CHAPTER 13

Analysing Longitudinal Data II –
Generalised Estimation Equations and
Linear Mixed Effect Models: Treating
Respiratory Illness and Epileptic Seizures

13.1 Introduction

13.2 Methods for Non-normal Distributions

13.3 Analysis Using R: GEE

13.3.1 Beat the Blues Revisited

To use the gee function, package gee (Carey et al., 2012) has to be installed and attached:

R> library("gee")

The gee function is used in a similar way to the lme function met in Chapter 12 with the addition of the features of the glm function that specify the appropriate error distribution for the response and the implied link function, and an argument to specify the structure of the working correlation matrix. Here we will fit an independence structure and then an exchangeable structure. The R code for fitting generalised estimation equations to the BtheB_long data (as constructed in Chapter 12) with identity working correlation matrix is as follows (note that the gee function assumes the rows of the data.frame BtheB_long to be ordered with respect to subjects):

R> osub <- order(as.integer(BtheB_long$subject))
R> BtheB_long <- BtheB_long[osub,]
R> btb_gee <- gee(bdi ~ bdi.pre + trt + length + drug,
+     data = BtheB_long, id = subject, family = gaussian,
+     corstr = "independence")

and with exchangeable correlation matrix:

R> btb_gee1 <- gee(bdi ~ bdi.pre + trt + length + drug,
+     data = BtheB_long, id = subject, family = gaussian,
+     corstr = "exchangeable")

The summary method can be used to inspect the fitted models; the results are shown in Figures 13.1 and 13.2.
Example R code and output for analyzing longitudinal data using GEE (Generalized Estimating Equations) in R:

```r
R> summary(btb_gee)

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

Model:
Link: Identity
Variance to Mean Relation: Gaussian
Correlation Structure: Independent

Call:
gee(formula = bdi ~ bdi.pre + trt + length + drug, id = subject,
data = BtheB_long, family = gaussian, corstr = "independence")

Summary of Residuals:

Min 1Q Median 3Q Max
-21.650 -5.849 0.113 5.584 28.187

Coefficients:

Estimate Naive S.E. Naive z Robust S.E. Robust z
(Intercept) 3.569 1.4833 2.41 2.2695 1.572
bdi.pre 0.582 0.0564 10.32 0.0916 6.355
trtBtheB -3.237 1.1296 -2.87 1.7746 -1.824
length>6m 1.458 1.1380 1.28 1.4826 0.983
drugYes -3.741 1.1766 -3.18 1.7827 -2.099

Estimated Scale Parameter: 79.3
Number of Iterations: 1

Working Correlation

[1,] 1 0 0 0
[2,] 0 1 0 0
[3,] 0 0 1 0
[4,] 0 0 0 1

Figure 13.1  R output of the summary method for the btb_gee model (slightly abbreviated).

13.3.2 Respiratory Illness

The baseline status, i.e., the status for month == 0, will enter the models as an explanatory variable and thus we have to rearrange the data.frame respiratory in order to create a new variable baseline:

```r
R> data("respiratory", package = "HSAUR2")
R> resp <- subset(respiratory, month > "0")
R> resp$baseline <- rep(subset(respiratory, month == "0")$status,
+ rep(4, 111))
R> resp$nstat <- as.numeric(resp$status == "good")
R> resp$month <- resp$month[, drop = TRUE]

The new variable nstat is simply a dummy coding for a poor respiratory status. Now we can use the data resp to fit a logistic regression model and GEE models with an independent and an exchangeable correlation structure as follows.

```r
R> resp_glm <- glm(status ~ centre + trt + gender + baseline
```
ANALYSIS USING R: GEE

R> summary(btb_gee1)

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

Model:
Link: Identity
Variance to Mean Relation: Gaussian
Correlation Structure: Exchangeable

Call:
gee(formula = bdi ~ bdi.pre + trt + length + drug, id = subject,
data = BtheB_long, family = gaussian, corstr = "exchangeable")

Summary of Residuals:
    Min 1Q Median 3Q Max
-23.96 -6.64 -1.11 4.26 25.45

Coefficients:

                        Estimate Naive S.E. Naive z Robust S.E. Robust z
(Intercept)          3.023 2.3039 1.3122 2.2320 1.3544
bdi.pre             0.648 0.0823 7.8741 0.0835 7.7583
trtBtheB           -2.169 1.7664 -1.2281 1.7361 -1.2495
length>6m           -0.111 1.7309 -0.0643 1.5509 -0.0718
drugYes             -3.000 1.8257 -1.6430 1.7316 -1.7323

Estimated Scale Parameter: 81.7
Number of Iterations: 5

Working Correlation

[1,] 1.000 0.676 0.676 0.676
[2,] 0.676 1.000 0.676 0.676
[3,] 0.676 0.676 1.000 0.676
[4,] 0.676 0.676 0.676 1.000

Figure 13.2  R output of the summary method for the btb_gee1 model (slightly abbreviated).

+ + age, data = resp, family = "binomial")
R> resp_gee1 <- gee(nstat ~ centre + trt + gender + baseline + + age, data = resp, family = "binomial", id = subject, + + corstr = "independence", scale.fix = TRUE, + + scale.value = 1)
R> resp_gee2 <- gee(nstat ~ centre + trt + gender + baseline + + age, data = resp, family = "binomial", id = subject, + + corstr = "exchangeable", scale.fix = TRUE, + + scale.value = 1)

The estimated treatment effect taken from the exchangeable structure GEE model is 1.299 which, using the robust standard errors, has an associated 95% confidence interval

R> se <- summary(resp_gee2)$coefficients["trttrt", + + "Robust S.E."]
R> coef(resp_gee2)["trttrt"] + + c(-1, 1) * se * qnorm(0.975)
R> summary(resp_glm)

Call:
glm(formula = status ~ centre + trt + gender + baseline + age,
    family = "binomial", data = resp)

Deviance Residuals:
     Min       1Q   Median       3Q      Max
-2.315   -0.855    0.434    0.895    1.925

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.90017    0.33765  -2.67  0.0077
centre2     0.67160    0.23957   2.80  0.0051
trttrt      1.29922    0.23684   5.49  4.1e-08
gendermale  0.11924    0.29467   0.40  0.6857
baselinegood 1.88203    0.24129   7.80  6.2e-15
age        -0.01817    0.00886  -2.05  0.0404

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 608.93 on 443 degrees of freedom
Residual deviance: 483.22 on 438 degrees of freedom
AIC: 495.2

Number of Fisher Scoring iterations: 4

Figure 13.3  R output of the summary method for the resp_glm model.

[1] 0.612 1.987

These values reflect effects on the log-odds scale. Interpretation becomes simpler if we exponentiate the values to get the effects in terms of odds. This gives a treatment effect of 3.666 and a 95% confidence interval of

R> exp(coef(resp_glm)="trttrt") +
+c(-1, 1) * se * qnorm(0.975))

[1] 1.84 7.29

The odds of achieving a 'good' respiratory status with the active treatment is between about twice and seven times the corresponding odds for the placebo.

13.3.3 Epilepsy

Moving on to the count data in epilepsy from Table ??, we begin by calculating the means and variances of the number of seizures for all interactions between treatment and period:

R> data("epilepsy", package = "HSAUR2")
R> itp <- interaction(epilepsy$period)
R> tapply(epilepsy$seizure.rate, itp, mean)

placebo.1  Progabide.1  placebo.2  Progabide.2  placebo.3  Progabide.3  placebo.4  Progabide.4
    9.36     8.58     8.29     8.42     8.79     8.13     7.96     6.71
ANALYSIS USING R: GEE

R> summary(resp_gee1)

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 = nstat ~ centre + trt + gender + baseline + age, 
id = subject, data = resp, family = "binomial", corstr = "independence", 
scale.fix = TRUE, scale.value = 1)

Summary of Residuals:
Min  1Q Median  3Q Max
-0.9313 -0.3062  0.0897  0.3302  0.8431

Coefficients:
Estimate   Naive S.E.   Naive z   Robust S.E.   Robust z
(Intercept) -0.9002   0.33765   -2.666   0.460   -1.956
centre2   0.6716   0.23957    2.803   0.357    1.882
trttrt  1.2992   0.23684    5.486   0.351    3.704
gendermale   0.1192   0.29467    0.405   0.443    0.269
baselinegood   1.8820   0.24129    7.800   0.350    5.376
age   -0.0182   0.00886   -2.049   0.013   -1.397

Estimated Scale Parameter: 1
Number of Iterations: 1

Working Correlation
[1,] 1 0 0 0
[2,] 0 1 0 0
[3,] 0 0 1 0
[4,] 0 0 0 1

Figure 13.4 R output of the summary method for the resp_gee1 model (slightly abbreviated).

R> tapply(epilepsy$seizure.rate, itp, var)

           placebo.1 Pregabide.1 placebo.2 Pregabide.2 placebo.3        Pregabide.3 placebo.4 Pregabide.4
placebo.1 102.8        332.7      66.7       140.7      215.3        193.0      58.2     126.9
placebo.2   49.7        173.3      38.4       103.5      106.1        101.4       91.9
placebo.3  103.0         84.4       89.2       158.8      192.1        169.0     104.5
Pregabide.1 374.8        381.5      91.7       144.4      123.0        329.1     110.5
Pregabide.2  77.3         97.3       77.3       111.7       77.3        106.4     110.5
Pregabide.3  75.5         87.4       29.1       141.4    121.7       177.5     104.5

Some of the variances are considerably larger than the corresponding means, which for a Poisson variable may suggest that overdispersion may be a problem, see Chapter 7.

We can now fit a Poisson regression model to the data assuming independence using the glm function. We also use the GEE approach to fit an independence structure, followed by an exchangeable structure using the following R code:

R> per <- rep(log(2),nrow(epilepsy))
R> epilepsy$period <- as.numeric(epilepsy$period)
R> summary(resp_gee2)

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: Exchangeable

Call:
  gee(formula = nstat ~ centre + trt + gender + baseline + age,
       id = subject, data = resp, family = "binomial", corstr = "exchangeable",
       scale.fix = TRUE, scale.value = 1)

Summary of Residuals:

  Min 1Q Median 3Q Max
-0.9313 -0.3062 0.0897 0.3302 0.8431

Coefficients:

  Estimate Naive S.E. Naive z Robust S.E. Robust z
(Intercept) -0.9002 0.4785 -1.881 0.460 -1.956
centre2 0.6716 0.3395 1.978 0.357 1.882
trt 1.2992 0.3356 3.871 0.351 3.704
gendermale 0.1192 0.4176 0.286 0.443 0.269
baselinegood 1.8820 0.3419 5.504 0.350 5.376
age -0.0182 0.0126 -1.446 0.013 -1.397

Estimated Scale Parameter: 1
Number of Iterations: 1

Working Correlation

[1,] 1.000 0.336 0.336 0.336
[2,] 0.336 1.000 0.336 0.336
[3,] 0.336 0.336 1.000 0.336
[4,] 0.336 0.336 0.336 1.000

Figure 13.5 R output of the summary method for the resp_gee2 model (slightly abbreviated).

R> names(epilepsy)[names(epilepsy) == "treatment"] <- "trt"
R> fm <- seizure.rate ~ base + age + trt + offset(per)
R> epilepsy_glm <- glm(fm, data = epilepsy, family = "poisson")
R> epilepsy_gee1 <- gee(fm, data = epilepsy, family = "poisson",
                       id = subject, corstr = "independence", scale.fix = TRUE,
                       + scale.value = 1)
R> epilepsy_gee2 <- gee(fm, data = epilepsy, family = "poisson",
                       + id = subject, corstr = "exchangeable", scale.fix = TRUE,
                       + scale.value = 1)
R> epilepsy_gee3 <- gee(fm, data = epilepsy, family = "poisson",
                       + id = subject, corstr = "exchangeable", scale.fix = FALSE,
                       + scale.value = 1)

As usual we inspect the fitted models using the summary method, the results are given in Figures 13.8, 13.9, 13.10 and 13.11.
**ANALYSIS USING R: RANDOM EFFECTS**

R> layout(matrix(1:2, nrow = 1))
R> ylim <- range(epilepsy$seizure.rate)
R> placebo <- subset(epilepsy, treatment == "placebo")
R> progabide <- subset(epilepsy, treatment == "Progabide")
R> boxplot(seizure.rate ~ period, data = placebo,
+ ylab = "Number of seizures",
+ xlab = "Period", ylim = ylim, main = "Placebo")
R> boxplot(seizure.rate ~ period, data = progabide,
+ main = "Progabide", ylab = "Number of seizures",
+ xlab = "Period", ylim = ylim)

![Boxplots of numbers of seizures in each two-week period post randomisation for placebo and active treatments.](image)

**Figure 13.6**  Boxplots of numbers of seizures in each two-week period post randomisation for placebo and active treatments.

**13.4 Analysis Using R: Random Effects**

As an example of using generalised mixed models for the analysis of longitudinal data with a non-normal response, the following logistic model will be fitted to the respiratory illness data

\[
\logit(P(\text{status} = \text{good})) = \beta_0 + \beta_1 \text{treatment} + \beta_2 \text{time} + \beta_3 \text{gender} \\
+ \beta_4 \text{age} + \beta_5 \text{centre} + \beta_6 \text{baseline} + u
\]

where \(u\) is a subject-specific random effect.

The necessary R code for fitting the model using the \texttt{glmer} function from package \texttt{lme4} ([Bates and Sarkar], [Bates]) is:

R> library("lme4")
R> layout(matrix(1:2, nrow = 1))
R> ylim <- range(log(epilepsy$seizure.rate + 1))
R> boxplot(log(seizure.rate + 1) ~ period, data = placebo,
+     main = "Placebo", ylab = "Log number of seizures",
+     xlab = "Period", ylim = ylim)
R> boxplot(log(seizure.rate + 1) ~ period, data = progabide,
+     main = "Progabide", ylab = "Log number of seizures",
+     xlab = "Period", ylim = ylim)

![Boxplots of log of numbers of seizures in each two-week period post randomisation for placebo and active treatments.](image)

Figure 13.7  Boxplots of log of numbers of seizures in each two-week period post randomisation for placebo and active treatments.

R> resp_lmer <- glmer(status ~ baseline + month +
+     trt + gender + age + centre + (1 | subject),
+     family = binomial(), data = resp)
R> exp(fixef(resp_lmer))

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>month.L</th>
<th>month.Q</th>
<th>month.C</th>
<th>trt</th>
<th>gender</th>
<th>age</th>
<th>centre2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.191</td>
<td>21.954</td>
<td>0.816</td>
<td>0.972</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>month.L</td>
<td>0.816</td>
<td>0.972</td>
<td>0.191</td>
<td>21.954</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>month.Q</td>
<td>0.972</td>
<td>0.191</td>
<td>21.954</td>
<td>0.816</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>month.C</td>
<td>0.191</td>
<td>21.954</td>
<td>0.816</td>
<td>0.972</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trt</td>
<td>0.701</td>
<td>8.725</td>
<td>1.269</td>
<td>0.975</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gendermale</td>
<td>0.701</td>
<td>8.725</td>
<td>1.269</td>
<td>0.975</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>0.701</td>
<td>8.725</td>
<td>1.269</td>
<td>0.975</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>centre2</td>
<td>0.701</td>
<td>8.725</td>
<td>1.269</td>
<td>0.975</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The significance of the effects as estimated by this random effects model and by the GEE model described in Section 13.3.2 is generally similar. But as expected from our previous discussion the estimated coefficients are substantially larger. While the estimated effect of treatment on a randomly sampled
ANALYSIS USING R: RANDOM EFFECTS

R> summary(epilepsy_glm)

Call:
glm(formula = fm, family = "poisson", data = epilepsy)

Deviance Residuals:
  Min     1Q   Median     3Q    Max
-4.436 -1.403  -0.503  0.484 12.322

Coefficients:
                     Estimate Std. Error z value Pr(>|z|)
(Intercept)     -0.130616    0.135619  -0.96 0.3355
base            0.022652     0.000509  44.48 < 2e-16
age             0.022740     0.004024   5.65 1.6e-08
trtProgabide   -0.152701     0.047805  -3.19 0.0014

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 2521.75 on 235 degrees of freedom
Residual deviance: 958.46 on 232 degrees of freedom
AIC: 1732

Number of Fisher Scoring iterations: 5

Figure 13.8  R output of the summary method for the epilepsy_glm model.

individual, given the set of observed covariates, is estimated by the marginal model using GEE to increase the log-odds of being disease free by 1.299, the corresponding estimate from the random effects model is 2.166. These are not inconsistent results but reflect the fact that the models are estimating different parameters. The random effects estimate is conditional upon the patient’s random effect, a quantity that is rarely known in practice. Were we to examine the log-odds of the average predicted probabilities with and without treatment (averaged over the random effects) this would give an estimate comparable to that estimated within the marginal model.
R> summary(epilepsy_gee1)

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

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

Call:
gee(formula = fm, id = subject, data = epilepsy, family = "poisson",
    corstr = "independence", scale.fix = TRUE, scale.value = 1)

Summary of Residuals:
    Min 1Q Median 3Q Max
-4.920 0.181 1.707 4.885 69.966

Coefficients:
                     Estimate Naive S.E. Naive z Robust S.E. Robust z
(Intercept)       -0.1306  0.135619  -0.963  0.36515  -0.358
base              0.0227  0.000509   44.476  0.00124  18.332
age               0.0227  0.004024    5.651  0.01158   1.964
trtProgabide     -0.1527  0.047805  -3.194  0.17111  -0.892

Estimated Scale Parameter: 1
Number of Iterations: 1

Working Correlation

[1,] 1 0 0 0
[2,] 0 1 0 0
[3,] 0 0 1 0
[4,] 0 0 0 1

Figure 13.9  R output of the summary method for the epilepsy_gee1 model (slightly abbreviated).
R> summary(epilepsy_gee2)

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

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

Call:
gee(formula = fm, id = subject, data = epilepsy, family = "poisson",
corstr = "exchangeable", scale.fix = TRUE, scale.value = 1)

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>-4.920</td>
<td>0.181</td>
<td>1.707</td>
<td>4.885</td>
<td>69.966</td>
</tr>
</tbody>
</table>

Coefficients:

<table>
<thead>
<tr>
<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>-0.1306</td>
<td>0.200442</td>
<td>-0.652</td>
<td>0.36515</td>
</tr>
<tr>
<td>base</td>
<td>0.0227</td>
<td>0.000753</td>
<td>30.093</td>
<td>0.00124</td>
</tr>
<tr>
<td>age</td>
<td>0.0227</td>
<td>0.005947</td>
<td>3.824</td>
<td>0.01158</td>
</tr>
<tr>
<td>trtProbide</td>
<td>-0.1527</td>
<td>0.070655</td>
<td>-2.161</td>
<td>0.17111</td>
</tr>
</tbody>
</table>

Estimated Scale Parameter: 1
Number of Iterations: 1

Working Correlation

```
[1,] 1.000 0.395 0.395 0.395
[2,] 0.395 1.000 0.395 0.395
[3,] 0.395 0.395 1.000 0.395
[4,] 0.395 0.395 0.395 1.000
```

Figure 13.10 R output of the summary method for the epilepsy_gee2 model (slightly abbreviated).
R> summary(epilepsy_gee3)
GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
gg S-function, version 4.13 modified 98/01/27 (1998)

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

Call:
gee(formula = fm, id = subject, data = epilepsy, family = "poisson",
corstr = "exchangeable", scale.fix = FALSE, scale.value = 1)

Summary of Residuals:
       Min 1Q Median 3Q Max
-4.920 0.181 1.707 4.885 69.966

Coefficients:
                     Estimate Naive S.E. Naive z Robust S.E. Robust z
(Intercept)   -0.1306 0.4522 -0.289 0.36515 -0.358
base          0.0227 0.0017 13.339 0.00124 18.332
age           0.0227 0.0134 1.695 0.01158 1.964
trtProgabide  -0.1527 0.1594 -0.958 0.17111 -0.892

Estimated Scale Parameter: 5.09
Number of Iterations: 1

Working Correlation
[1,]    1.000 0.395 0.395 0.395
[2,]    0.395 1.000 0.395 0.395
[3,]    0.395 0.395 1.000 0.395
[4,]    0.395 0.395 0.395 1.000

Figure 13.11 R output of the summary method for the epilepsy_gee3 model (slightly abbreviated).

R> summary(resp_lmer)

Fixed effects:
                        Estimate Std. Error t value Pr(>|t|)
(Intercept)             -1.6546   0.7762  -2.13  0.033
baselinegood            3.0890   0.5986   5.16  2.5e-07
month.L                 -0.2035   0.2796  -0.73  0.467
month.Q                 -0.0282   0.2792  -0.10  0.919
month.C                 -0.3557   0.2808  -1.27  0.205
trttrt                  2.1662   0.5516   3.93  8.6e-05
gendermale              0.2384   0.6661   0.36   0.720
age                     -0.0256   0.0199  -1.28   0.200
centre2                 1.0385   0.5418   1.92   0.055

Figure 13.12 R output of the summary method for the resp_lmer model (abbreviated).
Bibliography

