GSERM - Oslo 2018
Survival Model Extensions

January 19, 2018 (morning session)

Standard models (e.g.):

$$h(T_i|\mathbf{X}_i, \beta) = \frac{f(T_i|\mathbf{X}_i, \beta)}{S(T_i|\mathbf{X}_i, \beta)}$$

assume:

$$\int_0^\infty f(t)\,dt = 1 \;\forall\; i.$$

All observations will (eventually) experience the event of interest.

Mixture Cure Model

Assume (unobserved):

$$Y_i = \begin{cases} 1 \text{ for observations that will eventually fail,} \\ 0 \text{ for those that will not.} \end{cases}$$

For observations with $Y = 1$:

$$\begin{aligned} f(T_i|\mathbf{X}_i, \beta, Y_i = 1) &= g(T|\mathbf{X}_i, \beta) \\ F(T_i|\mathbf{X}_i, \beta, Y_i = 1) &= G(T|\mathbf{X}_i, \beta) \end{aligned}$$

For observations with $Y = 0$, $f(T)$ and $F(T)$ are undefined.

Mixture Cure Model (continued)

Define:

$$\Pr(Y_i = 1) = \delta_i.$$

Overall survival is then just:

$$S_i(T) = (1 - \delta_i) + \delta_i[1 - G_i(t)]$$

Then for $C_i = 1$:

$$\begin{aligned} L_i|C_i = 1 &= \Pr(Y_i = 1)\Pr(T_i = t|Y_i = 1, \mathbf{X}_i, \beta) \\ &= \delta_i g(T_i|\mathbf{X}_i, \beta) \end{aligned}$$

For $C_i = 0$:

$$\begin{aligned} L_i|C_i = 0 &= \Pr(Y_i = 0) + \Pr(Y_i = 1)\Pr(T_i > t_i|Y_i = 1, \mathbf{X}_i, \beta) \\ &= (1 - \delta_i) + \delta_i[1 - G(T_i|\mathbf{X}_i, \beta)] \end{aligned}$$

Mixture Cure Model: Likelihood

Implies:

$$\mathbf{L} = \prod_{i=1}^{N} \left[\delta_i g(T_i|\mathbf{X}_i, \beta)\right]^{C_i} \left\{(1-\delta_i) + \delta_i \left[1 - G(T_i|\mathbf{X}_i, \beta)\right]\right\}^{(1-C_i)}$$

and:

$$\begin{aligned} ln\mathbf{L} \quad = \quad & \sum_{i=1}^{N} C_i \left\{\ln(\delta_i) + \ln\left[g(T_i|\mathbf{X}_i, \beta)\right]\right\} \\ & + (1-C_i)\ln\left\{(1-\delta_i) + \delta_i\left[1 - G(T_i|\mathbf{X}_i, \beta)\right]\right\} \end{aligned}$$

Mixture Cure Model: Specification

Typically:

$$\delta_i = \frac{\exp(\mathbf{Z}_i\gamma)}{1+\exp(\mathbf{Z}_i\gamma)}$$

or:

$$\delta_i = \Phi(\mathbf{Z}_i\gamma).$$

Identified even if $\mathbf{Z} \equiv \mathbf{X}$.

Non-Mixture Cure Model (e.g. Sposto 2002)

N_i = number of pre-cancerous cell clusters, with:

$$N_i \sim \text{Poisson}(\lambda).$$

Pr(Cure) is:

$$\pi_i = \Pr(N_i = 0).$$

Time to cancer onset for cluster j of observation i is:

$$Z_{ij} \sim F(t),\ j = \{1, 2, ...N_i\}.$$

Non-Mixture Cure Model (continued)

Survival to first onset:

$$S(t) = \pi^{F(t)}$$

with hazard function:

$$h(t) = -\ln(\pi) f(t)$$

which reflects the fact that $\int_0^\infty h(t)dt = -\ln(\pi)$.

Non-Mixture Cure Model (continued)

Rewritten $S(t)$:

$$S(t) = \exp[\ln(\pi)F(t)].$$

Assuming:

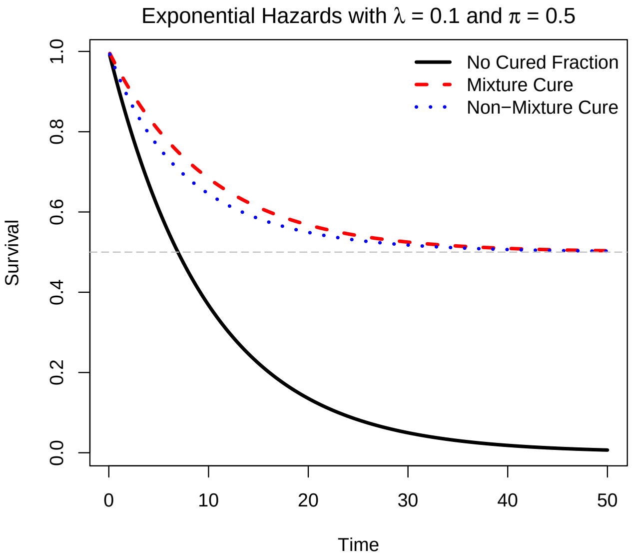
$$\pi_i = \exp[-\exp(\mathbf{X}_i\beta)]$$

we get:

$$S(t) = \exp\{[-\exp(\mathbf{X}_i\beta)]F(t)\}.$$

which is the Cox.

Mixture vs. Non-Mixture Models



Discrete-Time Cure Models

- Parametric / Cox $\longrightarrow$ Poisson
- Mixture Cure Model $\longrightarrow$ Zero-Inflated Poisson
- Non-Mixture Cure Model $\longrightarrow$ “Hurdle” Poisson

Software

R

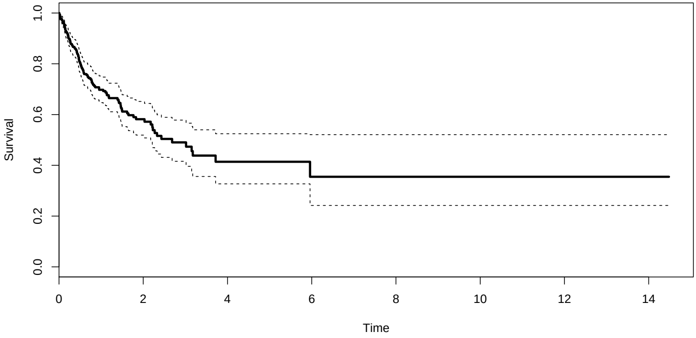
- `smcure` (semiparametric mixture models via EM)
- `semicure` (same; old)
- `nltm` (various; see Tsodikov 2003)
- `CR`, `NPHMC` (power analysis for cure models)

Stata

- `strsmix and strsnmix` (general parametric mixture & non-mixture cure models)
- `cureregr` (an old version)
- `lncure` (log-normal cure model)
- `spsurv` (discrete-time cure model)
- `zip / zinb` (discrete-time kludge)

A Simulated Example

```
> set.seed=7222009
> X<-rnorm(500)
> Z<-rbinom(500,1,0.5)
> T<-rweibull(500,shape=1.2,scale=1/(exp(0.5+1*X)))
> C<-rbinom(500,1,(0.4-0.3*Z))
> S<-Surv(T,C)
```



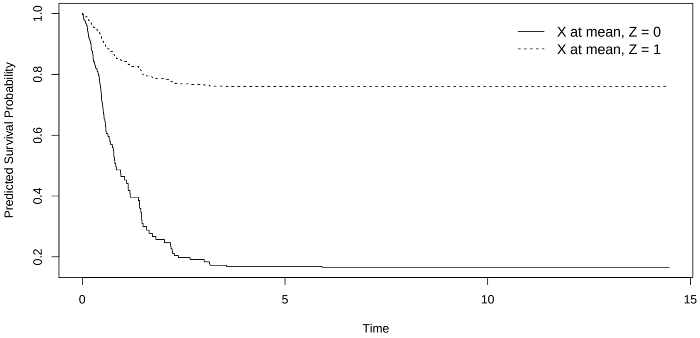
```
> coxph(S~X)
Call:
coxph(formula = S ~ X)

  coef exp(coef) se(coef)    z p
X 1.05      2.85    0.124 8.44 0

Likelihood ratio test=77.7  on 1 df, p=0  n= 500, number of events= 130


> coxph(S~X+Z)
Call:
coxph(formula = S ~ X + Z)

   coef exp(coef) se(coef)    z       p
X  1.08     2.956    0.122  8.9 0.0e+00
Z -1.59     0.204    0.230 -6.9 5.4e-12

Likelihood ratio test=140  on 2 df, p=0  n= 500, number of events= 130
```

Cure Model

```
> cure.fit<-smcure(S~X,cureform=~Z,data=data.cure,model="ph")

Program is running..be patient... done.

Call:
smcure(formula = S ~ X, cureform = ~Z, data = data.cure, model = "ph")

Cure probability model:
            Estimate Std.Error Z value Pr(>|Z|)
(Intercept)      1.6      0.39     4.1  3.4e-05
Z               -2.8      0.41    -6.7  2.5e-11


Failure time distribution model:
  Estimate Std.Error Z value Pr(>|Z|)
X      1.1      0.14     8.1  6.7e-16
```

An Interesting Plot

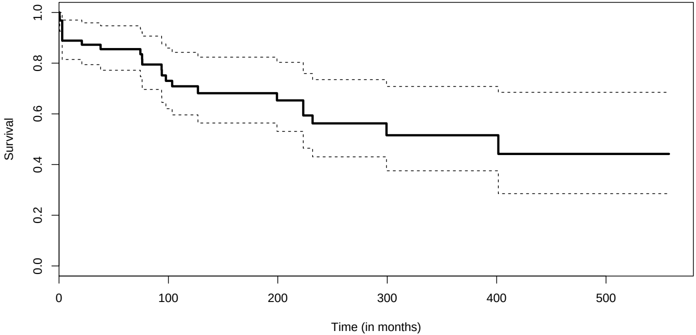
```
> cure.hat<-predictsmcure(cure.fit,c(rep(mean(X),times=2)),
                          c(0,1),model="ph")

> cure.pic<-plotpredictsmcure(cure.hat,type="S",model="ph")
```



An Example: Ceasefire Durability

Data are a subset used in Fortna (2004) (full data are here).

- $N = 63$
- Non-time-varying



Ceasefires: Cox Model

```
> CF.cox<-coxph(CF.S~tie+imposed+lndeaths+contig+onedem+twodem,
             data=CF,method="efron")
> CF.cox

Call:
coxph(formula = CF.S ~ tie + imposed + lndeaths + contig + onedem +
    twodem, data = CF, method = "efron")

            coef exp(coef) se(coef)      z       p
tie        1.845     6.327    0.557  3.314 0.00092
imposed    0.210     1.233    0.594  0.353 0.72000
lndeaths  -0.135     0.874    0.193 -0.699 0.48000
contigyes  2.898    18.143    0.948  3.058 0.00220
onedem     3.423    30.648    1.144  2.991 0.00280
twodem    -0.723     0.485    1.209 -0.598 0.55000

Likelihood ratio test=36.8  on 6 df, p=0.00000197  n= 63, number of events= 23
```

(hours of fiddling...)

A Typical Result

```
> CF.cure1.fit<-smcure(CF.S~tie+lndeaths+imposed,
                     cureform=~contig,data=CF,model="ph",
                     link="logit",emmax=500)

Program is running..be patient... done.

Call:
smcure(formula = CF.S ~ tie + lndeaths + imposed, cureform = ~contig,
    data = CF, model = "ph", link = "logit", emmax = 500)

Cure probability model:
            Estimate Std.Error Z value Pr(>|Z|)
(Intercept)     -3.4      12.4   -0.27     0.79
contig           2.1       7.4    0.28     0.78

Failure time distribution model:
         Estimate Std.Error Z value Pr(>|Z|)
tie          2.05      4.06    0.50     0.61
lndeaths    -0.37      0.34   -1.10     0.27
imposed      0.97      2.40    0.41     0.68
There were 50 or more warnings (use warnings() to see the first 50)
```

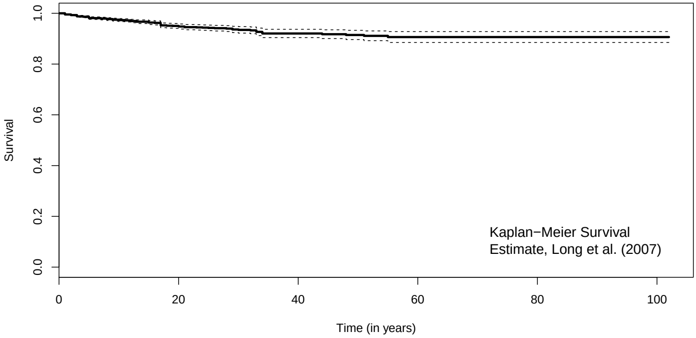
From Svolik (2008)

Consolidation status model[b]				
GDP per capita	2.121***	—	2.045***	2.121***
	(0.586)	—	(0.555)	(0.586)
GDP growth	−0.014	—	−0.048	−0.014
	(0.227)	—	(0.246)	(0.227)
Military (vs. *Not independent*)	−4.061**	—	−3.985**	−4.061**
	(1.895)	—	(1.857)	(1.895)
Civilian (vs. *Not independent*)	−0.421	—	−0.549	−0.421
	(1.097)	—	(1.067)	(1.097)
Monarchy (vs. *Not independent*)	−20.158	—	−15.844	−13.965
	(2888.609)	—	(680.185)	(891.870)
Parliamentary (vs. *Mixed*)	2.231	—	2.290	2.231
	(2.230)	—	(2.326)	(2.230)
Presidential (vs. *Mixed*)	−8.310**	—	−8.186**	−8.310**
	(3.958)	—	(4.035)	(3.958)
Intercept	−6.144**	—	−5.920**	−6.145**
	(2.646)	—	(2.644)	(2.647)

Another Example: Peace Duration

Long, Nordstrom and Baek (2007 *JOP*)

- Peace duration among allies
- Time-varying dyadic data, 1816-2001 ($NT = 57,819$)



Cox Model (replicating LNB)

```
> LNB.cox<-coxph(LNB.S~relcap+major+jdem+border+wartime+s_wt_glo+
                medarb+noagg+arbcom+organ+milinst+cluster(dyad),
                data=LNB,method="breslow")
> LNB.cox
Call:
coxph(formula = LNB.S ~ relcap + major + jdem + border + wartime +
    s_wt_glo + medarb + noagg + arbcom + organ + milinst + cluster(dyad),
    data = LNB, method = "breslow")


           coef exp(coef) se(coef) robust se      z        p
relcap   -1.431     0.239    0.614     0.683 -2.096 0.036000
major     1.137     3.118    0.241     0.280  4.064 0.000048
jdem     -0.987     0.373    0.367     0.380 -2.600 0.009300
border    1.931     6.897    0.190     0.206  9.378 0.000000
wartime  -0.359     0.699    0.367     0.467 -0.768 0.440000
s_wt_glo -0.284     0.752    0.332     0.355 -0.802 0.420000
medarb   -0.367     0.693    0.285     0.306 -1.202 0.230000
noagg    -0.463     0.630    0.126     0.152 -3.051 0.002300
arbcom    1.306     3.690    0.325     0.316  4.133 0.000036
organ     0.353     1.423    0.280     0.285  1.236 0.220000
milinst  -0.373     0.689    0.187     0.177 -2.101 0.036000
```

Cure Models

(hours of fiddling...)

```
> LNB.cure<-smcure(LNB.altS~relcap+major+jdem+border+wartime+s_wt_glo+
                   medarb+noagg+arbcom+organ+milinst,
                   cureform=~border,model="ph",data=LNB)

Program is running..be patient...
```

Cure Models (Stata Remix)

```
. stset count1, id(episode) f(buofmzmid==1)
. gen h0=0
. strsmix major jdem border wartime, bhazard(h0) distribution(weibull) link(logistic) k1
> (relcap major jdem border wartime s_wt_glo medarb noagg arbcom organ milinst)

                                                  Number of obs   =      57819
                                                  Wald chi2(4)    =      36.82
Log likelihood = -793.21263                       Prob > chi2     =     0.0000
------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
pi           |
       major |  -7.921296   3.764002    -2.10   0.035     -15.2986   -.5439877
        jdem |  -.6177566   .7656096    -0.81   0.420    -2.118324    .8828107
      border |  -1.943181   .3786093    -5.13   0.000    -2.685241    -1.20112
     wartime |   2.583909   1.051959     2.46   0.014     .5221065    4.645711
       _cons |   2.659179   .3980719     6.68   0.000     1.878972    3.439385
-------------+----------------------------------------------------------------
ln_lambda    |
      relcap |  -1.408332   .7129111    -1.98   0.048    -2.805613   -.0110523
       major |  -1.232928    .395653    -3.12   0.002    -2.008394   -.4574626
        jdem |   -1.69796   .4596442    -3.69   0.000    -2.598846   -.7970736
      border |   1.224114   .2622007     4.67   0.000     .7102103    1.738018
     wartime |     .42086   .4072876     1.03   0.301     -.377409    1.219129
    s_wt_glo |   -.274703   .3579769    -0.77   0.443    -.9763249    .4269188
      medarb |  -.8221547   .3503126    -2.35   0.019    -1.508755   -.1355545
       noagg |    -.68365   .1465971    -4.66   0.000     -.970975   -.3963251
      arbcom |   1.667284   .4562532     3.65   0.000     .7730438    2.561524
       organ |   .9298395   .3595899     2.59   0.010     .2250563    1.634623
     milinst |  -.4428979   .2251323    -1.97   0.049    -.8841491   -.0016468
       _cons |  -2.060399   .7260061    -2.84   0.005    -3.483344   -.6374528
-------------+----------------------------------------------------------------
ln_gamma     |
       _cons |   .0969349   .0733007     1.32   0.186    -.0467319    .2406018
------------------------------------------------------------------------------
```

Some Lessons

Cure models...

- ...Powerful
- ...Intuitive
- ...Temperamental
- ...Ask a lot of your data

[Break]

“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

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

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)

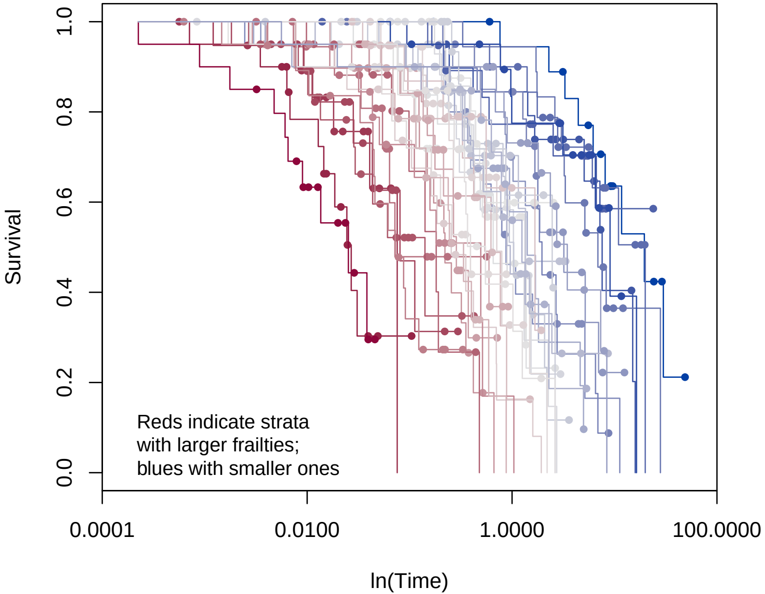
Stata

- 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

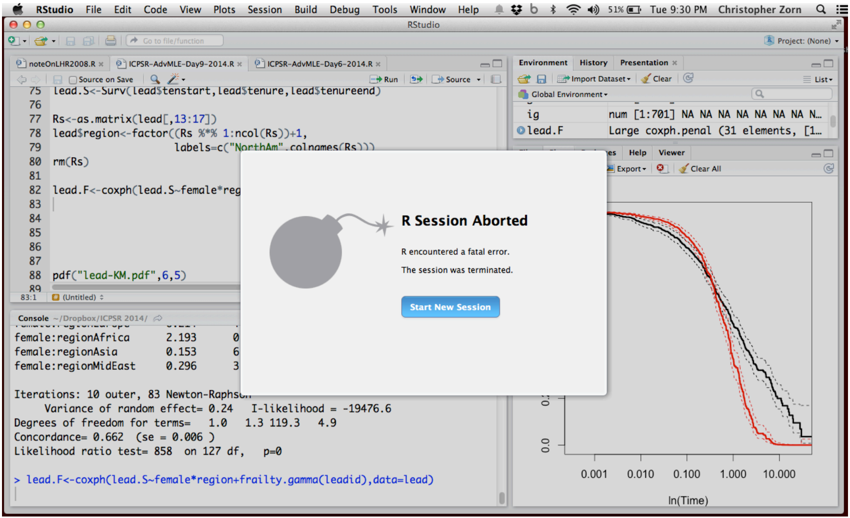
```
> cox.F<-coxph(S~X+frailty.gaussian(F),data=data)
> summary(cox.F)
Call:
coxph(formula = S ~ X + frailty.gaussian(F), data = data)

  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

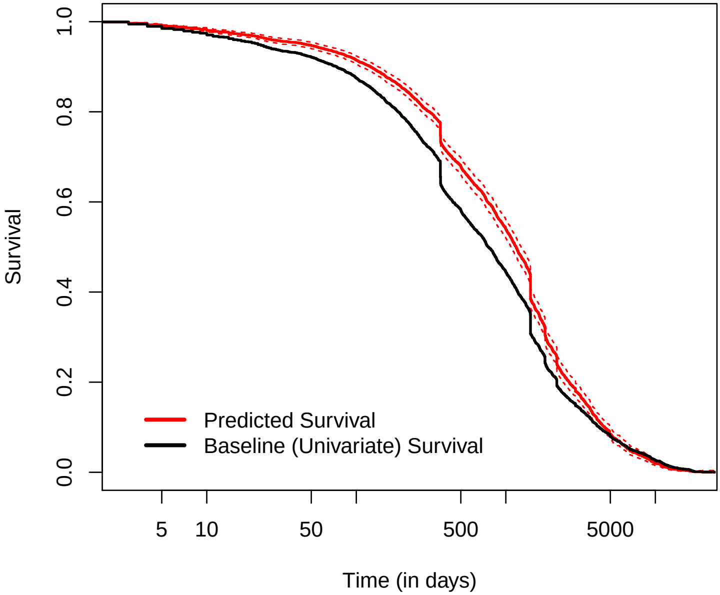
```
> lead.S<-Surv(lead$tenstart,lead$tenure,lead$tenureend)

> 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
Tue 9:30 PM Christopher Zorn
noteOnLHR2008.R
ICPSR-AdvMLE-Day9-2014.R
ICPSR-AdvMLE-Day6-2014.R
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*reg
pdf("lead-KM.pdf",6,5)
Environment History Presentation
Global Environment
ig num [1:701] NA NA NA NA NA NA NA N...
lead.F Large coxph.penal (31 elements, [1...
R Session Aborted
R encountered a fatal error.
The session was terminated.
Start New Session
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)
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

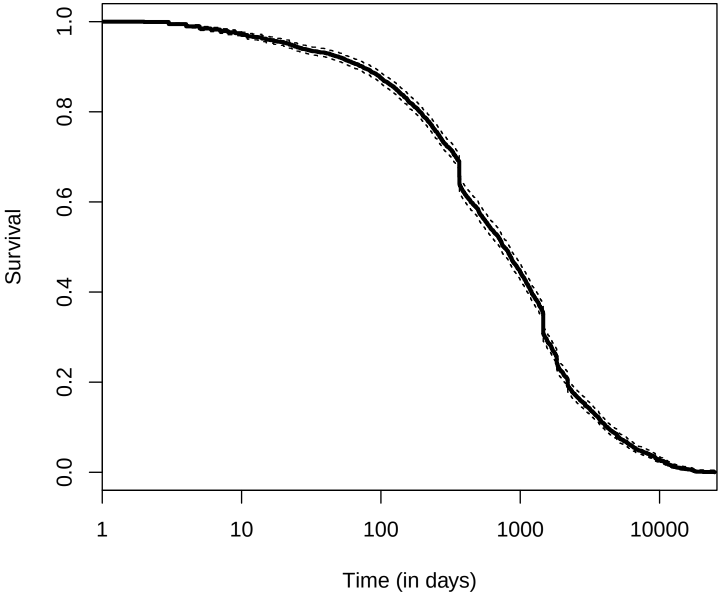
- HLMs for survival data / outcomes
- Combined fixed, random, and mixed effects (random-coefficient) models
- R: Implemented in `coxme`
- Stata: `stmixed` (parametric models)
- Terry Therneau has a nice vignette

```
> 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
```

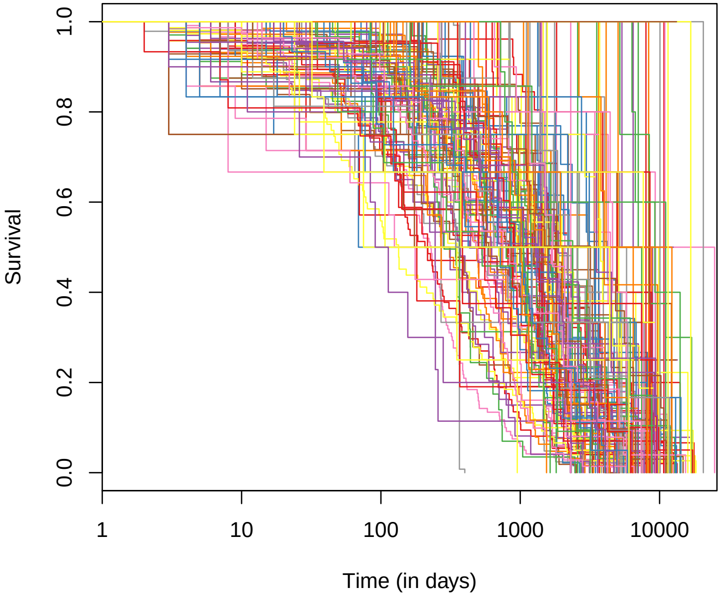
Stratify? Frailties? Clustering?

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

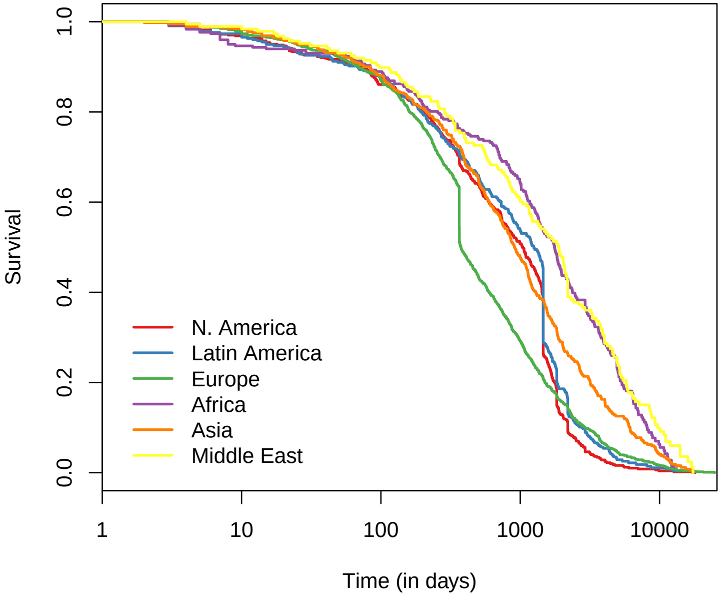
K-M Plot: Leaders



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

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.