Motivation

The outcome for the analysis that we will be conducting is the WHO 11-point ordinal scale for clinical improvement at 14 days, which ranges from 0 (uninfected and out of the hospital) to 10 (dead), with various stages of severity in between. We plan to use a Bayesian proportional odds model to assess the effectiveness of the therapy. Since this is a meta-analysis, we will be including these data from a collection of studies being conducted around the world.

Typically, in a proportional odds model one has to make an assumption about proportionality. In this case, while we are willing to make that assumption *within* specific studies, we are not willing to make that assumption *across* the various studies. This means we need to generate a separate set of intercepts for each study that we simulate.

In the proportional odds model, we are modeling the log-cumulative odds at a particular level. The simplest model with a single exposure/treatment covariate for a specific study or cluster k is

$$log \left(\frac{P(\text{score}_{k} < x)}{P(\text{score}_{k} \ge x) } \right) = \alpha_{xk} + \beta A,$$

where x ranges from 1 to 10, all the levels of the WHO score excluding the lowest level $x=0$. A is the treatment indicator, and is $A=1$ for patients who receive the treatment. α_{xk} is the intercept for each study/cluster k. β is interpreted as the log-odds ratio comparing the odds of the treated with the non-treated within each study. The proportionality assumption kicks in here when we note that β is constant for all levels of x. In addition, in this particular model, we are assuming that the log-odds ratio is constant across studies (not something we will assume in a more complete model). We make no assumptions about how the study intercepts relate to each other.

To make clear what it would mean to make a stronger assumption about the odds *across* studies consider this model:

$$log \left(\frac{P(\text{score}_{k} < x)}{P(\text{score}_{k} \ge x) } \right) = \alpha_{x} + b_k + \beta A,$$

where the intercepts for each study are related, since they are defined as $\alpha_{x} + b_k$, and share α_x in common. If we compare the log-odds of the treated in one study k with the log-odds of treated in another study j (so $A=1$ in both cases), the log-odds ratio is $b_j – b_k$. The ratio is independent of x, which implies a strong proportional odds assumption across studies. In contrast, the same comparison across studies based on the first model is $\alpha_{xj} – \alpha_{xk}$, which is *not* necessarily constant across different levels of x.

This is a long way of explaining why we need to generate different sets of intercepts for each study. In short, we would like to make the more relaxed assumption that odds are not proportional across studies or clusters.

The Dirichlet distribution

In order to generate ordinal categorical data I use the genOrdCat function in the `simstudy` package. This function requires a set of baseline probabilities that sum to one; these probabilities map onto level-specific intercepts. There will be a distinct set of baseline probabilities for each study and I will create a data set for each study. The challenge is to be able to generate unique baseline probabilities as if I were sampling from a population of studies.

If I want to generate a single probability (i.e. a number between 0 and 1), a good solution is to draw a value from a *beta* distribution, which has two shape parameters α and β.

Here is a single draw from $beta(3, 3)$:

```
set.seed(872837)
```

```
rbeta(1, shape1 = 3, shape2 = 3)
```

```
## [1] 0.568
```

The mean of the *beta* distribution is $\alpha/(\alpha + \beta)$ and the variance is $\alpha\beta/(\alpha+ \beta)^2(\alpha + \beta + 1)$. We can reduce the variance and maintain the same mean by increasing α and β by a constant factor (see addendum for a pretty picture):

```
library(data.table)

d1 <- data.table(s = 1, value = rbeta(1000, shape1 = 1, shape2 = 2))
d2 <- data.table(s = 2, value = rbeta(1000, shape1 = 5, shape2 = 10))
d3 <- data.table(s = 3, value = rbeta(1000, shape1 = 100, shape2 = 200))

dd <- rbind(d1, d2, d3)
dd[, .(mean(value), sd(value)), keyby = s]
```

```
##    s    V1     V2
## 1: 1 0.338 0.2307
## 2: 2 0.336 0.1195
## 3: 3 0.333 0.0283
```

The *Dirichlet* distribution is a multivariate version of the *beta* distribution where K values between 0 and 1 are generated, with the caveat that they sum to 1. Instead of α and β, the Dirichlet is parameterized by a vector of length K

$$\boldsymbol{\alpha} = \left(\alpha_1,\dots, \alpha_K\right)^T,$$

where there are K levels of the ordinal outcome. A draw from this distribution returns a vector $\boldsymbol{p} = (p_1, \dots, p_K)^T$ where $\sum_{i=1}^K p_i = 1$ and

$$E(p_k)=\frac{\alpha_k}{\sum_{i=1}^K \alpha_i}.$$

A draw from a Dirichlet distribution with $K=2$ is actually equivalent to a draw from a *beta* distribution where $\boldsymbol{\alpha} = (\alpha, \beta)^T$. Before, I generated data from a $beta(1, 2)$, and now here is a draw from $Dirichlet\left(\boldsymbol\alpha = (1,2)\right)$ using `rdirichlet` from the `gtools` package:

```
library(gtools)

dir <- rdirichlet(1000, alpha = c(1,2))
head(dir)
```

```
##        [,1]  [,2]
## [1,] 0.3606 0.639
## [2,] 0.4675 0.533
## [3,] 0.2640 0.736
## [4,] 0.0711 0.929
## [5,] 0.5643 0.436
## [6,] 0.0188 0.981
```

The first column has the same distribution as the $beta$ distribution from before; the mean and standard deviation are close to the values estimated above:

```
c(mean(dir[,1]), sd(dir[,1]))
```

```
## [1] 0.332 0.236
```

To ramp things up a bit, say we have $K = 5$, and the target mean values for each level are $\boldsymbol{p} = \left(\frac{1}{9}, \frac{2}{9}, \frac{3}{9}, \frac{2}{9}, \frac{1}{9} \right)$, one way to specify this is:

```
dir_1 <- rdirichlet(1000, alpha = c(1, 2, 3, 2, 1))
head(dir_1)
```

```
##        [,1]   [,2]   [,3]   [,4]   [,5]
## [1,] 0.1710 0.6637 0.0676 0.0633 0.0343
## [2,] 0.1130 0.1150 0.2803 0.4229 0.0689
## [3,] 0.1434 0.0678 0.3316 0.1721 0.2851
## [4,] 0.0250 0.1707 0.3841 0.2490 0.1712
## [5,] 0.0633 0.3465 0.4056 0.0853 0.0993
## [6,] 0.1291 0.1510 0.3993 0.2612 0.0593
```

Here are the observed means for each p_k, pretty close to the target:

```
apply(dir_1, 2, mean)
```

```
## [1] 0.111 0.221 0.328 0.229 0.112
```

Of course, we could generate data with a similar target $\boldsymbol{p}$ by multiplying $\boldsymbol\alpha$ by a constant c. In this case, we use $c=10$ and see that the average values for each p_k are also close to the target:

```
dir_2 <- rdirichlet(1000, alpha = c(10, 20, 30, 20, 10))
apply(dir_2, 2, mean)
```

```
## [1] 0.113 0.222 0.334 0.220 0.111
```

There is a key difference between specifying $\boldsymbol{\alpha}$ and $c\boldsymbol{\alpha}$. Just as in the *beta* distribution, as c grows larger, the variation within each p_k decreases. This will be useful when generating the study specific probabilities if we want explore different levels of variation.

Here’s the standard deviations from the two data sets just generated:

```
apply(dir_1, 2, sd)
```

```
## [1] 0.102 0.131 0.144 0.134 0.098
```

```
apply(dir_2, 2, sd)
```

```
## [1] 0.0333 0.0425 0.0508 0.0421 0.0333
```

Generating the baseline probabilities

A simple function that includes two key arguments – the base probabilities (which are really $\boldsymbol{\alpha}$) and a *similarity* index (which is really just the constant c) – implements these ideas to generate study-specific probabilities for each outcome level. As the *similarity* index increases, the variation across studies or sites decreases. The function includes an additional adjustment to ensure that the row totals sum exactly to 1 and not to some value infinitesimally greater than 1 as a result of rounding. Such a rounding error could cause problems for the function `genOrdCat`.

```
genBaseProbs <- function(n, base, similarity, digits = 8) {

  n_levels <- length(base)
  x <- rdirichlet(n, similarity * base)

  #--- ensure that each vector of probabilities sums exactly to 1

  x <- round(floor(x*1e8)/1e8, digits)   # round the generated probabilities
  xpart <- x[, 1:(n_levels-1)]           # delete the base prob of the final
level
  partsum <- apply(xpart, 1, sum)        # add the values of levels 1 to K-1
  x[, n_levels] <- 1 - partsum           # the base prob of the level K = 1 -
sum(1:[K-1])

  return(x)
}
```

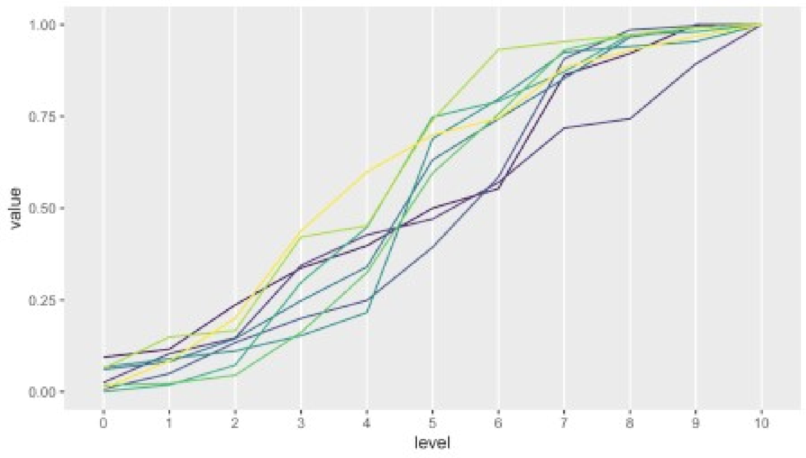
In this first example, I am generating 11 values (representing base probabilities) for each of 9 studies using a relatively low similarity index, showing you the first six studies:

```
basestudy <- genBaseProbs(
  n = 9,
  base =  c(0.05, 0.06, 0.07, 0.11, 0.12, 0.20, 0.12, 0.09, 0.08, 0.05, 0.05),
  similarity = 15,
)

round(head(basestudy), 3)
```

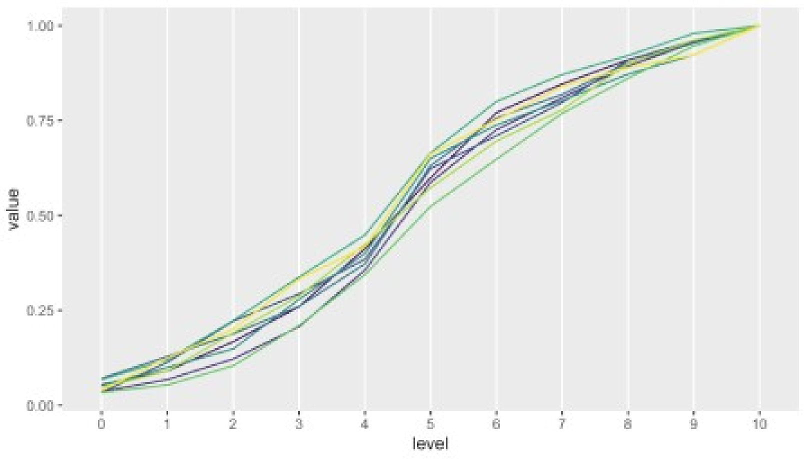
```
##       [,1]  [,2]  [,3]  [,4]  [,5]  [,6]  [,7]  [,8]  [,9] [,10] [,11]
## [1,] 0.094 0.022 0.121 0.100 0.061 0.102 0.053 0.309 0.059 0.078 0.000
## [2,] 0.025 0.079 0.043 0.197 0.083 0.044 0.099 0.148 0.025 0.150 0.107
## [3,] 0.007 0.042 0.084 0.066 0.049 0.145 0.191 0.323 0.078 0.012 0.003
## [4,] 0.061 0.021 0.063 0.104 0.092 0.292 0.112 0.110 0.113 0.026 0.008
## [5,] 0.067 0.023 0.021 0.042 0.063 0.473 0.108 0.127 0.016 0.013 0.046
## [6,] 0.001 0.018 0.054 0.225 0.150 0.301 0.043 0.081 0.100 0.008 0.020
```

A great way to see the variability is a cumulative probability plot for each individual study. With a relatively low *similarity* index, you can generate quite a bit of variability across the studies. In order to create the plot, I need to first calculate the cumulative probabilities:

```
library(ggplot2)
library(viridis)

cumprobs <- data.table(t(apply(basestudy, 1, cumsum)))
n_levels <- ncol(cumprobs)
cumprobs[, id := .I]

dm <- melt(cumprobs, id.vars = "id", variable.factor = TRUE)
dm[, level := factor(variable, labels = c(0:10))]

ggplot(data  = dm, aes(x=level, y = value)) +
  geom_line(aes(group = id, color = id)) +
  scale_color_viridis( option = "D") +
  theme(panel.grid.minor = element_blank(),
        panel.grid.major.y = element_blank(),
        legend.position = "none")
```



Here is a plot of data generated using a *similarity* index of 150. Variation is reduced pretty dramatically:



Using base probabilities to generate ordinal data

Now that we have these base probabilities, the last step is to use them to generate ordinal outcomes. I am generating the simplest of data sets: 9 "studies" each with 500 subjects, without any covariates or even treatment assignment. Since the `genOrdCat` requires an adjustment variable, I am adjusting everyone by 0. (This is something I need to fix – there should be no such requirement.)

```
library(simstudy)

d_study <- genData(9, id = "study")
d_ind <- genCluster(d_study, "study", numIndsVar = 500, "id")
d_ind[, z := 0]

d_ind
```

```
##       study   id z
##    1:     1    1 0
##    2:     1    2 0
##    3:     1    3 0
##    4:     1    4 0
##    5:     1    5 0
##   ---
## 4496:     9 4496 0
## 4497:     9 4497 0
## 4498:     9 4498 0
## 4499:     9 4499 0
## 4500:     9 4500 0
```

To generate the ordinal categorical outcome, we have to treat each study separately since they have unique baseline probabilities. This can be accomplished using `lapply` in the following way:

```
basestudy <- genBaseProbs(
  n = 9,
  base =  c(0.05, 0.06, 0.07, 0.11, 0.12, 0.20, 0.12, 0.09, 0.08, 0.05, 0.05),
  similarity = 50
)

list_ind  <- lapply(
  X = 1:9,
  function(i) {
    b <- basestudy[i,]
    d_x <- d_ind[study == i]
    genOrdCat(d_x, adjVar = "z", b, catVar = "ordY")
  }
)
```

The output `list_ind` is a list of data tables, one for each study. For example, here is the 5th data table in the list:

```
list_ind[[5]]
```

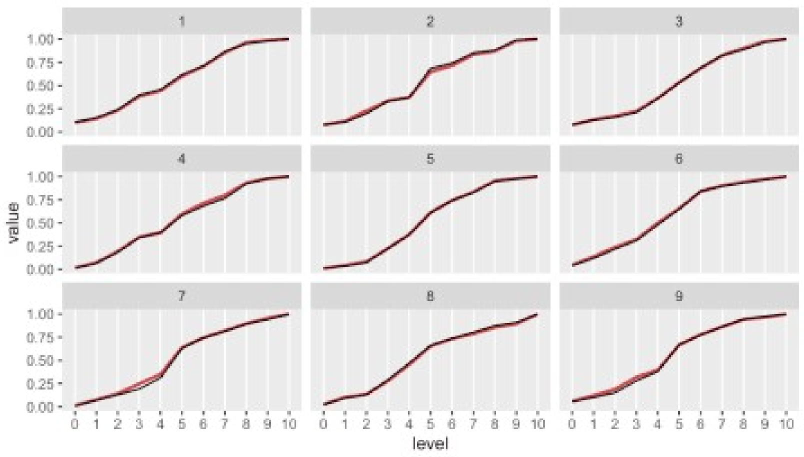
```
##       study   id z ordY
##   1:      5 2001 0    7
##   2:      5 2002 0    9
##   3:      5 2003 0    5
##   4:      5 2004 0    9
##   5:      5 2005 0    9
##  ---
## 496:      5 2496 0    9
## 497:      5 2497 0    4
## 498:      5 2498 0    7
## 499:      5 2499 0    5
## 500:      5 2500 0   11
```

And here is a table of proportions for each study that we can compare with the base probabilities:

```
t(sapply(list_ind, function(x) x[, prop.table(table(ordY))]))
```

```
##           1     2     3     4     5     6     7     8     9    10    11
##  [1,] 0.106 0.048 0.086 0.158 0.058 0.162 0.092 0.156 0.084 0.028 0.022
##  [2,] 0.080 0.024 0.092 0.134 0.040 0.314 0.058 0.110 0.028 0.110 0.010
##  [3,] 0.078 0.050 0.028 0.054 0.148 0.172 0.162 0.134 0.058 0.082 0.034
##  [4,] 0.010 0.056 0.116 0.160 0.054 0.184 0.102 0.084 0.156 0.056 0.022
##  [5,] 0.010 0.026 0.036 0.152 0.150 0.234 0.136 0.084 0.120 0.026 0.026
##  [6,] 0.040 0.078 0.100 0.092 0.170 0.168 0.196 0.050 0.038 0.034 0.034
##  [7,] 0.006 0.064 0.058 0.064 0.120 0.318 0.114 0.068 0.082 0.046 0.060
##  [8,] 0.022 0.070 0.038 0.160 0.182 0.190 0.074 0.068 0.070 0.036 0.090
##  [9,] 0.054 0.046 0.052 0.128 0.100 0.290 0.102 0.092 0.080 0.030 0.026
```

Of course, the best way to compare is to plot the data for each study. Here is another cumulative probability plot, this time including the observed (generated) probabilities in black over the baseline probabilities used in the data generation in red:



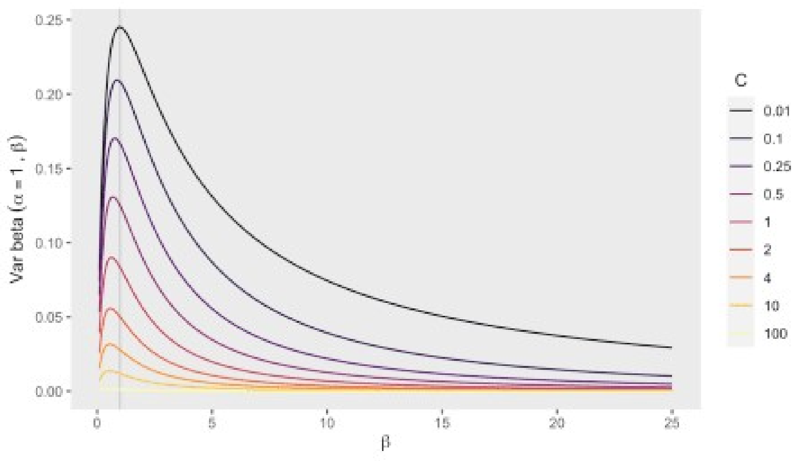
Sometime soon, I plan to incorporate something like the function `genBaseProbs` into `simstudy` to make it easier to incorporate non-proportionality assumptions into simulation studies that use ordinal categorical outcomes.

Addendum

The variance of the *beta* distribution (and similarly the *Dirichlet* distribution) decreases as \(\alpha\) and

\(\beta\) both increase proportionally (keeping the mean constant). I’ve plotted the variance of the *beta* distribution for \(\alpha = 1\) and different levels of \(\beta\) and \(C\). It is clear that at any level of \(\beta\) (I’ve drawn a line at \(\beta = 1\)), the variance decreases as \(C\) increases. It is also clear that, holding \(\alpha\) constant, the relationship of \(\beta\) to variance is not strictly monotonic:

```
var_beta <- function(params) {
  a <- params[1]
  b <- params[2]
  (a * b) / ( (a + b)^2 * (a + b + 1))
}

loop_b <- function(C, b) {
  V <- sapply(C, function(x) var_beta(x*c(1, b)))
  data.table(b, V, C)
}

b <- seq(.1, 25, .1)
C <- c(0.01, 0.1, 0.25, 0.5, 1, 2, 4, 10, 100)

d_var <- rbindlist(lapply(b, function(x) loop_b(C, x)))

ggplot(data = d_var, aes(x = b, y = V, group = C)) +
  geom_vline(xintercept = 1, size = .5, color = "grey80") +
  geom_line(aes(color = factor(C))) +
  scale_y_continuous(name = expression("Var beta"~(alpha==1~","~beta))) +
  scale_x_continuous(name = expression(beta)) +
  scale_color_viridis(discrete = TRUE, option = "B", name = "C") +
  theme(panel.grid = element_blank(),
        legend.title.align=0.15)
```


Var beta (α = 1 , β)
β
C