

BIOS 662 Fall 2018

Analysis of Variance, Part IV: A Case Study

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Strategy for Analysis

1. Consider data generation mechanism
2. Analysis plan: Specify model and assumptions; hypotheses to be tested; diagnostics to be performed
3. Summary statistics, tables, figures
4. Model fitting and diagnostics
5. Inference
6. Sensitivity analysis
7. Conclusions; summary; limitations (e.g., lack of power)

Hypothetical Example

- Survival times of patients following heart transplant surgery based on degree of mismatch (low, medium, high) of the tissue type between donor and recipient

Analysis Plan

- ANOVA model

$$Y_{ij} = \mu_i + \epsilon_{ij}$$

$i = 1, 2, 3$ denoting low, medium, high groups,
respectively

$j = 1, 2, \dots, n_i$ denoting the j^{th} patient in the i^{th}
group

$$n_1 = 14, \quad n_2 = 13, \quad n_3 = 12$$

Y_{ij} survival time in days

μ_i mean survival time in patients with type i mismatch

Analysis Plan cont.

- Primary hypotheses of interest: all pairwise comparisons

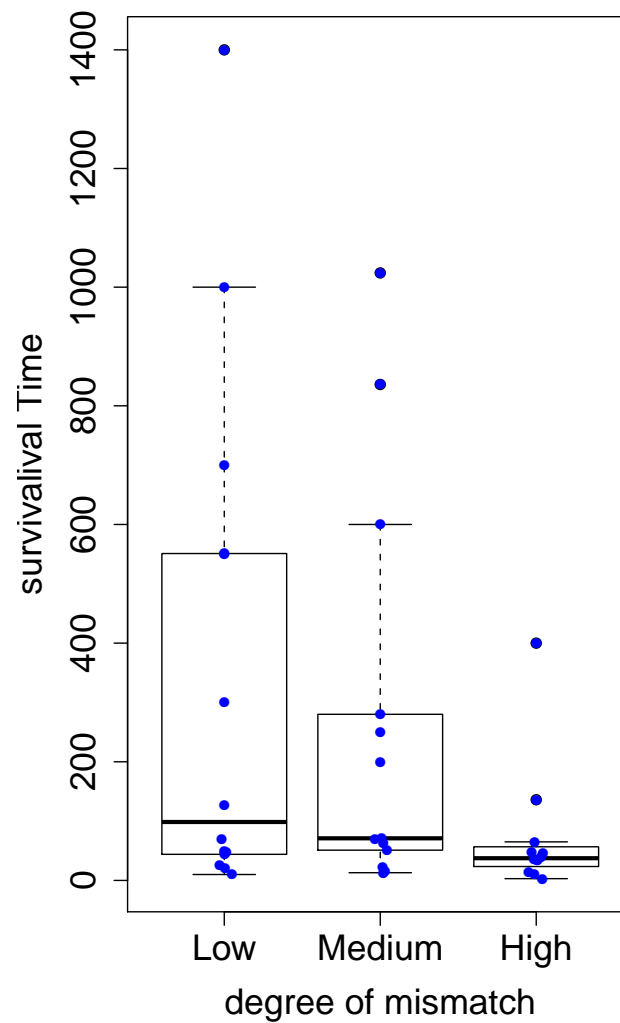
$$H_0 : \mu_1 = \mu_2, \quad H_0 : \mu_1 = \mu_3, \quad H_0 : \mu_2 = \mu_3$$

- Based on power considerations, decide $\alpha = 0.1$
- All pairwise comparisons using Tukey
- Further contrasts, group level means, etc. will be considered hypothesis generating/exploratory; thus no multiplicity adjustment
- Diagnostics, remedial measures, sensitivity analyses

Data

j	Low	Medium	High
1	44	15	3.0
2	551	280	136.0
3	127	1024	65.0
4	1400	836	400.0
5	1000	51	10.4
6	700	600	39.4
7	550	250	33.4
8	300	200	48.4
9	47	22	13.5
10	26	71	34.5
11	50	62	35.5
12	10	69	45.5
13	70	13	
14	20		

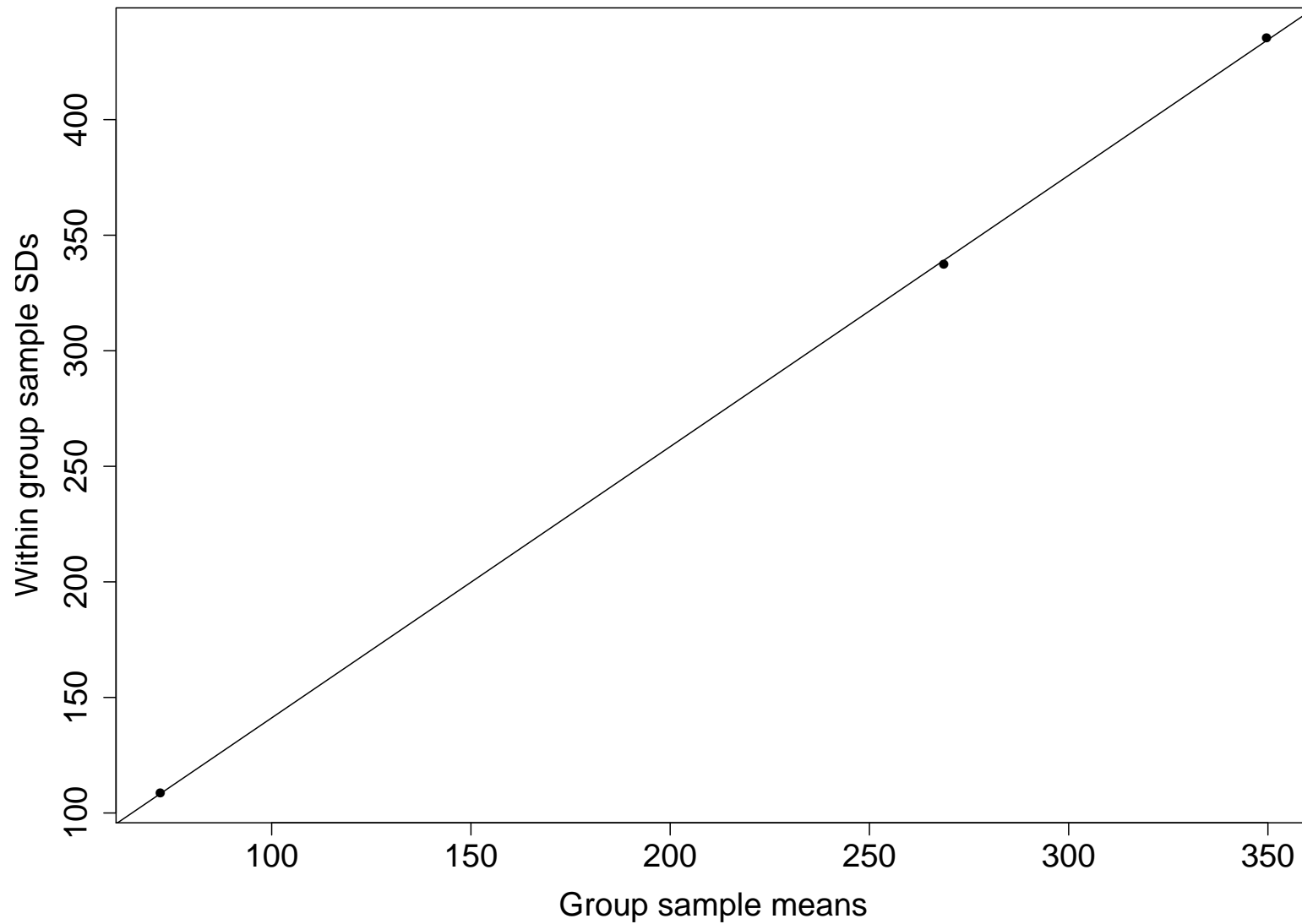
Boxplot With Raw Data



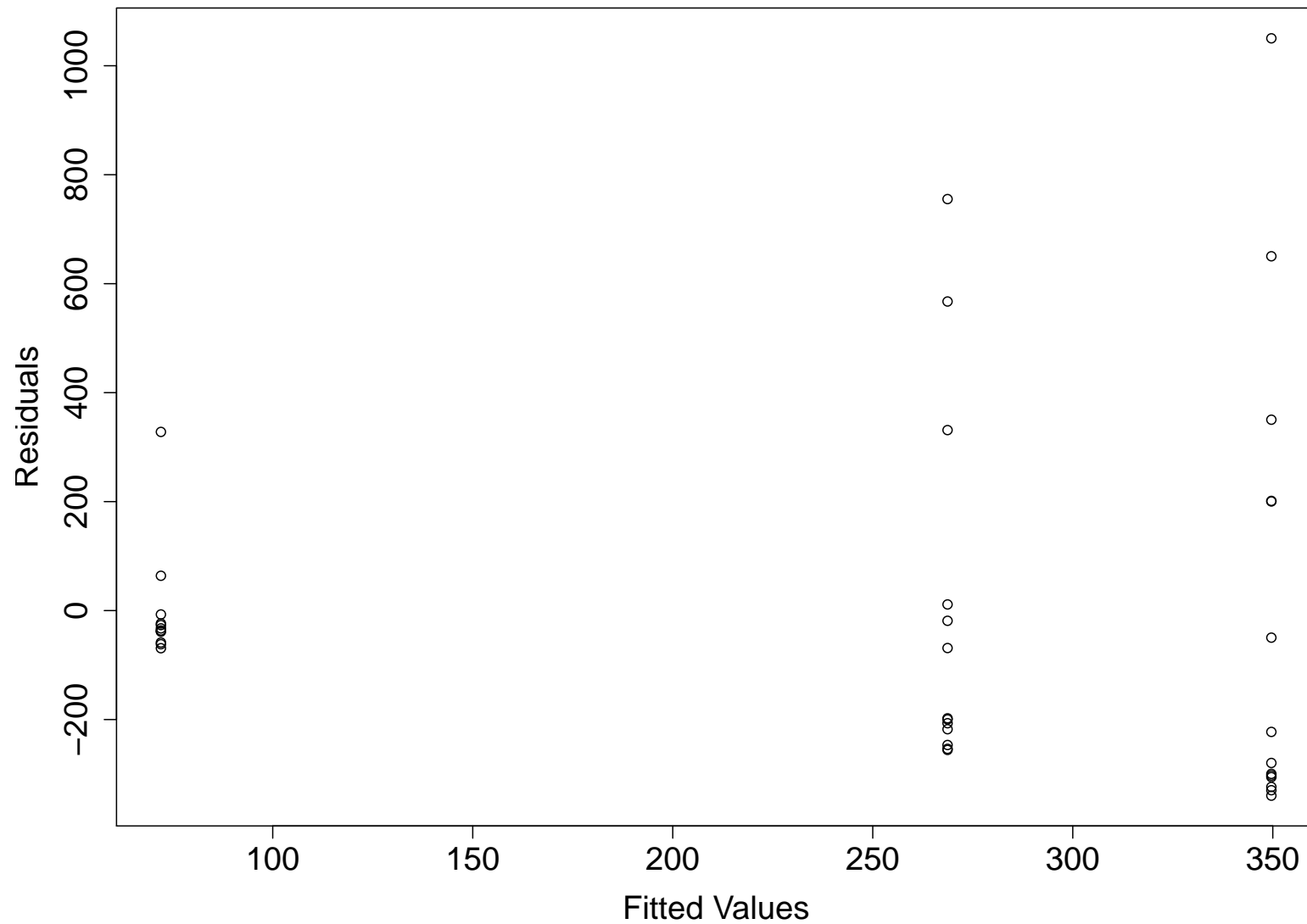
Summary Statistics

	Low	Medium	High
n	14	13	12
Mean	349.6	268.7	72.0
Median	98.5	71.0	37.5
SD	435.31	337.51	108.82
(Min, Max)	(10,1400)	(13, 1042)	(3,400)

Homogeneity of Variance Plot



Residual Plot



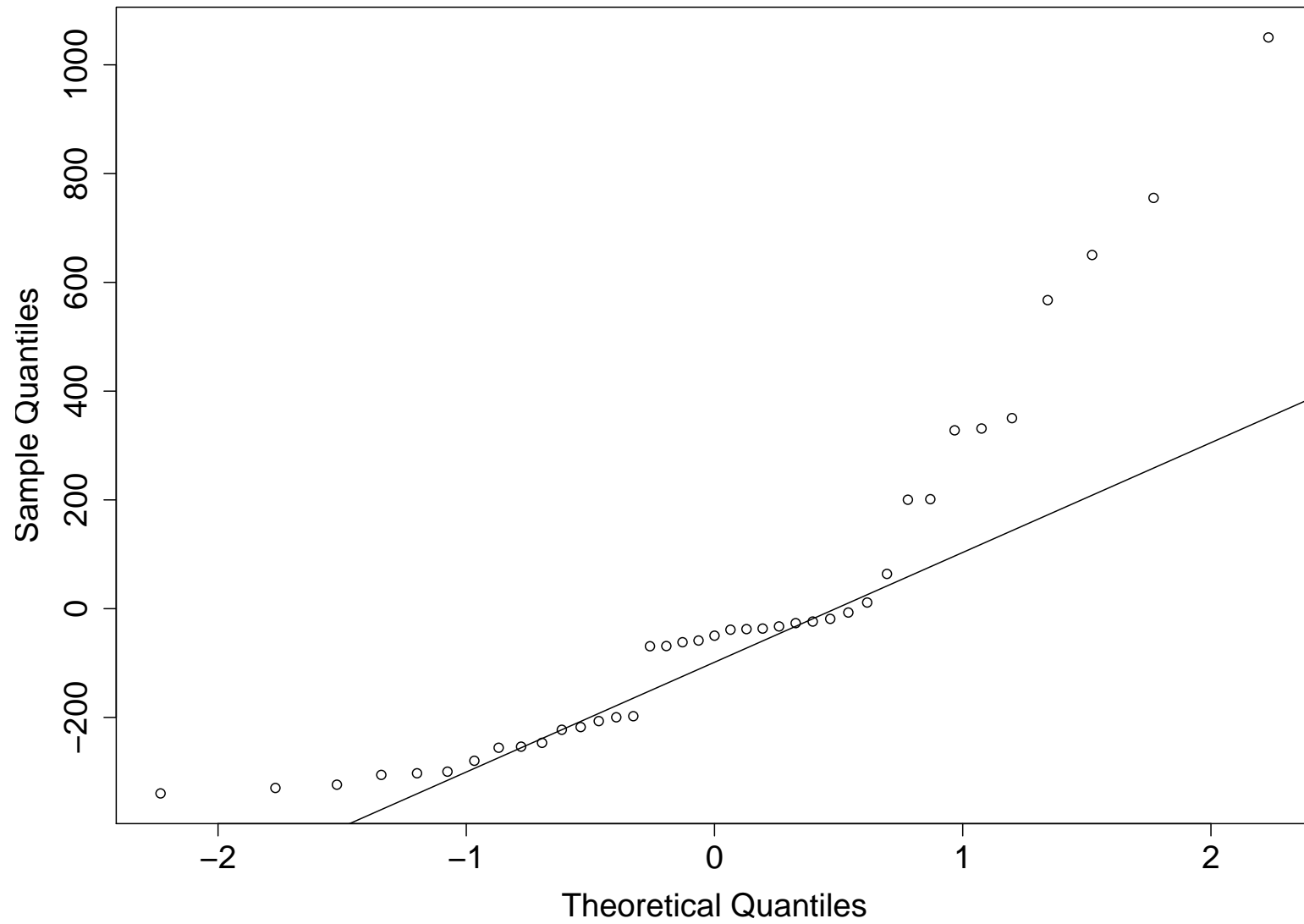
Modified Levene Test

Brown and Forsythe's Test for Homogeneity of survival Variance
ANOVA of Absolute Deviations from Group Medians

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
degree	2	452324	226162	2.46	0.0993
Error	36	3304203	91783.4		

QQ Plot

Normal Q-Q Plot



Box-Cox Transformation

- Recall: Family of transformations indexed by λ

$$Y_\lambda = \begin{cases} k_1(Y^\lambda - 1) & \text{for } \lambda \neq 0 \\ k_2 \log(Y) & \text{for } \lambda = 0 \end{cases}$$

where

$$k_2 = \left(\prod_{i,j} Y_{ij} \right)^{1/N} \quad \text{and} \quad k_1 = \frac{1}{\lambda k_2^{\lambda-1}}$$

- Choose λ that minimizes SSW
- SAS: macro on course website or proc transreg
R: MASS library, function boxcox()

Box-Cox Transformation

```
%macro boxcox(
    resp=,                /* name of response variable */
    model=,               /* independent variables in regression */
    id=,                  /* ID variable for observations */
    data=_last_,          /* input dataset */
    /* Various other parameters */
    lopower=-2,           /* low value for power */
    hipower=2,            /* high value for power */
    npower=21,            /* number of power values in interval */
    conf=0.95);           /* confidence coefficient of CI on power*/

data case_study;
    infile "anova_case.txt";
    input degree $ survival;

low=0; medium=0;
if degree="Low" then low=1;
if degree="Medium" then medium=1;

%boxcox(resp=survival,model=low medium,lopower=-2,hipower=2, npower=21);
%boxcox(resp=survival,model=low medium,lopower=-0.7,hipower=0.7, npower=15);
```

Box-Cox Transformation

Box-Cox Power (lambda)	Log Likelihood	Root mean squared error	0.95 Confidence Interval
-0.7	-209.436	214.896	
-0.6	-203.272	183.479	
-0.5	-198.035	160.423	
-0.4	-193.809	143.949	
-0.3	-190.648	132.742	
-0.2	-188.568	125.847	*
-0.1	-187.546	122.593	*
-0.0	-187.530	122.543	<+
0.1	-188.446	125.456	*
0.2	-190.213	131.268	
0.3	-192.746	140.080	
0.4	-195.970	152.149	
0.5	-199.812	167.904	
0.6	-204.212	187.955	
0.7	-209.113	213.124	

Box-Cox Transformation

```
proc transreg data=case_study ss2 pboxcoxtable details;  
  model boxcox(survival) = identity(low medium);
```

Box-Cox Transformation Information for survival

Lambda	R-Square	Log Like
-2.50	0.06	-390.086
-2.00	0.07	-333.778
-1.50	0.07	-280.235
-1.00	0.09	-232.441
-0.50	0.12	-198.035
0.00 +	0.14	-187.530 <
0.50	0.13	-199.812
1.00	0.12	-226.364
1.50	0.10	-261.488
2.00	0.09	-301.910
2.50	0.08	-345.720

< - Best Lambda

* - 95% Confidence Interval

+ - Convenient Lambda

Box-Cox Transformation

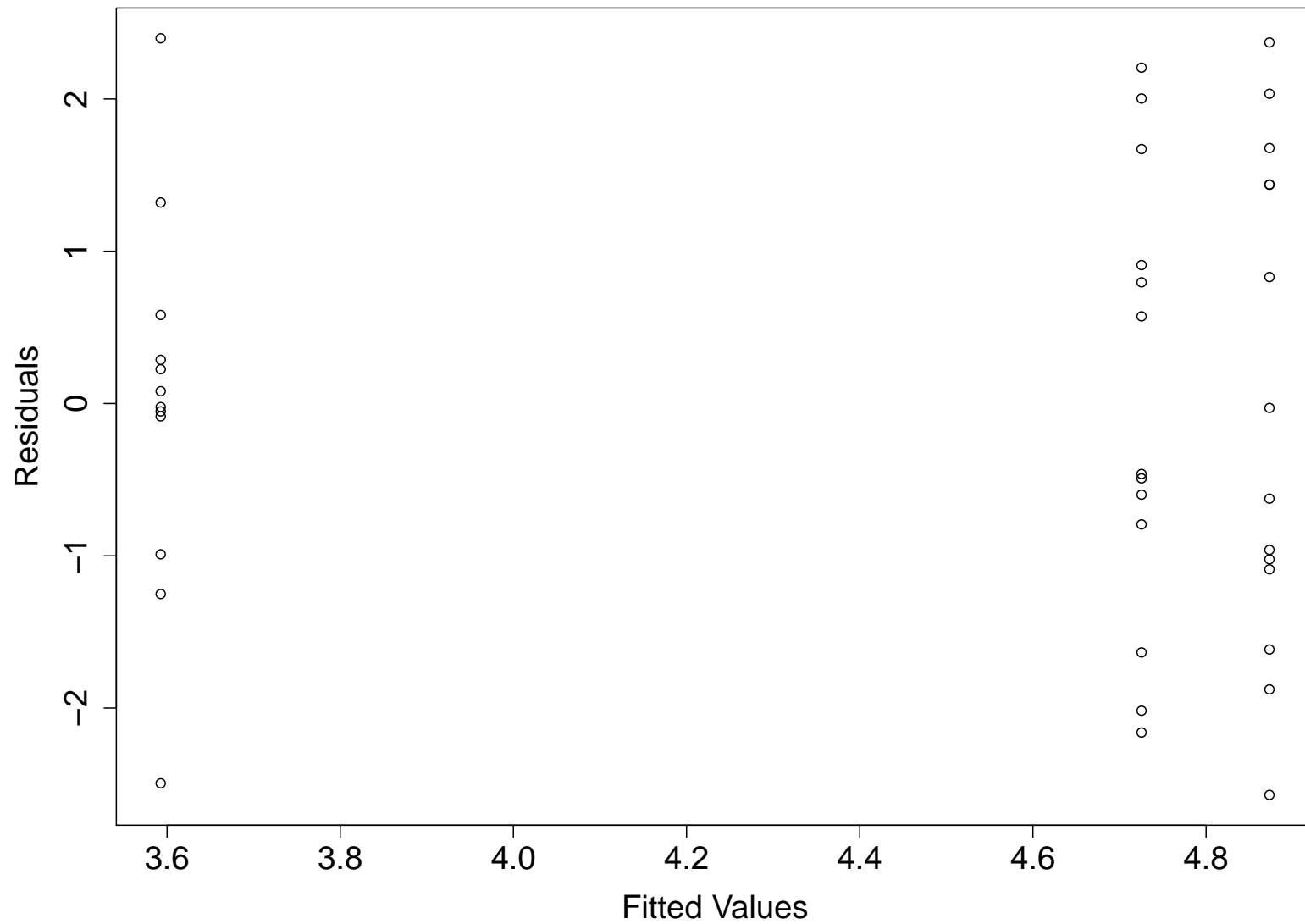
- Choose log transformation
- Run diagnostics again

Modified Levene Test

Brown and Forsythe's Test for Homogeneity of logsurvival Variance
ANOVA of Absolute Deviations from Group Medians

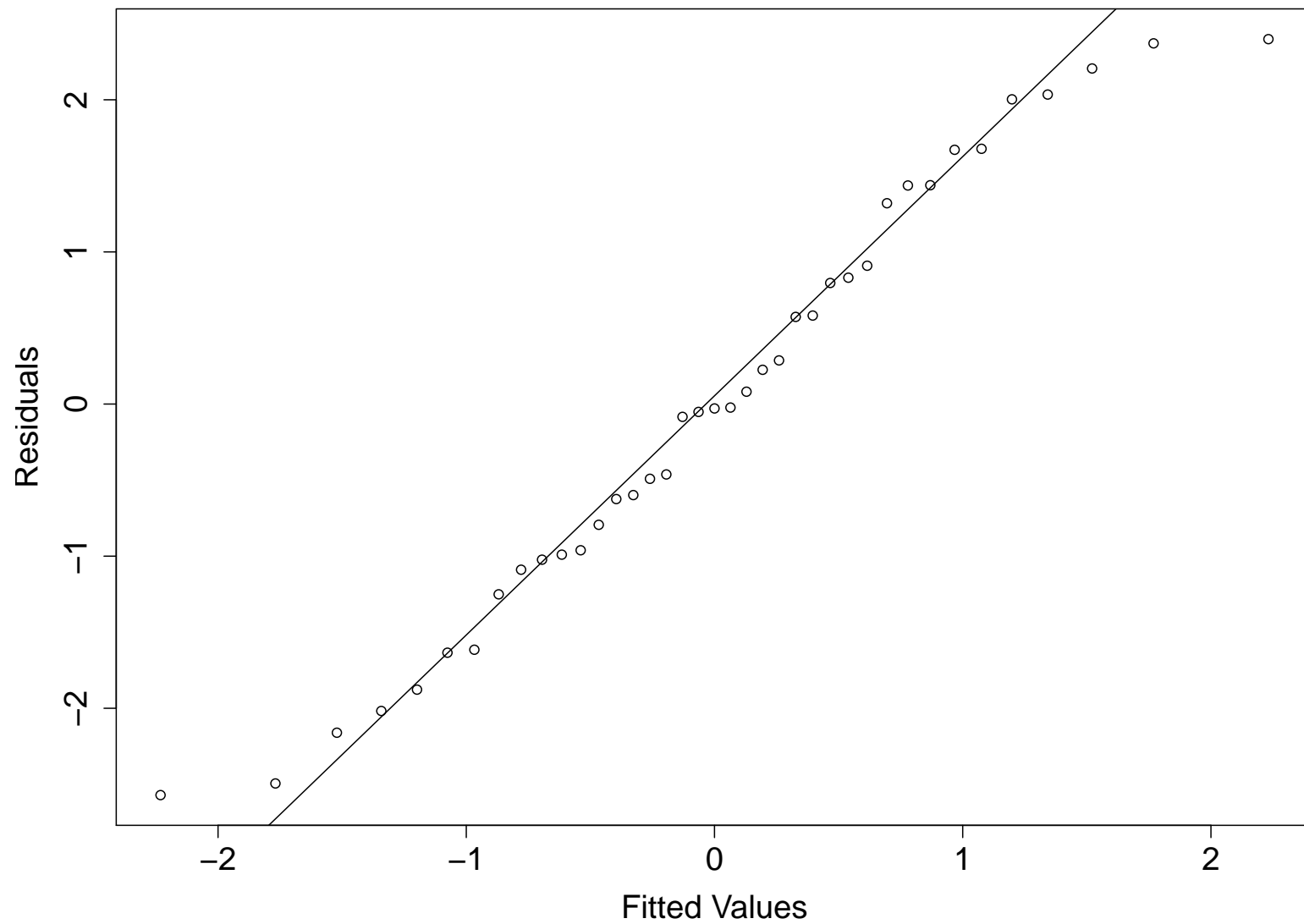
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
degree	2	2.2384	1.1192	1.52	0.2324
Error	36	26.5038	0.7362		

Residual Plot



QQ Plot

Normal Q-Q Plot



Tests for Normality

```
> fit <- aov(log(survival)~degree)
> qq <- qqnorm(fit$residuals,xlab="Fitted Values",ylab="Residuals")
> cor.test(qq$x,qq$y)
```

Pearson's product-moment correlation

sample estimates:

```
cor
0.9882992
```

```
> lillie.test(fit$residuals)
```

Lilliefors (Kolmogorov-Smirnov) normality test

```
data: fit$residuals
D = 0.0799, p-value = 0.766
```

```
> shapiro.test(fit$residuals)
```

```
data: fit$residuals
W = 0.9682, p-value = 0.3294
```

Box-Cox Transformation

- Diagnostics suggest adequate fit after log transformation
- Employ Tukey for all (3) pairwise comparisons of factor level means

Tukey Simultaneous 90% CIs

Tukey's Studentized Range (HSD) Test for logsurvival

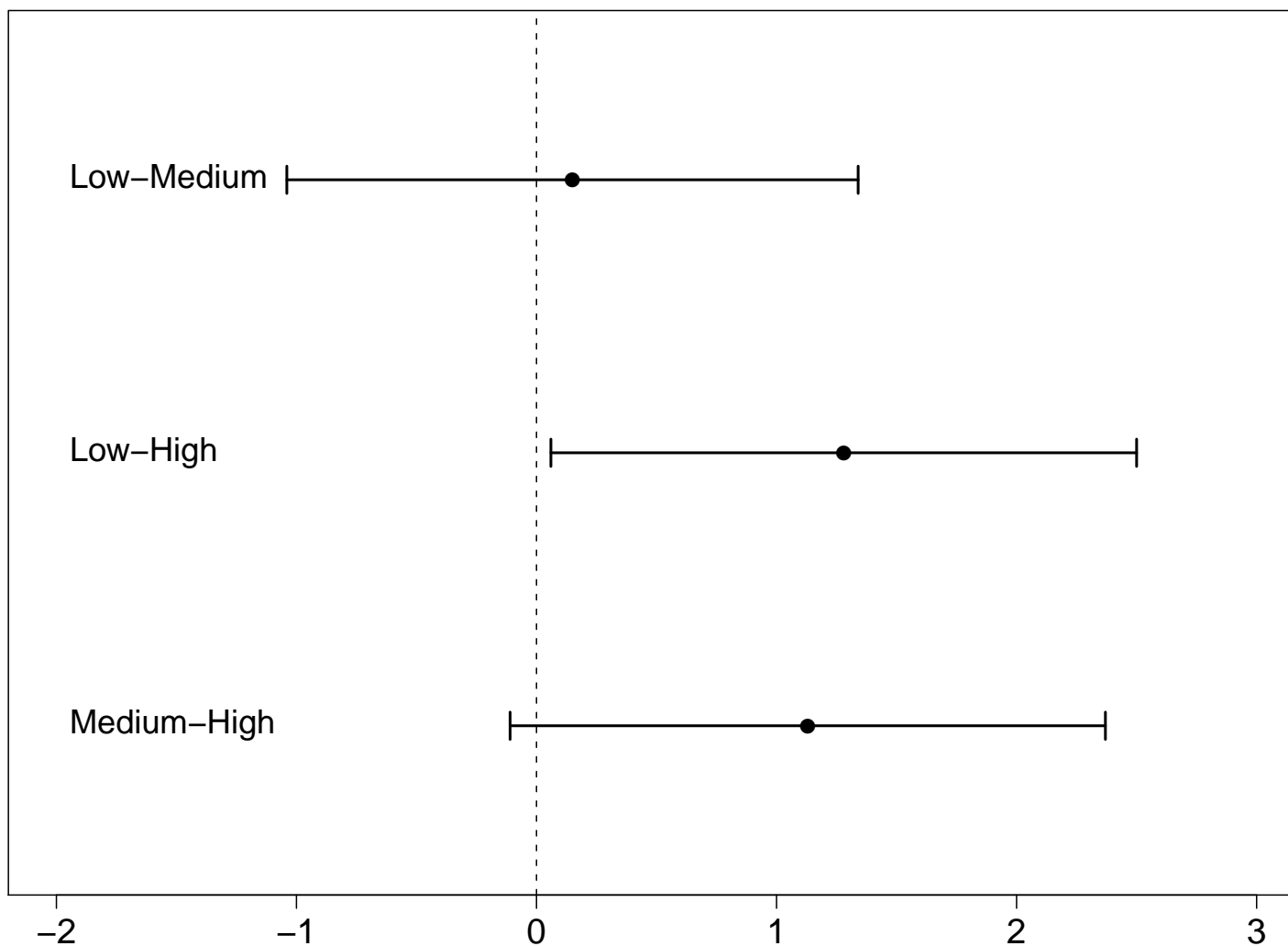
NOTE: This test controls the Type I experimentwise error rate.

Alpha	0.1
Error Degrees of Freedom	36
Error Mean Square	2.132024
Critical Value of Studentized Range	2.99758

Comparisons significant at the 0.1 level are indicated by ***.

		Difference			
degree		Between	Simultaneous 90%		
Comparison		Means	Confidence Limits		
Low	- Medium	0.1476	-1.0444	1.3397	
Low	- High	1.2805	0.0630	2.4980	***
Medium	- Low	-0.1476	-1.3397	1.0444	
Medium	- High	1.1329	-0.1061	2.3718	
High	- Low	-1.2805	-2.4980	-0.0630	***
High	- Medium	-1.1329	-2.3718	0.1061	

Tukey Simultaneous 90% CIs



Sensitivity Analyses: Bonferroni

Bonferroni (Dunn) t Tests for logsurvival

NOTE: This test controls the Type I experimentwise error rate, but it generally has a higher Type II error rate than Tukey's for all pairwise comparisons.

Comparisons significant at the 0.1 level are indicated by ***.

		Difference			
degree		Between	Simultaneous 90%		
Comparison		Means	Confidence Limits		
Low	- Medium	0.1476	-1.0969	1.3922	
Low	- High	1.2805	0.0094	2.5516	***
Medium	- Low	-0.1476	-1.3922	1.0969	
Medium	- High	1.1329	-0.1606	2.4263	
High	- Low	-1.2805	-2.5516	-0.0094	***
High	- Medium	-1.1329	-2.4263	0.1606	

Sensitivity Analyses: Wilcoxon Rank Sum

```
wilcox.test(low.survival,med.survival)
```

Wilcoxon rank sum test

W = 93, p-value = 0.943

alternative hypothesis: true location shift is not equal to 0

```
wilcox.test(low.survival,high.survival)
```

Wilcoxon rank sum test

W = 122, p-value = 0.05264

alternative hypothesis: true location shift is not equal to 0

```
wilcox.test(med.survival,high.survival)
```

Wilcoxon rank sum test

W = 115, p-value = 0.04571

alternative hypothesis: true location shift is not equal to 0

Contrasts

- It looks like low and medium degrees of mismatch are much better than a high degree of mismatch
- Consider using a contrast to test whether the mean survival time for patients with a high degree of mismatch differs from that of patients in the other two groups
- We want to test

$$H_0 : (\mu_1 + \mu_2)/2 - \mu_3 = 0 \quad \text{vs.} \quad H_A : (\mu_1 + \mu_2)/2 - \mu_3 \neq 0$$

- Letting $c_1 = 0.5$, $c_2 = 0.5$ and $c_3 = -1$, we have

$$L = \sum_{i=1}^3 c_i \mu_i \quad \text{with} \quad \sum_{i=1}^3 c_i = 0$$

Contrasts cont.

```
data case_study; set case_study;
logsurvival=log(survival);

if degree='Low' then mismatch=1;
  else if degree='Medium' then mismatch=2;
  else if degree='High' then mismatch=3;

proc glm data=case_study;
  class mismatch;
  model logsurvival = mismatch / clparm;
  estimate 'Low/med vs. high' mismatch 0.5 0.5 -1;
* or   contrast 'Low/med vs. high' mismatch 0.5 0.5 -1;
```

Parameter	Estimate	Standard Error	t Value	Pr > t	95% Conf. Limits	
Low/med vs. high	1.20668	0.50670	2.38	0.0227	0.1791	2.2343

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
Low/med vs. high	1	12.09150	12.09150	5.67	0.0227

Conclusions

- Conclude there is evidence of a marginally significant difference in mean log survival times between low and high (although not totally consistent across sensitivity analyses)
 - How to quantify/interpret on log scale?
 - Power of study to detect what size effects?
- Alternative analysis to test for trend?