Marginal Model for Categorical Data: Case Studies

A $2 \times 2$ Crossover Trial

- A crossover trial of efficacy of two treatments on cerebrovascular deficiency. Sixty-seven subjects from one center was used in the analysis for illustration.

- Two treatment arms (A: active drug, B: placebo) in the trial.

- Thirty-four patients received the active drug (A) followed by placebo (B); another 33 patients were treated in the reverse order.

- Binary outcome, 1: normal electrocardiogram reading, 0: abnormal reading.
Crossover design is one in which subjects are given a sequence of treatments with the objective of studying the difference between individual treatment.

- In crossover design, a subject can be considered as his/her own control to eliminate between subject variation, hence crossover design is more powerful than similar size parallel design.

- Period-by-treatment interactions may indicate carry over effect. A reasonable wash out period is needed.
> xover <- read.table("../data/xover1.data", col.names = c("id", "class", "y", "intercept", +   "trt", "period", "xover", "BA"))
> xover$trtA <- 1-xover$trt
> xover$trtAP <- xover$trtA*xover$period
> xoverw <- reshape(xover[,c("id", "y","period","BA")],
+   direction = "wide", v.names = "y", timevar = "period",idvar = "id")
> xoverw$respat <- ifelse(xoverw$y.0==0,2,3)
> xoverw$respat[(xoverw$y.0+xoverw$y.1)==2] <- 1
> xoverw$respat[(xoverw$y.0+xoverw$y.1)==0] <- 4

> #Table 8.1 in DHLZ book
> tab8.1 <- cbind(table(xoverw$BA,xoverw$respat),table(xoverw$BA),
+   table(xover$BA[xover$y==1],xover$period[xover$y==1]))
> dimnames(tab8.1) <- list(c("AB","BA"),c("(1,1)"","(0,1)"","(1,0)"","(0,0)"),
+   "Total","Period 1 Effective","Period 2 Effective"))
> tab8.1
   (1,1) (0,1) (1,0) (0,0) Total Period 1 Effective Period 2 Effective
AB  22  0  6  6  34     28        22
BA  18  4  2  9  33     20        22
What is the treatment effect if only period 1 data are considered?

\[
\text{Log odds ratio comparing the chance of being normal for drug vs. placebo using period 1 data}
\]

\[
\log\left(\frac{28 \times 13}{20 \times 6}\right)
\]

\[1\] \[1.109662\]

\[
\text{Standard error for the estimated log-odds ratio}
\]

\[
sqrt\left(\frac{1}{28} + \frac{1}{6} + \frac{1}{20} + \frac{1}{13}\right)
\]

\[1\] \[0.5738502\]

\[
\text{Z}
\]

\[
\frac{1.109662}{0.5738502}
\]

\[1\] \[1.933714\]

The estimated treatment effect based on the first period’s data is not significant. Combining the data from both periods could improve efficiency.

- Any within-subject correlation?
  - For patients treated with AB
  - For patients treated with BA

- Any carry-over effect (treatment-by-period interaction)?
Fit a GEE marginal model for the 2×2 Crossover Trial.

```r
> library(gee)
> summary(gee(y ~ trtA+period+trtAP, data = xover, cor = "exchangeable",
+ id = id, family = binomial, scale.fix = TRUE))
```

Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
running glm to get initial regression estimate
(Intercept) trtA period trtAP
 0.4307829 1.1096621 0.1753529 -1.0226507

GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
g ee S-function, version 4.13 modified 98/01/27 (1998)

Model:
Link: Logit
Variance to Mean Relation: Binomial
Correlation Structure: Exchangeable

Call:
gee(formula = y ~ trtA + period + trtAP, id = id, data = xover,
family = binomial, corstr = "exchangeable", scale.fix = TRUE)

Summary of Residuals:

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.8235294</td>
<td>-0.6060606</td>
<td>0.1764706</td>
<td>0.3529412</td>
<td>0.3939394</td>
</tr>
</tbody>
</table>
### Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Naive S.E.</th>
<th>Naive z</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.4307829</td>
<td>0.3562627</td>
<td>1.2091723</td>
<td>0.3562627</td>
<td>1.2091723</td>
</tr>
<tr>
<td>trtA</td>
<td>1.1096621</td>
<td>0.5738502</td>
<td>1.9337140</td>
<td>0.5738502</td>
<td>1.9337140</td>
</tr>
<tr>
<td>period</td>
<td>0.1753529</td>
<td>0.5056787</td>
<td>0.3467674</td>
<td>0.5056787</td>
<td>0.3467674</td>
</tr>
<tr>
<td>trtAP</td>
<td>-1.0226507</td>
<td>0.9846776</td>
<td>-1.0446231</td>
<td>0.9789663</td>
<td>-1.0446231</td>
</tr>
</tbody>
</table>

Estimated Scale Parameter: 1
Number of Iterations: 1

Working Correlation:

```
[,1] [,2]
[1,] 1.0000000 0.6401548
[2,] 0.6401548 1.0000000
```

> # Drop the interaction term
> summary (gee (y ~ trtA+period, data = xover, cor = "exchangeable",
+        id = id, family = binomial, scale.fix = TRUE))

... 

### Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Naive S.E.</th>
<th>Naive z</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.6660113</td>
<td>0.2842188</td>
<td>2.343304</td>
<td>0.2878956</td>
<td>2.313378</td>
</tr>
<tr>
<td>trtA</td>
<td>0.5690305</td>
<td>0.2287782</td>
<td>2.487258</td>
<td>0.2327207</td>
<td>2.445123</td>
</tr>
<tr>
<td>period</td>
<td>-0.2953176</td>
<td>0.2271589</td>
<td>-1.300048</td>
<td>0.2311211</td>
<td>-1.277761</td>
</tr>
</tbody>
</table>
Fit a GEE marginal model with working independent correlation.

\[
> \text{summary (gee (y \sim \text{trtA} + \text{period}, data = \text{xover}, cor = "independence",} \\
+ \text{id = id, family = binomial, scale.fix = TRUE))}
\]

... 

Model:
Link: Logit
Variance to Mean Relation: Binomial
Correlation Structure: Independent

... 

Coefficients:
\[
\begin{array}{cccccc}
(\text{Intercept}) & 0.6603929 & 0.3212796 & 2.0555081 & 0.2874920 & 2.297083 \\
\text{trtA} & 0.5581594 & 0.3784107 & 1.4750094 & 0.2332530 & 2.392936 \\
\text{period} & -0.2743154 & 0.3768179 & -0.7279787 & 0.2322731 & -1.181004
\end{array}
\]

Working Correlation
\[
\begin{array}{cc}
[,1] & [,2] \\
[1,] & 1 & 0 \\
[2,] & 0 & 1
\end{array}
\]
Fit a GEE marginal model with odds ratio and alternating logistic regression.

The \texttt{alr} package of R implements the ALR algorithm (http://www.biostat.harvard.edu/~carey/vcwww_4.html).

```r
> library(alr)
> # Model 1 in Table 8.2 of DHLZ
> x1 <- as.matrix(xover[,c("trtA", "period","trtAP")])
> xover.alr1 <- alr(xover$y ~ x1, id = xover$id,
+                 ainit = 0.01, depmodel = "exchangeable")
[1] "alternating logistic regression - Splus, @(#) alr.q 4.4 98/02/24"
[1] "Running glm to get initial estimates"
[1] 0.4307829 1.1096621 0.1753529 -1.0226507
[1] "nobs"
[1] 134
> summary (xover.alr1)

ALR: ALTERNATING LOGISTIC REGRESSION
alr S-function, version 4.4 98/02/24

Call:
alr(formula = xover$y ~ x1, id = xover$id, ainit = 0.01, depmodel = "exchangeable")

Summary of Residuals:

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
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<th>3Q</th>
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<td>0.1764706</td>
<td>0.3529412</td>
<td>0.3939394</td>
</tr>
</tbody>
</table>
```
Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.4307829</td>
<td>0.3562627</td>
<td>1.2091723</td>
</tr>
<tr>
<td>x1trtA</td>
<td>1.1096621</td>
<td>0.5738502</td>
<td>1.9337140</td>
</tr>
<tr>
<td>x1period</td>
<td>0.1753529</td>
<td>0.5056787</td>
<td>0.3467674</td>
</tr>
<tr>
<td>x1trtAP</td>
<td>-1.0226507</td>
<td>0.9789663</td>
<td>-1.0446231</td>
</tr>
</tbody>
</table>

Alpha:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td>3.537803</td>
<td>0.8200298</td>
<td>4.314238</td>
</tr>
</tbody>
</table>

Number of observations : 134
Number of Iterations : 5

> # Odds ratio between the two periods
> exp(3.54)
[1] 34.46692
Drop the interaction term from the above ALR model.

```r
> # Model 2 in Table 8.2 of DHLZ
> x2 <- as.matrix (xover[,c("trtA", "period")])
> xover.alr2 <- alr (xover$y ~ x2, id = xover$id,
+ ainit = 0.01, depmodel = "exchangeable")
```

> summary (xover.alr2)

**ALR: ALTERNATING LOGISTIC REGRESSION**

**alr S-function, version 4.4 98/02/24**

**Call:**

alr(formula = xover$y ~ x2, id = xover$id, ainit = 0.01, depmodel = "exchangeable")

**Summary of Residuals:**

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>-0.7761458</td>
<td>-0.5937025</td>
<td>0.2238542</td>
<td>0.3375072</td>
<td>0.4062975</td>
</tr>
</tbody>
</table>

**Coefficients:**

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.6744228</td>
<td>0.2882568</td>
</tr>
<tr>
<td>x2trtA</td>
<td>0.5689228</td>
<td>0.2335157</td>
</tr>
<tr>
<td>x2period</td>
<td>-0.2951299</td>
<td>0.2318499</td>
</tr>
</tbody>
</table>

**Alpha:**

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td>3.561692</td>
<td>0.8147993</td>
</tr>
</tbody>
</table>
A 3×3 Crossover Trial

• Three-period crossover trial of an analgesic drug for pain relieving.

• Three levels of analgesic (placebo, low, and high) were given to each of the 86 women.

• Women were randomized to one of the six possible orders for administering the three treatment levels.

• Ignoring the order of treatment, pain was relieved for 26% with placebo, 73% with low dose, and 78% with high dose.

• A cross-over study, the treatment changes each time.

• Binary outcome, 1: relief, 0: no relief.
> xover3 <- read.table("../data/xover3new.txt",col.names = c("id", "class",
+ "relief","intercept", "tx2", "tx3", "p2", "p3","ptx1", "ptx2", "ptx3"))

> xover3$period <- ifelse (xover3$p2 == 1, 2,ifelse (xover3$p3 == 1, 3, 1))
> xover3$tr <- ifelse (xover3$tx2 == 1, 2,ifelse (xover3$tx3 == 1, 3, 1))
>
> xover3 <- xover3[order(xover3$id,xover3$period),]
> xover3w <- reshape (xover3[,c("id", "relief","period","tr")],
+ direction = "wide", timevar = "period",idvar = "id")
> xover3w$grp[xover3w$tr.1==1] <- ifelse(xover3w$tr.2[xover3w$tr.1==1] == 2, 1, 2)
> xover3w$grp[xover3w$tr.1==2] <- ifelse(xover3w$tr.2[xover3w$tr.1==2] == 1, 3, 4)
> xover3w$grp[xover3w$tr.1==3] <- ifelse(xover3w$tr.2[xover3w$tr.1==3] == 1, 5, 6)
>
> xover3w$pat <- 1
> xover3w$pat[apply(xover3w[,c(2,4,6)],1,sum)==3] <- 8
> xover3w$pat[apply(xover3w[,c(2,4,6)],1,sum)==1] <- 2
> ind34 <- xover3w$pat==2&xover3w$relief.1==0
> xover3w$pat[ind34] <- ifelse(xover3w$relief.2[ind34] == 1, 3, 4)
> xover3w$pat[apply(xover3w[,c(2,4,6)],1,sum)==2] <- 7
> ind56 <- xover3w$pat==7&xover3w$relief.1==1
> xover3w$pat[ind56] <- ifelse(xover3w$relief.2[ind56] == 1, 5, 6)
>
> #Table 8.3 in DHLZ book
> tab8.3 <- cbind(table(xover3w$grp,xover3w$pat),table(xover3w$grp))
> dimnames(tab8.3) <- list(c("ABC","ACB","BAC","BCA","CAB","CBA"),
+ c("000","100","010","001","110","101","011","111","Total"))
> tab8.3

<table>
<thead>
<tr>
<th></th>
<th>000</th>
<th>010</th>
<th>001</th>
<th>110</th>
<th>101</th>
<th>011</th>
<th>111</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>ACB</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>BAC</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>BCA</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CAB</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CBA</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

> # Look at all periods, ignoring within-subject correlation
> xover3tab <- table(xover3$relief,xover3$tr)
> xover3tab[2,]/apply(xover3tab,2,sum)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2558140</td>
<td>0.7093023</td>
<td>0.8023256</td>
<td></td>
</tr>
</tbody>
</table>

> # Look at the data stratified by period
> with (xover3, ftable (period, relief, tr))

<table>
<thead>
<tr>
<th>tr 1 2 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>period relief</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

- Just from the above tables, it appears that the two different doses of the analgesic treatment (B and C) both did better than the placebo (A). The high dose may be slightly better than the low dose.
• Is there any carry-over effect?

```r
> xover3$ptx <- ifelse (xover3$ptx1 == 1, 1, ifelse (xover3$ptx2 == 1, 2, 3))
> xover3$ptx[xover3$period == 1] <- 0
> with (xover3, ftable (ptx, relief, tr))

   tr  1  2  3
ptx relief
  0  0 24  7  7
   1  7 20 21
  1  0  0  6  5
   1  0 23 26
  2  0 20  0  5
   1  9  0 22
  3  0 20 12  0
   1  6 18  0

> round(matrix(c(20*24/(7*7),21*7/(7*20),24*21/(7*7),
+ 18*20/(6*12),26*6/(23*5),22*20/(9*5)), nrow=2,byrow=T),2)

[,1] [,2] [,3]
[1,]  9.8  1.05 10.29
[2,]  5.0  1.36  9.78
```
We fit four models, assuming working independence (model 1) or unstructured correlation (model 2) and using odds ratios to characterize the associations (model 3, 4).

Model 1: Working independence correlation.

```r
> xover.gee <- gee(relief ~ p2 + p3 + tx2 + tx3 + ptx2 + ptx3,
+                   data = xover3, scale.fix = TRUE, id = id,
+                   family = binomial)

Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
running glm to get initial regression estimate
(Intercept)    p2     p3    tx2    tx3    ptx2    ptx3
  -1.0866229  0.4141734  0.5885481  1.9493789  2.222895   0.1922158 -0.8308649
> summary(xover.gee)

GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
gee S-function, version 4.13 modified 98/01/27 (1998)

Model:
Link:          Logit
Variance to Mean Relation: Binomial
Correlation Structure: Independent

Call:
gee(formula = relief ~ p2 + p3 + tx2 + tx3 + ptx2 + ptx3, id = id,
     data = xover3, family = binomial, scale.fix = TRUE)
```
Summary of Residuals:

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.8486709</td>
<td>-0.2522547</td>
<td>0.1751094</td>
<td>0.2431169</td>
<td>0.8180683</td>
</tr>
</tbody>
</table>

Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Naive S.E.</th>
<th>Naive z</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.0866229</td>
<td>0.3280932</td>
<td>-3.3119335</td>
<td>0.3171169</td>
<td>-3.4265694</td>
</tr>
<tr>
<td>p2</td>
<td>0.4141734</td>
<td>0.4609959</td>
<td>0.8984318</td>
<td>0.4188751</td>
<td>0.9887755</td>
</tr>
<tr>
<td>p3</td>
<td>0.5885481</td>
<td>0.4752612</td>
<td>1.2383678</td>
<td>0.4556855</td>
<td>1.2915665</td>
</tr>
<tr>
<td>tx2</td>
<td>1.9493789</td>
<td>0.3888244</td>
<td>5.0135193</td>
<td>0.4139646</td>
<td>4.7090470</td>
</tr>
<tr>
<td>tx3</td>
<td>2.2222895</td>
<td>0.3945988</td>
<td>5.6317689</td>
<td>0.4203606</td>
<td>5.2866265</td>
</tr>
<tr>
<td>ptx2</td>
<td>-0.1922158</td>
<td>0.5070045</td>
<td>-0.3791205</td>
<td>0.5120981</td>
<td>-0.3753495</td>
</tr>
<tr>
<td>ptx3</td>
<td>-0.8308649</td>
<td>0.4818407</td>
<td>-1.7243562</td>
<td>0.4199874</td>
<td>-1.9783093</td>
</tr>
</tbody>
</table>

Estimated Scale Parameter: 1
Number of Iterations: 1

Working Correlation

<table>
<thead>
<tr>
<th>[,1]</th>
<th>[,2]</th>
<th>[,3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1,]</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>[2,]</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>[3,]</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Model 2: Working unstructured correlation.

```r
> xover.gee <- gee (relief ~ p2 + p3 + tx2 + tx3 + ptx2 + ptx3,
+     data = xover3, scale.fix = TRUE,
+     family = binomial, corstr = "unstructured")
Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
running glm to get initial regression estimate
(Intercept)  p2    p3   tx2   tx3  ptx2  ptx3
-1.0866229  0.4141734  0.5885481  1.9493789  2.2222895 -0.1922158 -0.8308649
> summary (xover.gee)

GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
gee S-function, version 4.13 modified 98/01/27 (1998)

Model:
  Link: Logit
  Variance to Mean Relation: Binomial
  Correlation Structure: Unstructured

Call:
  gee(formula = relief ~ p2 + p3 + tx2 + tx3 + ptx2 + ptx3, data = xover3,
      family = binomial, corstr = "unstructured", scale.fix = TRUE)

Summary of Residuals:
    Min  1Q Median  3Q Max
-0.8453150 -0.2494076  0.1717964  0.2401164  0.8222795
```
Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Naive S.E.</th>
<th>Naive z</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.1017745</td>
<td>0.3259071</td>
<td>-3.3806403</td>
<td>0.3215724</td>
<td>-3.4262094</td>
</tr>
<tr>
<td>p2</td>
<td>0.3759339</td>
<td>0.4753671</td>
<td>0.7908287</td>
<td>0.4167114</td>
<td>0.9021444</td>
</tr>
<tr>
<td>p3</td>
<td>0.5462774</td>
<td>0.4608093</td>
<td>1.1854738</td>
<td>0.4504195</td>
<td>1.2128191</td>
</tr>
<tr>
<td>tx2</td>
<td>1.9884546</td>
<td>0.3801905</td>
<td>5.2301535</td>
<td>0.4163466</td>
<td>4.7759601</td>
</tr>
<tr>
<td>tx3</td>
<td>2.2538159</td>
<td>0.3878265</td>
<td>5.8114026</td>
<td>0.4252588</td>
<td>5.2998688</td>
</tr>
<tr>
<td>ptx2</td>
<td>-0.1252514</td>
<td>0.4811531</td>
<td>-0.2603150</td>
<td>0.5122957</td>
<td>-0.244904</td>
</tr>
<tr>
<td>ptx3</td>
<td>-0.8060278</td>
<td>0.4598286</td>
<td>-1.7528876</td>
<td>0.4167318</td>
<td>-1.9341644</td>
</tr>
</tbody>
</table>

Estimated Scale Parameter: 1
Number of Iterations: 3

Working Correlation

```
[,1]    [,2]    [,3]
[1,] 1.00000000 -0.17040570 0.03317488
[2,] -0.17040570 1.00000000 0.03673587
[3,] 0.03317488 0.03673587 1.00000000
```

- The results are similar. The two doses of treatments seemed to be highly effective and the difference between them is small (odds ratios $\sim 8$).
- There is a slight evidence for the carry-over effect after the high dose analgesic (OR is $exp(-0.81) = 0.4$).
- DHLZ Example 8.2 used different models, i.e. ALR, (models 1 and 2 in Table 8.4, p152) with similar conclusions.
Model 3: ALR with exchangeable correlation for the association (model 1 in Table 8.4 of DHLZ).

```r
> library(alr)
> x <- as.matrix(xover3[,c("p2", "p3", "tx2",
+ "tx3", "ptx2", "ptx3")])
> y <- xover3$relief
> xover.alr <- alr (y ~ x, id = xover3$id,
+ ainit = 0.01, depmodel = "exchangeable")
```

```
[1] "alternating logistic regression - Splus, @(#) alr.q 4.4 98/02/24"
[1] "Running glm to get initial estimates"
[1] -1.0866229 0.4141734 0.5885481 1.9493789 2.2222895 -0.1922158 -0.8308649
[1] "nobs"
[1] 258
> summary (xover.alr)

ALR: ALTERNATING LOGISTIC REGRESSION
alr S-function, version 4.4 98/02/24

Call:
alr(formula = y ~ x, id = xover3$id, ainit = 0.01, depmodel = "exchangeable")

Summary of Residuals:
     Min   1Q Median   3Q  Max
-0.8493048 -0.2529760  0.1745086  0.2431256  0.8169703
```
Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.0828026</td>
<td>0.3166356</td>
<td>-3.4197123</td>
</tr>
<tr>
<td>xp2</td>
<td>0.4183858</td>
<td>0.4206120</td>
<td>0.9947072</td>
</tr>
<tr>
<td>xp3</td>
<td>0.5935401</td>
<td>0.4582208</td>
<td>1.2953146</td>
</tr>
<tr>
<td>xtx2</td>
<td>1.9444196</td>
<td>0.4135581</td>
<td>4.7016844</td>
</tr>
<tr>
<td>xtx3</td>
<td>2.2184216</td>
<td>0.4190099</td>
<td>5.2944374</td>
</tr>
<tr>
<td>xptx2</td>
<td>-0.2095632</td>
<td>0.5156085</td>
<td>-0.4064387</td>
</tr>
<tr>
<td>xptx3</td>
<td>-0.8315376</td>
<td>0.4196590</td>
<td>-1.9814602</td>
</tr>
</tbody>
</table>

Alpha:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td>-0.2235135</td>
<td>0.3803329</td>
<td>-0.5876787</td>
</tr>
</tbody>
</table>

Number of observations : 258
Number of Iterations : 3
Model 4: ALR with unstructured correlation for the association (Model 2, Table 8.4).

For an unstructured correlation matrix, there are $n_i(n_i - 1)/2$ parameters. For the balanced design here we have $n_i = 3$ and 3 odds ratios to estimate. We need first make a design matrix with $n_i(n_i - 1) \times q$ ($6 \times 3$) elements where $q$ is the number of parameters to be estimated.

```r
> correctz <- matrix(c(1, 0, 0,
+                      0, 1, 0,
+                      1, 0, 0,
+                      0, 0, 1,
+                      0, 1, 0,
+                      0, 0, 1),
+                      ncol = 3, byrow = TRUE)
> xover.alr <- alr(y ~ x, id = xover3$id,
+                   z = correctz,
+                   zmast = 1,
+                   zlocs = rep(1:3, 86),
+                   ainit = rep(0.01, 3),
+                   depmodel = "general")
```

- The rows correspond to pairs (1,2), (1,3), (2,1), (2,3), (3,1), (3,2).
- Pairs of (1,2) and (2,1) share the same parameter, so they have the same values in their rows. So are (1,3) and (3,1); (2,3) and (3,2).
> summary (xover.alr)

... Summary of Residuals:

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.8445614</td>
<td>-0.2503970</td>
<td>0.1722254</td>
<td>0.2416136</td>
<td>0.8218775</td>
</tr>
</tbody>
</table>

Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.0964962</td>
<td>0.3203766</td>
<td>-3.4225233</td>
</tr>
<tr>
<td>xp2</td>
<td>0.3696734</td>
<td>0.4138135</td>
<td>0.8933333</td>
</tr>
<tr>
<td>xp3</td>
<td>0.5487134</td>
<td>0.4480590</td>
<td>1.2246452</td>
</tr>
<tr>
<td>xtx2</td>
<td>1.9818621</td>
<td>0.4145504</td>
<td>4.7807504</td>
</tr>
<tr>
<td>xtx3</td>
<td>2.2403497</td>
<td>0.4240615</td>
<td>5.2830774</td>
</tr>
<tr>
<td>xptx2</td>
<td>-0.1226300</td>
<td>0.5078993</td>
<td>-0.2414455</td>
</tr>
<tr>
<td>xptx3</td>
<td>-0.8022969</td>
<td>0.4159715</td>
<td>-1.9287305</td>
</tr>
</tbody>
</table>

Alpha:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td>-0.9643585</td>
<td>0.6067443</td>
<td>-1.5893986</td>
</tr>
<tr>
<td>a2</td>
<td>0.1366401</td>
<td>0.7075102</td>
<td>0.1931282</td>
</tr>
<tr>
<td>a3</td>
<td>0.2622779</td>
<td>0.6956535</td>
<td>0.3770237</td>
</tr>
</tbody>
</table>
ALR in SAS

The implementation of ALR is perhaps more mature in SAS:

data xover3;
   infile '../xover3new.txt';
   input id class relief inter tx2 tx3 p2 p3 ptx1 ptx2 ptx3;
run;

ALR with exchangeable correlation for the association.

proc genmod data = xover3 descending;
   class id;
   model relief = p2 p3 tx2 tx3 ptx2 ptx3 / dist = bin;
   repeated subject = id / logor = exch modelse;
run;

GEE Model Information

<table>
<thead>
<tr>
<th>Log Odds Ratio Structure</th>
<th>Exchangeable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Effect</td>
<td>id (86 levels)</td>
</tr>
<tr>
<td>Number of Clusters</td>
<td>86</td>
</tr>
<tr>
<td>Correlation Matrix Dimension</td>
<td>3</td>
</tr>
<tr>
<td>Maximum Cluster Size</td>
<td>3</td>
</tr>
<tr>
<td>Minimum Cluster Size</td>
<td>3</td>
</tr>
</tbody>
</table>

Algorithm converged.
GEE Fit Criteria

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>QIC</td>
<td>297.1377</td>
</tr>
<tr>
<td>QICu</td>
<td>297.1526</td>
</tr>
</tbody>
</table>

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Lower 95% Limit</th>
<th>Upper 95% Limit</th>
<th>Z</th>
<th>Pr &gt;</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.0828</td>
<td>0.3166</td>
<td>-1.7034</td>
<td>-0.4622</td>
<td>-3.42</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td>p2</td>
<td>0.4184</td>
<td>0.4206</td>
<td>-0.4060</td>
<td>1.2428</td>
<td>0.99</td>
<td>0.3199</td>
<td></td>
</tr>
<tr>
<td>p3</td>
<td>0.5935</td>
<td>0.4582</td>
<td>-0.3046</td>
<td>1.4916</td>
<td>1.30</td>
<td>0.1952</td>
<td></td>
</tr>
<tr>
<td>tx2</td>
<td>1.9444</td>
<td>0.4136</td>
<td>1.1339</td>
<td>2.7550</td>
<td>4.70</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>tx3</td>
<td>2.2184</td>
<td>0.4190</td>
<td>1.3972</td>
<td>3.0397</td>
<td>5.29</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>ptx2</td>
<td>-0.2096</td>
<td>0.5156</td>
<td>-1.2201</td>
<td>0.8010</td>
<td>-0.41</td>
<td>0.6844</td>
<td></td>
</tr>
<tr>
<td>ptx3</td>
<td>-0.8315</td>
<td>0.4197</td>
<td>-1.6541</td>
<td>-0.0090</td>
<td>-1.98</td>
<td>0.0475</td>
<td></td>
</tr>
<tr>
<td>Alpha1</td>
<td>-0.2235</td>
<td>0.3803</td>
<td>-0.9690</td>
<td>0.5219</td>
<td>-0.59</td>
<td>0.5567</td>
<td></td>
</tr>
</tbody>
</table>
ALR with unstructured correlation for the association.

```plaintext
proc genmod data = xover3 descending;
   class id;
   model relief = p2 p3 tx2 tx3 ptx2 ptx3 / dist = bin;
   repeated subject = id / logor = fullclust modelse;
run;
```

**GEE Model Information**

<table>
<thead>
<tr>
<th>Log Odds Ratio Structure</th>
<th>Fully Parameterized Clusters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Effect</td>
<td>id (86 levels)</td>
</tr>
<tr>
<td>Number of Clusters</td>
<td>86</td>
</tr>
<tr>
<td>Correlation Matrix Dimension</td>
<td>3</td>
</tr>
<tr>
<td>Maximum Cluster Size</td>
<td>3</td>
</tr>
<tr>
<td>Minimum Cluster Size</td>
<td>3</td>
</tr>
</tbody>
</table>

**Log Odds Ratio Parameter Information**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha1</td>
<td>(1, 2)</td>
</tr>
<tr>
<td>Alpha2</td>
<td>(1, 3)</td>
</tr>
<tr>
<td>Alpha3</td>
<td>(2, 3)</td>
</tr>
</tbody>
</table>

Algorithm converged.

**GEE Fit Criteria**
### Analysis Of GEE Parameter Estimates

#### Empirical Standard Error Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Error</th>
<th>95% Confidence Limits</th>
<th>Z</th>
<th>Pr &gt;</th>
<th>Z</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.0965</td>
<td>0.3204</td>
<td>-1.7244 -0.4686</td>
<td>-3.42</td>
<td>0.0006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p2</td>
<td>0.3697</td>
<td>0.4138</td>
<td>-0.4414 1.1807</td>
<td>0.89</td>
<td>0.3717</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p3</td>
<td>0.5487</td>
<td>0.4481</td>
<td>-0.3295 1.4269</td>
<td>1.22</td>
<td>0.2207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tx2</td>
<td>1.9819</td>
<td>0.4146</td>
<td>1.1693 2.7944</td>
<td>4.78</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tx3</td>
<td>2.2404</td>
<td>0.4241</td>
<td>1.4092 3.0715</td>
<td>5.28</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ptx2</td>
<td>-0.1226</td>
<td>0.5079</td>
<td>-1.1181 0.8729</td>
<td>-0.24</td>
<td>0.8092</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ptx3</td>
<td>-0.8023</td>
<td>0.4160</td>
<td>-1.6176 0.0130</td>
<td>-1.93</td>
<td>0.0538</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha1</td>
<td>-0.9644</td>
<td>0.6067</td>
<td>-2.1536 0.2248</td>
<td>-1.59</td>
<td>0.1120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha2</td>
<td>0.1366</td>
<td>0.7075</td>
<td>-1.2501 1.5233</td>
<td>0.19</td>
<td>0.8469</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha3</td>
<td>0.2623</td>
<td>0.6957</td>
<td>-1.1012 1.6257</td>
<td>0.38</td>
<td>0.7062</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Other possible choices for logor are: logorvar (allows the log OR to depend on another variable, e.g., center); ZFULL (fully specified z-matrix specified in ZDATA= data set) etc.
Seizure Data

- Clinical trial of 59 epileptics.
- For each patients, the number of epileptic seizures was recorded during a baseline period of eight weeks.
- Patients were randomized to be treated with the anti-epileptic drug progabide or placebo.
- Number of seizures was then recorded in four consecutive two-week intervals.
- Does progabide treatment reduce the rate of epileptic seizures?
- Count data.
A little data manipulation such that each person will have an additional row of baseline (or pre-treatment) data.

```r
> seize <- read.table("../data/seize.data",
+          col.names = c("id", "seizure", "week",
+                          "progabide", "baseline8", "age"))
> seize.base <- data.frame (id = seize$id, seizure = seize$baseline8, week = seize$week,
+                          progabide = seize$progabide, age = seize$age)
> seize.base <- seize.base[seize.base$week == 1,]
> seize.base$week <- 0
> seize.full <- rbind (seize[,-5], seize.base)
> seize.full <- seize.full[order(seize.full$id, seize.full$week),]
> seize.full$time <- ifelse (seize.full$week == 0, 8, 2)
> seize.full$post <- as.numeric (seize.full$week != 0)
> seize.full[1:10,]

   id seizure week progabide age time post
 1 1131    101     76       0  18   8   0
 2   113    101     11       1  18   2   1
 3   114    101     14       2  18   2   1
 4   115    101      9       3  18   2   1
 5   116    101      8       4  18   2   1
 6  1171    102     38       0  32   8   0
 7   117    102      8       1  32   2   1
 8   118    102      7       2  32   2   1
 9   119    102      9       3  32   2   1
10  120    102      4       4  32   2   1
```

Fit a Poisson family GEE model with exchangeable correlation (Table 8.11, textbook).

- Offset (a term with constant coefficient) is used to take into account that the time periods are different (8 weeks vs 2 weeks).

\[
\log(\mu_{ij}) = \log(t_{ij}\lambda_{ij}) = \log(t_{ij}) + \log \lambda_{ij} = \log(t_{ij}) + X_{ij}^T \beta.
\]

```r
> sg1 <- gee(seizure ~ post + progabide + post:progabide +
+   offset(log(time)),
+   data = seize.full, id = id, family = "poisson",
+   cor = "exchangeable")
```

Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
running glm to get initial regression estimate
(Intercept) post progabide post:progabide
1.34760922 0.11079814 0.02651461 -0.10368067

```r
> summary(sg1)
```

GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
gae S-function, version 4.13 modified 98/01/27 (1998)

Model:
Link: Logarithm
Variance to Mean Relation: Poisson
Correlation Structure: Exchangeable

Call:
gee(formula = seizure ~ post + progabide + post:progabide + offset(log(time))),
id = id, data = seize.full, family = "poisson", corstr = "exchangeable")

Summary of Residuals:

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-4.299107</td>
<td>-1.299107</td>
<td>2.020161</td>
<td>10.374640</td>
<td>147.048387</td>
</tr>
</tbody>
</table>

Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Naive S.E.</th>
<th>Naive z</th>
<th>Robust S.E.</th>
<th>Robust z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.3476092</td>
<td>0.1511851</td>
<td>8.913636</td>
<td>0.1573571</td>
<td>8.5640166</td>
</tr>
<tr>
<td>post</td>
<td>0.1107981</td>
<td>0.1547038</td>
<td>0.716196</td>
<td>0.1160997</td>
<td>0.9543358</td>
</tr>
<tr>
<td>progabide</td>
<td>0.0265146</td>
<td>0.2072721</td>
<td>0.127922</td>
<td>0.2218539</td>
<td>0.1195138</td>
</tr>
<tr>
<td>post:progabide</td>
<td>-0.103681</td>
<td>0.2199500</td>
<td>-0.471383</td>
<td>0.2136100</td>
<td>-0.4853736</td>
</tr>
</tbody>
</table>

Estimated Scale Parameter: 19.70269
Number of Iterations: 1

Working Correlation

<table>
<thead>
<tr>
<th></th>
<th>[1,]</th>
<th>[2,]</th>
<th>[3,]</th>
<th>[4,]</th>
<th>[5,]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1,]</td>
<td>1.000000</td>
<td>0.771588</td>
<td>0.771588</td>
<td>0.771588</td>
<td>0.771588</td>
</tr>
<tr>
<td>[2,]</td>
<td>0.771588</td>
<td>1.000000</td>
<td>0.771588</td>
<td>0.771588</td>
<td>0.771588</td>
</tr>
<tr>
<td>[3,]</td>
<td>0.771588</td>
<td>0.771588</td>
<td>1.000000</td>
<td>0.771588</td>
<td>0.771588</td>
</tr>
<tr>
<td>[4,]</td>
<td>0.771588</td>
<td>0.771588</td>
<td>0.771588</td>
<td>1.000000</td>
<td>0.771588</td>
</tr>
<tr>
<td>[5,]</td>
<td>0.771588</td>
<td>0.771588</td>
<td>0.771588</td>
<td>0.771588</td>
<td>1.000000</td>
</tr>
</tbody>
</table>

A negative coefficient for post:progabide suggests a greater reduction in number of seizures for the treatment group compared with the control group.
Illustration of *over-dispersed* seizure count data.

```r
> seizew <- reshape(seize[, c("id", "seizure", "week", "progabide")], 
+ direction = "wide", v.names = "seizure", timevar = "week", idvar = "id")
>
> Treated <- apply(seizew[seizew[,"progabide"]==1,3:6],2,var)/apply(
+ seizew[seizew[,"progabide"]==1,3:6],2,mean)
>
> Placebo <- apply(seizew[seizew[,"progabide"]==0,3:6],2,var)/apply(
+ seizew[seizew[,"progabide"]==0,3:6],2,mean)
>
> #Table 8.8 in DHLZ book, variance-to-mean ratios
>
> round(rbind(Treated,Placebo),2)

<table>
<thead>
<tr>
<th></th>
<th>seizure.1</th>
<th>seizure.2</th>
<th>seizure.3</th>
<th>seizure.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>38.78</td>
<td>16.71</td>
<td>23.75</td>
<td>18.91</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.98</td>
<td>8.04</td>
<td>24.50</td>
<td>7.31</td>
</tr>
</tbody>
</table>
```
We can also allow the dispersion parameter to differ between the treatment and placebo group by fitting Yan and Fine (2004)'s model.

```r
> library(geepack)
> sg2 <- geese (seizure ~ post + progabide + post:progabide + 
+     offset (log(time)), sformula = ~ progabide, 
+     data = seize.full, id = id, family = "poisson", 
+     corstr = "exchangeable")
> summary (sg2)
```

Call:
```
geese(formula = seizure ~ post + progabide + post:progabide +
     offset(log(time)), sformula = ~ progabide, id = id, data = seize.full,
     family = "poisson", corstr = "exchangeable")
```

Mean Model:
```
Mean Link: log
Variance to Mean Relation: poisson
```

Coefficients:
```
            estimate  san.se   wald    p
(Intercept)  1.34760922 0.1620151 69.186 1.110e-16
post        0.11079814 0.1203986 0.847 3.574e-01
progabide   0.02651461 0.2251817 0.014 9.062e-01
post:progabide -0.10368067 0.2159766 0.230 6.312e-01
```

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Scale Model:
   Scale Link: identity

Estimated Scale Parameters:
   estimate    san.se    wald    p
(Intercept) 14.228486  4.592945  9.596986  0.001948970
 progabide   9.910183  16.657605  0.353947  0.551887297

Correlation Model:
   Correlation Structure: exchangeable
   Correlation Link: identity

Estimated Correlation Parameters:
   estimate    san.se    wald    p
    alpha    0.7451173  0.08256208 81.44944 0

Returned Error Value: 0
Number of clusters: 59    Maximum cluster size: 5
For illustration, we assume an exchangeable correlation structure where the correlation may depend on age.

\[
\text{Cor}(Y_{ij}, Y_{ik}) = \rho_i \\
\log \left( \frac{1 + \rho_i}{1 - \rho_i} \right) = \alpha_1 + \text{Age}_i \alpha_2
\]

This model can be fitted using \texttt{geese}. The design matrix for the correlation model has to be constructed by hand. The matrix \textit{Z} has the same number of rows as the number of clusters (the covariate should be invariant within a cluster).

```r
> z <- cbind(1, seize.full$age[seize.full$week == 0])
> sg2 <- geese(seizure ~ progabide + post + post:progabide + 
+ offset(log(time)), sformula = ~ progabide,
+ data = seize.full, id = id, family = "poisson",
+ cor.link = "fisherz", zcor = z, corstr = "exchangeable")
> summary(sg2)
```

Call:
```
geese(formula = seizure ~ progabide + post + post:progabide +
      offset(log(time)), sformula = ~ progabide, id = id, data = seize.full,
      zcor = z, family = "poisson", cor.link = "fisherz", corstr = "exchangeable")
```

Mean Model:
```
Mean Link: log
Variance to Mean Relation: poisson
```
Coefficients:

<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>san.se</th>
<th>wald</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.4137</td>
<td>0.16974</td>
<td>6.9365</td>
<td>1.110223e-16</td>
</tr>
<tr>
<td>progabide</td>
<td>0.0035</td>
<td>0.2227</td>
<td>2.4998</td>
<td>9.873851e-01</td>
</tr>
<tr>
<td>post</td>
<td>0.1194</td>
<td>0.1448</td>
<td>6.8065</td>
<td>4.093612e-01</td>
</tr>
<tr>
<td>progabide:post</td>
<td>-0.3211</td>
<td>0.2880</td>
<td>1.2430</td>
<td>2.648795e-01</td>
</tr>
</tbody>
</table>

Scale Model:

Scale Link: identity

Estimated Scale Parameters:

<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>san.se</th>
<th>wald</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>13.3031</td>
<td>4.1888</td>
<td>10.086</td>
<td>0.001493814</td>
</tr>
<tr>
<td>progabide</td>
<td>14.3061</td>
<td>19.0404</td>
<td>0.5645</td>
<td>0.452439804</td>
</tr>
</tbody>
</table>

Correlation Model:

Correlation Structure: exchangeable

Correlation Link: fisherz

Estimated Correlation Parameters:

<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>san.se</th>
<th>wald</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha:1</td>
<td>5.8652</td>
<td>2.8087</td>
<td>4.3606</td>
<td>0.03677934</td>
</tr>
<tr>
<td>alpha:2</td>
<td>-0.1370</td>
<td>0.0813</td>
<td>2.8346</td>
<td>0.09225342</td>
</tr>
</tbody>
</table>

Returned Error Value: 0

Number of clusters: 59  Maximum cluster size: 5
Further Reading

- Chapter 8 of DHLZ.