

# STAT 222 Week 8

Survival Analysis  
mixed effects  
(aka "frailty")

```
> install.packages("coxme")
> library(coxme)
Loading required package: survival splines bdsmatrix nlme Matrix lattice
> data(eortc)
results of a breast cancer trial undertaken by the European Organization for Research and Treatment of Cancer.
There are 37 enrolling centers with enrollments ranging from 21 to 247 subjects. We start by fitting a simple
model with a random intercept per center. efit2
```

```
> dim(eortc)
[1] 2323 4
> head(eortc)
      y uncens center trt
2 506.1603      1      1 1
3 294.3800      1      1 1
4 383.9152      1      1 0
5 2441.8338      0      1 0
6 2442.2923      0      1 0
7 312.3571      1      1 1
```

```
> attach(eortc)
> table(uncens, center) centers have diff efficacy
```

center		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
uncens	0	15	38	11	53	42	14	53	9	12	10	18	156	13	34	12	10	81	7	10	6	9	16	8	14	24
center	1	48	48	23	51	74	21	67	14	44	20	24	91	26	18	22	16	102	27	11	29	21	19	33	39	67

```
> table(uncens) #uncens 0=alive, 1=dead
```

```
uncens
0      1
860 1463
```

```
> efit1 <- coxph(Surv(y, uncens) ~ trt, eortc) basic
```

Random effects are specified in the formula by a parenthesised expression which contains a vertical bar separating effects on the left from grouping variables on the right. In the case above we read it as an intercept (effect) per center (group).

```
> efit2 <- coxme(Surv(y, uncens) ~ trt + (1|center), eortc) coxme model
```

```
> fixed.effects(efit2)
      trt treatment effect
0.7086127
```

```
> print(efit2)
```

```
Cox mixed-effects model fit by maximum likelihood
Data: eortc
events, n = 1463, 2323
Iterations= 9 49
```

COXME

```
NULL Integrated Fitted
Log-likelihood -10638.71 -10520.65 -10478.84
```

	Chisq	df	p	AIC	BIC
Integrated loglik	236.11	2.00	0	232.11	221.53
Penalized loglik	319.74	28.69	0	262.37	110.67

```
Model: Surv(y, uncens) ~ trt + (1 | center)
```

Fixed coefficients

	coef	exp(coef)	se(coef)	z	p
trt	0.7086127	2.031171	0.06424398	11.03	0

*coxme*      *coxph*  
2.03 vs 1.86

Random effects

Group	Variable	Std Dev	Variance
center	Intercept	0.3292140	0.1083818

*big variability over centers*

*rand on  
Variance*

```
> summary(efit1)
```

*coxph*

Call:

```
coxph(formula = Surv(y, uncens) ~ trt, data = eortc)
n = 2323, number of events = 1463
```

*COX REGRESSION*

	coef	exp(coef)	se(coef)	z	Pr(> z )
trt	0.61826	1.85570	0.06343	9.747	<2e-16 ***

	exp(coef)	exp(-coef)	lower	.95	upper	.95
trt	1.856	0.5389	1.639	2.101		

Concordance= 0.563 (se = 0.006)

Rsquare= 0.044 (max possible= 1)

Likelihood ratio test= 105.7 on 1 df, p=0

Wald test = 95.01 on 1 df, p=0

Score (logrank) test = 98.04 on 1 df, p=0

*COMPARE models (back)*  
236 vs 105

# Stat 222 Week 8 n. 2

After integrating out the random effects, the log partial likelihood for the mixed effects model is 236.1. As a test of the random effects, we would normally compare this to efit1, the fit with no random effects which has a log partial likelihood of 105.7 The estimated standard deviation between centers of .33 is fairly substantial (more on this below). The difference is > 100 on one degree of freedom, which is highly significant

compare  
COX MC  
COX PH

The random effects  $\beta_j$  for each center  $j$  are in the risk score, a value of .33 for instance (one standard deviation above the mean) corresponds to a relative risk of  $\exp(.33) = 1.39$ , an almost 40% higher risk of death for subjects at that center

```
> stem(exp(ranef(efit2)[[1]]))
The decimal point is 1 digit(s) to the left of the |
 4 | 44
 6 | 42447
 8 | 679015556888
10 | 12458966
12 | 45670
14 | 159
16 | 27
> max(exp(ranef(efit2)[[1]])) [1] 1.768246
```

variability  
over centers

To look at random treatment effects within center we can add a nested effect

```
> efit3 <- coxme(Surv(y, uncens) ~ trt + (1 | center/trt), eortc)
> efit3
```

Cox mixed-effects model fit by maximum likelihood  
Data: eortc  
events, n = 1463, 2323  
Iterations= 10 54

Log-likelihood -10638.71 -10517.57 -10464.38

	Chisq	df	p	AIC	BIC
Integrated loglik	242.28	3.00	0	236.28	220.42
Penalized loglik	348.67	39.26	0	270.16	62.56

Model: Surv(y, uncens) ~ trt + (1 | center/trt)

Fixed coefficients

	coef	exp(coef)	se(coef)	z	p
trt	0.7420388	2.100213	0.08270483	8.97	0

Random effects

Group	Variable	Std Dev	Variance
center/trt	(Intercept)	0.20451052	0.04182455
center	(Intercept)	0.26273062	0.06902738

added term

This shows a further improvement in fit, but by much smaller amount.

```
> anova(efit2, efit3)
Analysis of Deviance Table
Cox model: response is Surv(y, uncens)
Model 1: ~trt + (1 | center)
Model 2: ~trt + (1 | center/trt) # a '3-level' model
loglik Chisq Df P(>|Chi|)
1 -10521
2 -10518 6.1727 1 0.01297 *
---
```

compare COX MC  
models

> #Also in vignette 4 The Minnesota Breast Cancer Family Study  
Source: Mixed Effects Cox Models Terry Therneau Mayo Clinic May 15, 2012

Further examples of coxme (compared with frailtyHL) in frailtyHL: A Package for Fitting Frailty Models with H-likelihood by Il Do Ha, Maengseok Noh and Youngjo Lee The R Journal Vol. 4/2, December 2012

shown in  
lecture

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> attach(eortc)
> table(uncens, center)
      center
uncens 1  2  3  4  5  6  7  8  9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
0  15 38 11 53 42 14 53  9 12 10 18 156 13 34 12 10 81  7 10  6  9 16  8 14 24
1  48 48 23 51 74 21 67 14 44 20 24  91 26 18 22 16 102 27 11 29 21 19 33 39 67
      center
uncens 26 27 28 29 30 31 32 33 34 35 36 37
0  10 14 13 45 16  7  6 20  7 36  5  6
1  27 52 48 110 27 25 19 52 45 49 37 17
> table(uncens) #uncens 0=alive, 1=dead
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          Chisq      df p      AIC      BIC
Integrated loglik 236.11  2.00 0 232.11 221.53
Penalized loglik 319.74 28.69 0 262.37 110.67

Model: Surv(y, uncens) ~ trt + (1 | center)
Fixed coefficients
      coef exp(coef) se(coef) z p
trt 0.7086127 2.031171 0.06424398 11.03 0

Random effects
Group Variable Std Dev Variance
center Intercept 0.3292140 0.1083818
> summary(efit1)
Call:
coxph(formula = Surv(y, uncens) ~ trt, data = eortc)
n = 2323, number of events = 1463
      coef exp(coef) se(coef) z Pr(>|z|)
trt 0.61826 1.85570 0.06343 9.747 <2e-16 ***
---
exp(coef) exp(-coef) lower .95 upper .95
trt 1.856 0.5389 1.639 2.101

Concordance= 0.563 (se = 0.006 )
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Cox mixed-effects model fit by maximum likelihood

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events, n = 1463, 2323
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NULL Integrated Fitted
Log-likelihood -10638.71 -10517.57 -10464.38

Chisq df p AIC BIC
Integrated loglik 242.28 3.00 0 236.28 220.42
Penalized loglik 348.67 39.26 0 270.16 62.56
```

Model: `Surv(y, uncens) ~ trt + (1 | center/trt)`

```
Fixed coefficients
coef exp(coef) se(coef) z p
trt 0.7420388 2.100213 0.08270483 8.97 0
```

Random effects

```
Group Variable Std Dev Variance
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