# Monday, Apr 18

## Sequential and Binary Regression Models

A sequential regression model can sometimes be estimated using several binary regression models.

**Example**: Consider again the `pneumo` data.

```
library(VGAM)
pneumo
```

```
  exposure.time normal mild severe
1           5.8     98    0      0
2          15.0     51    2      1
3          21.5     34    6      3
4          27.5     35    5      8
5          33.5     32   10      9
6          39.5     23    7      8
7          46.0     12    6     10
8          51.5      4    2      5
```

```
# sequential regression model
m <- vglm(cbind(normal, mild, severe) ~ exposure.time,
  family = cratio(link = "logitlink"), data = pneumo)
summary(m)
```

```
Call:
vglm(formula = cbind(normal, mild, severe) ~ exposure.time, family = cratio(link = "logitlink"),
    data = pneumo)

Coefficients:
                Estimate Std. Error z value Pr(>|z|)
(Intercept):1    -3.9664     0.4189   -9.47  < 2e-16 ***
(Intercept):2    -1.1133     0.7664   -1.45    0.146
exposure.time:1   0.0963     0.0124    7.79  6.9e-15 ***
exposure.time:2   0.0355     0.0206    1.72    0.085 .
---
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])

Residual deviance: 13.29 on 12 degrees of freedom

Log-likelihood: -29.22 on 12 degrees of freedom

Number of Fisher scoring iterations: 6

Warning: Hauck-Donner effect detected in the following estimate(s):
'(Intercept):1'
```

This model can be estimated using *two* logistic regression models. The first is a model for whether a miner

will develop pneumoconiosis (i.e., mild or severe). This logistic regression model can be estimated as follows.

```
m1 <- glm(cbind(mild + severe, normal) ~ exposure.time, family = binomial, data = pneumo)
summary(m1)$coefficients
```

```
              Estimate Std. Error z value  Pr(>|z|)
(Intercept)   -3.96635    0.41893  -9.468 2.857e-21
exposure.time  0.09627    0.01236   7.786 6.898e-15
```

Next we have the model for whether a miner with pneumoconiosis will develop severe pneumoconiosis (rather than mild). The logistic regression model for this probability can be estimated by effectively ignoring any observations where pneumoconiosis did not progress to mild or severe (i.e., exclude cases where it was normal).

```
m2 <- glm(cbind(severe, mild) ~ exposure.time, family = binomial, data = pneumo)
summary(m2)$coefficients
```

```
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.11342     0.8625  -1.291   0.1967
exposure.time  0.03547     0.0235   1.509   0.1312
```

We *cannot* estimate a sequential regression model with separate binary models if we want to constrain some parameters to be equal across the "steps" of the model (e.g., if we wanted to assume that the odds ratio for the effect of exposure was the same at each step as done below using the `parallel = TRUE` option.

```
m <- vglm(cbind(normal, mild, severe) ~ exposure.time,
  family = cratio(link = "logitlink", parallel = TRUE), data = pneumo)
summary(m)
```

```
Call:
vglm(formula = cbind(normal, mild, severe) ~ exposure.time, family = cratio(link = "logitlink",
    parallel = TRUE), data = pneumo)

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept):1  -3.6077     0.3542  -10.19  < 2e-16 ***
(Intercept):2  -2.8605     0.4426   -6.46  1.0e-10 ***
exposure.time   0.0849     0.0104    8.13  4.2e-16 ***
---
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])

Residual deviance: 18.3 on 13 degrees of freedom

Log-likelihood: -31.73 on 13 degrees of freedom

Number of Fisher scoring iterations: 5

Warning: Hauck-Donner effect detected in the following estimate(s):
'(Intercept):1'
```

## Proportional Odds Models

The logistic regression model for a binary response $Y_i = 0, 1$ can be written as

$$\log\left[\frac{P(Y_i = 1)}{1 - P(Y_i = 1)}\right] = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_k x_{ik}.$$

This can also be written as

$$\log\left[\frac{P(Y_i > 0)}{1 - P(Y_i > 0)}\right] = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_k x_{ik}.$$

Now let the response variable $Y_i = 1, 2, \ldots, R$ denote $R$ ordered response categories where order is implied by $Y_i$. A *proportional odds model* is a logistic regression model for each of the $R - 1$ possible "dichotomizations" of the categories such that

$$\log\left[\frac{P(Y_i > y)}{1 - P(Y_i > y)}\right] = \beta_0^{(y)} + \beta_1 x_{i1} + \cdots + \beta_k x_{ik}$$

for $y = 1, 2, \ldots, R - 1$. This defines a *system* of equations for each possible dichotomy. For example, suppose $R = 4$ and so $Y_i = 1, 2, 3, 4$. The model is then written as

$$\begin{aligned}
\log\left[\frac{P(Y_i > 1)}{1 - P(Y_i > 1)}\right] &= \beta_0^{(1)} + \beta_1 x_{i1} + \cdots + \beta_k x_{ik}, \\
\log\left[\frac{P(Y_i > 2)}{1 - P(Y_i > 2)}\right] &= \beta_0^{(2)} + \beta_1 x_{i1} + \cdots + \beta_k x_{ik}, \\
\log\left[\frac{P(Y_i > 3)}{1 - P(Y_i > 3)}\right] &= \beta_0^{(3)} + \beta_1 x_{i1} + \cdots + \beta_k x_{ik}.
\end{aligned}$$

The odds are proportional because (omitting the $i$ subscript for simplicity)

$$\frac{P(Y > y)}{1 - P(Y > y)} = e^{\beta_0^{(y)}} e^{\beta_1 x_1} \cdots e^{\beta_k x_k},$$

and so the odds ratio when we compare the odds at $x_1 = x_a$ to $x_1 = x_b$,

$$\frac{e^{\beta_0^{(y)}} e^{\beta_1 x_a} \cdots e^{\beta_k x_k}}{e^{\beta_0^{(y)}} e^{\beta_1 x_b} \cdots e^{\beta_k x_k}} = e^{\beta_1}$$

*does not depend on* $y$ (i.e., it does not depend how we dichotomize $Y$).

The system of equations allows us to express the probability of each response category as a function of the explanatory variables and parameters. From

$$\log\left[\frac{P(Y_i > y)}{1 - P(Y_i > y)}\right] = \beta_0^{(y)} + \beta_1 x_{i1} + \cdots + \beta_k x_{ik}$$

we get

$$P(Y_i > y) = \frac{\exp(\beta_0^{(y)} + \beta_1 x_{i1} + \cdots + \beta_k x_{ik})}{1 + \exp(\beta_0^{(y)} + \beta_1 x_{i1} + \cdots + \beta_k x_{ik})},$$

and then

$$P(Y_i = y) = P(Y_i > y - 1) - P(Y_i > y),$$

where $P(Y_i > 0) = 1$ and $P(Y_i > R) = 0$ by definition.

The distribution of a categorical response variable is assumed to be a *multinomial distribution*. The binomial distribution is a special case for when there are only $R = 2$ categories.

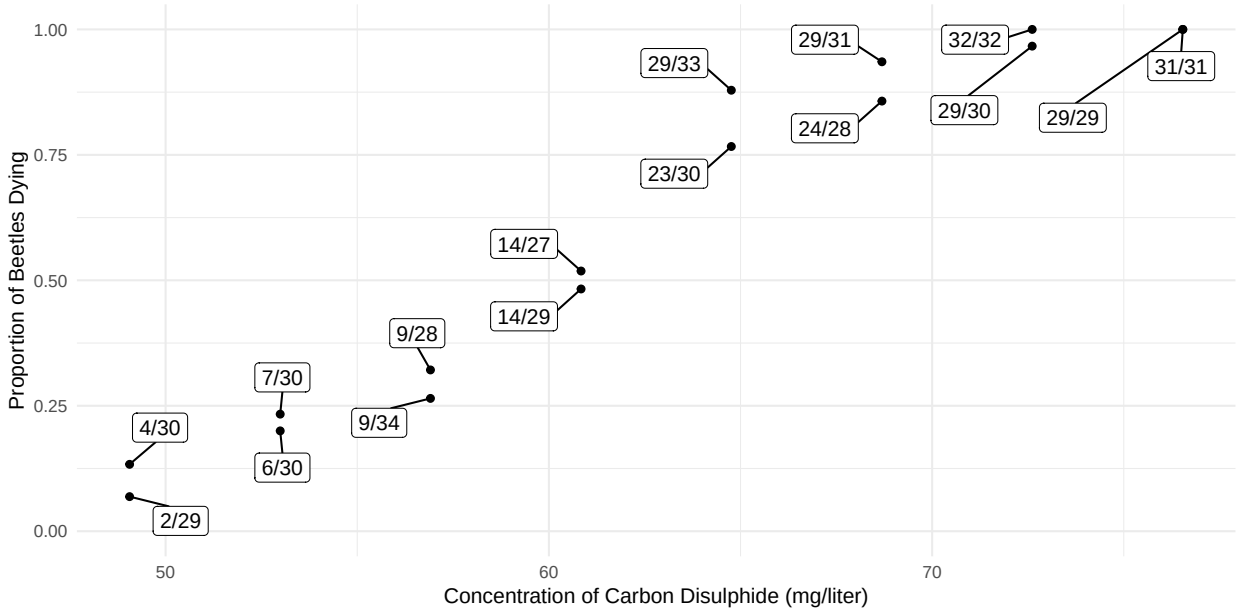
**Example**: Recall the `bliss` data that we used to demonstrate logistic regression.

```
library(trtools) # for bliss data
library(ggrepel) # for geom_repel_label

bliss$proportion <- paste(bliss$dead, "/", bliss$exposed, sep = "")
bliss$alive <- bliss$exposed - bliss$dead
bliss
```

```
   concentration dead exposed proportion alive
1          49.06    2      29       2/29    27
2          49.06    4      30       4/30    26
3          52.99    7      30       7/30    23
4          52.99    6      30       6/30    24
5          56.91    9      28       9/28    19
6          56.91    9      34       9/34    25
7          60.84   14      27      14/27    13
8          60.84   14      29      14/29    15
9          64.76   23      30      23/30     7
10         64.76   29      33      29/33     4
11         68.69   29      31      29/31     2
12         68.69   24      28      24/28     4
13         72.61   29      30      29/30     1
14         72.61   32      32      32/32     0
15         76.54   29      29      29/29     0
16         76.54   31      31      31/31     0
```

```
p <- ggplot(bliss, aes(x = concentration, y = dead/exposed)) +
  geom_point() + ylim(0, 1) + theme_minimal() +
  geom_label_repel(aes(label = proportion), box.padding = 0.75) +
  labs(x = "Concentration of Carbon Disulphide (mg/liter)",
    y = "Proportion of Beetles Dying")
plot(p)
```




```
m <- glm(cbind(dead, alive) ~ concentration, family = binomial, data = bliss)
summary(m)$coefficients
```

```
             Estimate Std. Error z value  Pr(>|z|)
(Intercept)   -14.8084    1.28976  -11.48 1.633e-30
concentration   0.2492    0.02138   11.65 2.250e-31
```

The `vglm` function from the **VGAM** package can be used to estimate a proportional odds model, but logistic regression is a special case when there are only $R = 2$ response categories.

```
library(VGAM) # for the vglm function and others
m <- vglm(cbind(alive, dead) ~ concentration, family = propodds, data = bliss)
cbind(coef(m), confint(m))
```

```
                          2.5 %   97.5 %
(Intercept)   -14.8084 -17.3363 -12.2806
concentration   0.2492   0.2073   0.2911
```

But note that we specify the *order* of the response categories in `cbind` from left to right when using `vglm`, which is opposite of how it is done when using `glm`.

Here we can plot the probabilities of the two categories as a function of concentration.

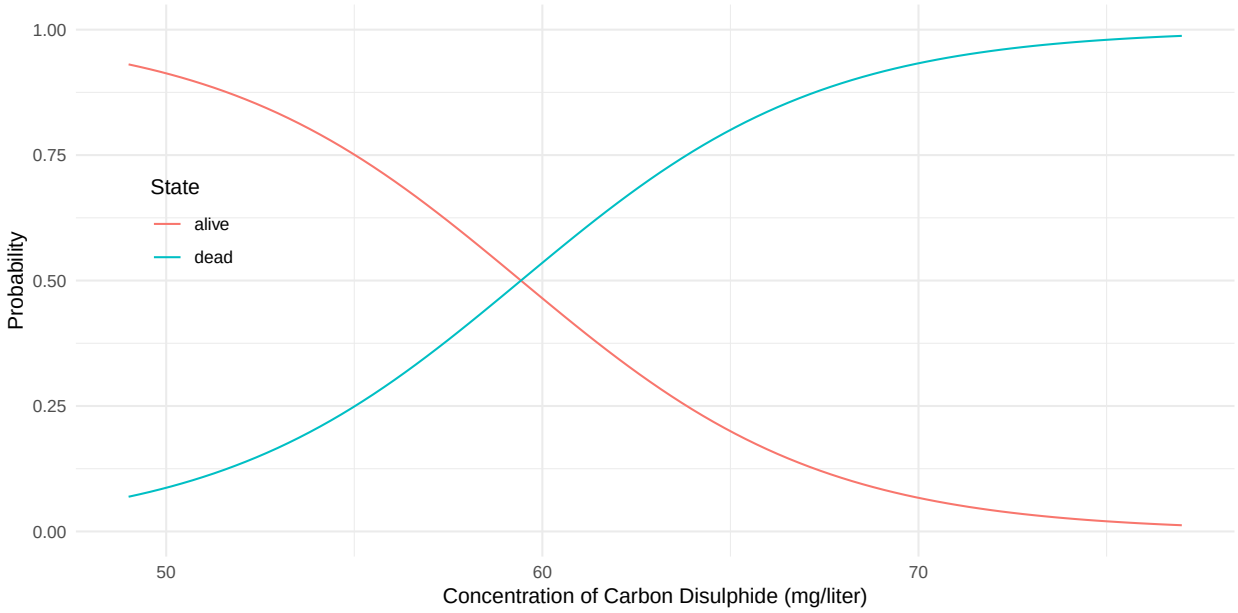
```
d <- data.frame(concentration = seq(49, 77, length = 100))
d <- cbind(d, predict(m, newdata = d, type = "response"))
head(d)
```

```
  concentration  alive    dead
1         49.00 0.9308 0.06920
2         49.28 0.9261 0.07388
3         49.57 0.9212 0.07884
4         49.85 0.9159 0.08412
5         50.13 0.9103 0.08971
6         50.41 0.9044 0.09563
```

```
library(tidyr)
d <- d %>% pivot_longer(cols = c(dead,alive),
  names_to = "state", values_to = "probability")
head(d)
```

```
# A tibble: 6 x 3
  concentration state probability
          <dbl> <chr>       <dbl>
1          49   dead       0.0692
2          49   alive      0.931
3          49.3 dead       0.0739
4          49.3 alive      0.926
5          49.6 dead       0.0788
6          49.6 alive      0.921
```

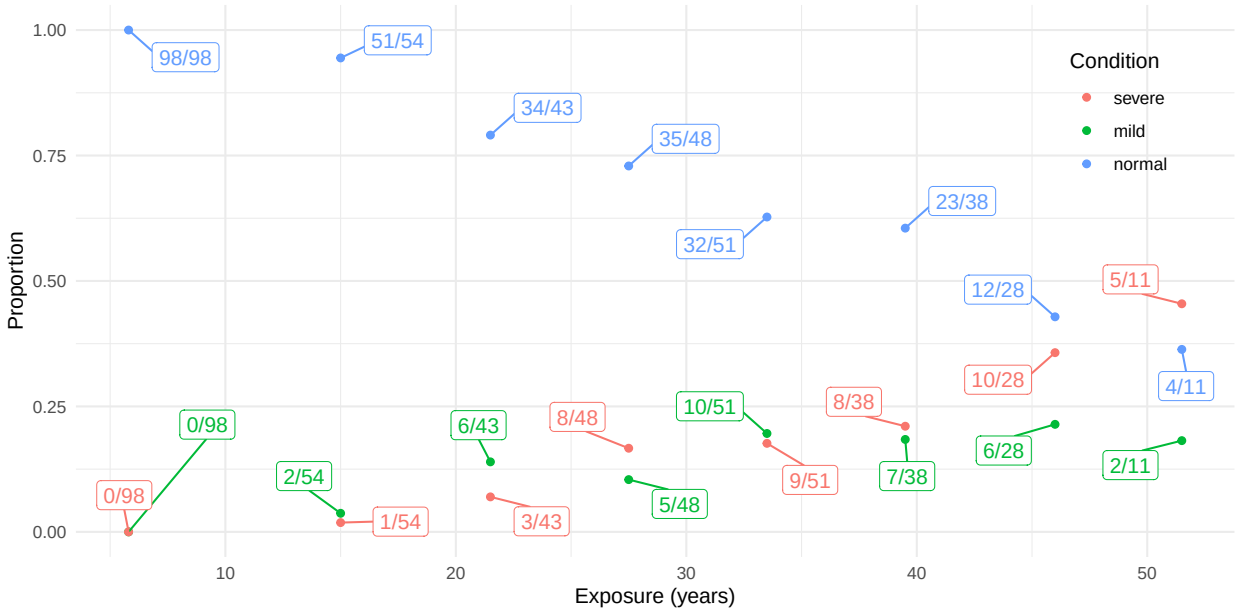
```
p <- ggplot(d, aes(x = concentration, y = probability)) +
  geom_line(aes(color = state)) +
  ylim(0, 1) + theme_minimal() + theme(legend.position = c(0.1, 0.6)) +
  labs(x = "Concentration of Carbon Disulphide (mg/liter)",
    y = "Probability", color = "State")
plot(p)
```




**Example**: Consider again the `pneumo` data frame included with the **VGAM** package.

```
print(pneumo)
```

```
  exposure.time normal mild severe
1           5.8     98    0      0
2          15.0     51    2      1
3          21.5     34    6      3
4          27.5     35    5      8
5          33.5     32   10      9
6          39.5     23    7      8
7          46.0     12    6     10
8          51.5      4    2      5
```



We can estimate a proportional odds model for these data as follows.

```
m <- vglm(cbind(normal, mild, severe) ~ exposure.time, family = propodds, data = pneumo)
summary(m)
```

```
Call:
vglm(formula = cbind(normal, mild, severe) ~ exposure.time, family = propodds,
    data = pneumo)

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept):1 -3.95572    0.26269   -15.1   <2e-16 ***
(Intercept):2 -4.86892    0.29628   -16.4   <2e-16 ***
exposure.time  0.09590    0.00749    12.8   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

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

Residual deviance: 13.4 on 13 degrees of freedom

Log-likelihood: -29.28 on 13 degrees of freedom

Number of Fisher scoring iterations: 18

Warning: Hauck-Donner effect detected in the following estimate(s):
'(Intercept):2'


Exponentiated coefficients:
exposure.time
        1.101
```

That "exponentiated coefficient" is the odds ratio for the effect of exposure time. We can also get that with a confidence interval as follows.

```
exp(cbind(coef(m), confint(m)))
```

```
                         2.5 %  97.5 %
(Intercept):1 0.019145 0.011441 0.03204
(Intercept):2 0.007682 0.004298 0.01373
exposure.time 1.100650 1.084618 1.11692
```

```
d <- data.frame(exposure.time = seq(5, 52, length = 100))
d <- cbind(d, predict(m, newdata = d, type = "response"))
head(d)
```

```
  exposure.time normal    mild  severe
1         5.000 0.9700 0.01774 0.01226
2         5.475 0.9686 0.01853 0.01282
3         5.949 0.9672 0.01935 0.01341
4         6.424 0.9658 0.02021 0.01402
5         6.899 0.9642 0.02111 0.01467
6         7.374 0.9626 0.02204 0.01534
```

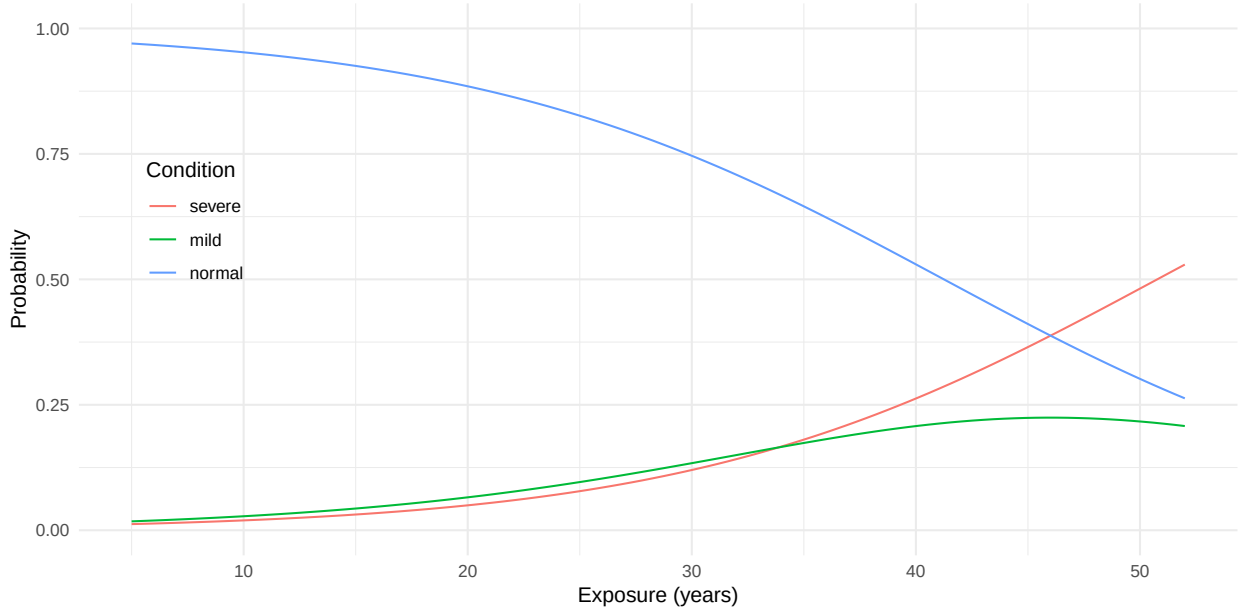
```
library(tidyr)
d <- d %>% pivot_longer(cols = c(normal, mild, severe),
```

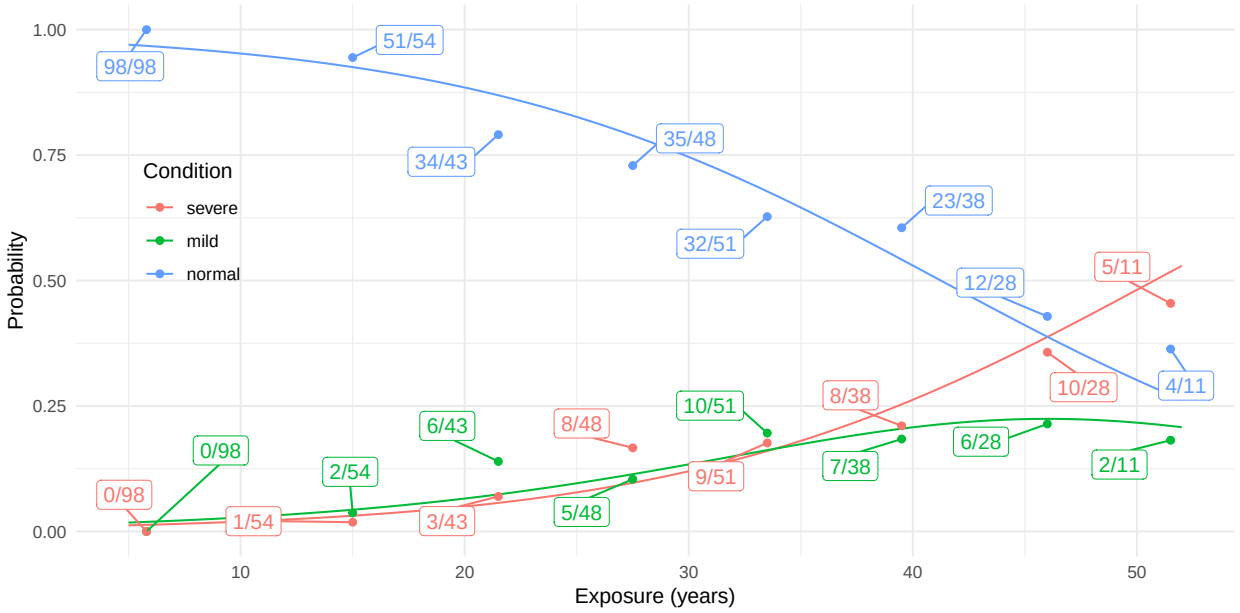
```
  names_to = "condition", values_to = "probability")
head(d)
```

```
# A tibble: 6 x 3
  exposure.time condition probability
          <dbl> <chr>           <dbl>
1             5 normal          0.970
2             5 mild            0.0177
3             5 severe          0.0123
4          5.47 normal          0.969
5          5.47 mild            0.0185
6          5.47 severe          0.0128
```

And then we can plot as usual. Here I have specified an order of the categories so that the colors are consistent with the plot of the raw data.

```
d$condition <- factor(d$condition, levels = c("severe","mild","normal"))
p <- ggplot(d, aes(x = exposure.time, y = probability)) +
  geom_line(aes(color = condition)) +
  ylim(0, 1) + theme_minimal() + theme(legend.position = c(0.1, 0.6)) +
  labs(x = "Exposure (years)", y = "Probability", color = "Condition")
plot(p)
```





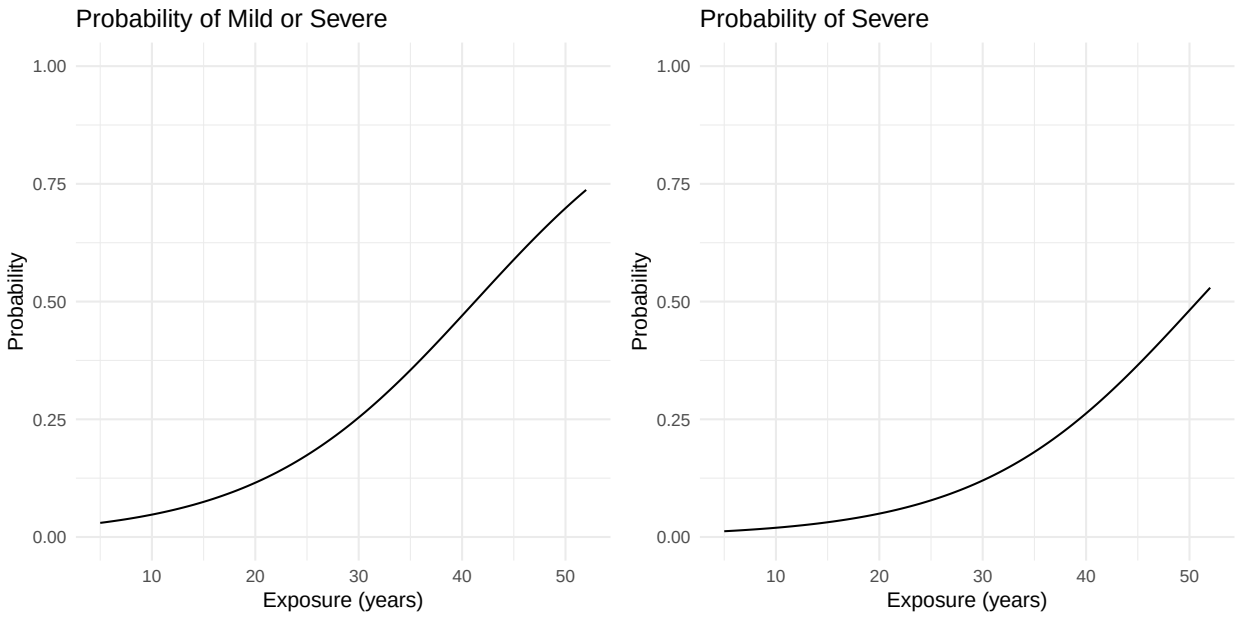

Another way to view the model is through *cumulative* probabilities that reflect the dichotomization.

```
d <- data.frame(exposure.time = seq(5, 52, length = 100))
d <- cbind(d, predict(m, newdata = d, type = "response"))

p <- ggplot(d, aes(x = exposure.time, y = mild + severe)) +
  geom_line() + ylim(0,1) + theme_minimal() +
  labs(x = "Exposure (years)", y = "Probability")
p1 <- p + ggtitle("Probability of Mild or Severe")

p <- ggplot(d, aes(x = exposure.time, y = severe)) +
  geom_line() + ylim(0,1) + theme_minimal() +
  labs(x = "Exposure (years)", y = "Probability")
p2 <- p + ggtitle("Probability of Severe")

cowplot::plot_grid(p1, p2)
```




Data that are not in aggregated form require a slightly different approach to enforce the ordering of the response categories.

**Example**: Consider the data frame `impairment` from the **trtools** package.

```
library(trtools)
head(impairment,3)
```

```
  impairment  ses events
1       none high      1
2       none high      9
3       none high      4
```

```
summary(impairment)
```

```
    impairment   ses         events
 impaired: 9   high:22   Min.   :0.00
 mild    :12   low :18   1st Qu.:2.00
 moderate: 7             Median :4.00
 none    :12             Mean   :4.28
                         3rd Qu.:6.25
                         Max.   :9.00
```

The ordering of the levels is not consistent with the ordering of impairment.

```
levels(impairment$impairment)
```

```
[1] "impaired" "mild"     "moderate" "none"
```

But the ordering can be changed using `factor`.

```
impairment$impairment <- factor(impairment$impairment,
  levels = c("none","mild","moderate","impaired"), ordered = TRUE)
levels(impairment$impairment)
```

```
[1] "none"     "mild"     "moderate" "impaired"
```

Now we can estimate a proportional odds model.

```
m <- vglm(impairment ~ ses + events, family = propodds, data = impairment)
cbind(coef(m), confint(m))
```

```
                       2.5 %  97.5 %
(Intercept):1 -0.8290 -1.7234  0.0654
(Intercept):2 -2.3237 -3.2651 -1.3823
(Intercept):3 -3.3202 -4.4298 -2.2106
seslow         1.1113  0.4004  1.8223
events         0.3187  0.1808  0.4567
```

Applying the exponential function provides odds ratios.

```
exp(cbind(coef(m), confint(m)))
```

```
                       2.5 % 97.5 %
(Intercept):1 0.43648 0.17846 1.0676
(Intercept):2 0.09791 0.03819 0.2510
(Intercept):3 0.03614 0.01192 0.1096
seslow        3.03846 1.49243 6.1860
events        1.37540 1.19816 1.5788
```

We can plot the estimated probabilities as we did in the previous example.

```
d <- expand.grid(ses = c("low","high"), events = seq(0, 9, length = 100))
d <- cbind(d, predict(m, newdata = d, type = "response"))
head(d)
```

```
   ses  events   none   mild moderate impaired
1  low 0.00000 0.4299 0.3408  0.13033  0.09896
2 high 0.00000 0.6961 0.2147  0.05430  0.03488
3  low 0.09091 0.4228 0.3428  0.13288  0.10157
4 high 0.09091 0.6900 0.2185  0.05569  0.03587
5  low 0.18182 0.4157 0.3446  0.13545  0.10424
6 high 0.18182 0.6837 0.2223  0.05711  0.03689
```

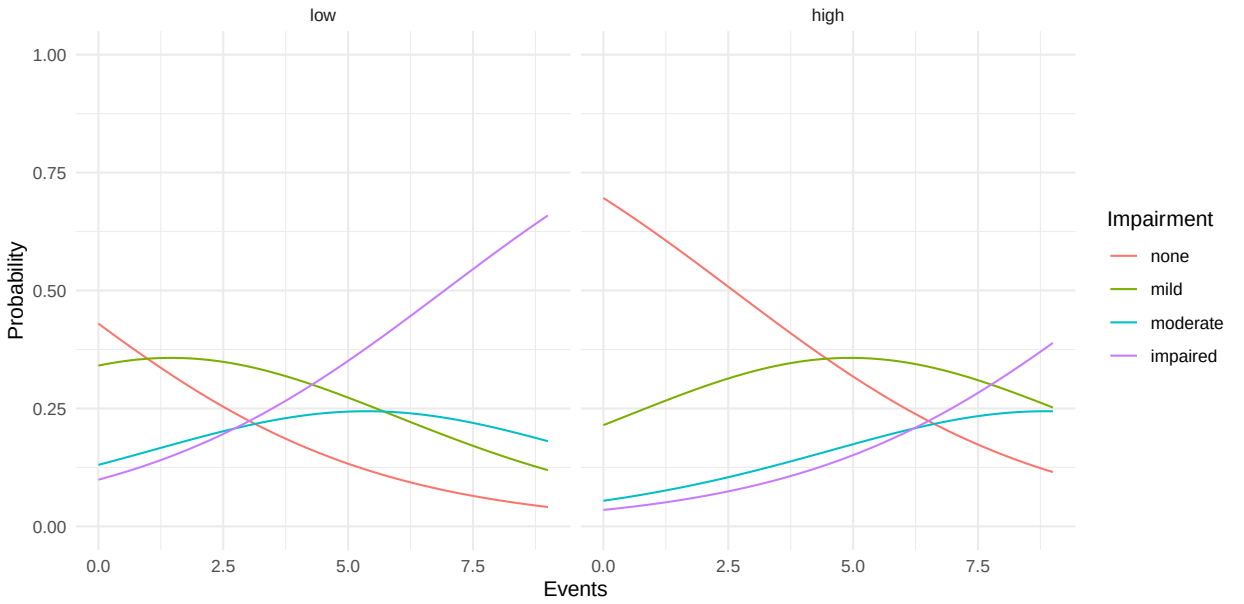
```
library(tidyr)
d <- d %>% pivot_longer(cols = c(none, mild, moderate, impaired),
  names_to = "impairment", values_to = "probability")
head(d)
```

```
# A tibble: 6 x 4
  ses   events impairment probability
  <fct>  <dbl> <chr>            <dbl>
1 low        0 none             0.430
2 low        0 mild             0.341
3 low        0 moderate         0.130
4 low        0 impaired         0.0990
5 high       0 none             0.696
6 high       0 mild             0.215
```

For our plot it would be nice to have the levels of impairment ordered. We can do this by (re)creating the factor and putting the levels in the desired order. Note that `ordered = TRUE` isn't necessary here.

```
d$impairment <- factor(d$impairment,
  levels = c("none","mild","moderate","impaired"))
p <- ggplot(d, aes(x = events, y = probability, color = impairment)) +
  geom_line() + ylim(0,1) + theme_minimal() + facet_wrap(~ ses) +
  labs(x = "Events", y = "Probability", color = "Impairment")
```

```
plot(p)
```




## The Interval-Censored Latent Variable Derivation

Assume a linear model for a *latent* (i.e., unobserved) response variable $Z_i$ such that

$$Z_i = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_k x_{ik} + \epsilon_i,$$

and assume that $Y_i$ arises from interval-censoring of $Z_i$. For example, with $R = 4$ intervals we would have

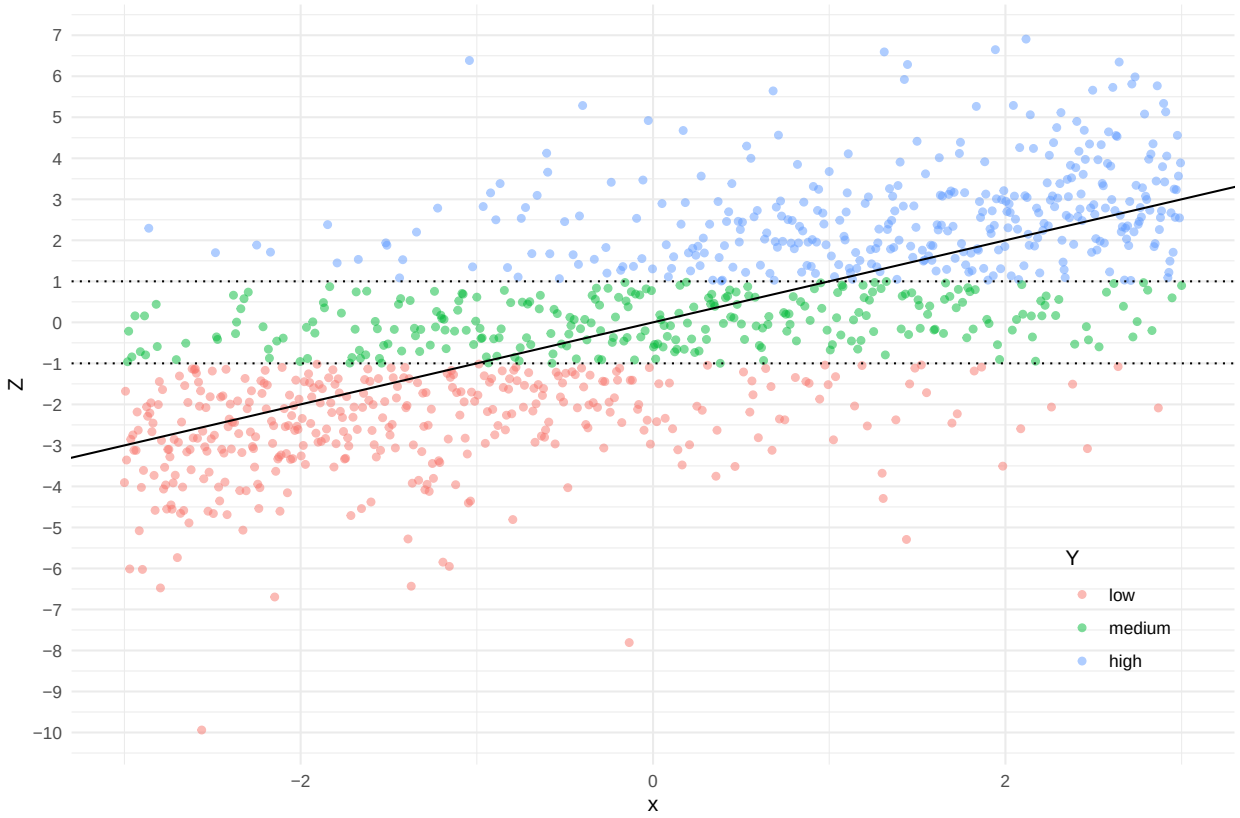
$$Y_i = \begin{cases} 1, & \text{if } Z_i \leq \delta_1, \\ 2, & \text{if } \delta_1 < Z_i \leq \delta_2, \\ 3, & \text{if } \delta_2 < Z_i \leq \delta_3, \\ 4, & \text{if } \delta_3 < Z_i, \end{cases}$$

where $\delta_1 < \delta_2 < \delta_3$.

If the distribution of $Z_i$ is *logistic* then the model for $Y_i$ is a proportional odds model. Other models can be derived by assuming different distributions of $Z_i$. However if the "thresholds" (i.e, $\delta_1, \delta_2, \ldots, \delta_{R-1}$) are unknown, then the origin and scale of $Z_i$ are not uniquely defined. This can be resolved by setting $\beta_0 = 0$ and the variance/scale parameter of $\epsilon_i$ to one.

**Example**: We can see the connection between interval-censoring and a proportional odds model using simulated data.

```
# create some data
set.seed(123)
x <- seq(-3, 3, length = 1000)
z <- x + rlogis(length(x))
y <- cut(z, c(-Inf, -1, 1, Inf), labels = c("low","medium","high"))
d <- data.frame(x = x, z = z, y = y)
```




If we *know* that $Y_i$ is interval-censored at $Y$ = -1 and $Y$ = 1 then we can estimate this model using `survreg` since it will handle the censoring.

```
library(dplyr)
d <- d %>%
   mutate(lower = case_when(y == "medium" ~ -1, y == "high" ~ 1)) %>%
   mutate(upper = case_when(y == "low" ~ -1, y == "medium" ~ 1))
```

Note that `case_when` will return `NA` values for other cases, which is what we want. Here are a few observations.

```
d[c(1,500,1000),]
```

```
             x       z      y lower upper
1    -3.000000 -3.9072    low    NA    -1
500  -0.003003  1.3035   high     1    NA
1000  3.000000  0.8972 medium    -1     1
```

Estimate a model for an interval-censored logistic-distributed response variable.

```
library(survival)
```

```
Warning: package 'survival' was built under R version 4.1.3
```

```
m <- survreg(Surv(lower, upper, type = "interval2") ~ x, dist = "logistic", data = d)
summary(m)$table
```

```
               Value Std. Error       z         p
(Intercept) -0.06696    0.07299 -0.9173 3.590e-01
x            1.05888    0.05962 17.7615 1.405e-70
Log(scale)   0.08994    0.05595  1.6074 1.080e-01
```

If we *do not know* where $Y_i$ is censored (but assume it is at the same values for all observations) then we can estimate the model using `vglm`.

```
d$y <- factor(d$y, levels = c("low","medium","high"), ordered = TRUE)
m <- vglm(y ~ x, family = propodds, data = d)
cbind(coef(m), confint(m))
```

```
                       2.5 %  97.5 %
(Intercept):1  0.8528  0.6985  1.0071
(Intercept):2 -0.9752 -1.1323 -0.8181
x              0.9678  0.8896  1.0459
```

Note that the estimates of $\beta_1$ are *similar* but not identical. This is due to having different information. In the proportional odds model the thresholds are *unknown* and must be estimated, whereas in the "survival" model they were treated as *known*.