coef)    z   Pr(>|z|)
X 0.522     1.685    0.104 5.02 0.00000051 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

  exp(coef) exp(-coef) lower .95 upper .95
X      1.69      0.593      1.37      2.07

Concordance= 0.577  (se = 0.015 )
Rsquare= 0.031   (max possible= 0.996 )
Likelihood ratio test= 25.2  on 1 df,   p=0.000000521
Wald test            = 25.2  on 1 df,   p=0.000000508
Score (logrank) test = 25.8  on 1 df,   p=0.000000382
```

Weibull Fit (No Frailty)

```
> weib.noF<-survreg(S~X,data=data,dist="weib")
> summary(weib.noF)

Call:
survreg(formula = S ~ X, data = data, dist = "weib")
             Value Std. Error     z        p
(Intercept)  1.595     0.1450 11.00 3.92e-28
X           -1.031     0.1974 -5.22 1.76e-07
Log(scale)   0.653     0.0383 17.04 3.98e-65

Scale= 1.92

Weibull distribution
Loglik(model)= -581   Loglik(intercept only)= -594
Chisq= 27 on 1 degrees of freedom, p= 0.00000023
Number of Newton-Raphson Iterations: 5
n= 800
```

Cox Fit With Frailty

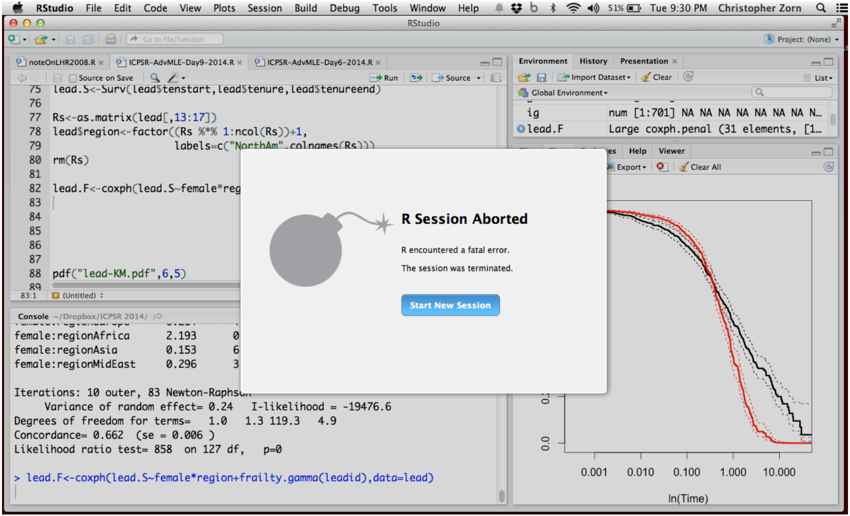
```
> cox.F<-coxph(S~X+frailty.gaussian(F),data=data)
> summary(cox.F)
Call:
coxph(formula = S ~ X + frailty.gaussian(F), data = data)

  n= 800, number of events= 381

                    coef se(coef) se2   Chisq DF   p
X                   1.01 0.112    0.112  81.9  1.0 0
frailty.gaussian(F)                     609.0 37.6 0

  exp(coef) exp(-coef) lower .95 upper .95
X      2.76      0.363      2.21      3.43

Iterations: 7 outer, 47 Newton-Raphson
     Variance of random effect= 1.8
Degrees of freedom for terms=  1.0 37.6
Concordance= 0.791  (se = 0.017 )
Likelihood ratio test= 414  on 38.5 df,   p=0
```

Weibull Fit With Frailty

```
> weib.F<-survreg(S~X+frailty.gaussian(F),data=data,dist="weib")

> summary(weib.F)

Call:
survreg(formula = S ~ X + frailty.gaussian(F), data = data, dist = "weib")
              Value Std. Error      z        p
(Intercept)  0.6188     0.2622   2.36 1.83e-02
X           -1.1386     0.1121 -10.16 3.12e-24
Log(scale)   0.0546     0.0417   1.31 1.91e-01

Scale= 1.06

Weibull distribution
Loglik(model)= -372   Loglik(intercept only)= -594
Chisq= 443 on 37 degrees of freedom, p= 0
Number of Newton-Raphson Iterations:  5 18
n= 800
```

Example: Leader Tenure

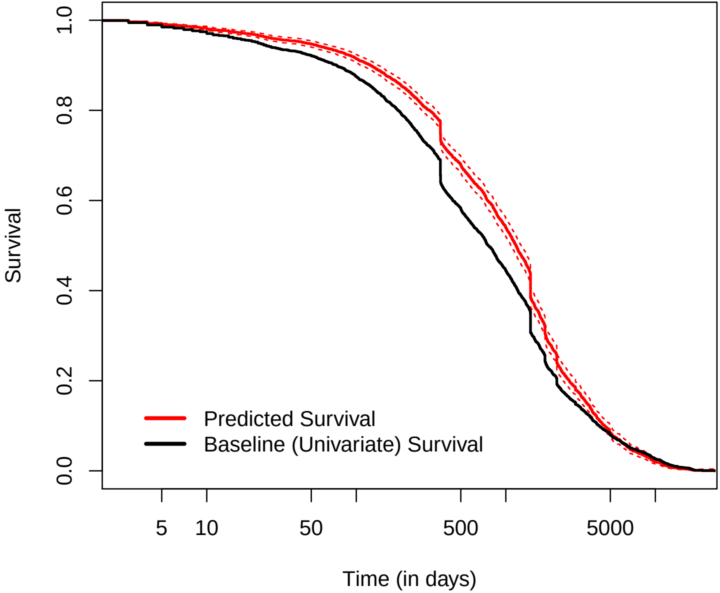
```
> lead.S<-Surv(lead$tenstart,lead$tenure,lead$tenureend)

> Rs<-as.matrix(lead[,13:17])
> lead$region<-factor((Rs %*% 1:ncol(Rs))+1,
                      labels=c("NorthAm",colnames(Rs)))
> rm(Rs)

> lead.F<-coxph(lead.S~female*region+frailty.gamma(leadid),data=lead)
```


RStudio File Edit Code View Plots Session Build Debug Tools Window Help
51% Tue 9:30 PM Christopher Zorn
RStudio
Go to file/function
Project: (None)
noteOnLHR2008.R
ICPSR-AdvMLE-Day9-2014.R
ICPSR-AdvMLE-Day6-2014.R
Source on Save
Run
Source
75 lead.S<-Surv(lead$tenstart,lead$tenure,lead$tenureend)
76
77 Rs<-as.matrix(lead[,13:17])
78 lead$region<-factor((Rs %*% 1:ncol(Rs))+1,
79 labels=c("NorthAm",colnames(Rs)))
80 rm(Rs)
81
82 lead.F<-coxph(lead.S~female*reg
83
88 pdf("lead-KM.pdf",6,5)
83:1
(Untitled)
Console ~/Dropbox/ICPSR 2014/
female:regionAfrica 2.193 0
female:regionAsia 0.153 6
female:regionMidEast 0.296 3
Iterations: 10 outer, 83 Newton-Raphson
Variance of random effect= 0.24 I-likelihood = -19476.6
Degrees of freedom for terms= 1.0 1.3 119.3 4.9
Concordance= 0.662 (se = 0.006)
Likelihood ratio test= 858 on 127 df, p=0
> lead.F<-coxph(lead.S~female*region+frailty.gamma(leadid),data=lead)
Environment History Presentation
Import Dataset
Clear
List
Global Environment
ig num [1:701] NA NA NA NA NA NA NA N...
lead.F Large coxph.penal (31 elements, [1...
Help Viewer
Export
Clear All
R Session Aborted
R encountered a fatal error.
The session was terminated.
Start New Session
0.0
0.001 0.010 0.100 1.000 10.000
ln(Time)

Let's Try That Again

```
> lead.F<-coxph(lead.S~female*region+frailty.gamma(ccode),data=lead)
Warning message:
In coxpenal.fit(X, Y, strats, offset, init = init, control, weights = weights,  :
  Inner loop failed to coverge for iterations 2 3

> summary(lead.F)
Call:
coxph(formula = lead.S ~ female * region + frailty.gamma(ccode),
    data = lead)

  n= 15222, number of events= 2806
   (22 observations deleted due to missingness)

                     coef    se(coef) se2    Chisq  DF  p
female                1.2427 0.462    0.4594   7.24   1 0.007100
regionLatinAm        -0.1259 0.208    0.0333   0.37   1 0.540000
regionEurope          0.0414 0.160    0.0545   0.07   1 0.800000
regionAfrica         -0.7047 0.160    0.0840  19.45   1 0.000010
regionAsia           -0.3896 0.164    0.0742   5.65   1 0.017000
regionMidEast        -0.7478 0.186    0.0986  16.13   1 0.000059
frailty.gamma(ccode)                         523.81 119 0.000000
female:regionLatinAm -1.8826 0.851    0.8495   4.89   1 0.027000
female:regionEurope  -1.5424 0.624    0.6212   6.11   1 0.013000
female:regionAfrica   0.7854 0.861    0.8556   0.83   1 0.360000
female:regionAsia    -1.8765 0.572    0.5666  10.76   1 0.001000
female:regionMidEast -1.2175 0.861    0.8551   2.00   1 0.160000

Iterations: 10 outer, 83 Newton-Raphson
     Variance of random effect= 0.24   I-likelihood = -19476.6
Degrees of freedom for terms=   1.0   1.3 119.3   4.9
Concordance= 0.662  (se = 0.006 )
Likelihood ratio test= 858  on 127 df,   p=0
```

Predicted vs. Actual



Extensions: Mixed-Effects Survival Models

- HLMs for survival data / outcomes
- Combined fixed, random, and mixed effects (random-coefficient) models
- R: Implemented in `coxme`
- Stata: `stmixed` (parametric models)
- Terry Therneau has a nice vignette

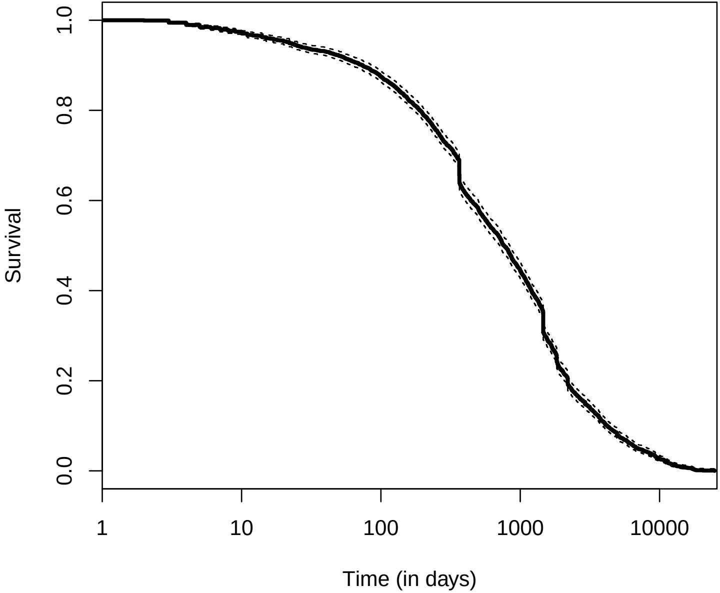
Mixed Effects Example

```
> lead.coxME<-coxme(lead.S~female + (1 | ccode/female),data=lead)
> lead.coxME
Cox mixed-effects model fit by maximum likelihood
  Data: lead
  events, n = 2806, 15222 (22 observations deleted due to missingness)
  Iterations= 38 160
                 NULL Integrated Fitted
Log-likelihood -19738     -19505 -19314

                  Chisq  df p AIC  BIC
Integrated loglik   465   3 0 459  441
 Penalized loglik   849 129 0 590 -177

Model:  lead.S ~ female + (1 | ccode/female)
Fixed coefficients
        coef exp(coef) se(coef)     z    p
female -0.07      0.93     0.22 -0.31 0.75

Random effects
 Group        Variable    Std Dev Variance
 ccode/female (Intercept) 0.279   0.078
 ccode        (Intercept) 0.487   0.237
```

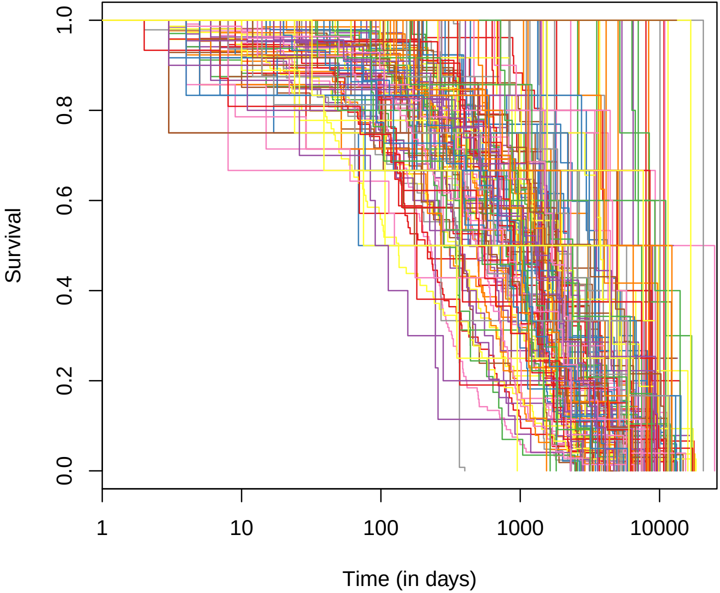
Stratify? Frailties? Clustering?

- Stratification $\approx$ "fixed effects"
- Frailties $\approx$ "random effects"
- "Robust" / cluster $\approx$ GEE / PCSEs, etc.
- Not all combinations are possible, or make sense

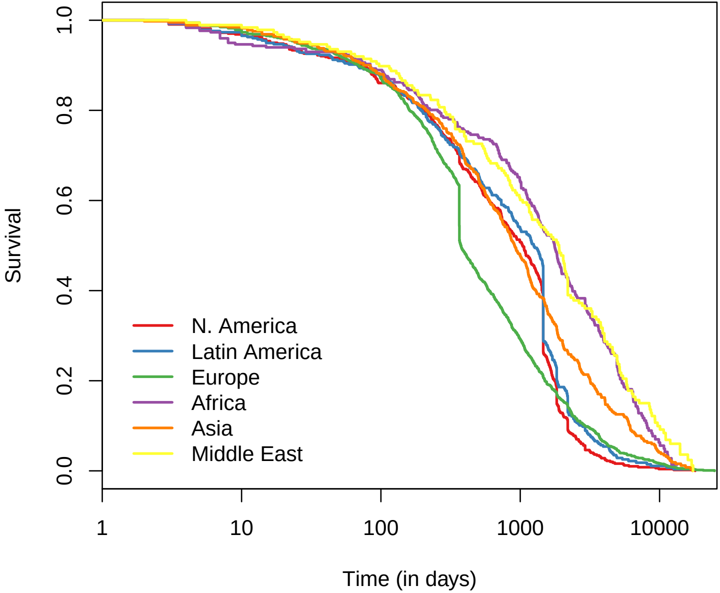
K-M Plot: Leaders



K-M Plot: Leaders (by country)



K-M Plot: Leaders (by region)



Strata + Frailty

```
> lead.Fstrat<-coxph(lead.S~female*strata(region)+
                    frailty.gamma(ccode),data=lead)
Warning message:
In coxpenal.fit(X, Y, strats, offset, init = init, control, weights = weights,
  Inner loop failed to coverge for iterations 2 3 4

> summary(lead.Fstrat)
Call:
coxph(formula = lead.S ~ female * strata(region) + frailty.gamma(ccode),
    data = lead)

  n= 15222, number of events= 2806
   (22 observations deleted due to missingness)

                         coef  se(coef) se2   Chisq  DF  p
female                    1.46 0.463    0.461   9.88   1 0.00170
frailty.gamma(ccode)                          594.82 121 0.00000
female:strata(region)regi -2.20 0.853    0.851   6.63   1 0.01000
female:strata(region)regi -1.75 0.625    0.623   7.81   1 0.00520
female:strata(region)regi  0.13 0.869    0.864   0.02   1 0.88000
female:strata(region)regi -2.07 0.573    0.568  13.04   1 0.00031
female:strata(region)regi -1.31 0.862    0.857   2.32   1 0.13000
```

Strata + Clustering

```
> lead.stratCl<-coxph(lead.S~female*strata(region)+
                       cluster(ccode),data=lead)

> summary(lead.stratCl)
Call:
coxph(formula = lead.S ~ female * strata(region) + cluster(ccode),
    data = lead)

  n= 15222, number of events= 2806
   (22 observations deleted due to missingness)

                                      coef exp(coef) se(coef) robust se     z
female                               1.234     3.436    0.453     0.288  4.28
female:strata(region)region=LatinAm -1.881     0.152    0.842     0.627 -3.00
female:strata(region)region=Europe  -1.618     0.198    0.610     0.415 -3.90
female:strata(region)region=Africa   0.473     1.605    0.849     0.382  1.24
female:strata(region)region=Asia    -1.711     0.181    0.555     0.342 -5.00
female:strata(region)region=MidEast -0.709     0.492    0.846     0.349 -2.03

Concordance= 0.503  (se = 0.002 )
Rsquare= 0.001   (max possible= 0.864 )
Likelihood ratio test= 13.8  on 6 df,   p=0.0323
Wald test            = 81.6  on 6 df,   p=1.67e-15
Score (logrank) test = 20.1  on 6 df,   p=0.00263,   Robust = 14.4  p=0.0255

  (Note: the likelihood ratio and score tests assume independence of
     observations within a cluster, the Wald and robust score tests do not).
```

Choices...

From the `frailty` documentation:

"Note that use of a frailty term implies a mixed effects model and use of a cluster term implies a GEE approach; these cannot be mixed."

```
> lead.FstratCl<-coxph(lead.S~female*strata(region)+frailty.gamma(ccode)+
                       cluster(ccode),data=lead)
Error in residuals.coxph(fit2, type = "dfbeta", collapse = cluster,
weighted = TRUE) :
  length of 'dimnames' [2] not equal to array extent
In addition: Warning message:
In coxpenal.fit(X, Y, strats, offset, init = init, control, weights = weights,
  Inner loop failed to coverge for iterations 2 3 4
```

Therneau, Terry M., Jun 27, 2011; 8:02am **Re: cluster() or frailty() in coxph**

693 posts

In reply to this post by Ehsan Karim

Addition of a cluster() term fits a Generalized Estimating Equations (GEE) type of model, addition of frailty() fits a random effects model (Mixed Effect or ME). In glm analysis (linear regression, logistic regression, etc) the arguments about the advantages/disadvantages of GEE ve ME would easily fill a volume. Most of this argument carries over to the coxph case; I find both approaches useful.

Caveats:

1. Coxph with cluster() only allows the "working independence" variance structure. The details for other variance structures were worked out by Alicia Z in her Iowa State PhD thesis, but I've never gotton around to implementing it.
2. For random effects, the coxme function is preferred.
3. In comparing GEE and ME one part of the arguement is that the former model is "marginal" and the second "conditional", and thus the coefficients from the models mean different things. I take this with a grain of salt. Remember that ALL models are wrong.

Terry Therneau

[hidden email] mailing list
https://stat.ethz.ch/mailman/listinfo/r-help
PLEASE do read the posting guide http://www.R-project.org/posting-guide.html
and provide commented, minimal, self-contained, reproducible code.

Topics We Didn't Cover

- Joint Models for Survival and Longitudinal Outcomes
  - e.g., survival + binary / multinomial / continuous variables
  - *inter alia* R package `JM` (Rizopolous 2010)
  - Recent reference is Viviani et al. (2014)
- Causal Inference (IVs, RDDs, matching, etc.)
- Variable Selection: regularization, bagging, boosting, stacking, lasso, etc.
- Bayesian approaches (esp. for high-dimensional competing risks & hierarchical models); see Ibrahim et al. (2005)
- New / better tools for interpretation and graphics (e.g. `simPH`)

General Tips

Journals:

- *Biometrics* / *Biometrika*
- *Statistics in Medicine*
- *Statistical Methods in Medical Research*
- *Lifetime Data Analysis*

Places:

- Biostatistics / Epidemiology / Public Health
- Statistics departments
- *Not* economics, psychology, etc.