Depression Study:

Longitudinal study of 340 subjects suffering from mental depression to compare the effectiveness of a new drug with a standard drug. Following 1 week, 2 weeks, and 4 weeks of treatment, each subject’s suffering from mental depression was classified as normal or abnormal.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Response at Three Times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NNN</td>
</tr>
<tr>
<td>Mild</td>
<td>Standard</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>New</td>
<td>31</td>
</tr>
<tr>
<td>Severe</td>
<td>Standard</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>New</td>
<td>7</td>
</tr>
</tbody>
</table>

Let,

- $t$ denote the time of measurement using score $t = \log_2(\text{week})$
- $Y_t = \begin{cases} 
1 & \text{normal} \\
0 & \text{abnormal} 
\end{cases}$
- $s = \begin{cases} 
1 & \text{severe} \\
0 & \text{mild} 
\end{cases}$
- $d = \begin{cases} 
1 & \text{new} \\
0 & \text{standard} 
\end{cases}$

The model is,

$$
\log \left[ \frac{P(Y_t = 1)}{P(Y_t = 0)} \right] = \alpha + \beta_1 s + \beta_2 d + \beta_3 t + \beta_4 (d \times t)
$$

with an interaction term $d \times t$ to allow a variable time effect under each treatment,

- time effect = $\begin{cases} 
\beta_3 & \text{if } d = 0 \text{ standard drug} \\
\beta_3 + \beta_4 & \text{if } d = 1 \text{ new drug} 
\end{cases}$

```r
> library(gee)
> depression=read.table("http://www.stat.ufl.edu/~dathien/STA4504/depression.txt", + header=TRUE)
> head(depression)
subject severity drug time response
1    1   mild std  0     normal
2    1   mild std  1     normal
3    1   mild std  2     normal
4    2   mild std  0     normal
5    2   mild std  1     normal
6    2   mild std  2     normal

> dep.gee1=gee(~ response ~ severity + drug*time, + id=subject, data=depression, family=binomial, corstr="exchangeable", + contrasts=list(drug=contr.treatment(2,base=2,contrasts=TRUE)))

(Intercept) severitysevere drugstd time drugstd:time
-0.08759224   -1.31391092   0.05960381   1.49985707   -1.01744498
```
> summary(dep.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: Exchangeable

**Call:**
gee(formula = (response == "normal") ~ severity + drug * time,
   id = subject, data = depression, family = binomial, corstr = "exchangeable",
   contrasts = list(drug = contr.treatment(2, base = 2, contrasts = TRUE)))

**Summary of Residuals:**

<table>
<thead>
<tr>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.94843397</td>
<td>-0.40683122</td>
<td>0.05156603</td>
<td>0.38832332</td>
<td>0.80238627</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>-0.02809866</td>
<td>0.1625499</td>
<td>-0.1728617</td>
<td>0.1741791</td>
</tr>
<tr>
<td>severitysevere</td>
<td>-1.31391033</td>
<td>0.1448627</td>
<td>-9.0700417</td>
<td>0.1459630</td>
</tr>
<tr>
<td>drug1</td>
<td>-0.05926689</td>
<td>0.2205340</td>
<td>-0.2687427</td>
<td>0.2285569</td>
</tr>
<tr>
<td>time</td>
<td>0.48246420</td>
<td>0.1141154</td>
<td>4.2278625</td>
<td>0.1199383</td>
</tr>
<tr>
<td>drug1:time</td>
<td>1.01719312</td>
<td>0.1877051</td>
<td>5.4191018</td>
<td>0.1877014</td>
</tr>
</tbody>
</table>

Estimated Scale Parameter: 0.985392
Number of Iterations: 5

**Working Correlation**

```
[,1]  [,2]  [,3]
[1,] 1.0000000000 -0.003432729 -0.003432729
[2,] -0.003432729 1.0000000000 -0.003432729
[3,] -0.003432729 -0.003432729 1.0000000000
```

- The test of $H_0: \beta_4 = 0$ (no interaction) is

  \[
  \frac{\hat{\beta}_4}{SE} = 5.42
  \]

  indicating a faster improvement for the new drug.

- When the initial diagnosis is severe ($s = 1$), the estimated odds of normal response are

  \[ \exp(-1.313911) = 0.27 \]

  times the estimated odds when initial diagnosis is mild, at each $d \times t$ combination

- At $t = 0$, the drug effect is only $\hat{\beta}_2 = -0.059604$ (as interaction term is 0). The odds ratio is

  \[ \exp(-0.059604) = 0.94 \approx 1 \]

  so in effect there is no drug effect at $t = 0$, which is after 1 week of treatment.

  The estimated odds of a normal response under the new drug at the end of the study ($t = 2$) is estimated to be

  \[ \exp(\hat{\beta}_2 + 2\hat{\beta}_4) = 7.2 \]

  times the estimated odds under the standard drug.
• Estimated time effects are

\[
\text{time effect} = \begin{cases} 
0.482412 & \text{if } d = 0 \text{ standard drug} \\
0.482412 + 1.017445 & \text{if } d = 1 \text{ new drug}
\end{cases}
\]

• Other interactions were not found to be significant, so not included.

• Estimated \( \rho \) in correlation matrix are close to 0 so we fit a model with independence correlation structure for comparison.

```r
> dep.gee2 = gee((response == "normal") ~ severity + drug*time, 
+ id=subject, data=depression, family=binomial, 
+ contrasts=list(drug=contr.treatment(2, base=2, contrasts=TRUE)))
```

(Intercept) severitysevere drugstd time drugstd:time
-0.08759224 -1.31391092 0.05960381 1.49985707 -1.01744498

> summary(dep.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: Independent

Call:
gee(formula = (response == "normal") ~ severity + drug * time, 
    id = subject, data = depression, family = binomial, 
    contrasts = list(drug = contr.treatment(2, base = 2, contrasts = TRUE)))

Summary of Residuals:

<table>
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<th></th>
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<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.94844242</td>
<td>-0.40683252</td>
<td>0.05155758</td>
<td>0.38830952</td>
<td>0.80242231</td>
</tr>
</tbody>
</table>

Coefficients:

Coefficients: Estimate Naive S.E. Naive z Robust S.E. Robust z
(Intercept) -0.02798843 0.1627083 -0.1720160 0.1741865 -0.1606808
severitysevere -1.31391092 0.1453432 -9.0400569 0.1459845 -9.0003423
drug1 -0.05960381 0.2205812 -0.2702126 0.2285385 -0.2608042
time 0.48241209 0.1139224 4.2345663 0.1199350 4.0222784
drug1:time 1.01744498 0.1874132 5.4288855 0.1876938 5.4207709

Estimated Scale Parameter: 0.9854113
Number of Iterations: 5

Working Correlation

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