Categorical Response Variables and the Incidental Parameters Problem

Statistics 516, Homework 5 (Solutions)

Lip Cancer in Scotland: The Random Effect of District

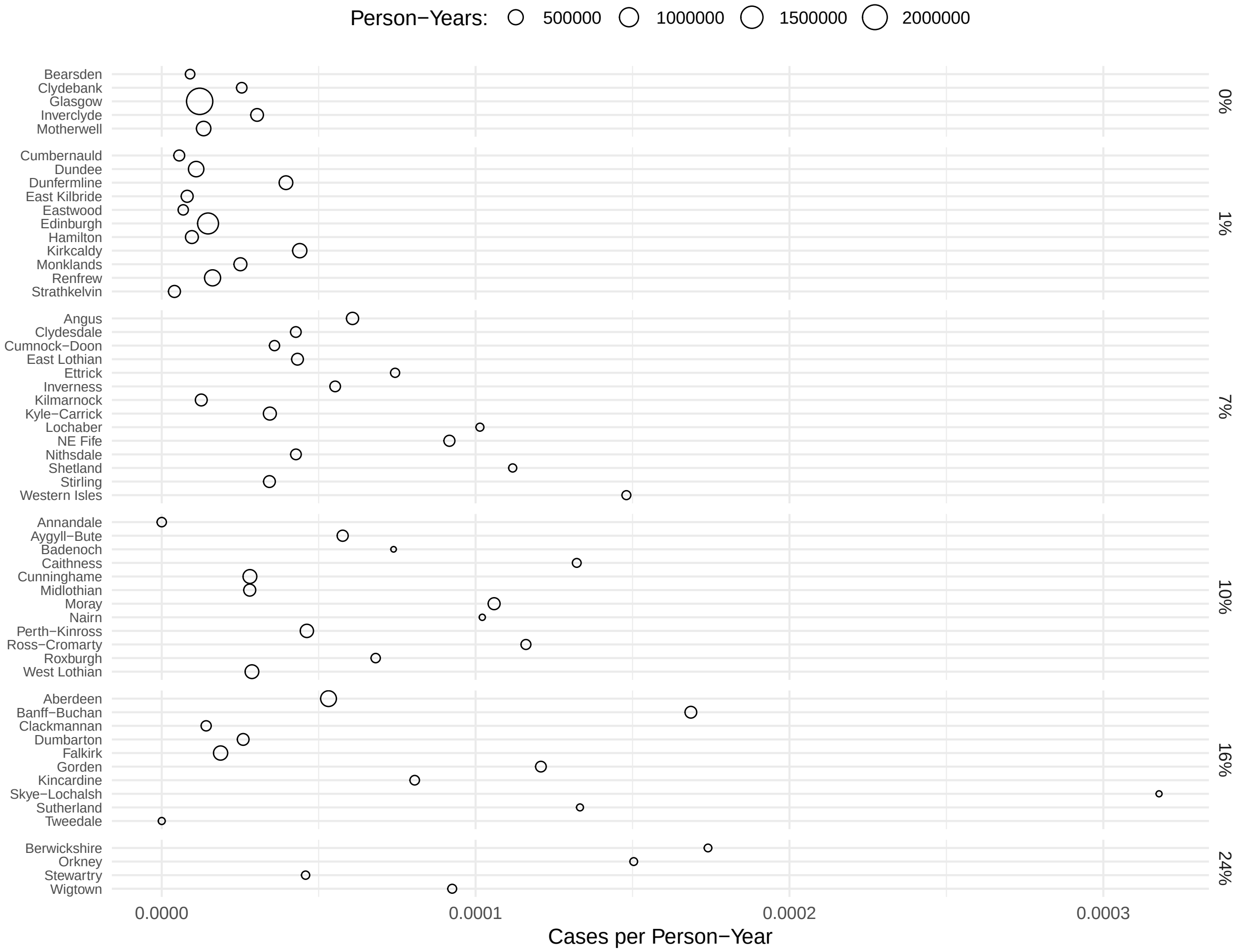
Recall the model for the lip cancer data from Scotland used in the third and fourth homework assignments. Here again is the code to process and plot the raw data showing the observed rate of lip cancer per person-year by percent of the population engaged in outdoor activity.

```r
library(epiR)
library(dplyr)
library(ggplot2)

data(epi.SClip)

lipcancer <- epi.SClip %>%
  mutate(district = factor(district, levels = rev(sort(unique(district))))) %>%
  mutate(percent = paste(prop.ag, "%", sep = "")) %>%
  mutate(percent = reorder(percent, prop.ag)) %>%
  select(district, cases, population, percent)

p <- ggplot(lipcancer, aes(y = district, x = cases/population)) +
  theme_minimal() + geom_point(aes(size = population), shape = 21) +
  facet_grid(percent ~ ., scales = "free_y", space = "free_y") +
  labs(y = NULL, x = "Cases per Person-Year", size = "Person-Years:") +
  scale_x_continuous(labels = scales::label_number()) +
  theme(axis.text.y = element_text(size = 7), legend.position = "top")
plot(p)
```



In the previous homework assignment you noted that there may be some over-dispersion which may be due to variation in the lip cancer rate over districts other than that accounted for by the percent of the population engaged in outdoor activity. To account for that over-dispersion you used a quasi-likelihood approach to "adjust" inferences to the over-dispersion. Another approach that could be used is to specify the effect of district as a *random effect*.[1]

1. Estimate a Poisson regression model like you did in the third homework assignment, but this time specifying a random "main effect" for district. Report the model parameter estimates and standard errors using `summary` or `lincon` so that I can verify that you estimated the model correctly.

   Solution: Here is how to estimate this mixed effects model.

   ```
   library(lme4)
   m <- glmer(cases ~ percent + offset(log(population)) + (1 | district),
     family = poisson, data = lipcancer)
   summary(m)
   ```

   ```
   Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
    Family: poisson  ( log )
   Formula: cases ~ percent + offset(log(population)) + (1 | district)
      Data: lipcancer
   ```

[1] In most cases when random effects are specified there are two or more observations per level of the factor(s) that define the random effect(s). Specifying the random effects can then help account for a lack of independence of observations from the same experimental/observational unit. But in some cases like this one a random effect can induce over-dispersion without dependencies among the observations because there is only one observation per unit.

```
     AIC      BIC   logLik deviance df.resid
   355.7    369.9   -170.9    341.7       49

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.5491 -0.4031 -0.0435  0.4107  1.4272

Random effects:
 Groups   Name        Variance Std.Dev.
 district (Intercept) 0.339    0.582
Number of obs: 56, groups:  district, 56

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -11.0362     0.3251  -33.95  < 2e-16 ***
percent1%    -0.0687     0.3932   -0.17  0.86127
percent7%     1.1837     0.3723    3.18  0.00148 **
percent10%    1.1775     0.3821    3.08  0.00206 **
percent16%    1.3654     0.3915    3.49  0.00049 ***
percent24%    1.8539     0.4770    3.89  0.00010 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
           (Intr) prcn1% prcn7% prc10% prc16%
percent1%  -0.825
percent7%  -0.873  0.722
percent10% -0.850  0.704  0.743
percent16% -0.830  0.688  0.725  0.707
percent24% -0.681  0.564  0.595  0.580  0.566
```

```
trtools::lincon(m)
```

```
             estimate     se    lower   upper   tvalue  df     pvalue
(Intercept) -11.03624 0.3251 -11.6734 -10.399 -33.9482 Inf 1.296e-252
percent1%    -0.06872 0.3932  -0.8395   0.702  -0.1748 Inf  8.613e-01
percent7%     1.18368 0.3723   0.4540   1.913   3.1793 Inf  1.476e-03
percent10%    1.17750 0.3821   0.4286   1.926   3.0818 Inf  2.058e-03
percent16%    1.36544 0.3915   0.5980   2.133   3.4874 Inf  4.878e-04
percent24%    1.85392 0.4770   0.9191   2.789   3.8869 Inf  1.016e-04
```

2. Using `contrast` or the **emmeans** package, estimate the expected number of cases of lip cancer per 100K person-years for each value of the percent of the population spent in outdoor activities.

   Solution: Here are the estimated rates of cases of lip cancer (per 100K person-years).

```
library(emmeans)
emmeans(m, ~percent, type = "response", offset = log(100000))
```

```
 percent rate    SE  df asymp.LCL asymp.UCL
 0%      1.61 0.524 Inf     0.852      3.05
 1%      1.50 0.334 Inf     0.973      2.32
 7%      5.26 0.956 Inf     3.685      7.51
 10%     5.23 1.051 Inf     3.526      7.75
 16%     6.31 1.379 Inf     4.111      9.69
 24%      10.28 3.591 Inf      5.187     20.39

Confidence level used: 0.95 
Intervals are back-transformed from the log scale 
```

3. In the third homework assignment I asked you to estimate and interpret rate ratios that compared the rate of lip cancer at 1%, 7%, 10%, 16%, and 24% versus 0% of the population involved in outdoor activity. This time estimate and interpret rate ratios that compare *consecutive* values of the percent of the population involved in outdoor activity (i.e., 0% versus 1%, 1% versus 7%, 7% versus 10%, and so on).

   Solution: I will show you a couple of ways to do this. One is to use `contrast`.

```
trtools::contrast(m, tf = exp,
  a = list(percent = c("1%","7%","10%","16%","24%"), population = 1),
  b = list(percent = c("0%","1%","7%","10%","16%"), population = 1),
  cnames = c("1% vs 0%", "7% vs 1%", "10% vs 7%", "16% vs 10%", "24% vs 16%"))
```

```
           estimate  lower upper
1% vs 0%     0.9336 0.4319 2.018
7% vs 1%     3.4987 1.9964 6.132
10% vs 7%    0.9938 0.5846 1.689
16% vs 10%   1.2068 0.6750 2.157
24% vs 16%   1.6298 0.7275 3.651
```

   With a little programming effort we can avoid so much tedious typing.

```
pa <- sort(unique(lipcancer$percent))[2:6]
pb <- sort(unique(lipcancer$percent))[1:5]
trtools::contrast(m, tf = exp,
  a = list(percent = pa, population = 1),
  b = list(percent = pb, population = 1),
  cnames = paste(pa, "vs", pb))
```

```
           estimate  lower upper
1% vs 0%     0.9336 0.4319 2.018
7% vs 1%     3.4987 1.9964 6.132
10% vs 7%    0.9938 0.5846 1.689
16% vs 10%   1.2068 0.6750 2.157
24% vs 16%   1.6298 0.7275 3.651
```

   The `contrast` function in the **emmeans** package can also be used to do consecutive paired comparisons.

```
emmeans::contrast(emmeans(m, ~percent, offset = log(1), type = "response"),
  method = "consec", infer = TRUE, adjust = "none")
```

```
 contrast  ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 1% / 0%   0.934 0.367 Inf     0.432      2.02    1  -0.175  0.8613
 7% / 1%   3.499 1.002 Inf     1.996      6.13    1   4.375  <.0001
 10% / 7%  0.994 0.269 Inf     0.585      1.69    1  -0.023  0.9818
 16% / 10% 1.207 0.358 Inf     0.675      2.16    1   0.634  0.5261
 24% / 16% 1.630 0.671 Inf     0.728      3.65    1   1.187  0.2353

Confidence level used: 0.95 
Intervals are back-transformed from the log scale 
Tests are performed on the log scale 
```

   Here is shortcut that gives both the estimated rates and consecutive pairwise comparisons.

```r
emmeans(m, consec ~ percent, offset = log(100000),
  type = "response", infer = TRUE, adjust = "none")
```

```
$emmeans
 percent  rate    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 0%       1.61 0.524 Inf     0.852      3.05    1   1.466  0.1426
 1%       1.50 0.334 Inf     0.973      2.32    1   1.838  0.0661
 7%       5.26 0.956 Inf     3.685      7.51    1   9.142  <.0001
 10%      5.23 1.051 Inf     3.526      7.75    1   8.229  <.0001
 16%      6.31 1.379 Inf     4.111      9.69    1   8.426  <.0001
 24%     10.28 3.591 Inf     5.187     20.39    1   6.675  <.0001

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale

$contrasts
 contrast  ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 1% / 0%   0.934 0.367 Inf     0.432      2.02    1  -0.175  0.8613
 7% / 1%   3.499 1.002 Inf     1.996      6.13    1   4.375  <.0001
 10% / 7%  0.994 0.269 Inf     0.585      1.69    1  -0.023  0.9818
 16% / 10% 1.207 0.358 Inf     0.675      2.16    1   0.634  0.5261
 24% / 16% 1.630 0.671 Inf     0.728      3.65    1   1.187  0.2353

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

Note that the value of the offset does not affect the rate ratios, but it does affect the estimated rates as I had to specify it here to give the estimated number of cases of lip cancer per 100K person-years. Here is how we could interpret these rate ratios.

The estimated rate of cases of lip cancer is about 6.6% less at 1% percent of the population engaged in outdoor activity than it is at 0%.

The estimated rate of cases of lip cancer is about 3.5 times higher (250% higher) at 7% percent of the population engaged in outdoor activity than it is at 1%.

The estimated rate of cases of lip cancer is about 1% less at 10% percent of the population engaged in outdoor activity than it is at 7%.

The estimated rate of cases of lip cancer is about 1.21 times higher (21% higher) at 16% percent of the population engaged in outdoor activity than it is at 10%.

The estimated rate of cases of lip cancer is about 1.63 times higher (63% higher) at 24% percent of the population engaged in outdoor activity than it is at 16%.

It may be worth noting that only one of these rate ratios is statistically significant at conventional significance levels. We can also "flip" the rate ratios to put the lower percent in the numerator of the ratio.

```r
emmeans(m, consec ~ percent, offset = log(100000),
  type = "response", infer = TRUE, adjust = "none", reverse = TRUE)$contrasts
```

```
 contrast  ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 0% / 1%   1.071 0.4212 Inf     0.496     2.315    1   0.175  0.8613
 1% / 7%   0.286 0.0818 Inf     0.163     0.501    1  -4.375  <.0001
 7% / 10%  1.006 0.2724 Inf     0.592     1.710    1   0.023  0.9818
 10% / 16% 0.829 0.2456 Inf     0.464     1.481    1  -0.634  0.5261
 16% / 24% 0.614 0.2525 Inf     0.274     1.375    1  -1.187  0.2353

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

We can interpret these rate ratios as follows.

The estimated rate of cases of lip cancer is about 1.07 times higher (7% higher) at 0% percent of the population engaged in outdoor activity than it is at 1%.

The estimated rate of cases of lip cancer is about 73% lower at 1% percent of the population engaged in outdoor activity than it is at 7%.

The estimated rate of cases of lip cancer is about 1.006 times higher (0.6% higher) at 7% percent of the population engaged in outdoor activity than it is at 10%.

The estimated rate of cases of lip cancer is about 17% lower at 10% percent of the population engaged in outdoor activity than it is at 16%.

The estimated rate of cases of lip cancer is about 39% lower at 16% percent of the population engaged in outdoor activity than it is at 24%.

Comparing Methods of Measuring Blood Oxygen Saturation

The data frame ox in the **MethComp** package is from a study comparing two methods of measuring blood oxygen saturation: chemical analysis or using a pulse oximeter.[2] Measurements were taken using both methods for each of 61 children. Multiple readings (replicates) were taken using each method in quick succession. For most children there were three replicates per method for a total of six measurements per child. Here are first few observations, sorted by the child (item).

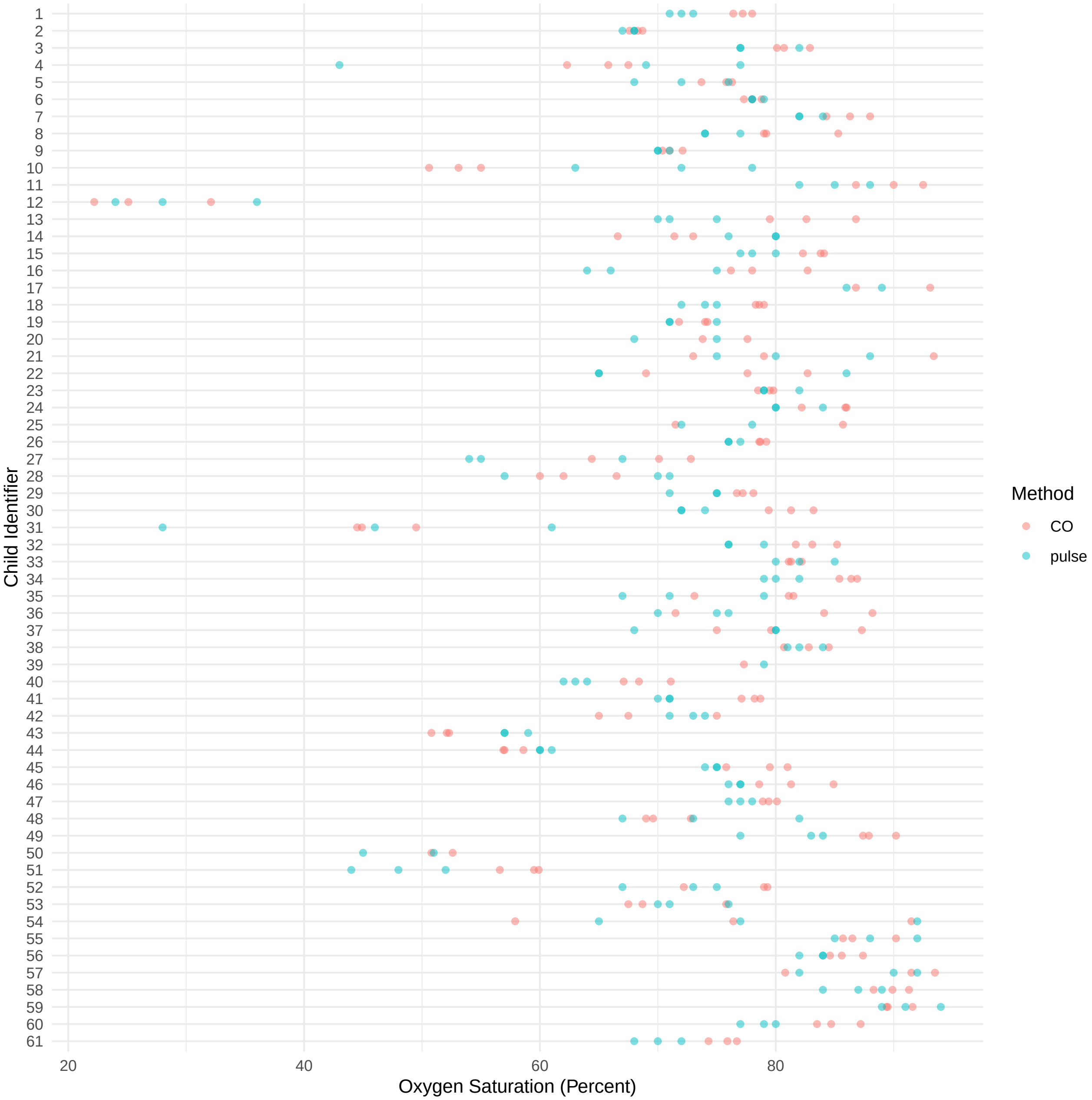
```
library(dplyr)
library(tibble) # to use the remove_rownames function
library(MethComp)
data(ox)
ox <- ox %>% arrange(item) %>% remove_rownames()
head(ox, 12)
```

```
    meth item repl    y
1     CO    1    1 78.0
2     CO    1    2 76.4
3     CO    1    3 77.2
4  pulse    1    1 71.0
5  pulse    1    2 72.0
6  pulse    1    3 73.0
7     CO    2    1 68.7
8     CO    2    2 67.6
9     CO    2    3 68.3
10 pulse    2    1 68.0
11 pulse    2    2 67.0
12 pulse    2    3 68.0
```

Note that here meth is the method of measuring oxygen saturation (CO is chemical analysis and pulse is pulse oximeter), item identifies the child, repl is the replicate, and y is the measurement of oxygen saturation. The plot below shows the raw data.

[2] Source: Carstensen, B. (2010). *Comparing clinical measurement methods: A practical guide.* Wiley.

```
library(ggplot2)
p <- ggplot(ox, aes(y = factor(item), x = y, color = meth)) +
  theme_minimal() + geom_point(alpha = 0.5) + scale_y_discrete(limits = rev) +
  labs(y = "Child Identifier", x = "Oxygen Saturation (Percent)", color = "Method")
plot(p)
```



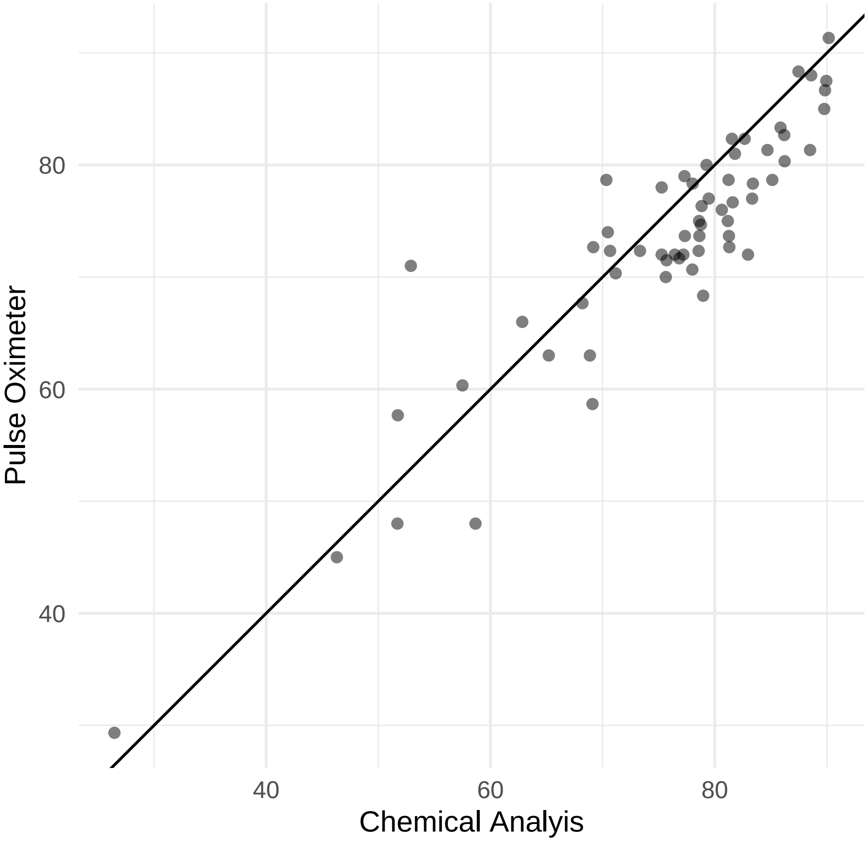
The plot shows some evidence of an "effect" for the child — i.e., children may naturally vary with respect to their average blood oxygen saturation. This can induce a lack of independence of the observations among those from the same child. We can also see this in a scatter plot of the average measurement for each child by method.[3]

[3] Using `coord_fixed()` forces a one-to-one aspect ratio of the axes, which is appropriate here since they are on the same scale.

```
library(tidyr) # to use the pivot_wider function
oxaverages <- ox %>% group_by(item, meth) %>%
  summarize(y = mean(y)) %>% pivot_wider(names_from = meth, values_from = y)

p <- ggplot(oxaverages, aes(x = CO, y = pulse)) + theme_minimal() +
  geom_abline(intercept = 0, slope = 1) +
  geom_point(alpha = 0.5) + coord_fixed() +
  labs(x = "Chemical Analyis", y = "Pulse Oximeter")

plot(p)
```



The lack of independence is suggested by the strong correlation between the average measurements. Here you will consider some different ways to account for this (or not).

1. Estimate the following four linear models with the oxygen saturation measurement as the response variable and the method of measurement as an explanatory variable: a model that ignores the effect of child (using the `lm` function), a marginal model estimated using generalized estimating equations that attempts to account for the lack of independence of observations from the same child (using the `geeglm` function), a fixed effects model with child used as a factor explanatory variable (using the `lm` function), and a mixed effects model with a random “main effect” for child (using the `lmer` function). For each model report the parameter estimates and standard errors using either the `summary` or `lincon` function so that I can verify that you estimated the model correctly. When using `geeglm` be sure to use the *sorted* data frame (see the code above) and an exchangeable correlation structure.

   Solution: First here is the model with no effect for child.

   ```
   m1 <- lm(y ~ meth, data = ox)
   trtools::lincon(m1)
   ```

```
            estimate     se  lower    upper tvalue  df     pvalue
(Intercept)   75.658 0.9002 73.888 77.42864 84.046 352 4.824e-235
methpulse     -2.477 1.2731 -4.981  0.02639 -1.946 352  5.245e-02
```

Here is the marginal model (note that the normal distribution and identity link function are the defaults).

```
library(geepack)
m2 <- geeglm(y ~ meth, family = gaussian(link = identity),
  id = item, corstr = "exchangeable", data = ox)
trtools::lincon(m2)
```

```
            estimate     se  lower  upper tvalue  df     pvalue
(Intercept)   75.650 1.5175 72.665 78.634  49.85 352 1.381e-161
methpulse     -2.477 0.6385 -3.733 -1.222  -3.88 352  1.248e-04
```

Here is the fixed effects model with a fixed effect for child. Note that I have trimmed the output a bit since there are 60 indicator variables for 61 levels of `item`.

```
m3 <- lm(y ~ meth + factor(item), data = ox)
trtools::lincon(m3)[1:5,]
```

```
              estimate     se    lower  upper tvalue  df     pvalue
(Intercept)     75.839 2.0553  71.7937 79.884 36.900 292 5.841e-112
methpulse       -2.477 0.5307  -3.5218 -1.433 -4.668 292  4.632e-06
factor(item)2   -6.667 2.8823 -12.3393 -0.994 -2.313 292  2.142e-02
factor(item)3    5.350 2.8823  -0.3227 11.023  1.856 292  6.444e-02
factor(item)4  -10.500 2.8823 -16.1727 -4.827 -3.643 292  3.188e-04
```

And here is the mixed effects model.

```
m4 <- lmer(y ~ meth + (1 | item), data = ox)
trtools::lincon(m4)
```

```
            estimate     se  lower  upper tvalue  df    pvalue
(Intercept)   75.650 1.4546 72.799 78.501 52.009 Inf 0.000e+00
methpulse     -2.477 0.5307 -3.517 -1.437 -4.669 Inf 3.033e-06
```

2. For each of the four models you estimated above, estimate (a) the expected blood oxygen saturation observed for each method, and (b) the difference in the expected blood oxygen saturation between the two methods. This can be done using `lincon`, `contrast`, or with the **emmeans** package, but be sure that you provide estimates and standard errors.

   Solution: I will use the **emmeans** package. I am going to use a shortcut that provides the answers to both (a) and (b).

```
emmeans(m1, pairwise ~ meth, infer = TRUE) # ignore
```

```
$emmeans
 meth  emmean  SE  df lower.CL upper.CL t.ratio p.value
 CO      75.7 0.9 352     73.9     77.4  84.050  <.0001
 pulse   73.2 0.9 352     71.4     75.0  81.290  <.0001

Confidence level used: 0.95 

$contrasts
 contrast   estimate   SE  df lower.CL upper.CL t.ratio p.value
 CO - pulse     2.48 1.27 352  -0.0264     4.98   1.946  0.0524

Confidence level used: 0.95 
```

```r
emmeans(m2, pairwise ~ meth, infer = TRUE) # marginal
```

```
$emmeans
 meth  emmean   SE  df asymp.LCL asymp.UCL z.ratio p.value
 CO      75.7 1.52 Inf      72.7      78.6  49.850  <.0001
 pulse   73.2 1.39 Inf      70.5      75.9  52.740  <.0001

Covariance estimate used: vbeta
Confidence level used: 0.95

$contrasts
 contrast   estimate    SE  df asymp.LCL asymp.UCL z.ratio p.value
 CO - pulse     2.48 0.638 Inf      1.23      3.73   3.880  0.0001

Confidence level used: 0.95
```

```r
emmeans(m3, pairwise ~ meth, infer = TRUE) # fixed effect
```

```
$emmeans
 meth  emmean    SE  df lower.CL upper.CL t.ratio p.value
 CO      75.7 0.378 292     74.9     76.4 200.080  <.0001
 pulse   73.2 0.378 292     72.4     73.9 193.530  <.0001

Results are averaged over the levels of: item
Confidence level used: 0.95

$contrasts
 contrast   estimate    SE  df lower.CL upper.CL t.ratio p.value
 CO - pulse     2.48 0.531 292     1.43     3.52   4.668  <.0001

Results are averaged over the levels of: item
Confidence level used: 0.95
```

```r
emmeans(m4, pairwise ~ meth, infer = TRUE) # random effect
```

```
$emmeans
 meth  emmean   SE   df lower.CL upper.CL t.ratio p.value
 CO      75.7 1.45 64.2     72.7     78.6  52.010  <.0001
 pulse   73.2 1.45 64.2     70.3     76.1  50.310  <.0001

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95

$contrasts
 contrast   estimate    SE  df lower.CL upper.CL t.ratio p.value
 CO - pulse     2.48 0.531 292     1.43     3.52   4.669  <.0001

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95
```

Note that for the fixed effects model the estimates of the expected blood oxygen saturation for each method are *averaged* over the children. They can vary from child to child as seen below which shows the estimates for the first three children.

```r
emmeans(m3, ~ meth | item, at = list(item = 1:3))
```

```
item = 1:
 meth  emmean   SE  df lower.CL upper.CL
 CO      75.8 2.06 292     71.8     79.9
 pulse   73.4 2.06 292     69.3     77.4

item = 2:
 meth  emmean   SE  df lower.CL upper.CL
 CO      69.2 2.06 292     65.1     73.2
 pulse   66.7 2.06 292     62.6     70.7

item = 3:
 meth  emmean   SE  df lower.CL upper.CL
 CO      81.2 2.06 292     77.1     85.2
 pulse   78.7 2.06 292     74.7     82.8

Confidence level used: 0.95
```

The estimate of the differences in these expectations, however, do not depend on the child.

```
emmeans(m3, pairwise ~ meth | item,
  at = list(item = 1:3), infer = TRUE)$contrast
```

```
item = 1:
 contrast   estimate    SE  df lower.CL upper.CL t.ratio p.value
 CO - pulse     2.48 0.531 292     1.43     3.52   4.668  <.0001

item = 2:
 contrast   estimate    SE  df lower.CL upper.CL t.ratio p.value
 CO - pulse     2.48 0.531 292     1.43     3.52   4.668  <.0001

item = 3:
 contrast   estimate    SE  df lower.CL upper.CL t.ratio p.value
 CO - pulse     2.48 0.531 292     1.43     3.52   4.668  <.0001

Confidence level used: 0.95
```

3. Compare the parameter estimates and standard errors you obtained for the quantities you estimated in the previous problem across the four models. Discuss briefly what did and did not change (much).

   Solution: The estimates of β_0 and β_1 are very similar across the four method, but there are some differences in the standard errors. This is also true when estimating the expected response for each method and the difference in the expected response between these two methods. The standard errors from the first approach which ignores the effect of child, which tend to be smaller for the expected response but larger for the difference, should not be trusted. The standard errors for the difference in the expected response between the two methods are more similar across the other approaches. The standard errors for the expected response are relatively similar between the marginal and mixed effects approaches. The standard error for the expected response for the fixed effects approach depend heavily on if we are making inferences for a given child or the average response across all children in the study.

4. Estimate a linear mixed effects model that specifies an *interaction* between the child and the method of measurement as a second random effect. Report the parameter estimates and standard errors, and estimate the quantities that you estimated in the second problem now using this model.

   Solution: Here is the estimated mixed effects model with the interaction.

```
m5 <- lmer(y ~ meth + (meth | item), data = ox)
trtools::lincon(m5)
```

```
            estimate     se  lower  upper tvalue  df    pvalue
(Intercept)   75.649 1.5285 72.653 78.645 49.493 Inf 0.0000000
methpulse     -2.476 0.6382 -3.727 -1.225 -3.879 Inf 0.0001047
```

Note that `(meth | item)` is the same thing as `(meth | item)`. The random "main effect" is implied. Here are the estimated quantities.

```
emmeans(m5, pairwise ~ meth, infer = TRUE)
```

```
$emmeans
 meth  emmean   SE df lower.CL upper.CL t.ratio p.value
 CO      75.7 1.53 60     72.6     78.7  49.490  <.0001
 pulse   73.2 1.40 60     70.4     76.0  52.300  <.0001

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95

$contrasts
 contrast   estimate    SE   df lower.CL upper.CL t.ratio p.value
 CO - pulse     2.48 0.638 59.5      1.2     3.75   3.878  0.0003

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95
```

Weight Gain in Rats Exposed to Thiouracil and Thyroxin

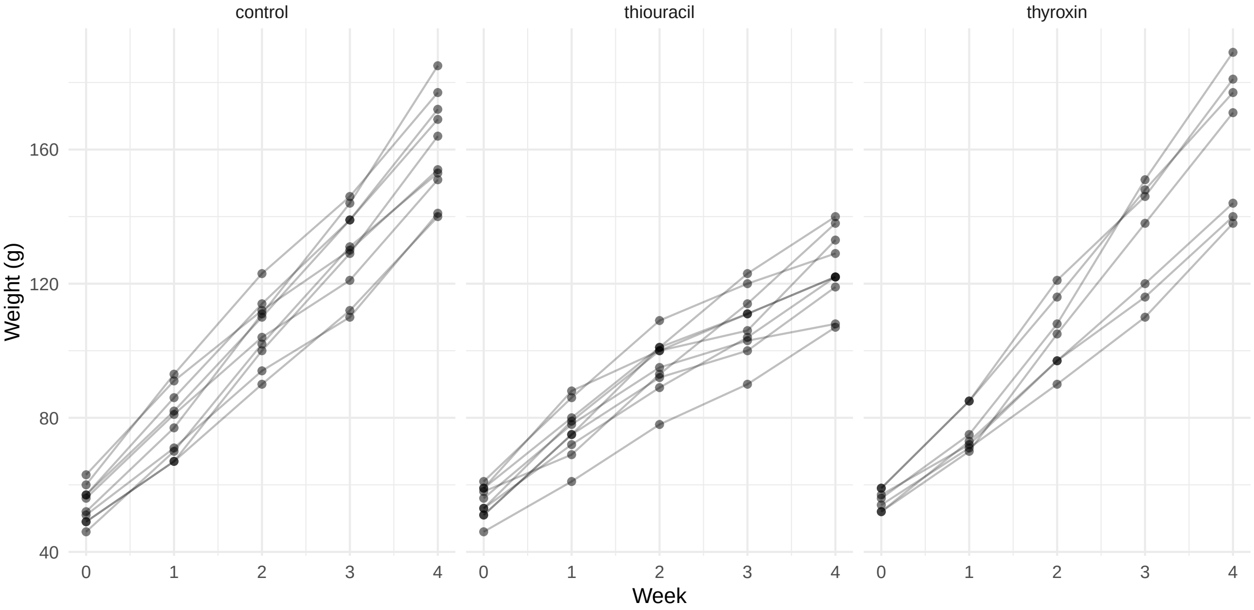
In the first homework assignment you encountered data from a study on the effects of thiouracil and thyroxin on growth of rats. Here are the first few rows of the data frame.

```
library(ALA)
head(rat,10)
```

```
    id treatment week weight
1    1   control    0     57
28   1   control    1     86
55   1   control    2    114
82   1   control    3    139
109  1   control    4    172
2    2   control    0     60
29   2   control    1     93
56   2   control    2    123
83   2   control    3    146
110  2   control    4    177
```

Note that the variable `id` identifies the rat and that there are multiple observations for each rat. The plot below shows the raw data with line segments joining observations from the same rat.

```
library(ALA)
library(ggplot2)
p <- ggplot(rat, aes(x = week, y = weight)) + theme_minimal() +
  geom_line(aes(group = id), alpha = 0.25) + geom_point(alpha = 0.5) +
  labs(x = "Week", y = "Weight (g)") + facet_wrap(~treatment)
plot(p)
```



In the first homework assignment we ignored the fact that there are multiple observations from each rat, but this may be important to take into account. We can think of the rat as being a factor with as many levels as there are rats (27), and that this categorical variable may have an "effect" in the sense that rats can vary in terms of their size, but also may grow at different rates (similar to what we observed for the Sitka spruce tree experiment from lecture). Here you will model the data using a random effects approach to account for the effect of rat.

1. In the seventh part of the *Weight Gain in Rats Exposed to Thiouracil and Thyroxin* problem on the first homework assignment you were asked to estimate a model with the model formula `weight ~ treatment:week`. This model can be written as

$$E(Y_i) = \begin{cases} \beta_0 + \beta_1 w_i, & \text{if the treatment for the } i\text{-th observation is control,} \\ \beta_0 + \beta_2 w_i, & \text{if the treatment for the } i\text{-th observation is thiouracil,} \\ \beta_0 + \beta_3 w_i, & \text{if the treatment for the } i\text{-th observation is thyroxin,} \end{cases}$$

where Y_i and w_i are the i-th observations of weight and week, respectively. Note that this model allows for differences in the growth rate depending on the treatment, but assumes that the expected weight at zero weeks is the same across treatments since at that point no drug had been administered. Now consider a mixed effects model with a random "main effect" for rat which can be written as

$$E(Y_{ij}) = \begin{cases} \beta_0 + \beta_1 w_{ij} + \delta_i, & \text{if the treatment for the } i\text{-th rat is control,} \\ \beta_0 + \beta_2 w_{ij} + \delta_i, & \text{if the treatment for the } i\text{-th rat is thiouracil,} \\ \beta_0 + \beta_3 w_{ij} + \delta_i, & \text{if the treatment for the } i\text{-th rat is thyroxin,} \end{cases}$$

where now Y_{ij} and w_{ij} are the weight and week for the j-th observation of the i-th rat. Here δ_i is a random parameter that represents the random effect of rat. Another model that allows for differences in the growth rate of rats by including an "interaction" between rat and week could be written as

$$E(Y_{ij}) = \begin{cases} \beta_0 + \beta_1 w_{ij} + \delta_i + \gamma_i w_{ij}, & \text{if the treatment for the } i\text{-th rat is control,} \\ \beta_0 + \beta_2 w_{ij} + \delta_i + \gamma_i w_{ij}, & \text{if the treatment for the } i\text{-th rat is thiouracil,} \\ \beta_0 + \beta_3 w_{ij} + \delta_i + \gamma_i w_{ij}, & \text{if the treatment for the } i\text{-th rat is thyroxin,} \end{cases}$$

where γ_i is a second random parameter for the interaction between rat and week. Estimate these two mixed effects models, and show the results using either `summary` or `lincon` so that I can verify that you estimated the model correctly. Note that you will still want to include the same fixed effects structure as the original model with the term `treatment:week`, but extend the model to include one or two random effects.

Solution: The first model can be estimated as follows.

```
m1 <- lmer(weight ~ treatment:week + (1 | id), data = rat)
trtools::lincon(m1)
```

```
                         estimate     se lower upper tvalue  df     pvalue
(Intercept)                 54.46 1.9310 50.67 58.24  28.20 Inf 5.521e-175
treatmentcontrol:week       26.32 0.6653 25.02 27.62  39.56 Inf  0.000e+00
treatmentthiouracil:week    17.38 0.6653 16.07 18.68  26.12 Inf 2.276e-150
treatmentthyroxin:week      26.90 0.7849 25.37 28.44  34.28 Inf 1.823e-257
```

The second model can be estimated as follows.

```
m2 <- lmer(weight ~ treatment:week + (week | id), data = rat)
trtools::lincon(m2)
```

```
                         estimate    se lower upper tvalue  df     pvalue
(Intercept)                 54.46 1.317 51.88 57.04  41.35 Inf  0.000e+00
treatmentcontrol:week       26.25 1.236 23.82 28.67  21.24 Inf 4.005e-100
treatmentthiouracil:week    17.53 1.236 15.11 19.95  14.19 Inf  1.128e-45
treatmentthyroxin:week      26.79 1.471 23.91 29.68  18.21 Inf  4.413e-74
```

2. Using the model you estimated with two random effects (i.e., the model with a random effect for the interaction between rat and week), estimate the expected weight of a rat at the fourth week for each treatment condition. Also estimate the three pairwise differences among these three expected weights. You can use `lincon`, `contrast`, or the **emmeans** package for this. Be sure to include standard errors and confidence intervals.

   Solution: Here is how we can do this with one statement using the **emmeans** package.

```
emmeans(m2, pairwise ~ treatment, at = list(week = 4), infer = TRUE, adjust = "none")
```

```
$emmeans
 treatment  emmean   SE   df lower.CL upper.CL t.ratio p.value
 control       159 5.04 24.4      149      170  31.660  <.0001
 thiouracil    125 5.04 24.4      114      135  24.730  <.0001
 thyroxin      162 6.04 24.3      149      174  26.780  <.0001

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95

$contrasts
 contrast              estimate   SE df lower.CL upper.CL t.ratio p.value
 control - thiouracil     34.87 7.18 24     20.0     49.7   4.854  0.0001
 control - thyroxin       -2.18 7.92 24    -18.5     14.2  -0.276  0.7852
 thiouracil - thyroxin   -37.06 7.92 24    -53.4    -20.7  -4.680  0.0001

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95
```

   An interesting thing about this model is that the tests of these pairwise differences are equivalent to testing the differences in the rates of change in weight between the treatment conditions. This is because the model is constrained so that the expected weight is the same for each treatment at week zero. For example, the difference in the expected weights between the control condition and the thiouracil treatment condition is

$$\beta_0 + \beta_1 4 - (\beta_0 + \beta_2 4) = (\beta_1 - \beta_2)4.$$

Note that we omit the terms δ_i and $\gamma_i w_{ij}$ because δ_i and γ_i both are modeled as having mean values of zero and so do not affect the expected weight for a given treatment condition and week if we are not conditioning on a particular rat. We can see the equivalence of these tests by testing the differences between the rates of change.

```
pairs(pairs(emmeans(m2, ~week|treatment, at = list(week = c(4,3)))),
  by = NULL, adjust = "none")
```

```
 contrast                                          estimate   SE df t.ratio p.value
 (week4 - week3 control) - (week4 - week3 thiouracil)     8.718 1.80 24   4.854  0.0001
 (week4 - week3 control) - (week4 - week3 thyroxin)      -0.546 1.98 24  -0.276  0.7852
 (week4 - week3 thiouracil) - (week4 - week3 thyroxin)   -9.264 1.98 24  -4.680  0.0001

Degrees-of-freedom method: kenward-roger
```

Seatbelt Use and Degree of Injury in Auto Accidents

The following data shows the number of auto accidents resulting in various levels of injury by victim gender, accident location, and whether not the victim was wearing a seat belt.[4]

```
seatbelt <- data.frame(gender = rep(c("female","male"), each = 4),
  location = rep(rep(c("urban","rural"), each = 2), 2), seatbelt = rep(c("no","yes"), 4),
  I1 = c(7287, 11587, 3246, 6134, 10381, 10969, 6123, 6693),
  I2 = c(175, 126, 73, 94, 136, 83, 141, 74),
  I3 = c(720, 577, 710, 564, 566, 259, 710, 353),
  I4 = c(91, 48, 159, 92, 96, 37, 188, 74),
  I5 = c(10, 8, 31, 17, 14, 1, 45, 12))
seatbelt
```

```
  gender location seatbelt    I1  I2  I3  I4 I5
1 female    urban       no  7287 175 720  91 10
2 female    urban      yes 11587 126 577  48  8
3 female    rural       no  3246  73 710 159 31
4 female    rural      yes  6134  94 564  92 17
5   male    urban       no 10381 136 566  96 14
6   male    urban      yes 10969  83 259  37  1
7   male    rural       no  6123 141 710 188 45
8   male    rural      yes  6693  74 353  74 12
```

The variables `I1` through `I5` denote the level of injury: *non injured* (`I1`), *injured but not transported by emergency medical services* (`I2`), *injured and transported by emergency medical services but not hospitalized* (`I3`), *injured and hospitalized but did not die* (`I4`), and *injured and died* (`I5`). The injury levels are ordered by severity. Note that the data are in aggregated form showing the number of accidents at each injury level for each combination of gender, location, and seat belt use. Use these data in the following.

1. Use the `vglm` function from the **VGAM** package to estimate a *sequential* regression model similar to a model we considered for the `pneumo` data in lecture on April 14. Use the injury level as the response variable, and use location and seat belt use as the explanatory variables, but not gender.[5] For this model do not specify any interactions. Note that the model should be specified with the injury levels ordered as listed above from I1 to I5. Use a logit link function. Do not use the `parallel` option for this model. Report the parameter estimates using `summary` so that I can verify that you specified the model correctly.

[4] Source: Agresti, A. (2013). *Categorical data analysis* (3rd ed). Hoboken, NJ: Wiley.

[5] Including location may be important as the severity of accidents may vary between urban and rural locations. Gender could be included as a (poor) proxy for weight, which could be related to severity of accidents — particular for those not wearing seat belts. In that case it would be important to include an interaction between gender (or, ideally, weight) and seat belt use. But for the purpose of this exercise we are going to keep the model very simple.

Solution: Here is the estimated model.

```
library(VGAM)
m <- vglm(cbind(I1,I2,I3,I4,I5) ~ seatbelt + location,
  family = cratio(link = "logitlink"), data = seatbelt)
summary(m)
```

```

Call:
vglm(formula = cbind(I1, I2, I3, I4, I5) ~ seatbelt + location,
    family = cratio(link = "logitlink"), data = seatbelt)

Coefficients:
                Estimate Std. Error z value Pr(>|z|)
(Intercept):1    -1.5326     0.0219  -70.02  < 2e-16 ***
(Intercept):2     2.1098     0.0626   33.72  < 2e-16 ***
(Intercept):3    -1.2063     0.0525  -22.99  < 2e-16 ***
(Intercept):4    -1.5210     0.1230  -12.36  < 2e-16 ***
seatbeltyes:1    -0.7487     0.0273  -27.41  < 2e-16 ***
seatbeltyes:2    -0.1606     0.0735   -2.19    0.029 *
seatbeltyes:3    -0.3514     0.0776   -4.53  6.0e-06 ***
seatbeltyes:4    -0.2177     0.2054   -1.06    0.289
locationurban:1  -0.7303     0.0268  -27.25  < 2e-16 ***
locationurban:2  -0.5052     0.0728   -6.94  3.9e-12 ***
locationurban:3  -0.6096     0.0762   -8.00  1.3e-15 ***
locationurban:4  -0.5251     0.2131   -2.46    0.014 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Names of linear predictors: logitlink(P[Y>1|Y>=1]), logitlink(P[Y>2|Y>=2]),
logitlink(P[Y>3|Y>=3]), logitlink(P[Y>4|Y>=4])

Residual deviance: 458.2 on 20 degrees of freedom

Log-likelihood: -329.6 on 20 degrees of freedom

Number of Fisher scoring iterations: 4

No Hauck-Donner effect found in any of the estimates
```

2. The sequential model you specified in the previous problem is effectively equivalent to four logistic regression models: one for whether an individual was injured (I2, I3, I4, or I5) or not injured (I1), another for whether an injured person was not transported (I2) or was transported (I3, I4, or I5), another for whether a transported person was hospitalized (I4 or I5) or was not hospitalized (I3), and finally a model for whether those that required hospitalization died (I5) or did not die (I4). The model you estimated in the previous problem can be used to compute odds ratios for the effect of using a seat belt (or not) with respect to each of these four situations. Report those four odds ratios and write a sentence for each odds ratio that explains how it is interpreted in terms of the statistical effect of wearing a seat belt (or not).

   Solution: We can estimate the same model as four logistic regression models. Note that this is not necessary to obtain the odds ratios as they can also be found by exponentiating the parameter estimates from the model estimated earlier. But it is illuminating to see how we can estimate the model above as four separate logistic regression models.

```
m1 <- glm(cbind(I2+I3+I4+I5,I1) ~ seatbelt + location,
  family = binomial, data = seatbelt)
summary(m1)$coefficients
```

```
              Estimate Std. Error z value   Pr(>|z|)
(Intercept)    -1.5326    0.02189  -70.02  0.000e+00
seatbeltyes    -0.7487    0.02731  -27.41 2.005e-165
locationurban  -0.7303    0.02680  -27.25 1.591e-163
```

```
m2 <- glm(cbind(I3+I4+I5,I2) ~ seatbelt + location,
  family = binomial, data = seatbelt)
summary(m2)$coefficients
```

```
              Estimate Std. Error z value   Pr(>|z|)
(Intercept)     2.1098    0.06227  33.880 1.298e-251
seatbeltyes    -0.1606    0.07341  -2.188  2.869e-02
locationurban  -0.5052    0.07277  -6.942  3.865e-12
```

```
m3 <- glm(cbind(I4+I5,I3) ~ seatbelt + location,
  family = binomial, data = seatbelt)
summary(m3)$coefficients
```

```
              Estimate Std. Error z value   Pr(>|z|)
(Intercept)    -1.2063    0.05203 -23.184 6.648e-119
seatbeltyes    -0.3514    0.07776  -4.519  6.221e-06
locationurban  -0.6096    0.07627  -7.993  1.317e-15
```

```
m4 <- glm(cbind(I5,I4) ~ seatbelt + location,
  family = binomial, data = seatbelt)
summary(m4)$coefficients
```

```
              Estimate Std. Error z value  Pr(>|z|)
(Intercept)    -1.5210     0.1222 -12.447 1.452e-35
seatbeltyes    -0.2177     0.2060  -1.057 2.906e-01
locationurban  -0.5251     0.2133  -2.462 1.383e-02
```

Notice that the parameter estimates and the standard errors from these four models are the same as those obtained above when using the `vglm` function. Here are the estimated odds ratios for seatbelt wearing. Note that since there is no interaction specified we do not need to condition on location.

```
pairs(emmeans(m1, ~seatbelt, type = "response"), infer = TRUE)
```

```
 contrast odds.ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 no / yes       2.11 0.0578 Inf         2      2.23    1  27.411  <.0001

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
Tests are performed on the log odds ratio scale 
```

```
pairs(emmeans(m2, ~seatbelt, type = "response"), infer = TRUE)
```

```
 contrast odds.ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 no / yes       1.17 0.0862 Inf      1.02      1.36    1   2.188  0.0287

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
```

```
Tests are performed on the log odds ratio scale
```

```
pairs(emmeans(m3, ~seatbelt, type = "response"), infer = TRUE)
```

```
 contrast odds.ratio   SE  df asymp.LCL asymp.UCL null z.ratio p.value
 no / yes       1.42 0.11 Inf      1.22      1.65    1   4.519  <.0001

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
Tests are performed on the log odds ratio scale 
```

```
pairs(emmeans(m4, ~seatbelt, type = "response"), infer = TRUE)
```

```
 contrast odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 no / yes       1.24 0.256 Inf      0.83      1.86    1   1.057  0.2906

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
Tests are performed on the log odds ratio scale 
```

We can interpret these odds ratios as follows.

The odds of an injury are about 2.11 times higher (110% higher) when not wearing a seatbelt.

The odds that an injured person would need to be transported is about 1.17 times higher (17% higher) when not wearing a seatbelt.

*The odds that a transported person would require hospitalization is about 1.42 times higher (42% higher) when not wearing a seatbelt.

The odds that a hospitalized person would die is about 1.24 times higher (24% higher) when not wearing a seatbelt.

Note that all but the last odds ratios are statistically significant at convention significance levels. We can also flip the odds ratios.

```
pairs(emmeans(m1, ~seatbelt, type = "response"), infer = TRUE, reverse = TRUE)
```

```
 contrast odds.ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 yes / no      0.473 0.0129 Inf     0.448     0.499    1 -27.411  <.0001

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
Tests are performed on the log odds ratio scale 
```

```
pairs(emmeans(m2, ~seatbelt, type = "response"), infer = TRUE, reverse = TRUE)
```

```
 contrast odds.ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 yes / no      0.852 0.0625 Inf     0.738     0.983    1  -2.188  0.0287

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
Tests are performed on the log odds ratio scale 
```

```
pairs(emmeans(m3, ~seatbelt, type = "response"), infer = TRUE, reverse = TRUE)
```

```
 contrast odds.ratio     SE  df asymp.LCL asymp.UCL null z.ratio p.value
 yes / no      0.704 0.0547 Inf     0.604      0.82    1  -4.519  <.0001

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
Tests are performed on the log odds ratio scale 
```

```
pairs(emmeans(m4, ~seatbelt, type = "response"), infer = TRUE, reverse = TRUE)
```

```
 contrast odds.ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 yes / no      0.804 0.166 Inf     0.537       1.2    1  -1.057  0.2906

Results are averaged over the levels of: location 
Confidence level used: 0.95 
Intervals are back-transformed from the log odds ratio scale 
Tests are performed on the log odds ratio scale 
```

We can interpret these odds ratios as follows.

The odds of an injury is reduced by a factor of about 0.47 (53% less) when wearing a seat belt.

The odds that an injured person would need to be transported is reduced by a factor of about 0.85 (15% less) when wearing a seat belt.

The odds that a transported person would need to be hospitalized decreases by a factor of about 0.7 (30% less) when wearing a seat belt.

The odds that a hospitalized person would die decreases by a factor of about 0.8 (20% less) when wearing a seat belt.