432 Class 21 Slides

github.com/THOMASELOVE/2019-432

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Preliminaries

```
library(skimr); library(MASS); library(robustbase)
library(quantreg); library(lmtest); library(sandwich)
library(boot); library(rms); library(survival)
library(OIsurv); library(survminer); library(broom)
library(tidyverse)

decim <- function(x, k) format(round(x, k), nsmall=k)</pre>
```

Today's Agenda

- Regression on Time-to-event data
 - Cox Proportional Hazards Model
- Robust Linear Regression Methods
 - with Huber weights
 - with bisquare weights (biweights)
 - Bounded Influence Regression & Least Trimmed Squares
 - Penalized Least Squares using ols in rms package
 - Quantile Regression on the Median

Survival Analysis / Cox Regression

A Survival Analysis Example

Source: Chen and Peace (2011) Clinical Trial Data Analysis Using R, CRC Press, section 5.1

```
brca <- read.csv("data/breast_cancer.csv") %>% tbl_df
```

The brca trial

The brca data describes a parallel randomized trial of three treatments, adjuvant to surgery in the treatment of patients with stage-2 carcinoma of the breast. The three treatment groups are:

- S+CT = Surgery plus one year of chemotherapy
- S+IT = Surgery plus one year of immunotherapy
- S+CT+IT = Surgery plus one year of chemotherapy and immunotherapy

The measure of efficacy were "time to death" in weeks. In addition to treat, our variables are:

- trial_weeks: time in the study, in weeks, to death or censoring
- last_alive: 1 if alive at last follow-up (and thus censored), 0 if dead
- age: age in years at the start of the trial

brca tibble

```
# A tibble: 31 \times 5
   subject treat trial weeks last alive
                                           age
   <fct> <fct>
                         <int>
                                 <int> <int>
 1 A01
      S+CT
                           102
                                        0
                                            55
2 A02 S+IT
                           192
                                       0
                                            62
3 A03 S+CT+IT
                           73
                                       0
                                            72
      S+CT
4 A04
                           58
                                            48
 5 A05
      S+CT
                           48
                                            26
6 A06
          S+IT
                           182
                                            52
7 A07
          S+IT
                          196
                                            50
8 A08
          S+CT
                          177
                                            49
9 A09
          S+IT
                                            62
                          191
10 A10
          S+CT+IT
                           36
                                       0
                                            60
# ... with 21 more rows
```

Analytic Objectives

This is a typical right-censored survival data set with interest in the comparative analysis of the three treatments.

- Does immunotherapy added to surgery plus chemotherapy improve survival? (Comparing S+CT+IT to S+CT)
- ② Does chemotherapy add efficacy to surgery plus immunotherapy? (S+CT+IT vs. S+IT)
- What is the effect of age on survival?

Create survival object

- trial_weeks: time in the study, in weeks, to death or censoring
- last_alive: 1 if alive at last follow-up (and thus censored), 0 if dead

So last_alive = 0 if the event (death) occurs.

What's next?

Create survival object

- trial_weeks: time in the study, in weeks, to death or censoring
- last_alive: 1 if alive at last follow-up (and thus censored), 0 if dead

So last_alive = 0 if the event (death) occurs.

```
brca$S <- with(brca, Surv(trial_weeks, last_alive == 0))
head(brca$S)</pre>
```

```
[1] 102 192 73 58+ 48+ 182+
```

Build Kaplan-Meier Estimator

```
kmfit <- survfit(S ~ treat, dat = brca)</pre>
print(kmfit, print.rmean = TRUE)
Call: survfit(formula = S ~ treat, data = brca)
            n events *rmean *se(rmean) median 0.95LCL
treat=S+CT 11
                  6
                       153
                               21.1 144
                                             102
treat=S+CT+IT 10
                  4 188 23.7 NA 139
treat=S+IT 10 5
                      188 17.9 192 144
           0.95UCL
treat=S+CT
               NΑ
treat=S+CT+IT NA
treat=S+IT
         NA
   * restricted mean with upper limit = 242
```

summary(kmfit)

> summary(kmfit)

Call: survfit(formula = S ~ treat, data = brca)

treat=S+CT

time n.risk n.event survival std.err lower 95% CI upper 95% CI 55 10 1 0.900 0.0949 0.732 1.000

63 8 1 0.787 0.1340 0.564 1.000 102 7 1 0.675 0.1551 0.430 1.000

133 6 1 0.562 0.1651 0.316 1.000 144 5 1 0.450 0.1660 0.218 0.927

217 1 1 0.000 NaN NA NA

treat=S+CT+IT

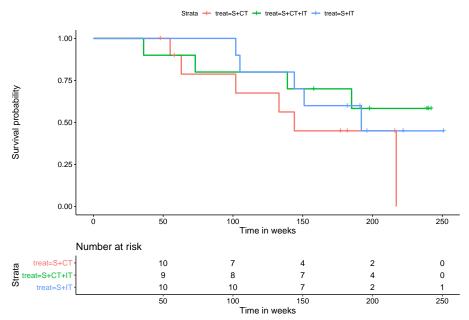
139 8 1 0.800 0.1265 0.587 1 139 8 1 0.700 0.1449 0.467 1 185 6 1 0.583 0.1610 0.340 1

treat=S+IT

time n.risk n.event survival std.err lower 95% CI upper 95% CI 102 10 1 0.90 0.0949 0.732 1.000

105 9 1 0.80 0.1265 0.587 1.000 144 8 1 0.70 0.1449 0.467 1.000

K-M Plot via survminer



K-M Plot via survminer (code)

Testing the difference between curves

```
survdiff(S ~ treat, dat = brca)
```

```
Call:
```

```
survdiff(formula = S ~ treat, data = brca)
```

```
N Observed Expected (0-E)^2/E (0-E)^2/V treat=S+CT 11 6 3.80 1.2772 1.7647 treat=S+CT+IT 10 4 5.62 0.4676 0.7725 treat=S+IT 10 5 5.58 0.0605 0.0981
```

Chisq= 1.9 on 2 degrees of freedom, p= 0.4

What do we conclude?

Fit Cox Model A: Treatment alone

```
modA <- coxph(S ~ treat, data = brca)
ModA
Call:
coxph(formula = S ~ treat, data = brca)
               coef exp(coef) se(coef) z
treatS+CT+IT -0.8313 0.4355 0.6547 -1.270 0.204
treatS+IT -0.5832 0.5581 0.6088 -0.958 0.338
Likelihood ratio test=1.75 on 2 df, p=0.4164
n= 31, number of events= 15
```

summary(modA)

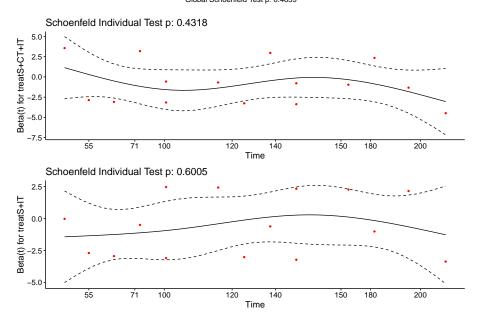
```
> summary(modA)
Call:
coxph(formula = S \sim treat, data = brca)
 n= 31, number of events= 15
            coef exp(coef) se(coef) z Pr(>|z|)
treatS+IT -0.5832 0.5581 0.6088 -0.958 0.338
          exp(coef) exp(-coef) lower .95 upper .95
treatS+CT+IT 0.4355 2.296 0.1207 1.571
treatS+IT 0.5581 1.792 0.1692 1.840
Concordance = 0.577 (se = 0.078)
Rsquare= 0.055 (max possible= 0.944)
Likelihood ratio test= 1.75 on 2 df, p=0.4164
Wald test = 1.82 on 2 df, p=0.403
Score (logrank) test = 1.89 on 2 df, p=0.3878
```

Check Proportional Hazards Assumption

cox.zph(modA)

```
rho chisq p
treatS+CT+IT -0.198 0.618 0.432
treatS+IT 0.138 0.274 0.601
GLOBAL NA 1.536 0.464
```

Graphical PH Test ggcoxzph(cox.zph(modA)) Global Schoenfeld Test p: 0.4639



Fit Cox Model B: Treatment + Age

```
modB <- coxph(S ~ treat + age, data = brca)
modB
Call:
coxph(formula = S ~ treat + age, data = brca)
               coef exp(coef) se(coef) z p
treatS+CT+IT -0.59960 0.54903 0.65741 -0.912 0.3617
treatS+IT -0.31161 0.73227 0.60936 -0.511 0.6091
    0.07807 1.08119 0.03672 2.126 0.0335
age
Likelihood ratio test=6.99 on 3 df, p=0.07224
n= 31, number of events= 15
```

summary(modB)

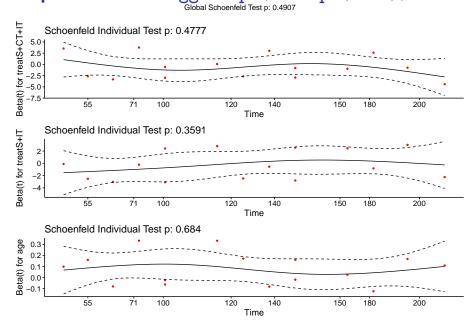
```
> summary(modB)
 Call:
 coxph(formula = S \sim treat + age. data = brca)
  n= 31, number of events= 15
                coef exp(coef) se(coef) z Pr(>|z|)
 treatS+CT+IT -0.59960 0.54903 0.65741 -0.912 0.3617
 treatS+IT -0.31161 0.73227 0.60936 -0.511 0.6091
 age 0.07807 1.08119 0.03672 2.126 0.0335 *
 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
            exp(coef) exp(-coef) lower .95 upper .95
 treatS+CT+IT 0.5490 1.8214 0.1514 1.992
 treatS+IT 0.7323 1.3656 0.2218 2.417
 age 1.0812 0.9249 1.0061 1.162
 Concordance= 0.701 (se = 0.083)
 Rsquare= 0.202 (max possible= 0.944 )
 Likelihood ratio test= 6.99 on 3 df, p=0.07224
 Wald test = 5.85 on 3 df, p=0.1192
github.com/THOMASELOVE/2019-432 432 Class 21 Slides
                                                2019-04-16
                                                        21 / 63
```

Proportional Hazards Assumption: Model B Check

cox.zph(modB)

```
rho chisq p
treatS+CT+IT -0.179 0.504 0.478
treatS+IT 0.244 0.841 0.359
age -0.106 0.166 0.684
GLOBAL NA 2.416 0.491
```

Graphical PH Test ggcoxzph(cox.zph(modB))



What to do if the PH assumption is violated

- If the PH assumption fails on a categorical predictor, fit a Cox model stratified by that predictor (use strata(var) rather than var in the specification of the coxph model.)
- If the PH assumption is violated, this means the hazard isn't constant over time, so we could fit separate Cox models for a series of time intervals.
- Use an extension of the Cox model that permits covariates to vary over time.

Visit

https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf for details on building the relevant data sets and models, with examples.

The crimestat data and an OLS fit

The crimestat data set

For each of 51 states (including the District of Columbia), we have the state's ID number, postal abbreviation and full name, as well as:

- crime the violent crime rate per 100,000 people
- **poverty** the official poverty rate (% of people living in poverty in the state/district) in 2014
- single the percentage of households in the state/district led by a female householder with no spouse present and with her own children under 18 years living in the household in 2016
- **trump** whether Donald Trump won the popular vote in the 2016 presidential election in that state/district (which we'll ignore for today)

The crimestat data set

crimestat <- read.csv("data/crimestat.csv") %>% tbl_df
crimestat

```
# A tibble: 51 \times 7
    sid state crime poverty single trump state.full
  <int> <fct> <dbl> <dbl> <dbl> <int> <fct><</pre>
1
      1 AT.
              427. 19.2
                           9.02
                                   1 Alabama
      2 AK
          636. 11.4 7.63
                                   1 Alaska
3
      3 A7.
          400. 18.2 8.31
                                   1 Arizona
4
          480. 18.7 9.41
      4 AR.
                                   1 Arkansas
5
      5 CA
             396. 16.4 7.25
                                   0 California
6
             309. 12.1 6.75
      6 CO
                                   0 Colorado
      7 CT
             237. 10.8 8.04
                                   0 Connecticut
                           6.52
8
      8 DE
              489. 13
                                   0 Delaware
9
      9 DC
             1244. 18.4 8.41
                                   O District of Colum~
10
     10 FL
              540.
                     16.6
                           8.29
                                   1 Florida
  ... with 41 more rows
```

Modeling crime with poverty and single

Our main goal will be to build a linear regression model to predict **crime** using centered versions of both **poverty** and **single**.

Our original (OLS) model

Significance of our coefficients?

tidy(mod1)



Robust Linear Regression with Huber weights

There are several ways to do robust linear regression using M-estimation, including weighting using Huber and bisquare strategies.

- Robust linear regression here will make use of a method called iteratively re-weighted least squares (IRLS) to estimate models.
- M-estimation defines a weight function which is applied during estimation.
- The weights depend on the residuals and the residuals depend on the weights, so an iterative process is required.

We'll fit the model, using the default weighting choice: what are called Huber weights, where observations with small residuals get a weight of 1, and the larger the residual, the smaller the weight.

Our robust model (using MASS::rlm)

```
rob.huber <- rlm(crime ~ pov_c + single_c, data = crimestat)</pre>
```

Summary of the robust (Huber weights) model

```
tidy(rob.huber)
```

Now, *both* predictors appear to have estimates that exceed twice their standard error. So this is a very different result than ordinary least squares gave us.

Glance at the robust model (vs. OLS)

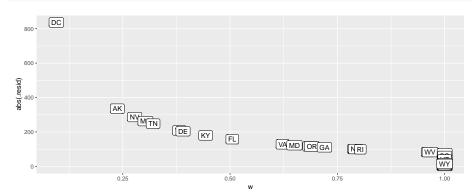
Understanding the Huber weights a bit

Let's augment the data with results from this model, including the weights used.

```
crime_with_huber <- augment(rob.huber, crimestat) %>%
    mutate(w = rob.huber$w) %>% arrange(w) %>% tbl_df
head(crime_with_huber, 3)
```

Are cases with large residuals down-weighted?

```
ggplot(crime_with_huber, aes(x = w, y = abs(.resid))) +
    geom_label(aes(label = state))
```



Conclusions from the Plot of Weights

- The district of Columbia will be down-weighted the most, followed by Alaska and then Nevada and Mississippi.
- But many of the observations will have a weight of 1.
- In ordinary least squares, all observations would have weight 1.
- So the more cases in the robust regression that have a weight close to one, the closer the results of the OLS and robust procedures will be.

summary(rob.huber)

Call: rlm(formula = crime ~ pov_c + single_c, data = crimestate
Residuals:

Coefficients:

Value Std. Error t value (Intercept) 343.7982 13.1309 26.1823 pov_c 11.9098 5.5058 2.1631 single_c 30.9868 10.5266 2.9437

Residual standard error: 59.14 on 48 degrees of freedom

Robust Linear Regression with the bisquare weighting function

Robust Linear Regression with the biweight

As mentioned there are several possible weighting functions - we'll next try the biweight, also called the bisquare or Tukey's bisquare, in which all cases with a non-zero residual get down-weighted at least a little. Here is the resulting fit. . .

Call:

```
rlm(formula = crime ~ pov_c + single_c, data = crimestat, psi
Converged in 13 iterations
```

Coefficients:

```
(Intercept) pov_c single_c
336.17015 10.31578 34.70765
```

Degrees of freedom: 51 total; 48 residual Scale estimate: 67.3

Coefficients and Standard Errors

```
tidy(rob.biweight)
```

```
A tibble: 3 \times 4
            estimate std.error statistic
 term
 <chr>>
              <dbl>
                       <dbl>
                                <dbl>
1 (Intercept)
              336.
                       12.7 26.5
             10.3 5.31 1.94
2 pov_c
3 single_c
               34.7
                       10.2
                              3.42
```

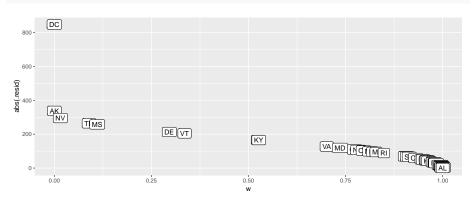
Understanding the biweights weights a bit

Let's augment the data, as above

```
crime with biweights <- augment(rob.biweight, crimestat) %>%
   mutate(w = rob.biweight$w) %>% arrange(w) %>% tbl df
head(crime with biweights, 3)
# A tibble: 3 \times 13
   sid state crime poverty single trump state.full pov_c
 <int> <fct> <dbl> <dbl> <int> <fct> <dbl> <dbl>
   2 AK 636. 11.4 7.63 1 Alaska -3.47
2 9 DC 1244. 18.4 8.41 0 District ~ 3.53
3 29 NV 636. 15.4 7.66 0 Nevada 0.527
# ... with 5 more variables: single c <dbl>, .fitted <dbl>,
#
   .se.fit <dbl>, .resid <dbl>, w <dbl>
```

Relationship of Weights and Residuals

```
ggplot(crime_with_biweights, aes(x = w, y = abs(.resid))) +
    geom_label(aes(label = state))
```



Conclusions from the biweights plot

Again, cases with large residuals (in absolute value) are down-weighted generally, but here, Alaska and Washington DC receive no weight at all in fitting the final model.

- We can see that the weight given to DC and Alaska is dramatically lower (in fact it is zero) using the bisquare weighting function than the Huber weighting function and the parameter estimates from these two different weighting methods differ.
- The maximum weight (here, for Alabama) for any state using the biweight is still slightly smaller than 1.

summary(rob.biweight)

Call: rlm(formula = crime ~ pov_c + single_c, data = crimestate
Residuals:

Coefficients:

Value Std. Error t value (Intercept) 336.1702 12.6733 26.5259 pov_c 10.3158 5.3139 1.9413 single_c 34.7077 10.1598 3.4162

Residual standard error: 67.27 on 48 degrees of freedom

Comparing OLS and the two weighting schemes glance(mod1) # OLS

A tibble: 1 x 11 r.squared adj.r.squared sigma statistic p.value df <dbl> <dbl> <dbl> <dbl> <int> 0.197 0.163 164. 5.88 0.00518 # ... with 5 more variables: logLik <dbl>, AIC <dbl>, # BIC <dbl>, deviance <dbl>, df.residual <int> glance(rob.biweight) # biweights # A tibble: 1×6

```
# A tibble: 1 x 6
sigma converged logLik AIC BIC deviance
<dbl> <lgl> <dbl> <dbl> <dbl> <dbl> <dbl> 1
67.3 TRUE -332. 672. 679. 1339850.
```

glance(rob.huber) # Huber weights

A tibble: 1 x 6

Bounded-Influence Regression

Bounded-Influence Regression and Least-Trimmed Squares

Under certain circumstances, M-estimators can be vulnerable to high-leverage observations, and so, bounded-influence estimators, like least-trimmed squares (LTS) regression have been proposed. The biweight that we have discussed is often fitted as part of what is called an MM-estimation procedure, by using an LTS estimate as a starting point.

The ltsReg function, which is part of the robustbase package (Note: **not** the ltsreg function from MASS) is what I use below to fit a least-trimmed squares model. The LTS approach minimizes the sum of the h smallest squared residuals, where h is greater than n/2, and by default is taken to be (n + p + 1)/2.

Least Trimmed Squares Model

lts1 <- ltsReg(crime ~ pov_c + single_c, data = crimestat)</pre>

Summarizing the LTS model

summary(lts1)\$coeff

```
Estimate Std. Error t value Pr(>|t|)
Intercept 339.14817 11.616766 29.194715 1.601245e-29
pov_c 16.99322 4.973459 3.416781 1.418337e-03
single_c 24.99819 9.136683 2.736024 9.073473e-03
```

MM estimation

Specifying the argument method="MM" to rlm requests bisquare estimates with start values determined by a preliminary bounded-influence regression, as follows...

summary(rob.MM)

Call: rlm(formula = crime ~ pov_c + single_c, data = crimestate
Residuals:

Coefficients:

Value Std. Error t value (Intercept) 336.3928 13.1929 25.4980 pov_c 10.5579 5.5318 1.9086 single_c 32.7755 10.5763 3.0990

Residual standard error: 75.79 on 48 degrees of freedom

Penalized Least Squares

Penalized Least Squares with rms

We can apply a penalty to least squares directly through the ols function in the rms package.

The pls fit

Linear Regression Model

```
ols(formula = crime ~ pov_c + single_c, data = crimestat, x =
    y = T, penalty = 1)
```

		Model Likelihood		Discrimination	
		Ratio Test		Indexes	
0bs	51	LR chi2	11.18	R2	0.197
sigma159.1209		d.f.	1.946198	R2 adj	0.164
d.f.	48.0538	Pr(> chi2)	0.0035	g	89.298

Residuals

```
Min
           1Q Median
                         3Q
                               Max
-284.24 -65.93 -16.68 15.66 807.01
```

How to Choose the Penalty in Penalized Least Squares?

The problem here is how to choose the penalty - and that's a subject I'll essentially skip today. The most common approach (that we've seen with the lasso) is cross-validation.

Meanwhile, what do we conclude about the fit here from AIC and BIC?

```
AIC(pls); BIC(pls)
```

d.f.

669.5781

d.f.

677,2014

Quantile Regression (on the Median)

Quantile Regression on the Median

We can use the rq function in the quantreg package to model the **median** of our outcome (violent crime rate) on the basis of our predictors, rather than the mean, as is the case in ordinary least squares.

```
rob.quan <- rq(crime ~ pov_c + single_c, data = crimestat)
glance(rob.quan)</pre>
```

```
# A tibble: 1 x 5
    tau logLik AIC BIC df.residual
    <dbl> <dbl> <dbl> <int>
1 0.5 -316. 638. 643. 48
```

summary(rob.quan)

```
Call: rq(formula = crime ~ pov_c + single_c, data = crimestat)
tau: [1] 0.5
```

Coefficients:

```
coefficients lower bd upper bd (Intercept) 344.75658 336.94534 366.23603 pov_c 10.54757 3.06714 28.95962 single_c 32.27249 4.45889 48.18925
```

Estimating a different quantile (tau = 0.70)

In fact, if we like, we can estimate any quantile by specifying the tau parameter (here tau = 0.5, by default, so we estimate the median.)

```
Call:
```

```
rq(formula = crime ~ pov_c + single_c, tau = 0.7, data = crime
```

Coefficients:

```
(Intercept) pov_c single_c
379.72818 19.30376 32.15827
```

Degrees of freedom: 51 total; 48 residual

Conclusions

Comparing Five of the Models

Estimating the Mean

Fit	Intercept CI	pov_c CI	single_c Cl
OLS	(318.6, 410.2)	(-3.13, 35.35)	(-12.92, 60.60)
Robust (Huber)	(320.0, 367.6)	(0.89, 22.93)	(9.93, 52.05)
Robust (biweight)	(310.7, 361.5)	(-0.30, 20.94)	(14.39, 55.03)
Robust (MM)	(310.0, 362.8)	(-0.50, 21.62)	(11.62, 53.94)

 $\textbf{Note} : \mbox{Cls}$ estimated for OLS and Robust methods as point estimate $\pm \ 2$ standard errors

Estimating the Median

Fit	Intercept CI	pov_c CI	single_c CI
Quantile (Median) Reg	(336.9, 366.2)	(3.07, 28.96)	(4.46, 48,19)

Comparing AIC and BIC

Fit	AIC	BIC
OLS	669.7	677.4
Robust (Huber)	670.8	678.5
Robust (biweight)	671.7	679.4
Robust (MM)	671.6	679.3
Quantile (median)	637.5	643.3

Some General Thoughts

- When comparing the results of a regular OLS regression and a robust regression for a data set which displays outliers, if the results are very different, you will most likely want to use the results from the robust regression.
 - Large differences suggest that the model parameters are being highly influenced by outliers.
- Oifferent weighting functions have advantages and drawbacks.
 - Huber weights can have difficulties with really severe outliers.
 - Bisquare weights can have difficulties converging or may yield multiple solutions.
 - Quantile regression approaches have some nice properties, but describe medians (or other quantiles) rather than means.