Lesson 11: Numerical Problems

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Learning Objectives

1. Identify and troubleshoot logistic regression analysis when there are low or zero observations for the cross section of the outcome and a predictor
2. Identify and troubleshoot logistic regression analysis when there is complete separation between the two outcome groups
3. Identify and troubleshoot logistic regression analysis when there is multicollinearity between variables

Three Numerical Problems

- Issues that may cause numerical problems:

    1. Zero cell count

    2. Complete separation

    3. Multicollinearity

- All may cause large estimated coefficients and/or large estimated standard errors

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Zero cell count in a contingency table

- If no observations at any intersection of the covariate and outcome

- Zero cell in a contingency table should be detected in descriptive statistical analysis stage

- Example of one covariate with outcome:

Outcome	Covariate (x)			Total
	1	2	3	
1	7	12	20	39
0	13	8	0	21
Total	20	20	20	60

Zero cell count: example (1/2)

- Example of logistic regression with **one** covariate:

```
ex1_m = glm(outcome ~ x, data = ex1,
                 family = binomial)
```

Outcome	Covariate (x)			Total
	1	2	3	
1	7	12	20	39
0	13	8	0	21
Total	20	20	20	60

Zero cell count: example (2/2)

Outcome	Covariate (x)			Total
	1	2	3	
1	7	12	20	39
0	13	8	0	21
Total	20	20	20	60

- Example of logistic regression with **one** covariate:

```r
ex1_m = glm(outcome ~ x, data = ex1,
              family = binomial)
```

- Coefficient estimates

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	−0.62	0.47	−1.32	0.19	−1.60	0.27
xTwo	1.02	0.65	1.57	0.12	−0.23	2.35
xThree	20.19	2,404.67	0.01	0.99	−148.07	NA

Coefficient estimate is large and standard error is large! Estimated odds ratio is very large and confidence interval cannot be computed.

- Odds ratio

Characteristic	**OR**	**95% CI**	**p-value**
x			
One	—	—	
Two	2.79	0.79, 10.5	0.12
Three	583,822,601	0.00,	>0.9

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Ways to address zero cell

1. Add one-half to each of the cell counts

- Technically works, but not the best option
- Rarely useful with a more complex analysis: may work for simple logistic regression
- Nicky would say worst option because manipulating the data that does not work on individual level

2. Collapse the categories to remove the 0 cells

- We could collapse groups 2 and 3 together if it makes clinical sense
- Good idea if this makes clinical sense OR there is no difference between groups

3. Remove the category with 0 cells

- This would mean we reduce the total sample size as well
- Not a good idea: we would remove people from our dataset. Why would we do that?

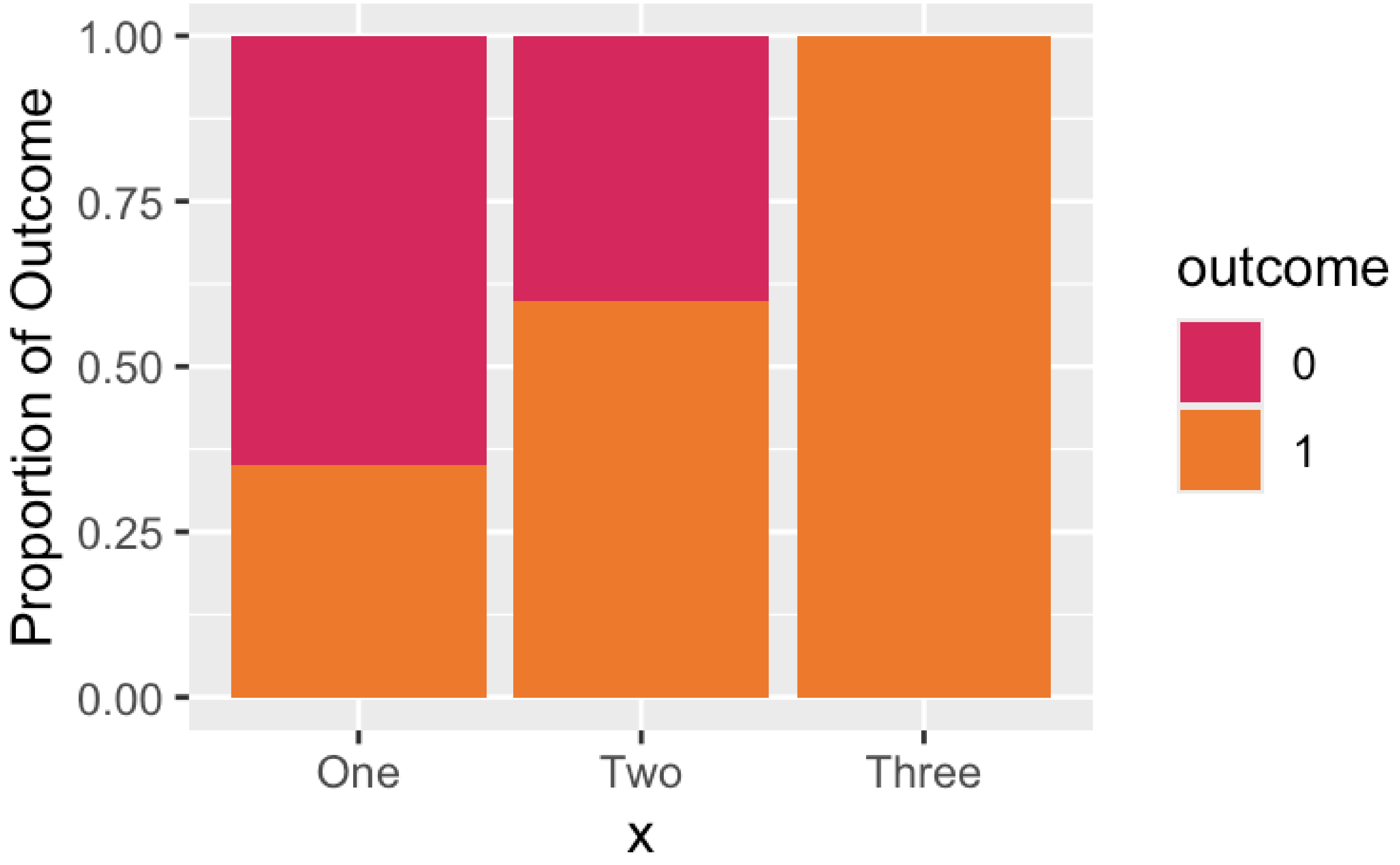
4. If the variable is ordinal, treat it as continuous

- Good idea if you have seen evidence that there is a linear trend on log-odds scale

Decide on how to address zero cell

- Look at the proportions across the predictor, X:

```
ggplot(data = ex1, aes(x = x, fill = outcome)) +
       geom_bar(stat = "count", position = "fill") +
       labs(y = "Proportion of Outcome")
```



- Combining groups 2 and 3 together *may not be a good idea*.
- **Their proportions of the outcome do not look similar.**
- The predictor has an *ordinal quality*, so this is making me think a *continuous approach might be good*.

2. Collapse the categories of predictor: first check if close enough!

Just to be safe: I'd check the Fisher's Exact test for the 2x2 table of groups 2 and 3:

```
ex1_1 = ex1 %>%
  filter(x != "One") %>%
  mutate(x = factor(x, levels = c("Two", "Three")),
         outcome = factor(outcome, levels=c("1", "0")))

fisher.test(x = table(ex1_1$x, ex1_1$outcome))
```

```
	Fisher's Exact Test for Count Data

data:  table(ex1_1$x, ex1_1$outcome)
p-value = 0.003276
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 0.000000 0.442286
sample estimates:
odds ratio 
         0 
```

Remember, I'm using Fisher's Exact test because I have a zero cell count! If the expected cell count was > 5, I could use a difference in proportions or Chi-squared test.

2. Collapse the categories of predictor

NOT APPROPRIATE, but let's run through the thought experiment

Combine groups 2 and 3:

```
ex1_23 = ex1 %>%
              mutate(x = factor(x, levels = c("One", "Two", "Three"),
                                   labels = c("One", "Two-Three", "Two-Three")))
ex1_23_glm = glm(outcome ~ x, data = ex1_23, family = binomial)
tbl_regression(ex1_23_glm, exponentiate=T) %>% as_gt() %>%
  tab_options(table.font.size = 38)
```

Characteristic	OR	95% CI	p-value
x			
One	—	—	
Two-Three	7.43	2.32, 26.3	0.001

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

- Based on our previous visual, I don't think this is a good idea
- Look at the estimated OR comparing group 2 to group 1 from our original model: 2.79 (95% CI: 0.79, 10.5)
  - Looks different than the estimated OR in the above table

3. Remove the category with 0 cells

Remove group 3 from the data:

```
ex1_two = ex1 %>% filter(x != "Three")
ex1_two_glm = glm(outcome ~ x, data = ex1_two, family = binomial())
tbl_regression(ex1_two_glm, exponentiate=T) %>% as_gt() %>%
  tab_options(table.font.size = 38)
```

Characteristic	OR	95% CI	p-value
x			
One	—	—	
Two	2.79	0.79, 10.5	0.12

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

- Not a good idea because we lose information (sample size goes down!)
- **And really bad when we have other predictors!!**

4. Treat predictor as continuous

- When we treat a predictor as continuous, we need to make sure we have **linearity between continuous predictor and log-odds**
- Cannot test this before fitting the logistic regression with the continuous predictor
  - Try taking the logit of a probability of 1… it's infinity!
- Test linearity by fitting logistic regression with the continuous predictor, then visually examining if predicted probabilities from that model match with approximate sample proportions
  - Checking: Did linear assumption completely warp the original trend?

```
ex1_cont = ex1 %>% mutate(x = as.numeric(x))
ex1_cont_glm = glm(outcome ~ x, data = ex1_cont, family = binomial())
tbl_regression(ex1_cont_glm, exponentiate=T) %>% as_gt() %>%
  tab_options(table.font.size = 38)
```

Characteristic	OR	95% CI	p-value
x	6.22	2.63, 18.0	<0.001

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

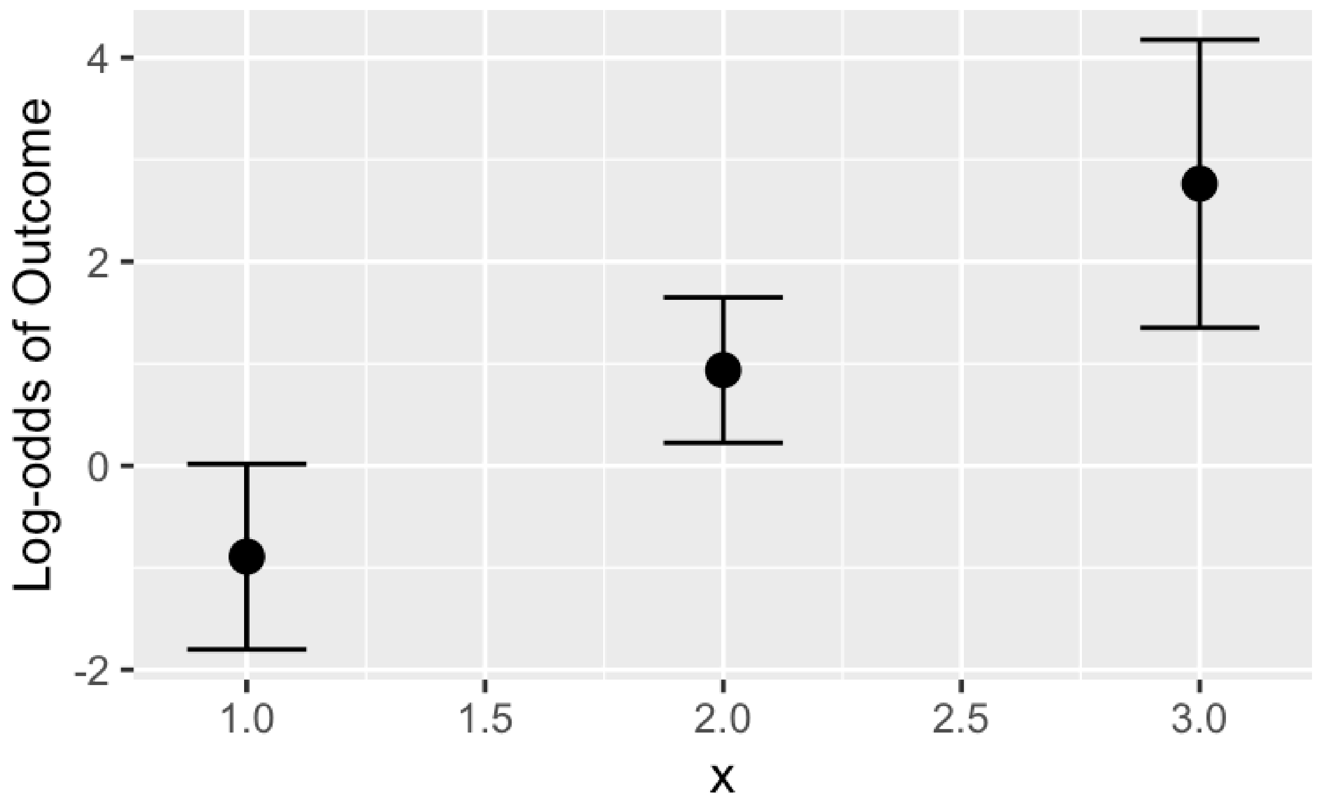
4. Treat predictor as continuous: check linearity assumption (1/2)

- You may think we need to look at the fitted log-odds to check linearity
  - BUT fitted log-odds were constrained to the linearity assumption, so it will automatically be linear!

```r
newdata = data.frame(x = c(1, 2, 3))
pred = predict(ex1_cont_glm, newdata, se.fit=T, type = "link")
LL_CI1 = pred$fit - qnorm(1-0.05/2) * pred$se.fit
UL_CI1 = pred$fit + qnorm(1-0.05/2) * pred$se.fit

pred_link = data.frame(x = newdata, Pred = pred$fit, LL_CI1, UL_CI1)
```

▶ Plotting fitted log-odds

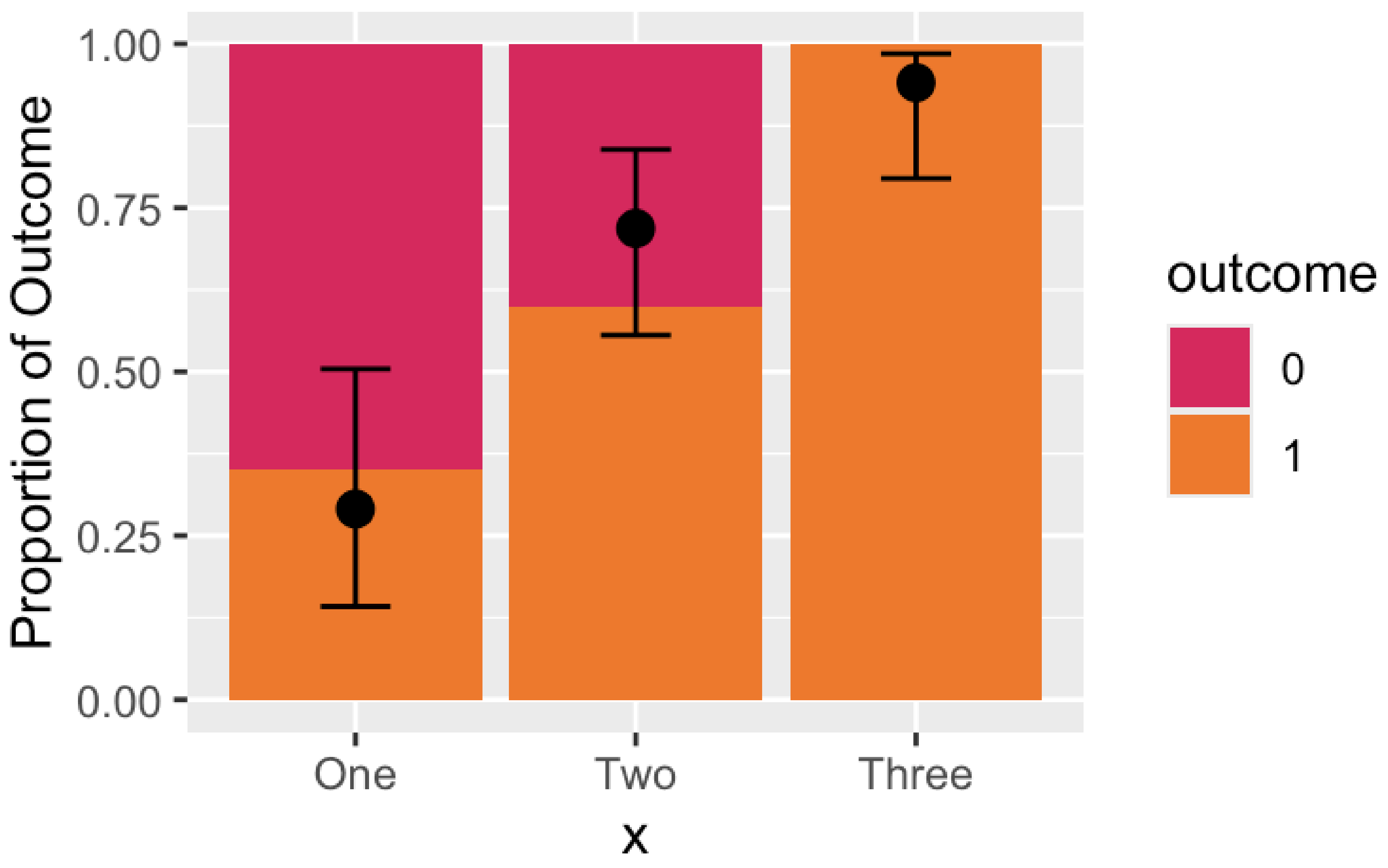


4. Treat predictor as continuous: check linearity assumption (2/2)

```
newdata = data.frame(x = c(1, 2, 3))
pred = predict(ex1_cont_glm, newdata, se.fit=T, type = "link")
LL_CI1 = pred$fit - qnorm(1-0.05/2) * pred$se.fit
UL_CI1 = pred$fit + qnorm(1-0.05/2) * pred$se.fit

pred_link = cbind(Pred = pred$fit, LL_CI1, UL_CI1) %>% inv.logit()
pred_prob = as.data.frame(pred_link) %>% mutate(x = c("One", "Two", "Three"))
```

- Plotting sample and predicted probabilities



- Do the predicted probabilities (from the model with continuous x) align with the sample proportions?

This looks pretty good. We've mostly captured the trend of the outcome proportion!

Zero cell count when we have multiple predictors

- Note that we may not see the zero count cells in a single predictor
  - But we may have issues if there is an interaction!
  - This is why I suggested we keep an eye out for cell counts below 10 in our lab!
- If you see a **big coefficient estimate** with a **big standard deviation** for a specific category or interaction…
  - …this may mean that a **low cell count for that category is causing you issues!**

Zero cell count: summary

My suggestion is to try possible solutions in this order

1. For group with zero cell count, see if there is an adjacent group that makes sense to combine it with

2. If that does not make sense (or obscures your data) AND your data has an inherent order, then you can try treating it as continuous.

3. Remove the zero count group and all the observations in it (not a very good solution)

4. Add a half count to each cell (only works for a single predictor)

Poll Everywhere Question 1

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3. Identify and troubleshoot logistic regression analysis when there is multicollinearity between variables

Complete Separation

- **Complete separation:** occurs when a collection of the covariates completely separates the outcome groups
  - Example: Outcome is “gets senior discount at iHop” and the only covariate you measure is age
  - Age will completely separate the outcome
  - No overlap in distribution of covariates between two outcome groups

- Problem: the maximum likelihood estimates do not exist
  - Likelihood function is monotone
  - In order to have finite maximum likelihood estimates we must have some overlap in the distribution of the covariates in the model

Poll Everywhere Question 2

Complete Separation: example (1/2)

- We get a warning when we have complete separation

```r
y = c(0,0,0,0,1,1,1,1)
x1 = c(1,2,3,3,5,6,10,11)
x2 = c(3,2,-1,-1,2,4,1,0)
ex3 = data.frame(outcome = y, x1 = x1, x2= x2)
ex3
```

```
  outcome x1 x2
1       0  1  3
2       0  2  2
3       0  3 -1
4       0  3 -1
5       1  5  2
6       1  6  4
7       1 10  1
8       1 11  0
```

```r
m1 = glm(outcome ~ x1 + x2, data = ex3, family=binomial)
```

```
Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred
```

- Outcomes of 0 and 1 are completely separated by `x1`
  - If `x1 > 4` then outcome is 1
  - If `x1 < 4` then outcome is 0

Complete Separation: example (2/2)

Coefficient estimates:

```
tidy(m1, conf.int=T) %>% gt() %>%
  tab_options(table.font.size = 35) %>%
  fmt_number(decimals = 2)
```

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	−66.10	183,471.72	0.00	1.00	−10,644.72	10,512.52
x1	15.29	27,362.84	0.00	1.00	−3,122.69	NA
x2	6.24	81,543.72	0.00	1.00	−12,797.28	NA

- Coefficient estimate of x1 is large
- Standard error of x1's coefficient is large
- But also the coefficients and standard errors for the intercept and x2 are large!

Complete Separation

- The occurrence of complete separation in practice **depends on**
  - Sample size
  - Number of subjects with the outcome present
  - Number of variables included in the model

- Example: 25 observations and only 5 have "success" outcome
  - 1 variable in model may not lead to complete separation
  - More variables = more dimensions that can completely separate the observations

- In most cases, the occurrence of complete separation is not bad for clinical importance
  - But rather a numerical coincidence that causing problem for model fitting

Poll Everywhere Question 3

Complete Separation: Ways to address issue

- Collapse categorical variables in a meaningful way
  - Easiest and best if stat methods are restricted (common for collaborations)
  - Other reasons why you MUST stay with logistic regression

- Exclude x1 from the model
  - Not ideal because this could lead to biased estimates for the other predicted variables in the model

- Firth logistic regression (best option in terms of statistical properties)
  - Uses penalized likelihood estimation method
  - Basically takes the likelihood (that has no maximum) and adds a penalty that makes the MLE estimatable

Firth logistic regression

```
library(logistf)
m1_f = logistf(outcome ~ x1 + x2, data = ex3, family=binomial)
summary(m1_f) # Cannot use tidy on this :(
```

```
logistf(formula = outcome ~ x1 + x2, data = ex3, family = binomial)

Model fitted by Penalized ML
Coefficients:
                  coef  se(coef)   lower 0.95 upper 0.95     Chisq          p
(Intercept) -2.9748898 1.7244237 -15.47721665 -0.1208883 4.2179522 0.03999841
x1           0.4908484 0.2745754   0.05268216  2.1275832 5.0225056 0.02501994
x2           0.4313732 0.4988396  -0.65793078  4.4758930 0.7807099 0.37692411
            method
(Intercept)      2
x1               2
x2               2

Method: 1-Wald, 2-Profile penalized log-likelihood, 3-None

Likelihood ratio test=5.505687 on 2 df, p=0.06374636, n=8
Wald test = 3.624899 on 2 df, p = 0.1632538
```

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Multicollinearity

- **Multicollinearity** happens when one or more of the covariates in a model can be predicted from other covariates in the same model

- This will cause unreliable coefficient estimates for some covariates in logistic regression, as in an ordinary linear regression

- Looking at correlations among pairs of variables is helpful but not enough to identify multicollinearity problem
  - Because multicollinearity problems may involve relationships among more than two covariates

Multicollinearity: example (1/2)

- Table below is a simulated data with
  - $x_1 \sim \text{Normal}(0, 1)$
  - $x_2 = x_1 + \text{Uniform}(0, 0.1)$
  - $x_3 = 1 + \text{Uniform}(0, 0.01)$
- Therefore, x_1 and x_2 are highly correlated, and x_3 is nearly collinear with the constant term

Table 4.38 Data Displaying Near Collinearity Among the Independent Variables and Constant

Subject	x_1	x_2	x_3	y
1	0.225	0.231	1.026	0
2	0.487	0.489	1.022	1
3	−1.080	−1.070	1.074	0
4	−0.870	−0.870	1.091	0
5	−0.580	−0.570	1.095	0
6	−0.640	−0.640	1.010	0
7	1.614	1.619	1.087	0
8	0.352	0.355	1.095	1
9	−1.025	−1.018	1.008	0
10	0.929	0.937	1.057	1

Multicollinearity: example (2/2)

- Four logistic regression models using data in the previous slide
- Consequence of multicollinearity: large coefficient estimates and/or standard errors

Table 4.39 Estimated Coefficients and Standard Errors from Fitting Logistic Regression Models to the Data in Table 4.38

Var.	Coeff.	Std. Err.	Coeff.	Std. Err.	Coeff.	Std. Err.	Coeff.	Std. Err.
x_1	1.4	1.0	104.2	256.2			79.8	272.6
x_2			−103.4	256.0			−78.3	272.5
x_3					1.8	20.0	−11.1	206.6
Cons.	−1.0	0.8	−0.3	1.3	−2.7	21.1	11.4	27.8
	Model 1: x1 only		Model 2: x1 and x2		Model 3: x3 only		Model 4: x1, x2, x3	
			Large coefficients and SE		Large SE		Large coefficients and SE	

Multicollinearity: how to detect

- Multicollinearity only involves the covariates
  - No specific issues to logistic regression (vs. linear regression)
  - Techniques from 512/612 work well for logistic regression model

- In more complicated dataset/analysis, we may not be able to detect multicollinearity using the coefficient estimates/SE

- **Variance inflation factor (VIF) approach:** well-known approach to detect multicollinearity

Variance Inflation Factor (VIF) Approach

- Computed by regressing each variable on all the other explanatory variables
  - For example: $E(x_1 | x_2, x_3, \ldots) = \alpha_0 + \alpha_1 x_2 + \alpha_2 x_3$
- Calculate the coefficient of determination, R^2
  - Proportion of the variation in x_1 that is predicted from x_2, x_3,...

$$VIF = \frac{1}{1 - R^2}$$

- Each covariate has its own VIF computed
- Get worried for multicollinearity if VIF > 10
- Sometimes VIF approach may miss serious multicollinearity
  - Same multicollinearity we wish to detect using VIF can cause numerical problems in reliably estimating R^2

Multicollinearity: Ways to address the issue

- Exclude the redundant variable from the model
- Scaling and centering variables
  - When you have transformed a continuous variable
- Other modeling approach (outside scope of this class)
  - Ridge regression
  - Principle component analysis

- **Please take a look at the** BSTA 512/612 lesson **that included multicollinearity**

Poll Everywhere Question 4

Learning Objectives

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